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RESEARCH ARTICLE

ROLE OF COMBINED PLEURAL FLUID CHOLESTEROL AND TOTAL PROTEIN FOR DIFFERENTIATING EXUDATIVE FROM TRANSUDATIVE PLEURAL EFFUSION IN A TERTIARY CARE CENTRE-AN OBSERVATIONAL STUDY

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Abstract

Introduction: Identifying whether the pleural effusion is exudative or transudative is the first step in making a diagnosis.Light\'s criteria, have been accepted more widely than any other criteria for discriminating between transudative and exudative effusions.But incorrectly labels 15–20% of transudative effusions as exudates. We investigate if comparable results may be obtained using pleural fluid cholesterol and pleural fluid total protein.

Objectives: To compare combined pleural fluid cholesterol and pleural fluid total protein with Light's criteria in differentiating exudative and transudative effusion and find its significance.

Methods: This is a hospital based cross sectional study conducted in the Department of Respiratory medicine, GMC, Kannur over a period of one year on 120 patients who presented with pleural effusion,and fulfilling the inclusion and exclusion criteria. The pleural fluid sample obtained from each patient was taken for analysis,and nature of effusion by using Light's criteria and combined pleural fluid cholesterol+total protein was noted. The final diagnosis based on clinical diagnosis along with HPR and/or culture was set as the gold standard. Mc Nemar's Chi-square test was applied to compare Light's criteria and Pleural fluid cholesterol+total protein with gold standard.The diagnostic parameters like sensitivity, specificity, PVP, PVN and accuracy of Light's criteria and pleural fluid cholesterol+ total protein to predict exudates were estimated.

Results: We found out that there is significant difference in the classification of transudate and exudate by Light's criteria with respect to gold standard (p-value 0.001). Kappa value 0.722 shows a significant substantial agreement between Light's criteria and gold standard test (p-value <0.001). The sensitivity ,specificity, PVP,PVN and accuracy of Light's criteria to predict exudate was 100.00%,63.33%, 89.11%,100.00%, and 90.83% respectively. Also, there is significant difference in the classification of transudate and exudate by Pleural fluid cholesterol+total protein with respect to gold standard (p-value 0.031). Kappa value 0.875 shows a significantly almost perfect agreement between pleural fluid Cholesterol+Total protein and gold standard test (p-value <0.001).The sensitivity, specificity, PVP,PVN and accuracy of Pleural fluid Cholesterol+Total protein to predict

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exudate was 93.33%, 100.00%, 100.00%,83.33%, and 95.00% respectively.

Conclusion: As compared to Light's criteria, Pleural fluid cholesterol+total protein shows a high agreement with gold standard to distinguish exudative and transudative effusion and can be used as an alternative to Light's criteria.

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Introduction:-

Normally,the pleural space contains a few millilitres of pleural fluid only. Via the visceral pleura, capillaries in the parietal pleura, interstitial spaces of the lungs, and channels in the diaphragm, fluid can enter the pleural space. It is eliminated by the parietal pleura's lymphatic system. When lymphatics are blocked or pleural fluid production exceeds its absorption, pleural fluid builds up. In conjunction with the clinical history, physical examination, and radiography, the pleural fluid analysis provides critical diagnostic information about pleural effusion. Identifying whether the pleural effusion is exudative or transudative is the first step in making a diagnosis.[1]

Light's criteria, which have a sensitivity and specificity of 99 percent and 98 percent, respectively, have been accepted more widely than any other criteria for discriminating between transudative and exudative effusions.Exudative effusion is defined by the Light's criteria as having one or more of the following:(1) A pleural-to-serum protein ratio greater than 0.5; (2) A pleural-to-serum LDH ratio >0.6; (3) Pleural fluid LDH greater than 2/3 of the upper limit of serum LDH.[2]

The fundamental drawback of Light's criteria is that they misclassify 15-20% of transudative pleural effusions as exudative, particularly in patients with congestive heart failure taking diuretics.[3] Many patients with congestive heart failure (CHF) have protein levels in the exudative range. In 1965, this phenomenon was first observed by Pillay et al. and it was later confirmed by Chakko et al. This might cause these patients to undergo pointless investigations.[4,5] Pleural cholesterol may serve as a biomarker to distinguish between exudative and transudative pleural effusions because several studies indicate that it is elevated in pleural exudates.[4,5] Pleural cholesterol levels are considered to rise as a result of cellular degeneration (leukocytes and erythrocytes) and vascular leakage due to increased permeability. Independent of serum cholesterol levels, exudative effusions appear to have higher pleural cholesterol levels.[5] An Indian study that used combined pleural fluid cholesterol and total protein to differentiate exudative and transudative effusion demonstrated 100% sensitivity and specificity.[6]

Aim of the study is to find out the role of combined pleural fluid cholesterol and total protein in differentiating exudative from transudative pleural effusions,and to compare combined pleural fluid cholesterol and total protein with Light's criteria in differentiating exudative and transudative effusion and find its significance.

We investigate if comparable results may be obtained using pleural fluid cholesterol and total protein to streamline the diagnostic process and eliminate the requirement for a concurrent blood sample. The study also tries to estimate the usefulness of these parameters where Light's criteria fails.

Methods:-

1. Study Design: Hospital based cross sectional study.
2. Study Setting: Department of Respiratory Medicine, Government medical college, Kannur.
3. Study Period: The study was conducted for a period of 1 Year, from May 2021 to May 2022.
4. Sample Size: $\frac{(1.96)2\text{sensitivity x}(1\text{-sensitivity})}{(d)2\text{prevalence}}$

Where sensitivity=87.9% ;1- sensitivity =12.1 %; d:10%of relative precision
Prevalence=45%(based on a pilot study conducted in the year 2020)
Final sample size: 118~120
5. Sampling: Consecutive sampling
6. Study Population: Patients with pleural effusion attending the Department of Respiratory medicine, GMC, Kannur.

7.Inclusion Criteria: Patients aged between 19 -64 yrs. with clinical, radiological or sonographic evidence of pleural effusion attending the Department of Respiratory medicine, GMC, Kannur.
6. Exclusion Criteria
1. Those patients in whom thoracentesis can't be done (coagulopathy, chest wall infections, hemodynamically unstable patients)
2. Minimal pleural effusion (<1cm detected by imaging studies)
3. Empyema
4. Post traumatic pleural effusion
5. Haemothorax (PCV >45%)

Methodology:-

Subjects were selected according to inclusion and exclusion criteria.The written informed consent was obtained from them .After a detailed history and clinical examination, a chest X-ray was done to localize pleural effusion. A pretested piloted questionnaire was used to gather information regarding sociodemographic characteristics, clinical profile and lab parameters. Diagnostic tapping of the pleural fluid was done. Blood samples were also sent for routine investigations like blood routine, liver function tests, renal function tests and electrolytes along with serum ldh. Further investigations, if needed, such as sputum AFB, sputum culture,sputum cytology, ECG, Echo, USG abdomen and pelvis, CT scan of the chest,bronchoscopy, FNAC, biopsy were also done to determine the aetiology of pleural effusion .

The nature of effusion by using Light's criteria and combined pleural fluid cholesterol and total protein were noted. The final diagnosis based on clinical diagnosis along with HPR and/or culture was set as the gold standard, to which the pleural fluid parameters under study are compared.

Variables Studied:
Age,Gender,Pleural fluid examination

Data Analysis
All the statistical analysis were done using IBM SPSS Statistics Version 26. All the categorical variables were presented as in frequency or in percentage. Mc Nemar's Chi-square test was applied to compare Light's criteria and pleural fluid cholesterol+ total protein with gold standard. Overall agreement of Light's criteria and pleural fluid cholesterol+total protein was estimated by Cohen's Kappa value. The diagnostic parameters like sensitivity, specificity, PVP, PVN and accuracy of Light's criteria and pleural fluid cholesterol+ total protein to predict exudates were estimated. All the statistical tests were two tailed. A p-value <0.05 was considered as statistically significant.

Result:-

Total 120 patients were included in this study.

We observed that the majority of the participants belonged to the more than >50 years age group(45%) .There was male predominance, accounting for 65% of the total number. Almost 78% of the study participants were educated. 38% were belonging to the middle class and 37.5% to lower class. Around 58% were unemployed.(Table .1)

Table 1:- Sociodemographic and baseline characteristics of the study participants (N=120).

Characteristics	Frequency (%)
Age group	
<30 years	23 (19.2)
31-50 years	43 (35.8)
>50 years	54 (54.0)
Sex	
Male	78 (65.0)
Female	42 (35.0)
Education	
Uneducated	26 (21.6)
Educated	94 (78.4)
Socio economic status	

Upper	29 (24.2)
Middle	46 (38.3)
Lower	45 (37.5)
Employment	
Employed	51 (42.5)
Unemployed	69 (57.5)

The right hemithorax was most commonly affected (40%).(Fig.1) The commonest diagnosis noted was tuberculosis (29%), followed by adenocarcinoma (19%)(Fig.2).

Around 63% were suffering from some form or the other comorbidity. The most common comorbidity noted was hypoalbuminemia (34%) followed by HTN (24%).(Fig.3) The commonest clinical presentation was fever 72%, followed by cough 60% and dyspnoea 54%.(Fig.4)

We observed that around 16% of the cases were diagnosed to be transudative and the rest 84% were diagnosed as exudative using Light's criteria.(Table 2).

Table 2:-Distribution of pleural effusion based on Light's criteria among the study participants (N=120).

	Exudative	**Transudate**
Light's criteria	101 (84.2)	19 (15.8)

Out of 120 cases, 11(9.2%) cases were classified as transudative by gold standard and exudative by Light's criteria.19 (15.8%) cases were classified as transudative by both the test. 90(75.0%) cases were classified as exudative by both the test.However there is significant difference in the classification of transudative and exudative by Light's criteria with respect to gold standard (p-value 0.001). Kappa value 0.722 shows a significant substantial agreement between Light's criteria and gold standard test (p-value <0.001).(Table.3) The specificity, sensitivity, PVN, PVP and accuracy of Light's criteria was 63.33%, 100.00%, 100.00%, 89.11% and 90.83% respectively. (Table.4)

Table 3:- Comparison of Light's criteria and Gold Standard.

Light's criteria		**Gold Standard**		**Total**	**Kappa value & p-value**	**Mc-Nemar's Chi square p- value**
		Transudative	Exudative			
Transudative	No.	19	0	19	0.722 & <0.001	0.001
	%	15.8	0	15.8		
Exudative	No.	11	90	101		
	%	9.2	75	84.2		
Total	No.	30	90	120		
	%	25.0	75.0	100		

Table 4:- Diagnostics parameters of Light's criteria to predict exudate.

Statistic	**Value**	**95% Confidence Interval (Lower limit – upper limit)**
Specificity	63.33%	43.86% - 80.07%
Sensitivity	100.00%	95.98% - 100.00%
Predictive Value Negative (PVN)	100.00%	-
Predictive Value Positive (PVP)	89.11%	83.64% - 92.91%
Accuracy	90.83%	84.19% - 95.33%

We observed that around 30% of the cases were diagnosed to be transudative and the rest 70% were diagnosed as exudative using pleural fluid cholesterol+total protein.(Table.5)

Table 5:- Distribution of pleural effusion based on Pleural fluid Cholesterol >60mg/dL and Protein >3g/dL among the study participants (N=120).

	Exudative	**Transudate**
Pleural fluid Cholesterol >60mg/dL and Protein >3g/dL	84 (70.0)	36 (30.0)

Out of 120 cases , 6(5.0%) cases were classified as exudative by gold standard and transudative by Pleural fluid cholesterol+total protein. 30 (25.0%) cases were classified as transudative by both the test. 84 (70.0%) cases were classified as exudative by both the test. However, there is significant difference in the classification of transudative and exudative effusion by Pleural fluid cholesterol+total protein with respect to gold standard (p-value 0.031). Kappa value 0.875 shows a significantly almost perfect agreement between Pleural fluid cholesterol+total protein and gold standard test (p-value <0.001). (Table.6)

The specificity, sensitivity, PVN,PVP and accuracy of Pleural fluid cholesterol+total protein to predict exudate was 100.00%, 93.33%, 83.33%, 100.00% and 95.00% respectively.(Table.7)

Table 6:- Comparison of Pleural Fluid Cholesterol +Total protein and Gold Standard.

Pleural Fluid Cholesterol+ Total protein		**Gold Standard**		**Total**	**Kappa value & p-value**	**Mc-Nemar's Chi square p- value**
		Transudative	Exudative			
Transudative	No.	30	6	36	0.875 & <0.001	0.031
	%	25.0	5.0	30.0		
Exudative	No.	0	84	84		
	%	0.0	70.0	70.0		
Total	No.	30	90	120		
	%	25.0	75.0	100.0		

Table 7:- Illustrates the diagnostic parameters of pleural fluid cholesterol+total protein to predict exudate with respect to Gold standard test.

Statistic	**Value**	**95% Confidence Interval (Lower limit – upper limit)**
Specificity	100.00%	88.43% - 100.0%
Sensitivity	93.33%	86.05% - 97.51%
Predictive Value Negative (PVN)	83.33%	69.77% - 91.55%
Predictive Value Positive (PVP)	100.00%	-
Accuracy	95.00%	89.43% - 98.14%

As compared to Light's criteria, Pleural fluid cholesterol+total protein shows a high agreement with Gold standard to distinguish exudative and transudative effusion.(Fig 5)

Discussion:-

Our study findings showed that majority (45%) of the participants belonged to the age group more than >50 years.In a similar study by Bista et al the mean age of the patient was found to be 45.88±18.25yrs.[7] Majority of the patients were males (65%).This was found to be in line with the finding from another study by Bista et al, who showed that males were more commonly affected(51.9%) with pleural effusions. ([7]) Also we find out that majority of the patients were educated (78.4%), most of them belonged to middle class (38.3%) and 57.5% were unemployed. .With respect to the clinical presentation, we observed that right hemithorax (40%) was most commonly affected. This was consistent with similar study by Rungta R et al and Jha RK et al where majority (53.5%) of patients had right sided effusion.([8])The commonest diagnosis noted was tuberculosis (29.2%). Around 63% were suffering from some or other form of comorbidity, hypoalbuminemia (54.2%) being the most common. The commonest clinical presentation was fever (72%), followed by cough (60%) and dyspnoea (54%). This finding was found to be comparable to findings from Patel et al, who also observed that TB was the most common reason for pleural effusions admitted in Indian settings. ([9]) Our findings were also found to be similar to findings established by Bista et al, who showed that tuberculosis was the most common cause of exudative pleural effusions, and the most common presenting complaint was fever.[7]

In our study the clinical diagnosis along with diagnosis made by HPR and/or culture was taken as gold standard. Out of 120 cases, 19 (15.8%) cases were classified as transudative by both Light's criteria and Gold standard.90 (75.0%) cases were classified as exudative by both the test. Light's criteria misclassified 11(9.2%) transudative as exudative and correctly identified all exudative effusion. However there is significant difference in the classification of transudative and exudative by Light's criteria with respect to gold standard (p-value 0.001). Kappa value 0.722 shows a significant substantial agreement between Light's criteria and Gold standard (p-value <0.001). In a similar study by Bista et al, Light's criteria misclassified more number of (19.7%) transudative as exudative and few (2.4%) exudative as transudative.[7] Out of 120 cases , 30 (25.0%) cases were classified as transudative by both Pleural fluid cholesterol+total protein and Gold standard. 84 (70.0%) cases were classified as exudative by both the test. 6(5.0%) cases were misclassified as transudative by Pleural fluid cholesterol+total protein while correctly identified all transudative effusion. However, there is significant difference in the classification of transudative and exudative by Pleural fluid cholesterol+total protein with respect to Gold standard (p-value 0.031). Kappa value 0.875 shows a significantly almost perfect agreement between Pleural fluid cholesterol+total protein and Gold standard test (p-value <0.001). In the study by Bista et al, using combined pleural fluid cholesterol and total protein more number of transudatives where misclassified compared to our study ie 7(8.6%)cases were misclassified as transudative where as similar to our study all transudative effusions were correctly identified.([7])

The analysis showed that Light's criteria had sensitivity, specificity, PPV, NPV, accuracy of 100%, 63.33%, 89.11%, 100% and 90.83% respectively to predict exudative. Study by Bista et al, showed a lower sensitivity and speficity for Light's criteria compared to our study ie 96.6% and 30.4% respectively.[7] Study by Patel et al showed lower sensitivity (98%) and NPV 92% and higher specificity (100%) and PPV (100%) for Light's compared to our study.[9] In our study sensitivity, specificity, PVP, PVN and accuracy of Pleural fluid cholesterol+total protein to differentiate exudative effusion was 93.33%, 100.00%, 100%, 83.33%, and 95.00% respectively. In the study by Bista et al, using Pleural fluid cholesterol >60mg/dL and total protein >3g/dL showed a lower sensitivity but similar specificity compared to our study ie 87.9% 100% respectively with a significant p value of <0.001.[7] However, our findings were observed to show lower sensitivity but similar specificity when compared to another study done by Patel et al, who observed a sensitivity and specificity of 100% and 100% respectively.[9] To conclude, in our study Pleural fluid cholesterol+total protein shows a high agreement with Gold standard to distinguish exudative and transudative effusion, compared to Light's criteria and can be used as an alternative to Light's criteria.

Despite all, our study had certain limitations:

1. We had a smaller sample size to evaluate the effect outcome on all independent variables
2. Limitations of this study are generally attributed to the observational nature of this study
3. The findings are generalisable only to similar study settings, as the study was conducted only from one single centre in south India.

Conclusion:-

To conclude, in our study we found that majority of the patients who presented with pleural effusions were males, most common age group affected was >50yrs, most common presenting symptoms were fever and cough and most common comorbidity was hypoalbuminemia. Our study showed that Tuberculosis was the most common cause of pleural effusion, hence keen observation is required to diagnose and treat those cases. In our study as compared to Light's criteria, Pleural fluid cholesterol+total protein shows a high agreement with gold standard to distinguish exudative and transudative effusion and can be used as an alternative to Light's criteria. However larger studies are required to make definite conclusions.

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