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Pleural Fluid Cholesterol Level in Differentiating Exudate from Trasudate Pleural Effusion

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ABSTRACT

Correlation of pleural fluid cholesterol level with light's criteria to differentiate exudate from transudate pleural effusion. Classification of transudate and exudate clinically was done independently based on the light's criteria. Pleural fluid cholesterol levels of 100 selected patients were obtained. The cholesterol levels were compared with the earlier obtained data to study its specificity and sensitivity in differentiating exudate from transudate effusion. It was found that pleural fluid cholesterol in comparison to protein values in differentiating exudate from transudate showed a sensitivity of 79.55%, specificity of 91.07%, the positive predictive value of 87.50%, the negative predictive value of 85.00%, with a P-value of <0.001. Comparison of pleural fluid cholesterol with LDH values showed a sensitivity of 86.36% specificity of 94.64%, the positive predictive value of 92.68%, the negative predictive value of 89.83%, with a P-value of <0.001. Also, a comparison of pleural fluid cholesterol to light's criteria showed a sensitivity of 100% and 86.4% in the transudative group and sensitivity of 100% and 91.1 % in the exudative group, respectively. Routine measurement of pleural fluid cholesterol may serve as a valuable diagnostic indicator for differentiating exudate from transudate effusion.

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INTRODUCTION

Accumulation of the excess fluid in the pleural cavity – pleural effusion, is a fluid-filled space around the lung, which can limit the expansion of lung, thus impairing breathing (Jameson *et al.*, 2018). It could develop as a consequence of excessive formation from the related structures – parietal pleurae, interstitial spaces of the lung, or the peritoneal cavity; or maybe a result of reduced fluid drainage by the associated lymphatics.

Conditions like congestive cardiac failure, nephrotic syndrome, hypoalbuminemia, liver cirrhosis can cause increased capillary permeability of the lung vasculature, probably mediated by the release of cytokines and inflammatory mediators like VEGF, consequently, producing a transudative effusion (Murray and Nadel, 1987). Whereas, conditions like – post-cardiac surgery when retained blood syndrome ensues, empyema of lung secondary to bacterial pneumonia, parapneumonic effusions, carcinoma lung or metastasis to pleurae – can cause an exudative effusion

Diagnosis is usually based on the presentation, examination and a chest x-ray. Fluid usually should accumulate more than 300ml to be clini-

cally detectable. An exudate and transudate can be further differentiated using laboratory methods by analysis of protein and lactate dehydrogenase levels of the pleural fluid and serum, where the fluid can define an exudate to serum protein ration >0.5 and fluid to serum LDH ration >0.6 (Wang, 1985).

An exudate can also be characterised by the presence of fluid cholesterol >45mg/dL, LDH >0.45 upper limit of that of serum, and a protein >2.9g/dL

Cholesterol levels are assumed to have a higher sensitivity and specificity in comparison to the light's criteria in differentiating exudate from a transudate, based on which the present study was undertaken to compare the reliability of fluid cholesterol levels as a diagnostic indicator for differentiation. (Cecil *et al.*, 2012)

Aim

Correlation of pleural fluid cholesterol level with light's criteria to differentiate exudate from transudate pleural effusion

Primary objective

To assess cholesterol level in pleural fluid.

Secondary objective

To assess the total cholesterol level in the pleural fluid to differentiate exudate and transudate.

Study design

This prospective case study was conducted in Department of General Medicine, Vinayaka Mission Medical College, Karaikal after obtaining approval from the Ethics Review Committee of the Vinayaka Mission Medical College, Karaikal. Written informed consent was taken from all participating patients after explaining the study in their language. Patients were recruited from all units in the inpatient department.

Inclusion criteria

a) Age above 18 years of either gender

b) patients with pleural effusion diagnosed clinically &radiologically

c) all cases irrespective of duration

d) patients willing to give consent

Exclusion criteria

Patients with

a) pyothorax

b) chylothorax

c) haemothorax

d) traumatic pneumothorax

e) pregnancy.

We screened 108 patients for pleural effusion, and 100 patients who satisfied the inclusion and exclusion criteria were included in the study. A detailed history regarding the nature and duration of the presenting symptoms was obtained from each patient. List of symptoms regarding breathlessness on exertion, fever, cough and expectoration, pleuritic chest pain, abdominal pain, lower limbs swelling, decreased urine output, loss of appetite, facial puffiness, multiple joint pain, weight loss were enquired. They were also evaluated with the available investigation regarding pleural effusion: Pleural fluid-Protein, LDH, cholesterol level, Serum protein, Serum LDH.

Patients were classified (according to (Lee and Olak, 1994)) as having

a) Exudative effusion if one of the following was met

1. Pleural fluid protein level > 2.9 g/dL (conversion to g/L, multiply by 10)

2. Fluid lactate dehydrogenase (LDH) level greater than two-thirds of the upper limit of the standard serum value

3. Fluid cholesterol level > 45 mg/dl.

b) Effusions were classified as transudative if none of the above criteria was met, or if two of the following conditions were met

1. Fluid LDH level less than or equal to 2/3rd of the upper limit of the standard serum value (222 U/L)

2. Fluid cholesterol level less than or equal to 45 mg/dl.

As the simultaneous serum values of the patients were not consistently available, a criterion suggested by Heffner et al., which does not base on the simultaneous serum values, was chosen. (Figure 1)

RESULTS

Out of 100 patients, 83 patients were males, and 17 patients were females in this study, as depicted in Figure 2. In this study group, the age group of 51-60 years constituted the majority of patients (Figure 3). Diabetes is considered the most common comorbidity in our study (Table 1). The above table (Table 2)shows a comparison of Cholesterol group with Protein group. In Cholesterol group when comparing with Protein group transudates were 44 and exudates were 56. The above table (Table 3) depicts the Cholesterol test was comparatively better than
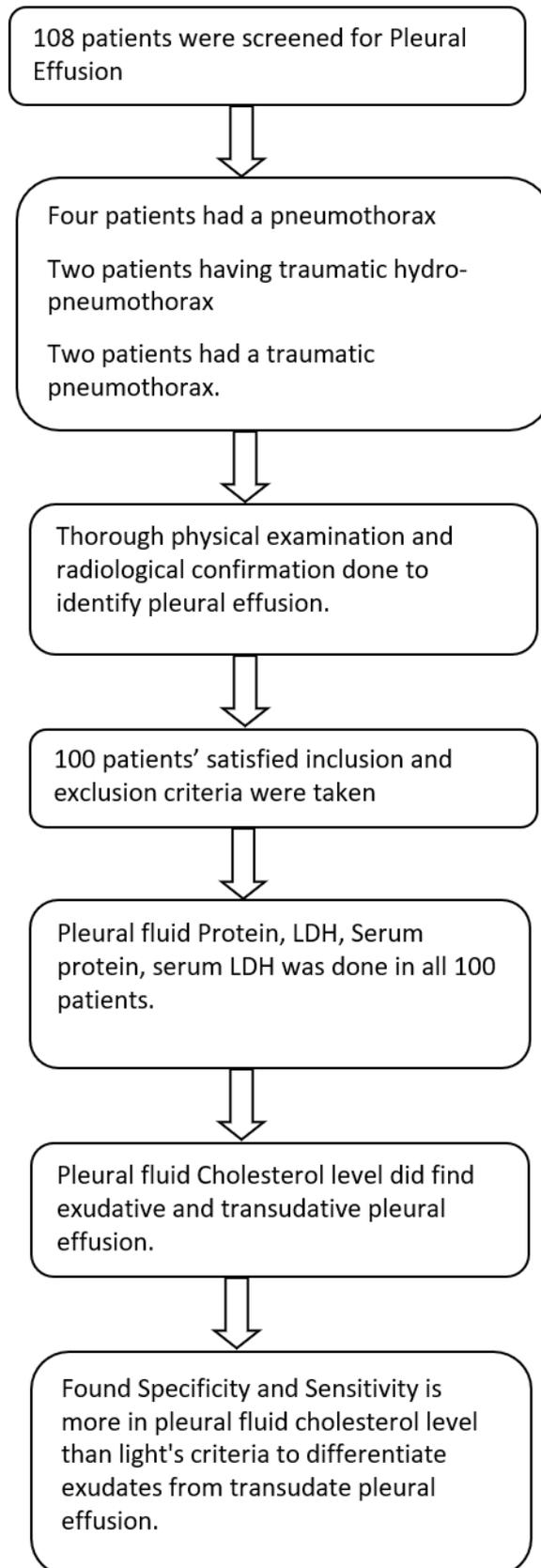
Figure 1: Methodology

Table 1: Frequency distribution of co-morbid conditions in the study patients

S. No	Co-morbid Conditions	Present (%)	Absent (%)	Transudate (%)	Exudate (%)
1.	Diabetes Mellitus	63	37	-	-
2.	Hypertension	45	55	-	-
3.	Tuberculosis	33	67	-	33
4.	Chronic Kidney disease	23	77	23	-
5.	Congestive Cardiac Failure	3	97	3	-
6.	Pancreatitis	16	84	-	16
7.	Malignancy	7	93	-	7
8.	Alcoholics	80	20	18	-
9.	Smokers	77	23	-	-

Table 2: Comparison of cholesterol with protein group

		Crosstab			
			Pleural fluid cholesterol group		Total
			Transudate	Exudate	
PLF protein	Transudate	Count	35	5	40
SR protein		%	79.5	8.9	40
group	Exudate	Count	9	51	60
		%	20.5	91.1	60
Total		Count	44	56	100
		%	100	100	100

Pearson Chi-Square = 51.197 ** P < 0.0001

Table 3: Cholesterol Group variables in comparison with protein group

Sensitivity	Specificity	Positive Predictive value	Negative Predictive value	Diagnostic accuracy	False Positivity rate	False negativity rate	Positive LR	Negative LR
79.55%	91.07%	87.50%	85.00%	86.00%	8.93%	20.45%	8.91	0.22

Table 4: Test Result Variable(s): Pleural fluid cholesterol group

Area	Std. Error	Asymptotic Sig.^{b}	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.863	.040	.000	.783	.942

Table 5: Comparison of LDA group vs cholesterol group

		Crosstab			
			Pleural fluid cholesterol group		Total
			Transudate	Exudate	
PLF LDH	Transudate	Count	38	3	41
SR LDH		%	86.4	5.4	41
group	Exudate	Count	6	53	59
		%	13.6	94.6	59
Total		Count	44	56	100
		%	100	100	100

Table 6: Cholesterol Group Variables in comparison with LDH group

Sensitivity	Specificity	Positive Predictive value	Negative Predictive value	Diagnostic accuracy	False Positivity rate	False negativity rate	Positive LR	Negative LR
86.36%	94.64%	92.68%	89.83%	91.00%	5.36%	13.64%	16.12	0.14

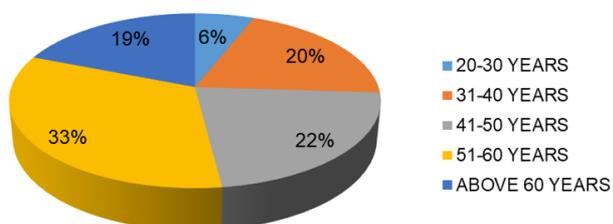**Table 7: Values for the area under the curve in pleural fluid cholesterol group**

		Test Result Variable(s): Pleural fluid cholesterol group		
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.913	.033	.000	.848	.977

Table 8: Statistical analysis of various groups

				Statistic				
		95% Confidence Interval for Mean						
	Mean	Lower Bound	Upper Bound	Median	Std. Deviation	Minimum	Maximum
Serum LDH	231.02	211.17	250.87	180.50	100.02	122.00	451.00
Serum protein	6.10	5.94	6.26	6.10	0.81	5.00	11.60
Pleural Fluid Protein	3.42	3.24	3.59	3.60	0.88	1.64	5.80
Pleural Fluid LDH	222.83	206.23	239.43	219.00	83.64	118.00	386.00
Pleural Fluid Cholesterol	40.09	36.87	43.31	47.20	16.23	12.00	76.30
Age	50.010	47.560	52.460	52.500	12.350	20.00	84.00
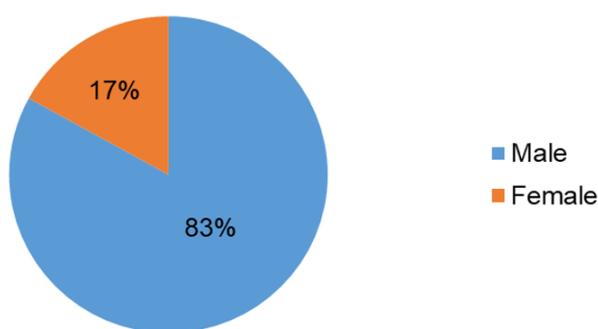
Figure 2: Sex distribution of the study patients

Figure 4: Area under the Curve

Figure 3: Age-wise frequency distribution of the study patients

the protein group, where the P-value is <0.0001, which is very highly significant.

The area is 0.863 with standard error 0.040. The asymptomatic 95% Confidence Interval lower bound was 0.783 and upper bound 0.942 (Table 4, Figure 4). The above table (Table 5) shows a comparison of Cholesterol group with LDH group. In
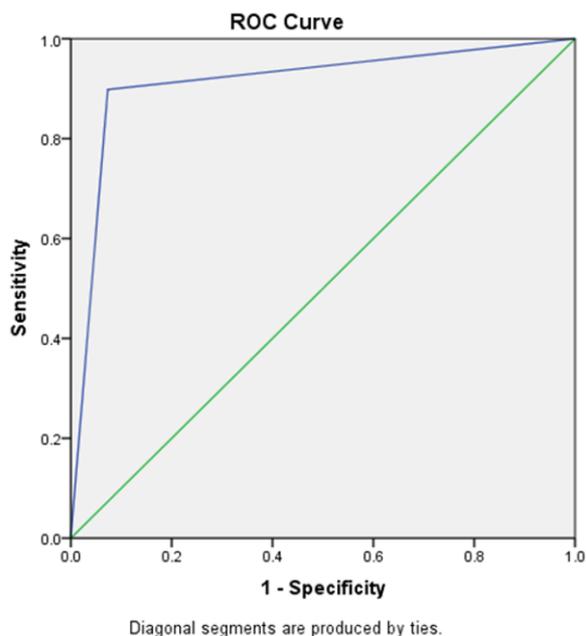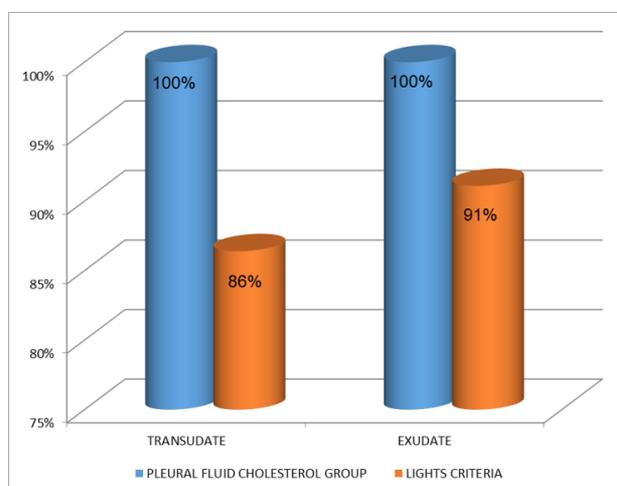
Figure 5: Area under the Curve

Figure 6: Comparison of sensitivity for pleural fluid cholesterol and light's criteria

Cholesterol group when comparing with LDH group transudates were 44 and exudates were 56. The above table (Table 6) depicts the cholesterol test was comparatively better than the LDH group, where the P-value is <0.0001, which is very highly significant. The area is 0.913 with standard error 0.033. The asymptomatic 95% Confidence Interval lower bound was 0.848 and upper bound 0.977 (Table 7, Figure 5). Table 8 shows the mean serum LDH levels to be 231.02 and mean serum protein as 6.10mg.dl. This figure shows Pleural Fluid Cholesterol Sensitivity is 100% in both transudative and exudative type, whereas 86.4% in transudative and 91.1% in exudative type according to light's criteria. (Figure 6)

DISCUSSION

The present study indicates that Pleural fluid Cholesterol may serve as a valuable diagnostic indicator as compared to light's criteria to differentiate exudates from transudates. In this study, the total number of patients with pleural effusion were 100, in which 83 were males, 17 were females. In this study, the age group between 51-60 years were 33%, between 41-50 years were 22%, between 31-40 years were 20%, above 60 years were 19% and between 20-30 years were 6%. In this study, out of 100 patients, 63 were diabetic, and 37 were non-diabetic, 45 patients were hypertensive, and 55 patients were non-hypertensive. Tubercular pleural effusion was of exudative type. Out of 33 patients suffering from tuberculosis, Pleural Fluid Cholesterol levels classified everyone to be having an exudative type of pleural effusion, whereas, light's criteria gave confusing results in 6 patients.

As per the study done by (Patel and Choudhury, 2013), the sensitivity and specificity in classifying a transudate based on the cholesterol levels, with a cut – off point of greater than 60mg/dL, was found to be 98% and 100% respectively, where one of the patients with a tuberculous effusion of the assessed 49 patients was classified wrongly as transudate. Although, there was found to be no misdiagnosis of 11 transudate patients.

In the same way, Chronic kidney disease patients with pleural effusion have transudative type of effusion which were classified correctly in all study subjects by pleural fluid cholesterol measurement compared to light's criteria which classified 5 of 23 study subjects as the exudative type of pleural effusion.

A study by (Mitra, 2012), Symptomatic pleural effusion was present in 6.74% patients of CKD (stages 3 to 5) and 5.88% of post-transplant patients.

(Mitra, 2012) in their study showed an incidence of 6.7% for symptomatic pleural effusion among the chronic kidney disease patients – stage 3 to 5, and 5.88% among the post-transplant group.

(Kumar *et al.*, 2015), in their study, showed that most of the unilateral, blood-tinged, lymphocyte-predominant, exudative effusions among the chronic kidney disease patients were secondary to tuberculosis; with TB being a leading cause of pleural effusions among the CKD patients only secondary to cardiac failure with a reported incidence of 28% and 31% respectively. Of the 35 patients they have assessed, unilateral effusion was found in 57%, of which majority of effusions were moderate (60%) followed by minimal (25%) and massive (15%). The other significant causes

they have described are uremic effusion (14%), parapneumonic effusions(11%), malignancy (9%) and connective tissue disorders (2%).

Moreover, 8 of 18 patients who were suffering from alcoholic liver disease and had pleural effusion were classified as exudative type as per light's criteria whereas, all were classified correctly into the group of transudative effusion by Pleural fluid Cholesterol measurement.

Pleural effusion in alcoholics can be related to a study done by Jalal Assouad et al., which suggested that Passage of ascites through diaphragmatic defects appears to be the leading cause of PE complicating cirrhosis.

According to Jose (Alonso, 2010), ~10% of cirrhotic patients with pleural effusion due to the hepatic cause have protein concentrations in the exudate range as a result of diuresis. (Paramothayan and Barron, 2002), in their study had similar results as that of our study with pleural fluid cholesterol diagnosing six cirrhotic cases correctly as transudates whereas 1 of 6 was a false negative according to light's criteria.

And also, malignancy and related pleural effusion were of an exudative type which was classified correctly in all seven patients by Pleural fluid Cholesterol. Still, light's criteria classified one of the patients as transudative effusion. These indicate the efficacy of Pleural fluid Cholesterol over Light's criteria for the classification of pleural effusion.

(Hamm *et al.*, 1987), showed when exudates differed from transudates with a cut-off level of 60mg/dL, 5% were incorrectly segregated. They also showed that in the malignant effusions, the mean cholesterol level was 94mg/dL, and the elevated cholesterol levels in the exudates were not dependant on the serum cholesterol levels.

(Guleria *et al.*, 2003), suggested criteria that exudative can be best recognised with pleural fluid cholesterol levels and triglyceride levels more than or equal to 60mg/dL and 40mg/dL respectively, and, a fluid to serum ratio of cholesterol and triglyceride greater than or equal to 0.4 and 0.3 respectively. They also demonstrated a sensitivity and specificity of 88% and 100% respectively for the pleural fluid cholesterol, and, 98% and 84% respectively for fluid to serum cholesterol ratio, with an accuracy of 92% for fluid cholesterol among the exudates group which were on a comparison basis superior to the criteria proposed by the light et al.

(Light *et al.*, 1972) suggested criteria with fluid serum protein ratio greater than 0.5, fluid LDH more than or equal to $2/3^{rd}$ upper limit of that of serum and a ratio of fluid to serum LDH more than 0.6, suggesting a sensitivity and specificity of 99% and 98% respectively in classifying an exudate from a transudate, but, which when evaluated by other researches failed to show the same result; with reproduced values from other studies showing a specificity ranging in between 70-86%. Also, it was highlighted that of the patients with transudate variant, 25% were classified as having exudate by light's criteria.

Mis-diagnosis of exudate from a transudate can be a leading factor for increased morbidity, misuse of, and increased cost of health care resources; mainly by the alteration of treatment leading to inappropriate management. This suggests a necessity of tests with higher diagnostic accuracy.

In our study, we found a significantly low misdiagnosis rate with the use of fluid cholesterol levels for classification, in comparison to light's criteria.

All these on a conclusive basis, with synergistic support, form our personal experience about this study showing a higher sensitivity and specificity of 100% draw a suggestion that the pleural fluid cholesterol might be a new landmark in the pleural exudate diagnosis, and it could be a promising test for avoiding misdiagnosis.

Limitations of the study

For one thing, the detailed mechanism of cholesterol in the pathogenic process has not been systematically investigated; second, the standard cut-off value of pleural cholesterol has not been founded, there were several cut-off values ranged from 38 to 65 mg/dl. Further work should aim to identify the cut-off value of pleural cholesterol that provides optimal diagnostic accuracy.

CONCLUSIONS

In conclusion, pleural fluid cholesterol showed higher accuracy, specificity and sensitivity, statistically significant P value of <0.0001 when compared to the light's criteria. It also facilitates in the reduction of healthcare-associated costs by cutting down investigations like plasma protein and LDH, serum protein and LDH. Hence, in short, assessment of pleural fluid cholesterol is way more efficient, cost-effective and an easy method for classifying exudate from transudate and must be applied in routine clinical practice. As the study involved a small sample size, we suggest that further studies on large samples are warranted.

ACKNOWLEDGEMENT

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