

DIAGNOSTIC VALUE OF PLEURAL C- REACTIVE PROTEIN IN PLEURAL EFFUSION IN TERTIARY CARE CENTRE IN KUMAON REGION OF UTTARAKHAND

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Abstract

Background: ur study aims to provide a diagnosis biomarker CRP as an indicator for pleural effusion and assess the diagnostic value of pleural CRP for differentiating between exudative and transudative pleural effusion in the Uttarakhand (part of India) population. **Materials and Methods:** This cross sectional, institution-based, observational single centre study was conducted at the Department of General Medicine, Government medical college and associated Dr Sushila Tiwari Government Hospital. The study included IPD and OPD patients of pleural effusion. The study excluded patients not willing to consent, Patient below 16years, Patients on treatment for pleural effusion and PLWHA. **Result:** When comparing hematological parameters, a significantly higher mean Hb (p= 0.013), mean ESR (p= 0.008), mean pleural LDH (p= 0.001), mean ADA (p =0.001), mean Protien (p= 0.001), mean TLC (p= 0.002), and mean CRP (p= 0.001) was observed in Exudative group compared to Transudative group. It was also noted that there was a significant difference in the distribution of patients according to CRP levels (p= 0.001). The patients had Sensitivity of 69% while Specificity was 78.6%, PPV was 81.6%, NPV was 64.7% and Accuracy was 73.0% with respect to CRP levels. **Conclusion:** The present study concludes that levels of CRP are significantly correlated in pleural effusion patients. Thus, CRP could prove as good marker and can be used as an indicator for pleural effusions and assess the diagnostic value of CRP for differentiating between exudative and transudative pleural effusion at an early stage of disease.

INTRODUCTION

Pleural effusion is an abnormal collection of fluid build-up in pleural space or cavity between lungs and chest cavity.^[1] The presence of fluid in a normal amount (approx. 0.1 to 0.2 mL/kg) provides lubrication and avoids frictional stress to the lungs caused by breathing.^[2,3] The global incidence of pleural effusion in industrialized countries is approx. 3 million cases per annum. Pleural effusion is one of the most common causes of morbidity and mortality in pulmonary conditions.^[4]

The pleural effusion can be classified into transudative and exudative, based on reformed Light's criteria.^[5,6] Exudative pleural effusion occurs due to pleural infection, injury, inflammation, or lymphatic obstruction. The common causes include viral infection, pneumonia, pleural or pulmonary tuberculosis, malignancy, and inflammatory disorders such as chylothorax (lymphatic obstruction or thoracic duct injury),

haemothorax (post trauma), rheumatoid arthritis, post-cardiac injury syndrome, asbestosis and systemic lupus erythematosus. Transudative develops by systemic illness caused due to increase and decrease in capillary hydrostatic pressure and osmotic pressure respectively in the pleural space. The leading causes of transudate pleural effusion are congestive heart failure, nephrotic syndrome, hepatic disorders like cirrhosis, and hypoalbuminemia.

Differentiating an exudative from transudative effusion always involves the analysis of pleural fluid depending on Light's criteria.^[6] If the pleural fluid lactate dehydrogenase (LDH)/serum LDH > 0.6, and/or pleural fluid LDH is more than two-thirds the normal upper limit for serum, and/or pleural fluid protein/serum protein > 0.5 is deemed as exudative, whereas transudative pleural effusion if none of these criteria are met. The major drawback of these criteria is that about 25% of pleural effusions due to Congestive heart failure are considered as exudates

(according to Light's criteria).^[7] Unfortunately, pleural fluid analysis lacks enough sensitivity and specificity to determine the cause. This ultimately results in invasive procedures which involve thorascopies and closed pleural biopsies. The diagnosis of disease etiology in pleural effusions, and the number of potential accurate biomarkers on pleural fluid specimens have streamlined clinical diagnostic pathways.

C-reactive protein (CRP), identified as "acute-phase proteins", is secreted by hepatocytes in the liver and gets released in response to various stimuli. They are initially synthesized during inflammatory processes, allow enhanced protection against pathogens and help in a rapid return to a homeostatic state during infection, and limit tissue damage. The primary pro-inflammatory mediators, such as interleukin-6 and tumour necrosis factor trigger the induction of CRP in the liver.^[8]

In the case of pneumonia-affected individuals, CRP levels are increased in serum/plasma and play a valuable role in disease diagnosis.^[9] Multiple studies have confirmed that CRP could act as a possible biomarker for pleural infection because the circulating CRP may leak into the pleural cavity and increased concentration levels could help in diagnosis. Although, an increasing number of studies have reported that both pleural and serum CRP could play a role in the diagnosis of pleural effusion.^[10-13]

However, there is not a "one size fits all" approach to diagnosis and management as patients with pleural disease represent a heterogeneous population. Here, our study aims to provide a diagnosis biomarker pleural CRP as an indicator for pleural effusions and assess the diagnostic value of CRP for differentiating between exudative and transudative pleural effusion among Indian population.

MATERIALS AND METHODS

After obtaining approval from Institutional Ethics Committee, this cross sectional, institution-based, observational single Centre study was conducted at the Department of General Medicine, Government medical college and associated Dr Sushila Tiwari Government Hospital. This study was conducted for a duration of 21 months (January 2021 – September 2022).

Study Population

The present study included all patients with pleural effusion visiting the OPD or IPD of our tertiary care

Centre. An informed consent was obtained from all patients before enrolling for the study. The patients were then divided into two groups based on the Light's criteria:

- I. Exudative Pleural Effusion
- II. Transudative Pleural Effusion

The study included IPD and OPD patients of pleural effusion. The study excluded patients not willing to consent, Patient below 16 years, Patients on treatment for pleural effusion and PLWHA.

Methodology

A detailed history according to preset questionnaire and a detailed clinical examination of patients was done, once the patients were enrolled for the study. All patients with clinical and radiological diagnosis of pleural effusion underwent pleural fluid analysis comprising of protein, sugar, LDH, cytology, AFB, culture. Renal function tests, complete blood count, liver function tests, serum protein and LDH, sputum gram stain and culture and sensitivity. CRP were measured in all cases of pleural effusion.

Light's criteria was used to classify the patients into exudative and transudative pleural effusion. Transudative group was further subjected to find the cause of transudative by subjecting them to ultrasound abdomen, echocardiogram. Exudative pleural effusion was studied under four categories: parapneumonic effusion, tuberculous effusion, malignant effusion, and others. The diagnosis of malignant effusion was made when malignant cells were found on pleural fluid cytologic examination.

Statistical Analysis

SPSS version 25.0 analyzed the Excel data when it was loaded. Quantitative (numerical variables) data was given as mean and standard deviation, whereas qualitative (categorical variables) data was provided as frequency and percentage. The student t-test was used to compare the two groups' mean values, while the chi-square test analyzed their frequency differences. If $p < 0.05$, it was statistically significant.

RESULTS

It was observed that 58.0% patients were in Exudative Group while 42.0% patients were in Transudative Group. It was observed that under Exudative group, mean age was 45.34 ± 19.56 years while under Transudative group, mean age was 49.29 ± 19.21 years. It was observed that under Exudative group, mean BMI was 25.84 ± 1.52 while under Transudative group, mean BMI was 26.24 ± 1.43 . [Table 1]

Table 1: showing comparison of mean age, gender distribution and BMI of patients between two groups.

		Diagnosis		p value
		Exudative	Transudative	
		Mean \pm SD	Mean \pm SD	
Age		45.34 \pm 19.56	49.29 \pm 19.21	0.319
Gender	Male	31 (53.4%)	26 (61.9%)	0.399
	Female	27 (46.6%)	16 (38.1%)	
Total		58 (58.0%)	42 (42.0%)	
BMI		25.84 \pm 1.52	26.24 \pm 1.43	0.184

Table 2: showing comparison of distribution of patients according to smoking habits, alcohol, dyspnoea grading, chest pain, cough, fever, COPD, Diabetes mellitus, Hypertension, CAD, Ascites.

	Diagnosis				p value
	Exudative		Transudative		
	Frequency	%	Frequency	%	
Smoking	19	32.8%	15	35.7%	0.758
Alcohol	4	6.9%	5	11.9%	0.388
Dyspnea Grade 0	20	34.5%	17	40.5%	0.550
Dyspnea Grade 1	31	53.4%	20	47.6%	
Dyspnea Grade 2	5	8.6%	5	11.9%	
Dyspnea Grade 3	2	3.4%	0	0.0%	
Chest pain	25	43.1%	18	42.9%	0.980
Cough	42	72.4%	21	50.0%	0.022*
Fever	24	41.4%	9	21.4%	0.036*
COPD	7	12.1%	4	9.5%	0.757
Diabetes Mellitus	8	13.8%	14	33.3%	0.020*
Hypertension	4	6.9%	16	38.1%	0.001*
CAD	2	3.4%	17	40.5%	0.001*
Ascites	18	31.0%	18	42.9%	0.224

It was observed that under Exudative and Transudative group with respect to smoking, alcohol abuse and Dyspnea Grades. Exudative group showed that 43.1% patients had chest pain and Transudative group showed 42.9% patients had chest pain. Cough and Fever were significantly more among Exudative group (72.4% and 41.4% respectively) compared to Transudative group (50.0% and 21.4% respectively).

It was observed that in Exudative group, 12.1% patients had COPD and in Transudative group, 9.5% patients had COPD. In Exudative group, 13.8% of the patients had DM and in Transudative group, 33.3% patients had DM. It was observed that in Exudative group, 6.9% patients had HTN and in Transudative group, 38.1% patients had HTN. 3.4% of the patients in Exudative group had CAD and 40.5% patients in Transudative group had CAD. Among Exudative group, 31.0% patients had Ascites and among Transudative group, 42.9% patients had Ascites.

Table 3: showing comparison between various haematological and biochemical parameters.

	Diagnosis		p value
	Exudative	Transudative	
	Mean ± SD	Mean ± SD	
TLC	12463.79 ± 17528.17	10042.86 ± 4057.94	0.255
Platelets	282413.79 ± 134191.93	297714.29 ± 128331.56	0.665
Hb	11.56 ± 3.13	10.24 ± 1.93	0.013*
ESR	56.21 ± 32.58	40.52 ± 17.94	0.008*
pleural LDH	659.07 ± 796.43	439.93 ± 599.55	0.001*
ADA	37.6 ± 25.02	13.06 ± 16.23	0.001*
Glucose	109.45 ± 62.51	127.5 ± 56.81	0.050
Protein	4.97 ± 1.39	2.63 ± 1.34	0.001*
TLC	4988.79 ± 2532.36	6236.26 ± 2233.33	0.002*

The mean Hb, ESR, pleural LDH, ADA, Protein and TLC was significantly more among Exudative group compared to Transudative group.

Table 4: showing comparison between various haematological and biochemical parameters.

	Diagnosis		p value
	Exudative	Transudative	
	Mean ± SD	Mean ± SD	
Lymphocytes	69.03 ± 32.8	70.05 ± 31.43	0.784
Neutrophil	23.16 ± 30.73	21.31 ± 23.8	0.279
CRP	13.41 ± 40.4	1.58 ± 2.2	0.001*
T. protein	6.4 ± 1.05	6.35 ± 0.78	0.248
Albumin	3.24 ± 0.61	3.11 ± 0.57	0.257
Globulin	3.15 ± 0.82	3.24 ± 0.69	0.692

The mean CRP was significantly more among Exudative group compared to Transudative group. However, there was no significant difference in mean Lymphocytes (p value 0.784), mean Neutrophil (p value 0.279), mean total protein (p value 0.248), mean Albumin (p value 0.257) and mean Globulin (p value 0.692) when Exudative group was compared with Transudative Group.

The area under curve for CRP in predicting Exudative diagnosis was 0.712 with 95% CI of 0.610 – 0.814. Using Receiver Operating Curve, the cut off value of CRP found to be 1.51 correlating with Exudative diagnosis. The patients had Sensitivity of 69% while Specificity was 78.6%, PPV was 81.6%, NPV was 64.7% and Accuracy was 73.0% with respect to CRP levels.

DISCUSSION

Pleural effusion is an abnormal collection of fluid build-up in pleural space or cavity between lungs and chest cavity.^[1] The global incidence of pleural effusion in industrialized countries is approx. 3 million cases per annum. Pleural effusion usually results from excess fluid production and decreased lymphatic absorption. The most frequent causes of exudative pleural effusion are pneumonia, tuberculosis (TB), pulmonary embolisms, and diseases that cause pleuro-renal syndromes, such as systemic lupus erythematosus. The most frequent causes of transudative pleural effusion are fluid overload, heart failure, and nephrotic syndrome. Uraemic pleurisy (exudative PE), a diagnosis of exclusion that continues or recurs after intensive hemodialysis, is another significant contributing factor (HD).^[14]

The mean age of patients in exudative group was 45.34 ± 19.56 years and transudative group was 49.29 ± 19.21 years. Male predominance was observed in both the groups. However, no significant difference was found in the gender between the two groups. Similarly, male predominance was also seen in a study by Chandrik Babu et al. 34.2% of the patients were men and about 65.8% of them were women.^[15] In another study done by Waffa et al,^[16] also Male subjects reported pleural effusion more than female and the mean age around 55 years of age.

Mean BMI in the present study was 25.84 ± 1.52 and 26.24 ± 1.43 in exudative and transudative groups, respectively. Non-vegetarian diet (77.6% and 76.2%) was preferred by subjects in both the groups compared to vegetarian diet (22.4% and 23.8%). Most of the study subjects were non-smokers. However, a significant difference was observed in the mean number of smoking packs consumed by smoker in the two groups (30.00 ± 10.00 vs 23.00 ± 9.60 ; $p=0.041$). Only 6.9% and 11.9% of the subjects consumed alcohol in exudative and transudative groups, respectively. In a systematic review,^[17] it was found that the commonest risk factor was smoking ($n = 9$) followed by alcohol intake ($n = 8$). Symptoms from most common to least common include dyspnoea, weight loss, chest pain, fever, sputum, and black sputum production.

The clinical manifestations of pleural effusion are variable and often are related to the underlying disease process. The most commonly associated symptoms are progressive dyspnoea, cough, and pleuritic chest pain. The most prevalent symptom of pleural effusion is dyspnoea, which has less to do with hypoxemia and more to do with the diaphragm and chest wall deformation that occurs during respiration. Despite very minor changes in gas exchange, evacuation of pleural fluid reduces dyspnoea in many individuals.

Chest pain was seen in 43.1% and 42.9% of the patients in exudative and transudative groups, respectively. Other common presenting symptoms of the patients were also noted. It was observed that there was a significant difference in distribution of patients according to presence of cough, fever when exudative group was compared with transudative group (p value 0.022 and 0.036, respectively). None of the patient had haemoptysis in both the groups. COPD was seen in 12.1% of the exudative group patients and 9.5% of the transudative group patients. Cough in patients with pleural effusion is often mild and non-productive.^[18] Chest discomfort from pleural irritation increases the risk of an exudative aetiology, such as mesothelioma, pleural infection, or pulmonary infarction.^[19]

Comorbidities of the patients were also reported in our study. Diabetes mellitus (13.8% vs 33.3%; $p=0.020$), hypertension (6.9% vs 38.1%; $p=0.001$) and CAD (3.4% vs 40.5%; $p=0.001$) was significantly more prevalent in transudative group compared to exudative group. It was observed that under the Exudative group, 69.0% of the patients had no Ascites while 31.0% of the patients had Ascites. Similarly, it was observed that under Transudative group, 57.1% of the patients had no Ascites while 42.9% of the patients had Ascites.

In the present study, complete routine blood tests of the patients showed that in comparison to the Transudative group, the Exudative group had significantly higher mean HB ($p = 0.013$), mean ESR ($p = 0.008$), mean pleural LDH ($p = 0.001$), mean ADA ($p = 0.001$), mean protein ($p = 0.001$), and mean TLC ($p = 0.002$). When the Exudative group was compared to the Transudative Group, there was no discernible change in mean TLC (p value 0.255), mean Platelets (p value 0.665), or mean Glucose (p value 0.050). Similarly, significantly higher mean CRP (p value 0.001) in Exudative group was compared with Transudative Group. However, there was no significant difference in mean Lymphocytes (p value 0.784), mean Neutrophil (p value 0.279), mean T.protein (p value 0.248), mean Albumin (p value 0.257) and mean Globulin (p value 0.692) when Exudative group was compared with Transudative Group. However, Babu et al. showed that only serum globulin was shown to be statistically significant between transudate and exudate pleural fluid, whereas albumin and protein were discovered to be statistically insignificant. Makwana et al.^[20] observed that the empyema group had the greatest ratio of pleural fluid protein to serum protein (1.26); The empyema group also had the greatest pleural fluid LDH to serum LDH ratio (30.45), which was followed by parapneumonic effusions (4.19). Following empyema, pleural fluid ADA was considerably greater in tuberculous effusion. Shafahi and colleagues,^[21] found that the respective means for serum glucose, LDH, protein, and albumin were 162.35 ± 84.239 , 409.25 ± 5.87 , and 3.40 g/dl. Analysis of the white blood cell count in

pleural fluid revealed that the lymph type was more prevalent than the PMN.

When the patients in the exudative group of our study were tested for other conditions, it was observed that 19% of the patients had malignancy, 8.6% had Para pneumonia, and 72.4% had TB. On the contrary, Izhakian et al,^[12] showed that none of the patients in their study group had tuberculous effusion whereas 119 (53.1%) had malignant effusion; 38 (16.9%) had parapneumonic effusion; and 23 (10.2%) were lung transplant recipients. Congestive heart failure, which can occur at later ages, is the most prevalent cause of transudative pleural effusion, according to research by Rismantab and colleagues.^[22] Exudative effusions caused by infectious diseases like TB and parapneumonic effusion typically affect people who are younger than cancer patients.

On recording the CRP levels of the patients in the present study, it was observed that under the Exudative group, 31.0% of the patients had CRP <1.51 while 69.0% of the patients had CRP ≥1.51. Similarly, it was observed that under Transudative group, 78.6% of the patients had CRP <1.51 while 21.4% of the patients had CRP ≥1.51. There was significant difference in distribution of patients according to CRP levels when Exudative group was compared with Transudative group (p value <0.001).

The ROC curve of the present study revealed an AUC of 0.712 (95% CI= 0.61-0.814) with a sensitivity, specificity, PPV, NPV and accuracy of 69%, 78.6%, 81.6%, 64.7%, and 73%, respectively. Chandrik Babu et al,^[15] observed that with a statistically significant value of less than 0.05, the CRP value in the pleural fluid was determined to be 1.05–1.09 in transudative pleural fluid and 5.98–7.45 in exudative fluid. Pleural Fluid CRP cut off value was analysed using a ROC curve, and it was discovered that a cut off value of 1.05 had a sensitivity of 75.4% and a specificity of 77.6% for identifying exudative and transudative Pleural Fluid. Rismantab et al,^[22] reported that CRP levels were 13.3–37.1 mg/dl in exudative pleural effusion and 3.5–4.3 mg/dl in the transudate group; this difference was statistically significant (p=0.008). An AUC of 0.85 (CI 95%= 0.78-0.90) was found using ROC analysis, demonstrating a fair degree of diagnostic accuracy (p 0.001). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 96.3%, 72.1%, 86.0%, and 91.7%, respectively, for the 3.31 mg/dl cut-off point for the CRP level of pleural effusion.

Izhakian et al,^[12] also showed that CRP was an effective marker for differentiating parapneumonic effusion from post-lung transplantation effusion (1.93 mg/dL cut-off value, 75% sensitivity, and 56% specificity), malignant effusion (0.88 mg/dL cut-off value, 87% sensitivity, and 64% specificity; and heart failure effusion (0.49 mg/dL cut-off value, 93% sensitivity, and 72% specificity).

CONCLUSION

The present study concludes that levels of CRP were significantly correlated with exudative pleural effusion. Thus, CRP could prove as good marker and can be used as an indicator for exudative pleural effusion. Diagnostic value of CRP could be assessed for differentiating between exudative and transudative pleural effusion at an early stage of disease. However, our findings are primary which needs some other trials to validate our results.

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