RESEARCH ARTICLE

PLEURAL FLUID LDH-CHOLESTEROL AND ADA LEVELS: USEFUL BIOCHEMICAL MARKERS IN COMPARISON TO LIGHT'S CRITERIA FOR MORE RAPID AND ACCURATE EVALUATION OF PLEURAL EFFUSION

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ABSTRACT
Background: Early and decisive evidence of pleural effusion as transudative or exudative nature is of considerable importance for further diagnostic procedure and therapeutic implication.
Aims & Objective: To evaluate the utility of PF LDH-Cholesterol including Triglycerides level and ADA levels and comparing it with Light's criteria for rapid and accurate evaluation of Pleural effusion mainly exudates.
Materials and Methods: Total of 100 cases of Pleural effusion studied from July 2011 to September 2012. All the cases were evaluated by clinical, biochemical, cytological analysis of pleural effusion to diagnose underlying cause and different methods were compared for its diagnostic value, its sensitivity and specificity.
Results: Out of all the effusions, 94 were exudative and 6 were transudative in nature. The commonest cause of effusion was tuberculous (58 cases) followed by malignancy (24 cases). 62 patients showed ratio of pleural fluid and serum protein <0.05. Pleural fluid LDH more than 200 was found in 90 patients. Pleural fluid to serum LDH ratio was .0.6 in 85 patients. Analysis of lipid from pleural fluid showed 83 patients had pleural fluid cholesterol levels > 60 mg/dl. 86.2% of patients with TB and 79.16% of malignancy patients had pleural fluid cholesterol levels > 60 mg/dl with pleural fluid to serum cholesterol ratio of >0.4. Pleural fluid triglyceride levels were >40 mg/dl in 50% of the patients. Pleural fluid LDH levels were 135 ± 37 in transudative effusion while it was 676 ± 414, 559 ± 225 and 678 ± 513 in exudative, tuberculous and malignant effusion respectively. Similarly ratio of pleural fluid to serum LDH was <0.6 in transudative while it was 2.68 ± 3.27, 1.93 ± 1.15 and 1.61 ± 1.13 in exudative, tuberculous and malignant effusion respectively. Pleural fluid ADA levels were 20 ± 17, 53.5 ± 43, 65.48 ± 39.9 and 24.29 ± 24.72 in transudative, exudative, tuberculous and malignant effusions respectively. It was found that the specificity of separating transudate and exudates and positive predictive value was 100% with light's criteria, pleural fluid LDH levels and pleural fluid to serum LDH ratio. Sensitivity and specificity of ADA in tuberculous effusion is 79.31% and 76.16% respectively.
Conclusion: In clinical setting Light's criteria generally distinguish the exudative from transudative pleural effusion. Current study supports other studies in stating that the alternative criteria like PF LDH-Cholesterol and ADA levels must be considered as a good alternative.
Key Words: Pleural Fluid LDH; Pleural Fluid Cholesterol; Adenosine Deaminase (ADA); Light's Criteria; Exudates; Pleural Effusion

Introduction

Pleural effusion is commonly encountered by chest physicians accounting for approximately 4% of attendance to chest clinics.[1] It is important to establish an accurate etiological diagnosis, so that the patient may be treated in the most appropriated and rational manner. First and foremost step in management of pleural effusion is to identify the nature of fluid and distinguish transudative effusion from exudative effusion. Exudative effusions require to be separated into infectious causes, non-infectious causes and malignancy. In most cases problem is solved by following the light's criteria.[2] These criteria are based on the fact that elevation of pleural fluid proteins and lactate dehydrogenase is seen in pleural inflammations. The lights criteria includes, (a) Pleural fluid protein/Serum protein ratio of more than 0.5; (b) Pleural fluid LDH/Serum LDH ratio of more than 0.6; and (c) Pleural fluid LDH more than 200 units/l. However, often a diagnostic dilemma arises and no cause may be found in about 15% of cases, in spite of careful evaluation.[2]

Tuberculosis is the most common cause of effusion in India as compared to the Western countries where malignancy and para-pneumonic effusions are more common. The clinical, biochemical and cytological parameters of tubercular effusion are shared by malignancy, both being exudates and predominantly lymphocytic effusions.[3] This can pose a significant diagnostic dilemma. Variety of tests is available for differential diagnosis. Adenosine deaminase enzyme activity, gamma interferon, polymerase chain reaction, lysozyme measurement, pleural fluid tuberculous protein antibodies and various tumour markers like

CA15-3, squamous cell carcinoma antigen, etc have been used to differentiate TB from non TB effusions. Other diagnostic tests including flow cytometry, chromosomal analysis of malignant cells, LDH isoenzymes assay, and tumor marker assays, immunohisto chemical tests, and carcino embryonic antigen (CEA), are used to differentiate between benign and malignant effusions.[3,4]

These tests are not easily available even in a tertiary care hospital and they are very costly. Therefore, there is a need for defining the best diagnostic and cost effective approach to quickly diagnose cause pleural effusions. Currently biochemical parameters are used for classifying pleural effusion. Hence attempts have been made to identify markers, which allow a more accurate and rapid diagnosis.

PF LDH is used for diagnosis. All exudative pleural effusions show elevated LDH levels and simultaneous measurement of pleural fluid and serum LDH showed the following: Pleural fluid LDH more than 2/3rd the upper limit of normal for blood LDH level. Pleural fluid: serum values of LDH of more than 0.6. It has been found that Pleural fluid LDH more than 200 units/l mostly indicate the exudative nature also the extremely higher value suggest underlying malignancy.[3-5]

PF lipid levels are also a useful marker. Cholesterol levels were more than 60 mg/dl in cases of exudates whereas transudates have a cholesterol levels below 60 mg/dl. Increased presence of lipids imparts a milky or opalescent colour to the effusion and such an effusion that contains chyle is called chylothorax. The level of cholesterol is not much different in chylous and non-chylous effusions, but there is a marked difference in the triglyceride levels. The mean triglyceride level in a chylous effusion was 249 mg/dl and in a non-chylous effusion was 33 mg/dl.[6-8]

Adenosine Deaminase (ADA) levels are found to be markedly elevated in case of tuberculous effusions as compared to malignant effusions (values more than 45 U/L.). Thus ADA estimation in the pleural fluid is a sensitive method to differentiate tuberculous from non-tuberculous effusions. This is especially useful in patients with exudative pleural effusions with negative cytology and absent lymphocytosis.[4-6]

This study discusses the role of some of the biochemical markers like PF LDH-cholesterol and ADA for investigating pleural disease, in a clinical setup.

Materials and Methods

The present study was prospective and observational in nature. It has been conducted to study the significance of Pleural fluid LDH, Cholesterol and ADA levels in comparison to light's criteria for rapid and accurate evaluation of pleural effusion especially the exudates. All the cases presenting with significant amount of pleural effusion at either indoor and/or outdoor department of Pulmonary Medicine during a time period of July 2011 to September 2012 were included in the study. Written informed consent was obtained from all the patients before including them in the study.

All these patients' pleural effusions were aspirated by standard procedure and taking strict aseptic precaution and safety measures. In case where there was difficulty in aspiration, USG guidance was obtained for completing the procedure. All patients' findings like detailed history, clinical examination, routine blood investigations, sputum examination, chest X-rays, USG of thorax and pleural fluid analysis and others were noted in a prepared proforma.

The samples of pleural fluid were sent in different departments: (a) for fluid protein, sugar, ADA, LDH, cholesterol, triglyceride, CRP and others in department of biochemistry; (b) for cell count, cell type and other analysis in department of pathology; and (c) for AFB stain, Gram stain and others in department of microbiology as per hospital procedures. The pleural fluid LDH, ADA and Cholesterol, triglyceride and CRP levels were estimated.

All the tests were directed towards identifying the etiology and probable cause of pleural effusion and its clinical correlation was also carried out. Effusions were considered malignant when malignant cells are demonstrated in cytological examination or in a biopsy specimen. Pleural effusions were considered parapneumonic when there was an acute febrile illness with purulent sputum and pulmonary infiltrates in the absence of malignancy or obvious disease causing transudate. Tuberculosis was diagnosed after evaluating various parameters like demonstration of mycobacteria etc. Congestive heart failure was diagnosed by enlarged heart, pulmonary venous congestion on x-ray, peripheral oedema, response to CHF treatment and absence of any other pathology. Final diagnosis was made after correlation of clinical, radiological, pathological and biochemical data for evaluation of usefulness of novel markers.

Statistical Analysis: Data was represented as actual frequencies, percentage, mean and standard deviation, compared and analyzed using simple statistics.

Results

Total 100 patients with pleural effusions studied in the given time duration of this study. Out of all the effusions, 94 were exudative and only 6 were transudative in nature. The commonest type of effusion was found to be tuberculous (58 cases) followed by malignancy (24 cases), sympneumonic effusion (20 cases) as shown in table 1.

Table-1: Types and diagnosis of Pleural Effusion

Diagnosis	Transudates	Exudates
Tuberculosis	1	57
Malignancy	2	22
Empyema	0	5
Pancreatitis	0	4
Chronic renal failure/ Congestive cardiac failure	2	0
Pyogenic effusion	0	2
Sympneumonic	0	2
Eosinophilic Parasitic Effusion	0	1
Pseudochylus	0	1
Undiagnosed	1	0
Total	6	94

Table-2: Biochemical Analysis of Pleural fluid (Light's criteria)

Diagnosis	PF/S. Protein		PF LDH		PF/S.LDH	
	>0.5	<0.5	>200	<200	>0.6	<0.6
TB (58)	25	33	55	3	55	3
Malignancy (24)	10	14	21	4	18	6
Empyema (5)	3	2	4	1	4	1
Pancreatitis (4)	0	4	4	0	3	1
CRF/CCF (2)	0	2	0	2	0	2
Pyogenic effusion (2)	0	2	2	0	2	0
Sympneumonic (2)	0	2	2	0	1	1
Eosinophilic Parasitic Effusion (1)	0	1	1	0	1	0
Pseudochylus (1)	0	1	1	0	1	0
Undiagnosed (1)	0	1	0	1	0	1
Total	38	62	90	10	85	15

Table-3: Lipid values in pleural effusion

Diagnosis	Cholesterol (mg/dl)			Triglyceride (mg/dl)		
	FL > 60	FL < 60	FL/S ratio >0.4	FL>40	FL < 40	FL/S ratio >0.3
TB	50 (86.2)	8 (13.8)	50	31 (53.5)	27 (46.5)	46
Malignancy	19 (79.2)	5 (20.8)	18	8 (33.3)	16 (66.7)	14
Empyema	4 (80.0)	1 (20.0)	3	3 (60.0)	2 (40.0)	4
Pancreatitis	3 (75.0)	1 (25.0)	3	2 (50.0)	2 (50.0)	2
CRF/CCF	2 (100.0)	0	2	2 (100.0)	0	1
Pyogenic effusion	1 (50.0)	1 (100.0)	1	1 (50.0)	1 (50.0)	2
Sympneumonic	2 (100.0)	0	1	2 (100.0)	0	2
Eosinophilic Parasitic Effusion	1 (100.0)	0	1	0	1 (100.0)	2
Pseudochylus	1 (100.0)	0	1	1 (100.0)	0	2
Undiagnosed	0	1 (100.0)	1	0	1 (100.0)	2
Total	83	17		50	50	

Table-4: Different biological parameters in transudate, exudates, tuberculosis and malignant pleural effusion

Parameters	Transudates	Exudates	Tuberculous	Malignant
PF/S. Protein	0.29 ± 0.1	0.45 ± 0.28	0.48 ± 0.3	0.43 ± 0.23
PF LDH	135 ± 37	676 ± 414	559 ± 225	678 ± 513
PF LDH /S.LDH	0.36 ± 0.12	2.68 ± 3.27	1.93 ± 1.15	1.61 ± 1.13
PF ADA	20 ± 17	53.5 ± 43	65.48 ± 39.9	24.29 ± 24.72
PF Cholesterol	80 ± 30	82.84 ± 37.33	86.62 ± 36.08	75.8 ± 35
PF/S. Cholesterol	0.48 ± 0.17	0.65 ± 0.29	0.69 ± 0.29	0.53 ± 0.24
PF Triglyceride	51.5 ± 26	48.73 ± 31.7	53.72 ± 35.25	37 ± 21
PF/S. Triglyceride	0.40 ± 0.2	0.47 ± 0.27	0.47 ± 0.25	0.40 ± 0.3

Values are expressed in Mean ± SD.

Table-5: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of various laboratory parameters for transudate and exudates separation

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PF/S. Protein	40.42	0	86.36	0
PF LDH	95.74	100	100	60
PF LDH /S.LDH	90.42	100	100	40
PF ADA	96.91	100	100	50
PF Cholesterol	83.5	33.33	97.59	58.82
PF/S. Cholesterol	85.56	0	96.51	0
PF Triglyceride	49.48	33.33	96	2
PF/S. Triglyceride	73.19	66.66	98.61	7.14

Table-6: Pleural fluid ADA

Diagnosis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Tuberculous	79.31	76.19	72.73	82.14
Non-Tuberculous	28.57	24.14	21.43	31.82

Out of total 100 patients, 62 showed ratio of pleural fluid and serum protein <0.05. Pleural fluid LDH more than 200 was found in 90 patients. Pleural fluid to serum LDH ratio was .0.6 in 85 patients. Disease wise distribution and its biochemical analysis as per light's criteria has been shown in table 2. High value of the PF LDH is being noted in the TB and malignancy.

Table 3 shows analysis of lipids from the pleural fluid. Out of total 100 patients, 83 had pleural fluid cholesterol levels > 60 mg/dl. It was found that 86.2% of patients with TB and 79.16% of malignancy patients had pleural fluid cholesterol levels > 60 mg/dl with pleural fluid to serum cholesterol ratio of >0.4. Pleural fluid triglyceride levels were >40 mg/dl in 50% of the patients.

Table 4 shows mean value and standard deviation of different biological parameters in transudate, exudates, tuberculosis and malignant pleural effusion. Pleural fluid LDH levels were 135 ± 37 in transudative effusion while it was 676 ± 414, 559 ± 225 and 678 ± 513 in exudative, tuberculous and malignant effusion respectively. Similarly ratio of pleural fluid to serum LDH was <0.6 in transudative while it was 2.68 ± 3.27, 1.93 ± 1.15 and 1.61 ± 1.13 in exudative, tuberculous and malignant effusion respectively. Pleural fluid ADA levels were 20 ±

17, 53.5 ± 43, 65.48 ± 39.9 and 24.29 ± 24.72 in transudative, exudative, tuberculous and malignant effusions respectively. It was observed that ratio of plural fluid/serum protein was < 0.5 in both transudate and exudates.

Table 5 shows Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of various laboratory parameters for transudate and exudates separation. It was found that the specificity of separating transudate and exudates and positive predictive value was 100% with light's criteria, pleural fluid LDH levels and pleural fluid to serum LDH ratio. Sensitivity was 100% with pleural fluid LDH and cholesterol levels.

Table 6 shows the diagnostic value of ADA levels in tuberculous pleural effusion. It was found that sensitivity and specificity of ADA in Tuberculous effusion is 79.31% and 76.16% respectively.

Discussion

Pleural effusion is commonly encountered condition in clinical practice and diagnosis of cause by examination of fluid is vital and recommended first step in the management. Various biochemical tests have been used in diagnosis of pleural effusion. This study has evaluated the diagnostic value of different biochemical tests used for evaluation of pleural fluid.

In the present study majority of pleural effusions were of exudative nature (94%). As the most of cardiac, renal and liver disease patients first approach the Internal medicine department of hospital, most of the transudative effusions were managed further by medicine department and number of transudative effusions were very less to Pulmonary medicine department of the hospital.

Comparison of different diagnosis for pleural effusions and values of different laboratory parameters from different studies has been shown in table 7. In this study tuberculosis pleural effusion was found in 58% of patients while it varies in different studies. Malignant pleural effusion is 24% which is comparable to Valdes (1991)[9] and Valdes (1996)[10]. Parapneumonic pleural effusion is Thiruvengadam (1962)[11], A. Dambal (1998)[12]. CCF effusion is 2% which is comparable to Thiruvengadam (1962)[11], A. Dambal (1998)[12], and Hirsch (1979)[13].

Table-7: Values (in Mean ± SD) of Different Laboratory Parameters

Parameters	Studies	Transudates	Exudates	Tuberculosis	Malignancy
PF/S. Protein	K.N. Ram[14]	0.32±0.12	-	0.74±0.13	0.63±0.13
	S.Kaval[15]	0.29±0.1	0.74±0.23	0.79±0.23	0.59±0.15
	Present Study	0.29± 0.1	0.45±0.28	0.48±0.3	0.43±0.23
PF LDH	Valdes[16]	98.3±65.5	-	783.3±21.6	513.9±843
	K.N. Ram[14]	63.5±14.3	183.4±74.4	182.8±-61.9	158.2±107.5
	Present Study	135±37	676±414	559±225	678±513
PF/S. LDH	Valdes[16]	0.39±0.21	-	4.68±15.5	2003±3.31
	K.N. Ram[14]	0.41±0.06	1.58±0.88	1.59±4.75	1.44±1.53
	Present Study	0.36±0.12	2.68±3.27	1.93+-1.15	1.61±1.13
PF Cholesterol	Valdes[16]	28.5±12.8	-	96.5±28	88.13±30
	K.N. Ram[14]	42.1±8.6	117.6±46.9	110.2±43.2	143.4±39.3
	Present Study	80±30	82.84±37.33	86.62±36.08	75.8±35

Table-8: Sensitivity, Specificity, Positive Predictive Value (PPV) Negative Predictive Value (NPV) of Different Laboratory Parameters for Transudates and Exudates

Parameters	Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PF/S. Protein	Valdes[16]	89	89	46	74
	K.N. Ram[14]	81.5	100	100	72
	Light[17]	96	98	99	98
	Present Study	40.42	0	86.36	0
PF LDH	Valdes[16]	61	95	97	50
	K.N. Ram[14]	81.5	100	100	72
	Light[17]	70	100	100	61
	John heffner[18]	88	81.8	93.9	68.3
	Present Study	95.74	100	100	60
PF/S. LDH	Valdes[16]	81.6	84.6	94	65
	K.N. Ram[14]	89	100	100	81
	Light[17]	86	98	99	77
	John heffner[18]	91.4	85	95.1	75.7
	Present Study	90.42	100	100	40

Table-9: PF LDH and cholesterol levels

Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Marina costa[19]	99	98	-	-
Present study	100	33.33	97.98	100

Table-10: Mean values of ADA in tuberculous and non tuberculous pleural effusion

Studies	Tuberculous	Non tuberculous
PK Sinha et al[20]	76.8	14.50
Gilhotra et al[21]	82.9	28.42
Piras MA et al[22]	83.04	17.26
Baldev Raj et al[23]	99.56	20.58
SK Sharma et al[24]	95.8	30.7
Subhakar et al[25]	66.41	17.32
Present study	65.48	24.29

Table-11: Sensitivity, Specificity, NPV and PPV OF ADA in Tuberculous + Non tuberculous pleural effusion. Cut off value (40 IU/L)

Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
B.R.Maldhure[26]	100	34.78	44.44	100
P.K.Sinha et al[20]	100	100	-	-
Baldev Raj et al[23]	100	100	-	-

In this study, mean value of PF LDH in transudates, exudates, tuberculosis and malignancy is 135 ± 37, 676 ± 414, 559 ± 225, 678 ± 513 respectively which is comparable to Valdes et al [16] study. In the present study, mean value of PF LDH/S.LDH in transudates, exudates, tuberculosis and malignancy is 0.36 ± 0.12, 2.68 ± 3.27, 1.93 ± 1.15, 1.61 ± 1.13 respectively which is comparable

to K. N. Ram et al[14] study.

It is evident from the results that the pleural fluid LDH >200 mg/dl and ratio of pleural fluid to serum LDH>0.6, pleural fluid cholesterol >60 mg/dl, Pleural Fluid/Serum Cholesterol > 0.4 indicates exudative effusion.

Comparison of different studies for sensitivity and specificity of various biochemical parameters has been shown in table 8. Pleural fluid LDH levels sensitivity, Specificity, PPV, NPV in present study was 95.74%, 100%, 100%, 60% respectively which was comparable to Lights et al[17], KN Ram et al[14] and John Heffner's et al[18] study. PF.LDH/S.LDH Sensitivity, Specificity, PPV, NPV in present study was 90.42%, 100%, 100%, 40% respectively which is comparable to Lights et al[17], KN Ram et al[14] and John Heffner's et al [18] study. From this table we can say that Light's criteria are most sensitive and specific criteria to differentiate between exudates and transudates.

Pleural fluid LDH and cholesterol levels has sensitivity of 100%, specificity of 33.33%, positive predictive value of 97.98% and negative predictive value of 100% in the present study. Another study by marina costa et al[19] has shown the sensitivity of 99% and specificity of 98% with the same laboratory parameter.

In present study, mean value of ADA level was 65.48 in tubercular effusion and 24.29 in nontubercular effusions which is comparable to other studies as shown in table 9. This suggest that high levels of ADA in pleural fluid is more diagnostic towards tuberculosis.

Sensitivity, Specificity, NPV and PPV of ADA in tuberculous and non-tuberculous pleural effusion of the present study and its comparison with other similar studies has been shown in table 10. In the present study, sensitivity of ADA levels was found to be 79.31% which is lower than studies by B R Maldhure et al, P. K. Sinha et al, Baldev Raj et al which showed 100% sensitivity. Similarly specificity was 76.19% in the present study for pleuarla fluid ADA level which was 100% in studies by P. K. Sinha et al and Baldev Raj et al. Thus, pleural fluid ADA levels can be a useful marker for distinguishing tubercular effusions.

Conclusion

In conclusion, Light's criteria are most sensitive and specific parameter to differentiate between transudates and exudates and are most widely being used. Pleural ADA is a specific and sensitive parameter to differentiate between tuberculous and non tuberculous pleural effusion and it is becoming popular and vital tool to differentiate tuberculous from non tuberculous cases of pleural effusion which is quite handful in countries like India where tuberculosis is prevalent everywhere. The association of LDH and pleural fluid cholesterol classified 100% of the exudates, with efficacy similar to that of Light's criteria. Cholesterol levels were about as useful as Light's criteria. The association of LDH and cholesterol allows us to bypass blood analysis for the diagnosis of exudates. Our study supports other studies in stating that the vital role and cost effectiveness of these novel biochemical markers alone with protein value in comparison to long list of markers in evaluation of pleural effusion and recommends their use.

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