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Research Paper

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KEYWORDS : pleural effusion, transudate, exudate.

Serum- Pleural Fluid Albumin Gradient in The Evaluation of Pleural Effusion

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ABSTRACT

Pleural effusion is a common complication of many disease processes where differentiation between transudate & exudate is necessary to assist in differential diagnosis. Presently Light's criteria are used to distinguish between transudate & exudates. But many pleural effusions are misclassified by using these criteria. Objective of the present study was to assess the usefulness of Serum Pleural fluid Albumin gradient as a marker to differentiate exudates from transudate

INTRODUCTION:

Pleural efusion is one of the commonest presenting features, which can be due to varied etiology ranging from relatively benign to highly malignant conditions. Recent advanced techniques have increased the accuracy of distinguishing transudative from exudative effusions and to chemically analyse and culture pleural fluids have improved the sensitivity and specificity of diagnostic procedures. However, despite the employment of extensive diagnostic procedures the cause remains elusive in as many as 20 percent of the cases.

Light's Criteria[1]had a better success in differentiating between transudate and exudates since it is based on a combination of both protein and LDH criteria. Several studies evaluating the alternative criteria were published with shared opinion regarding the sensitivity and specificity of Serum Pleural Albumin Gradient. In keeping with the raised hope of probable superiority of combination of tests, which include albumin gradient[1], it was decided to carry out the comparative study of Light's criteria Vs Serum Pleural fluid Albumin Gradient to differentiate Exudates from Transudates.

AIMS AND OBJECTIVES

To assess the usefulness of Serum-Pleural fluid Albumin Gradient (SPAG) as a marker to differentiate EXUDATE from TRANSUDATE.

To compare the efficacy of Serum-Pleural fluid Albumin Gradient (SPAG) with Light's criteria.

MATERIALS AND METHODS

- Study period - June 2010 to June 2011.
- 88 patients who were admitted in our hospital were taken in the study.
- Pleural fluid and serum specimen were drawn from each patient preferably simultaneously, but within 24 hrs was accepted.
- EXCLUSION CRITERIA : Obscure diagnosis
  Undiagnosed cases
  Frank hemothorax
- The effusions were classified as transudates or exudates on the basis of their diagnosis.

OBSERVATION AND RESULTS

In total 88 cases were analyzed of which 72 were exudates (81.81%) and 16 were transudates (18.18%). Of the exudative effusions, 30 were Tuberculous (41.67%), and 22 were malignant (30.56%). Of the transudative effusions, 5 cases of CCF (31.25%) and 4 cases each of CRF and cirrhosis (25% each) were present

Age of the patients in this study ranged from 14-18 years, the mean age being 46.2yrs (SD-15.9yrs)

There was a significant difference between the mean ages of patients with tuberculous effusion 39.1 yrs (SD=15.84) and malignant effusion 53.14yrs (SD=15.84) (p=0.017).

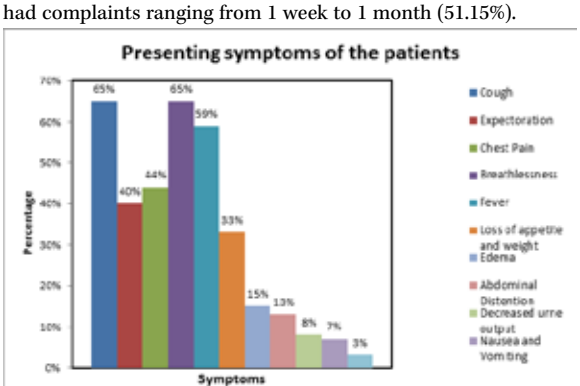
Mean age for patients with trasudates was 50.6yrs (SD=15.97yrs) and for patients with CCF mean age of 60.2yrs, patients with CRF mean age of 46.5, and Cirrhosis 49.5yrs.

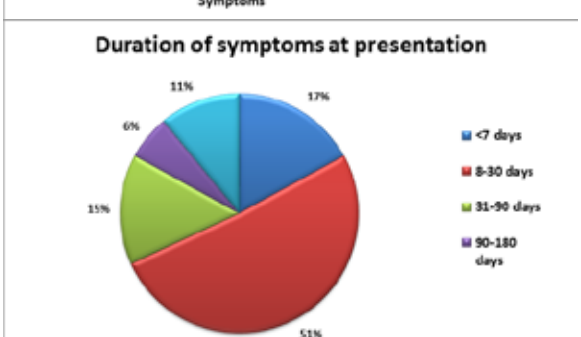
Of the 88 cases of effusion, 62 were male (70.5%) and 26 were female (29.5%).

Of the exudates, 53 were male and 19 were female with significant disparity in sex distribution in case of tuberculosis where male: female was 5:1.

In case of exudates no significant difference between right and left sided effusions were noted, where as in case of transudates clinically right sided effusions were twice as common as left (68.75% vs.31.25%).

Cough, expectoration, breathlessness, fever and chest pain were the predominant presenting symptoms. Majority of the patients had complaints ranging from 1 week to 1 month (51.15%).





Tuberculosis was diagnosed based on pleural biopsy, pleural fluid cytology, culture or AFB staining, pleural fluid ADA, spu-

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tum AFB, pleural fluid lymphocyte predominance, Lymph node biopsy and Mantoux test. In 6 cases, a presumptive diagnosis of tuberculosis was made considering the clinical features, ESR, pleural fluid lymphocyte, relief of symptoms and resolution of effusion with ATT, all of which suggested a tuberculous etiology to be most likely.

Pleural biopsy was suggestive of TB pleuritis in 5 out of 8 patients on whom it was done.

Pleural fluid ADA (>43U/L) suggestive of tuberculous effusion was positive in 12 out of 13 patients in whom it was done.

Mantoux test was positive in 9 out of 17 patients who were tested.

Table : Comparison of Light's criteria and SPAG in the 2 groups.

Parameter		Exudates n-67	Transudates n-16
PF-S protein ratio	Mean	0.67	0.33
	Range	0.37-0.95	0.05-0.62
	SD	0.12	0.17
PF-S LDH Ratio	Mean	2.165	0.58
	Range	0.02-19.7	0.07-1.94
	SD	3.30	0.46
PF-LDH	Mean	1998	328
	Range	8-24700	70-1272
	SD	3971	308
SPAG	Mean	0.87	1.78
	Range	0-3.4	1.3-2.8
	SD	0.568	0.52

In this study, mean SPAG for transudate is 1.78 gm/dl, for tubercular effusion 0.84gm/dl, for malignant effusions 1.10gm/dl and the mean SPAG for synpneumonic effusion is 0.61 gm/dl. All the exudates groups had a lower SPAG than transudate

The differences in the mean values for tubercular, synpneumonic and transudative effusions was statistically significant (p= 0.007)

Table : Mean SPAG in each group

Exudates	SPAG-mean (gm/dl)	Range	SD
TB	0.84	0-3.4	0.63
Malignant	1.1	0-2.2	0.51
Synpneumonic	0.61	0.2-1.1	0.38
Miscellaneous	0.56	0.1-1.2	0.36
Transudates	1.78	1.3-2.8	0.52

There was a significant difference between the mean SPAG values among the various groups of transudates but in view of the small sample size, statistical significance was not calculated.

Table : SPAG in transudates

Transudate	Mean SPAG (gm/dl)
CCF(5)	2.26
CRF(4)	1.55
Cirrhosis(4)	1.50
Rest(3)	1.66

Of the exudates, 10 were wrongly classified as transudates by SPAG criteria, whereas 1 was misclassified using Light's criteria. Of the transudates, 5 were misclassified by Light's criteria, but none by SPAG

Table : Classification of effusions using Light's and SPAG criteria

Effusion	Misclassified by		Sensitivity%
	Light's	SPAG	
TB (30)	None	03	90
Malignant (22)	None	07	68.2
Synpneumonic (8)	1	None	87.5
Miscellaneous (7)	None	None	100
Transudate (16)	5	None	68.8

SPAG-Serum Pleural Fluid Albumin Gradient

Empyema (frank pus), 5 cases, were all classified as exudates by Light's criteria and transudates by SPAG and the erratic results were explainable because of the low sensitivity of the machine to correctly analyze the sample in case of thick pus. Hence, empyema was not considered for the statistical analysis.

Overall, in the above study of 67 cases of exudates and 16 cases of transudates, the following results have been obtained **.**

Table : Results of the study

Criteria	Sensitivity%	Specificity%	PPV%	NPV%
PF-S Protein ratio >0.5	95.5	93.8	98.5	83.3
PF-S LDH ratio >0.6	85.7	80	91	71
PF-LDH>2/3rd upper limit of normal	79.4	75	93	48
LIGHT'S CRITERIA	98.51	68.75	92.96	91.67
SPAG	85.07	100	100	61.54

PF-Pleural Fluid S-Serum SPAG-Serum Pleural Fluid Albumin Gradient
PPV-Positive Predictive value NPV-Negative Predictive value

DISCUSSION

The criteria used to distinguish between transudate and exudate have been based on the biochemical parameters proposed by Light et al, though only few studies have shown the results as satisfactory as reported by Light et al. Thus, no single chemical test or a series of tests have yet proved to be completely reliable. Hence, the search for diagnostic improvisations is kept alive.

A total of 88 patients were taken up for study of which, 72 patients (81.8%) were diagnosed to have exudative effusion and 16 patients (18.18%) were diagnosed to have transudative effusion.

Of the exudative effusions, 30 were tuberculous (41.7%), 22 were malignant (30.6%), 8 synpneumonic (11.11%), 7 miscellaneous (9.8%) and 5 were empyema (6.94%). Of the transudates, CCF accounted for 5 cases (31.25%), CRF and cirrhosis - 4 cases each (25% each) and 1 case each of acute renal failure, nephritic syndrome and constrictive pericarditis (6.25% each).

Age of the patients in this study ranged from 14-80years, the mean being 46.2 yrs (SD =15.9). The maximum incidence of effusions were between 3rd and 7th decade. There was a significant difference between the mean age of presentation of tuberculous effusion (39.1 yrs) and malignant effusions (53.14yrs). Even among transudates, there was a significant age difference between patients with CCF (60.2yrs) and those with CRF and cirrhosis (46.5 and 49.5yrs).

Sixty two out of 88 patients were male (70.5%) and 26 were female (29.5%). Of the exudates (n=72), 53 were male and 19 were

female. There was a significant disparity in sex distribution in case of tuberculosis where male: female was 5:1.

Cough (65%), dyspnoea (65%), fever (59%), chest pain (44%), expectoration (40%), and loss of appetite and weight (33%) were the predominant symptoms at presentation.

Number of patients presenting with symptoms of 1 week to 1 month duration was maximum (51.1%) and 83% of patients had a history of less than 3 months duration. 25% of patients were smokers and an equal number were alcoholics.

On chest X-Ray, 39 patients had right sided effusion, 36 left sided and 13 had bilateral effusion. 7 out of 72 patients (9.72%) with exudative effusions had bilateral effusion while the rest (65/72) were unilateral. In case of transudates, the number of bilateral effusions were significantly higher compared to exudates (6/16)-37.5%.

Moderate pleural effusions were the most common in both the groups-exudates (87.5%) and transudates (75%) whereas minimal and massive effusions were seen in 3 and 10 cases respectively.

Among the tuberculosis patients, 2 were sputum positive for AFB, 5 out of 8 were pleural biopsy positive, 12 out of 13 had high pleural fluid ADA levels (>43U/L) and 9 out of 17 patients were Mantoux positive. While 2 cases were associated with Pott's spine, 1 was associated with abdominal tuberculosis. ESR was significantly high in all the 30 patients. Pleural fluid cell count ranged from 100-2700 cells/mm3. Twenty three of the 30 patients had a lymphocytic predominance with a mean of 75% while 6 had neutrophil predominant effusions. 6 patients were started on empirical ATT based on the clinical features, high ESR, lymphocyte predominant fluid and follow up revealed relief of symptoms in all 6 patients.

Total WBCs in transudates exceeded 1000cells/mm3 in 2 cases with 1 case having 1400 cells and the other 1800cells /mm3. In case of tuberculosis, malignancy and transudates, the pleural fluid was lymphocyte predominant-75% (SD=23), 82.3% (SD=15), 70% (SD=25.3) respectively. Neutrophil predominance in the pleural fluid was seen in case of synpneumonic, empyema and miscellaneous causes of exudates.

Carcinoma lung (7), lymphoma (4), metastatic carcinoma with unknown primary (4), were the major causes of malignant effusions followed by carcinoma breast, leukemia and carcinoma stomach, ovary and cervix. All cases were pleural fluid cytology positive for malignancy.

In this study, mean SPAG for transudates is 1.78gm/dl and 0.84gm% for tuberculous effusion, 1.10 gm% for malignancy and 0.61 gm% for synpneumonic effusions. All the exudate groups had a lower SPAG than transudates {0.87 (Ex) vs 1.78 (Tr)}. The difference in mean values for tuberculosis, synpneumonic effusions and transudative effusions was statistically significant (p=0.007). There was also a significant difference between the mean SPAG values among cases of CCF and the rest of the transudates, but in view of the small sample size, statistical significance was not calculated.

Five cases of empyema (frank pus) which were initially considered were not taken into biochemical statistical analysis as the biochemical reports were erratic in view of the low sensitivity of the analyzer to analyze thick pus and the values unreliable as per the clinical biochemistry department.

As noted in the table below ,Light's excellent results have not been fully reproduced in several studies with respect to sensitivity and specificity. A large number of prospective studies have reported specificities of only between 70-86%, in contrast to 98% claimed by Light (Hamm[2] .Peterman[3], Costa M[4], Rcth[5], Valdes[6], Burgers[7]). Another major disadvantage of Light's criteria is the misclassification of transudate effusions as exudates in patients with CCF on diuretic therapy- a phenomenon first noted by Pillay[8] and confirmed by Chakko[9] . In the present study, Light's criteria, was very sensitive but not specific. This conforms to the other studies listed.

Table: Comparative study of Light's criteria.

Author	Misclassification		Sn%	Sp%	PPV%	NPV%
	E%	T%				
Light 1972	0.9	2	99	98	99	98
Hamm 1987	Nil	30	100	70	77.5	100
Valdes 1990	5.3	21.5	94.6	78.4	92	83
Roth BJ 1990			100	72		
Berrin & Turgay 1993			100	100		
Ibrahim Akurt 1993			100	81		
Ram 1995	7.3	Nil	93	100	100	87
Romero 1995	2	23	97	77	96	40
Burgess 1995	4	19	98	83	93	96
Costa M 1995	1.5	22.4	98	81.6	93.6	95
Heffner JE 1996			97.9	74.3		
Muzaffar M et al 1996			100	81	95	100
Lakhotia M et al 1996			100	100		
J M Porcel 1999			98.3	76.1	94.7	91.1
Present study	1.3	31.3	98.5	68.8	92.9	91.67

Table: Comparative study of SPAG

Author	Sn%	Sp%	PPV%	NPV%
Roth BJ 1990	95	100	--	--
Berrin & Turgay 1993	76	100	--	--
Ibrahim Akurt 1993 (61)	91.9	100	--	--
Burgess LJ 1995	87	92	96	77
Heffner JE et al 1996	86.9	91.8	95.8	76.3
Muzaffar M et al 1996	63	81	92	39
Ebrahim Razi Et al 2000	82.9	95	93.5	86.6
A K Das et al 2004	96.1	93	-	-
Manaswini M et al 2008	92	85	92	85
Present study	85.07	100	100	61.5

Sn-Sensitivity **Sp-Specificity**

In this study, as noted in the above ,Light's criteria was superior to SPAG in case of exudates, whereas, 5 out of 16 cases of transudates were misclassified as exudates. One was due to protein criteria and the other 4 due to LDH criteria. The cases were 2 patients of CRF, 2 of cirrhosis, and 1 CCF. The probable explanation is that, with diuresis, free water leaves the pleural compartment first, while protein and LDH leave later and a pleural fluid analysis done after few days of diuresis, as was the case in this study, would meet the exudative range of protein and LDH criteria. Hence the importance of albumin gradient, which may add to the accuracy in detecting transudates in patients receiving diuretic therapy[10]. In those cases which were misclassified as exudates by Light's criteria, applying albumin criteria all 5 were

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correctly classified as transudates.

In summary, Light's criteria in this study of 83 patients was 98.5% sensitive at identifying exudates; however, these criteria were not as specific (68.75%). The albumin gradient is 100% specific and still fairly sensitive (85%). Thus, serum-pleural fluid albumin gradient is a reliable criterion for identifying transudates especially in patients who are on diuretic therapy as Light's criteria tend to misclassify these as exudates.

CONCLUSION

SPAG is reasonably sensitive and very specific, in contrast to Light's criteria, which is sensitive but not specific.

If a disease is known to cause an exudative effusion and is classified so by Light's criteria, it is an exudate in all probability, whereas, in diseases known to cause transudate effusion, if Light's criteria classifies it as exudate and SPAG as transudate, the fluid in all probability is a transudate.

The diagnostic accuracy of these tests in the differentiation of exudative and transudative effusions can be increased by combining both SPAG and Light's criteria in suspected cases of transudative effusions.

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