Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 07, 2023

Original Research Article

A Prospective Study on Etiology of Pleural Effusion with Special Reference to Cholinesterase Level in Pleural Fluids of Patients Admitted to a Tertiary Care Hospital

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Article History: **Received:** 12.05.2023 **Revised:** 15.06.2023 **Accepted:** 25.07.2023

ABSTRACT

Background

Pleural effusion may occur in different infections or as a complication of pulmonary disease, malignant disease. Exudative pleural effusion results from local or systemic disease that directly injure the pleural surface. To know intrapleural pathology, correct diagnosis of pleural effusion is essential. For this many parameters have been proposed for segregation of exudates from transudates. Cholinesterase level in pleural effusion of diverse etiologies helps to differentiate between transudates and exudates.

Methods

The study was conducted in the Department of General Medicine, SCB Medical College & Hospital, Cuttack during the period from June 2019 to September 2020. 100 consecutive patients admitted were included in the study group. Thoracocentesis was done in all patients and samples were sent for biochemical, microbiological and cytological tests. Cholinesterase estimation was done by photometer 5010V5+. Final diagnosis was done by clinical, biochemical, cytological and microbiological results.

Results

Out of 100 cases, 78 cases were male and 22 cases were females, with male: female ratio 3.4:1. Tubercular effusion was the most common cause followed by congestive cardiac failure. Fever was the most common clinical presentation (62%). The mean total cell count was more in exudate (2911.820+/1511.48). The pleural fluid cholinesterase level of 943.5U/L was 96% sensitive and 93% specificity.

Conclusion

Pleural fluid cholinesterase level of 943.5U/dl gives a more reasonable sensitivity and specificity (96% sensitive and 93% specific) to differentiate from exudates and transudates , while that of 981U/dl is more specific(92.6% sensitive and >99% specific) and can be taken as taken as gold standard as specificity approaches 100%. The result of present study revealed that pleural fluid cholinesterase is the most accurate parameter for the differentiation of transudates and exudates.

Keywords: Pleural fluid, exudates, transudates, cholinesterase.

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INTRODUCTION

Pleural effusions may occur with many different infections or as a complication of pulmonary disease. Pleural effusions frequently complicate malignant disease, heart disease, liver disease, kidney disease and collagen vascular disease. Approximately one million patients develop pleural effusion each year.[1]

Exudative pleural effusion results from local or systemic diseases that directly injure the pleural surface. The diagnostic focus for exudative effusions is to recognize intrapleural pathology. The correct diagnosis of the underlying disease is essential for rational management of the pleural effusion.[2]

Some of the exudative pleural effusion which remains undiagnosed even after thorough investigation, is known as idiopathic pleural effusion.

The criteria established by Light et al. in 1972 have been used widely to differentiate the exudative effusion from transudate effusion. This criteria often misclassified many transudates as exudates.[3]

For this reason, different parameters like the pleural fluid cholesterol level, pleural fluid to cholesterol ratio[4], pleural fluid to serum bilirubin ratio[5], serum effusion albumin gradient[6], pleural fluid alkaline phosphatase[7], pleural fluid ADA[8], pleural fluid uric acid levels[9], acute phase reactants[10], cytokine levels in pleural fluid[11] have been proposed for segregation of exudates from transudates. But none of them have been proved to be superior to Light's criteria. Carber et al[12] analyzed the cholinesterase level in pleural effusion of diverse etiologies and found significant difference in the average level between transudates and exudates.

Manju Sharma et al. [13] in 2002 found that estimation of pleural fluid to serum cholinesterase ratio had a better discriminatory capacity than Light's criteria, with a cut off value of 0.24.

AIMS AND OBJECTIVE

The aim of the study is to know the different etiological factors for diagnosis of pleural effusion and to study usefulness of pleural fluid cholinesterase level and pleural fluid to serum choline esterase ratio in differentiating exudative and transudative effusions and to compare its diagnostic efficacy with that of Light's criteria.

MATERIALS AND METHODS

This study was carried out in the Department of General Medicine, SCB Medical College & Hospital, Cuttack during the period June 2019 to September 2020. 100 consecutive patients admitted to Department of General Medicine during this period with clinical and radiological evidence of pleural effusion were included in our study group. Essential investigations were done to find out clinical diagnosis.

Thoracocentesis was done in all patients and samples were sent for following tests. 1. Biochemical tests - Glucose, protein, albumin, LDH, ADA, and choline esterase. 2. Cytological tests - total cell count, differential count, examination of malignant cells. 3. Microbiological tests - Gram staining, ZN staining for AFB and bacterial culture. Thoracocentesis was done as per protocol and maintaining asepsis in all patients using 20G needle and 10ml syringe in sitting position. Pleural tap was done in the intercostal space just above the rib, in the posterior axillary line. About 10ml of the fluid aspirated and was sent for biochemical, cytological, and microbiological tests. Exclusion criteria: Hemothorax, patients having more than one etiology, patients using oral contraceptive pills, anticancer drugs, MAO inhibitors were excluded, as all these drugs have the potentiality to alter serum cholinesterase.

Cholinesterase estimation in pleural fluid and serum was done by photometer 5010 V5+ manufactured by Robert Riele GmbH and CoKG, Berlin, Germany. The normal range of serum cholinesterase by this method is 5600-11200 IU/L in males and 4200-10800 IU/L in females. Final diagnosis was achieved by using proper history, clinical examination, routine investigations, radiological studies and pleural fluid cytological and microbiological results.

Light's criteria classify pleural effusion as exudates if one or more of the following criteria fulfilled. 1.Pleural fluid /serum protein ratio > 0.5, 2. Pleural fluid/ serum LDH ratio >0.6, 3. Pleural fluid LDH>1/3rd of upper normal limit of serum LDH. If none of the criteria are fulfilled the fluid is considered as transudate.

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Statistical Analysis

Statistical significance was interpretated using Chi-square test and Fischer's exact test. The level of agreement of Light's criteria has been done using symmetric measure kappa. Statistical analysis of efficacy of each parameter was done using Receiver operator curve (ROC) in IBM SPSS statistics version 19. The study protocol included Name, age, sex, address, brief clinical history, general examination, systemic examination, and laboratory investigations.

OBSERVATION

Out of total 140 patients admitted to the Medicine wards of SCB Medical College & Hospital, Cuttack, 100 patients were selected after exclusion as per selection criteria. Out of which 22% were females while 78% were males. Male to female ratio 3.4:1. Males found to have more exudative pleural effusion (64.5%) than transudative effusions (22.2%). This observation was not statistically significant (p value 0.69). Pleural effusion was found in all age groups, maximum patients were in age group of fifth decade followed by fourth decade. Female patients were in the age group of 20 to 40 years. Males were more common in above 40 years age groups (Table-1). Mean age of present study was 47±15.4 in males and 33.5±10 in females. Tuberculosis was common below 40 years age group, malignant pleural effusion was present above 50 years of age. Parapneumonic effusions were more common in old ages, mean age 69.5±17.2 years. Exudates were evenly distributed among all age groups; transudates were mainly seen in older age group. Most common cause among males as well as females were tuberculosis (Table-2).

In the study population fever, chest pain, cough, breathlessness, and weight loss were the chief complaints while pallor, lymphadenopathy, edema, and ascites were the most common clinical finding, found beside that of pleural effusion (Table-3). In present study, correlation of the clinical features with the type of pleural fluid was done and found to have significant association between some of the symptoms with exudate and transudate. Pleural effusions in present study were mild, moderate, and severe. Most of the cases (62%) were moderate pleural effusion. The mean total cell count (TLC) in pleural fluid was more in exudates (2911.820±1511.48) than transudates (629.213±576.15) (Table-4). Even though it was not statistically significant, with mean difference 2282.607 and standard error difference is 78.51(p value 0.121). Receptor operating characteristic curve(ROC) analysis of pleural fluid (PF), TLC showed area under curve was 0.849, cut off value of 610cells/mm3 will give 85% sensitivity and 77% specificity.

There is no much difference between the lymphocyte percentages in exudates (52.81±32.504) when compared to transudates (43.06±21.461). Mean difference is 9.9, which was statistically not significant (p value 0.267). ROC analysis of lymphocyte percentage in pleural fluid shows area under curve is 0.59 with no cut off value, was sensitive as well as specific.

38.70% of transudate are classified as exudates using Light's criteria. 14.81% of the exudates classified using Light's criteria were actually misclassified which were actually transudates. Sensitivity and specificity of Light's criteria were 100% and 61.29% respectively (Table -5).

ROC analysis of different parameters showed area under curve is more in pleural fluid ADA and pleural fluid albumin followed by pleural fluid protein (Table-6). Sensitivity is more in pleural fluid to serum protein ratio with a cut off value of 0.42, while specificity is more with pleural fluid to serum LDH ratio and pleural fluid to serum protein ratio with a cut off value 3.5g/dl.

Pleural fluid cholinesterase levels of 943.5 U/L gives reasonable sensitivity and specificity of 96% and 93% respectively, while that of 981U/L is more specific and can be taken as gold standard value with sensitivity of 92.6% and specificity of >99%. Serum cholinesterase levels are more sensitive than specific and none of the value can be used to diagnose the type of fluid, rather the ratio of pleural fluid cholinesterase is more predictive. Pleural fluid to serum cholinesterase ratio value of 0.429 is 85% sensitive and specific. (Table 7)

Light's criteria misclassified around 12% of total cases, when it was combined with serum fluid protein gradient >3.1gm/dl, misclassification came down to 5% but this combination had same effect when the LDH had been removed from Light's criteria (5%). Number of misclassification by pleural fluid to serum protein ratio, pleural fluid ADA and pleural fluid/serum cholinesterase ratio were almost same (12%). Pleural fluid cholinesterase misclassified only 5% of cases, but equivalent to that by pleural fluid/serum protein ratio plus serum pleural fluid protein gradient.

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Age groups in years	Male	Female	Total (%)
10-20	5	0	5
20-30	8	10	18
30-40	12	10	22
40-50	23	0	23
50-60	15	2	17
>60	15	0	15
Total	78	22	100

Table-1 Age and Sex distribution of study population. (N=10 0)

Final diagnosis	**Female**	**Male**	**Total (%)**
CCF	5	17	22
Liver cirrhosis	0	5	5
CDT	5	2	7
Empyema	0	3	3
Hypoproteinemia	0	2	2
Lymphoma	2	1	3
Malignancy	0	12	12
Nephrotic syndrome	0	2	2
Synpneumonic effusion	0	10	10
Tubercular	10	22	32
Liver abscess	0	2	2

Table-2 Etiological factors according to sex distribution. (N=1 00)

Clinical features	**Number of patients**	**Percentage**
Fever	62	62%
Breathlessness	50	50%
Chest pain	38	38%
Cough	30	30%
Weight loss	30	30%
Anemia	30	30%
Edema	40	40%
Lymphadenopathy	12	12%
Ascites	37	37%

Type of fluid	Number	Mean	Standard Deviation	Std error
Exudate	69	2911.820	1511.48	181.96
Transudate	31	629.213	576.15	103.45

Table- 4 Pleural fluid total cell count (TLC/mm3) according to type of fluid

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According to Light's criteria		According to final diagnosis		Total
		Exudate	Transudate	
Exudate	Count % within LC ex/tr	69(85.18%)	12(14.81%)	81 (100%)
Transudate	Count % within LC ex/tr	0(0%)	19 (100%)	19 (100%)
Total	Count % within LC ex/tr	69 (69%)	31 (31%)	100 (100%)

Table -5 Segregation of fluid according to Light's Criteria compared with that of final diagnosis

LC-Light's criteria; ex-exudate, tr-transudate

Parameters	Area under curve	Cut off value	Sensitivity (%)	Specificity (%)
PF protein	0.887	2.9g/dl	92.6%	85
		3./5g/dl	63	93
PF/Serum protein ratio	0.875	0.506	89	85
		0.42	96.3	77
PF LDH	0.835	135U/L	89	77
PF/ Serum LDH ratio	0.875	0.597	89.5	93
PF albumin	0.906	1.15g/dl	85	85
Ser-PF albumin gradient	0.422	1.2g/dl	-	-
PF ADA	0.915	23.25U/L	89	85

Table-6 Receptor operating characteristic (ROC) curve analysis of different parameters

Test variable	Area under curve	Cut off value	Sensitivity	Specificity
PF Cholinesterase	0.98	943.5U/L 981U/L	96% 92.6%	93% >99%
Serum cholinesterase	0.638	2353U/L	66.7%	70%
PF/Serum cholinesterase	0.883	0.429	85%	85%

Table-7 ROC Analysis of pleural fluid cholinesterase parameter s

DISCUSSION

In this present study out of 100 patients, 22% were females and 78% were males with male: female ratio 3.4:1. In accordance with studies by Roth et al.[14] and Eduardo GP et al. [15] both showing male predominance. This may be due to the fact that males are more exposed to different infections, because of outdoor activity lifestyle. In this study males male showed more exudative effusion (64.5%) than transudative (22.2%). This is similar to study done by Burgress L J et al. [16]

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Tuberculosis was common below 40 years of age in present study but malignant cause of pleural effusion was more in elderly age group above 50 years. Our study is similar to Valdes et al. [17] study, they found 69.4% of tubercular effusion were below 40 years and 83% malignant effusions were above 50 years.

In our study we found moderate pleural effusion in (62.5%) of cases, Kalaajieh W K et al.[18] found 50.9% as moderate pleural effusion. One of the case of massive pleural effusion in our study was due to cirrhosis of liver which is not commonly seen, but reported by Jimenez D et al. [19]

In our study third common cause is malignant effusion (12.5%), tubercular effusion was most common cause but in study of Marcelo A C et al. [20] they found was the commonest cause of effusion (40%) cases, followed by tubercular effusion (28%). The pleural fluid to serum cholinesterase ratio had been recommended by Eduardo et al. and Manju Sharma et al.[13] as an initial tool in the diagnosis of pleural effusion had misclassified (12.5%) cases, equivalent to the number misclassified by Light's criteria in this study. The best cut off value proposed by statistical analysis 0.429, is having a sensitivity and specificity of 85% which is inferior to the pleural fluid cholinesterase only.

Pleural fluid cholinesterase levels came to clinical interest when Cabrer B et al. [12] analyzed cholinesterase level in different etiologies of pleural effusion and found significant difference between them. Eduardo in 1996 proposed a cut off value of 1140IU/L to discriminate between exudate and transudates. The ratio of pleural fluid to serum cholinesterase, they found a cut off value 0.23. The percentage of cases misclassified by different parameters, Light's criteria 7.8%, pleural fluid choline esterase level 8.5%, pleural fluid to serum cholinesterase ratio 1.3%, and the study concluded that pleural fluid to serum cholinesterase ratio is the best parameter among all. Sevim T et al.[21] from Turkey in their study pleural fluid cholinesterase level>1700IU/L misclassified around 10.3% of patients, while pleural fluid to serum cholinesterase ratio misclassified only 3.8% cases when cut off value was taken 0.29%.

The criteria used for differentiating exudates and transudates like Light's criteria, total leucocyte count in pleural fluid, pleural fluid protein, pleural LDH, pleural fluid to serum ratio of protein and LDH, serum pleural fluid albumin gradient had been compared with pleural fluid cholinesterase and pleural fluid to serum cholinesterase ratio and had been found that pleural fluid cholinesterase is having a better sensitivity and specificity than other above mentioned criteria.

CONCLUSION

Pleural fluid cholinesterase level of 943.5U/dl gives more reasonable sensitivity and specificity (96% sensitive and 93% specific) to separate exudates and transudates, while that of 981U/dl is more specific (92.6% sensitive and >99% specific) and can be taken as taken as gold standard as specificity approaches 100% and number of misclassification by this method is lowest. Light's criteria which is having 100% sensitivity in diagnosing exudative effusion misclassified a large number of transudates and this misclassification can be partially corrected by serum pleural fluid protein gradient with a cut off value >3.1g/dl and pleural fluid cholinesterase with a cut off value 981IU/L is having a good sensitivity and high specificity, can be used for separating exudates from transudates. The result of present study reveals that pleural fluid cholinesterase is the most accurate parameter for the separation of transudates and exudates. However this needs further confirmation by larger studies.

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