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Role of C-Reactive Protein as a marker for discrimination of Exudative and Transudative Pleural Effusion

Saeed Anwar, Naveed Ikram, Sohail Ahmad ✉

Department of Chest Medicine, Liaquat National Hospital, Karachi – Pakistan

Corresponding Author:
Sohail Ahmad
Department of Chest Medicine,
Liaquat National Hospital,
Karachi – Pakistan
Email: dr.ahmad15@gmail.com

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ABSTRACT

Background: Pleural effusion is a common clinical presentation that demands to be differentiated into exudative and transudative varieties for appropriate diagnosis and treatment. Though Light's criteria are the gold standard for diagnosis, they also have their limitations, particularly in specific clinical contexts. C-reactive protein (CRP), an acute-phase reactant, has been proposed as a possible biomarker here.

Objective: To evaluate the diagnostic utility of pleural fluid CRP in distinguishing between exudative and transudative pleural effusions.

Methodology: This cross-sectional study comprised 88 patients with radiologically proven pleural effusion in Liaquat National Hospital, Karachi. Pleural and serum samples were subjected to biochemical parameters such as CRP. Patients were divided into two groups; as exudative group (54) and transudative group (34) based on Light's criteria, and CRP values between both groups were compared.

Results: Mean pleural fluid CRP concentrations were much greater in exudative effusions (12.7 ± 35.4 mg/dL) compared to transudative effusions (3.4 ± 4.1 mg/dL; $p < 0.001$). CRP was positive in 94.4% of cases with exudative effusions and 32.3% of cases with transudative effusions. The results indicate that pleural CRP is a good biomarker in distinguishing the type of pleural effusion.

Conclusion: Pleural fluid CRP is a sensitive, widely available, and inexpensive marker for differentiating exudative from transudative effusions. Used with Light's criteria and clinical experience, it improves diagnostic accuracy and allows early and proper management.

Keywords: Pleural Effusion; C-reactive Protein (CRP); Exudative Effusion; Transudative Effusion; Light's Criteria

Introduction

Pleural effusion is an abnormal collection of fluid within the pleural space and is a frequent clinical presentation of diverse medical disorders.[1] The etiology and nature of pleural effusions are varied, from benign systemic illness to severe local disease. The treatment of pleural effusion relies on proper identification of the underlying cause, and hence the differentiation between exudative and transudative effusions is an important step in the diagnostic process.[2]

Transudative pleural effusion is one form of fluid accumulation within the pleural space that is caused by systemic factors altering the balance between hydrostatic and oncotic pressures, instead of local pleural disease.[3] It is usually due to conditions like congestive heart failure, liver cirrhosis, and nephrotic syndrome. In such situations, elevated capillary pressure or reduced plasma oncotic pressure causes passive filtration of fluid into the pleural space. Transudative effusions are usually pale yellow, clear, and low in protein and lactate dehydrogenase (LDH). Unlike exudative effusions, they do not involve inflammation of the pleura and therefore usually do not contain a high cell count or inflammatory markers such as CRP. Identification of a transudative effusion is important, as it may indicate a systemic disease that needs to be treated for the underlying condition and not for invasive diagnostic tests.

Exudative pleural effusion results when local injury or inflammation of the pleura is accompanied by enhanced capillary permeability or compromised lymphatic drainage. This allows protein-rich fluid and inflammatory cells to leak into the pleural space. Pneumonia (parapneumonic effusion), tuberculosis, malignancy, pulmonary embolism, and autoimmune conditions like rheumatoid arthritis or lupus are some of the more frequent reasons for exudative effusions. Exudative fluid is usually turbid or cloudy and has high levels of protein, lactate dehydrogenase (LDH), and inflammatory markers such as C-reactive protein (CRP).[4] In contrast to transudates, exudates may need further examination, such as microbiological, cytological, or histological analysis to establish the exact etiology. Exudative effusion identification is vital in order to provide targeted treatment and management for the underlying disease process.

Light's criteria play important role in distinguishing between exudative and transudative pleural effusions, which in turn influence the diagnostic strategy and management.[5] By these standards, a pleural effusion is defined as exudative if any one of the following conditions applies: (1) the pleural fluid protein to serum protein ratio is more than 0.5, (2) the pleural fluid LDH to serum LDH ratio is more than 0.6, or (3) pleural fluid LDH is greater than two-thirds of the upper limit of normal for serum LDH. If all these are not fulfilled, the effusion is transudative. Light's criteria are extremely sensitive for detecting exudative effusions, usually due to local inflammation or malignancy. But they can sometimes mistakenly categorize transudates as exudates, especially in diuretic patients. In spite of this drawback, Light's criteria are still a standard and valuable tool in the initial assessment of pleural effusion.

C-reactive protein (CRP) is an acute-phase reactant that is primarily synthesized in the liver in response to inflammatory stimuli and is a possible marker for this. CRP increases considerably during systemic and local inflammatory processes, thus being a helpful indicator in infectious and inflammatory diseases.[6] In pleural effusions, pleural fluid CRP levels have been reported to be significantly elevated in exudative disease, specifically due to infection like parapneumonic effusions and empyema. Transudative effusions tend to present with low CRP levels because there is no local inflammation.

Pleural fluid CRP can be measured relatively easily, quickly, and inexpensively, making it an accessible choice in clinical practice. Several studies have investigated its diagnostic utility and hypothesized that it can be an effective addition to conventional biochemical markers. CRP would not only be useful in distinguishing exudative from transudative effusions but also in determining specific etiologies within exudative effusions, like differentiating between tuberculous and parapneumonic effusions.[7]

While promising results, our studies and other literature do vary in terms of optimal cutoff values and diagnostic precision. These differences can be attributed to discrepancies in study design, patient populations, and laboratory techniques. Thus, more research must be done to confirm the diagnostic utility of CRP in pleural effusion and make it standardized in various health care systems.

This research is conducted to assess the diagnostic utility of pleural fluid CRP to differentiate between transudative and exudative pleural effusions and determine its efficacy as an adjunct marker that can enhance the diagnostic strategy and aid clinicians in the early and proper management of pleural conditions.

Objective

To evaluate the diagnostic utility of pleural fluid CRP in distinguishing between exudative and transudative pleural effusions.

Methodology

This observational, cross-sectional study was conducted at Liaquat National Hospital, Karachi from March 2023 to December 2023 after obtaining approval from the institutional ethics review board. A total of 88 patients who presented with pleural effusion and underwent diagnostic thoracentesis were included in the study.

Inclusion criteria included 18 years and older adult patients with radiologically proven pleural effusion, in whom enough pleural fluid samples were available for analysis of biochemistry. Exclusion was made of patients who had been treated with antibiotics, steroids, or diuretics for more than a week before thoracentesis to prevent confounding alterations in pleural fluid biochemistry. Patients with hemothorax, chylothorax, or post-trauma effusions were excluded.

Pleural fluid was obtained under aseptic conditions and submitted for standard analysis such as protein, LDH, glucose, and CRP. At the same time, blood was drawn to obtain serum protein and serum LDH. Pleural effusions were graded as exudative or transudative according to Light's criteria.

CRP in pleural fluid was determined by the high-sensitivity immunoturbidimetric assay. The value was expressed in mg/L. Statistical analysis was carried out through SPSS version 27. Continuous values were presented as mean ± standard deviation, while categorical values were presented as frequency and percentages. The independent sample t-test was used to compare the mean pleural fluid CRP levels in exudative and transudative groups. A p-value of less than 0.05 was taken as statistically significant.

Results

Figure 1 shows gender distribution in patients with exudative and transudative pleural effusion. In the exudative group (n = 34), there were 58.8% male (20 patients) and in transudative group (n = 54), there were 55.6% male (30 patients). Female was a little more represented in the exudative group than in the transudative.

The age was slightly increased in the transudative group (65.3 vs 60.2 years, p = 0.048). Infection history, especially TB or pneumonia, was much more frequent in exudative cases (53.7% vs 11.7%, p < 0.001), whereas congestive heart failure was the most frequent cause of transudative effusions (73.5% vs 9.2%, p < 0.001). Malignancy was also more common in exudative cases (p = 0.018), but chronic liver disease and end-stage renal disease did not have any statistically significant difference. Mean pleural fluid CRP concentrations were markedly higher in exudative effusions (12.7 ± 35.4 mg/dL) than in transudative effusions (3.4 ± 4.1 mg/dL), which raises the possibility that CRP could distinguish between the two (Table 1).

Table 1. Demographic and Clinical Characteristics Related to Pleural Effusion Etiology

Variable	Exudative (n = 54)	Transudative (n = 34)	p-value
Mean Age (years)	60.2 ± 16.7	65.3 ± 14.3	0.048
Male Gender [n (%)]	30 (55.6%)	20 (58.8%)	0.77
History of Infection (e.g., TB/Pneumonia)	29 (53.7%)	4 (11.7%)	<0.001
Malignancy (Active or History)	15 (27.7%)	2 (5.9%)	0.018
Congestive Heart Failure	5 (9.2%)	25 (73.5%)	<0.001
Chronic Liver Disease	4 (7.4%)	7 (20.5%)	0.07
End-Stage Renal Disease	6 (11.1%)	2 (5.8%)	0.23
CRP (mg/dL) Mean ± SD	12.7 ± 35.4	3.4 ± 4.1	-

In exudative cases, 94.4% (51/54) were CRP positive, whereas 32.3% (11/34) of transudative cases were CRP positive. This was statistically significant (p < 0.001) and shows that CRP is highly raised in exudative effusions and could be a good diagnostic test to differentiate between exudative and transudative cases (Table 2).

Discussion

Pleural effusion, or the accumulation of fluid within the pleural space, is a common clinical finding.[8] Proper identification as exudative or transudative is important in diagnosis and management, as it determines the necessity for further investigation and the therapeutic approach. C-reactive protein (CRP) is an acute-phase protein synthesized in the liver in response to inflammation. It increases dramatically in infections, tissue damage, or inflammation.[9] In pleural effusion, high levels of CRP particularly in pleural fluid may be used to differentiate between exudative and transudative effusions and are very useful for the detection of infectious origins like parapneumonic effusions. As it is very sensitive, CRP is a

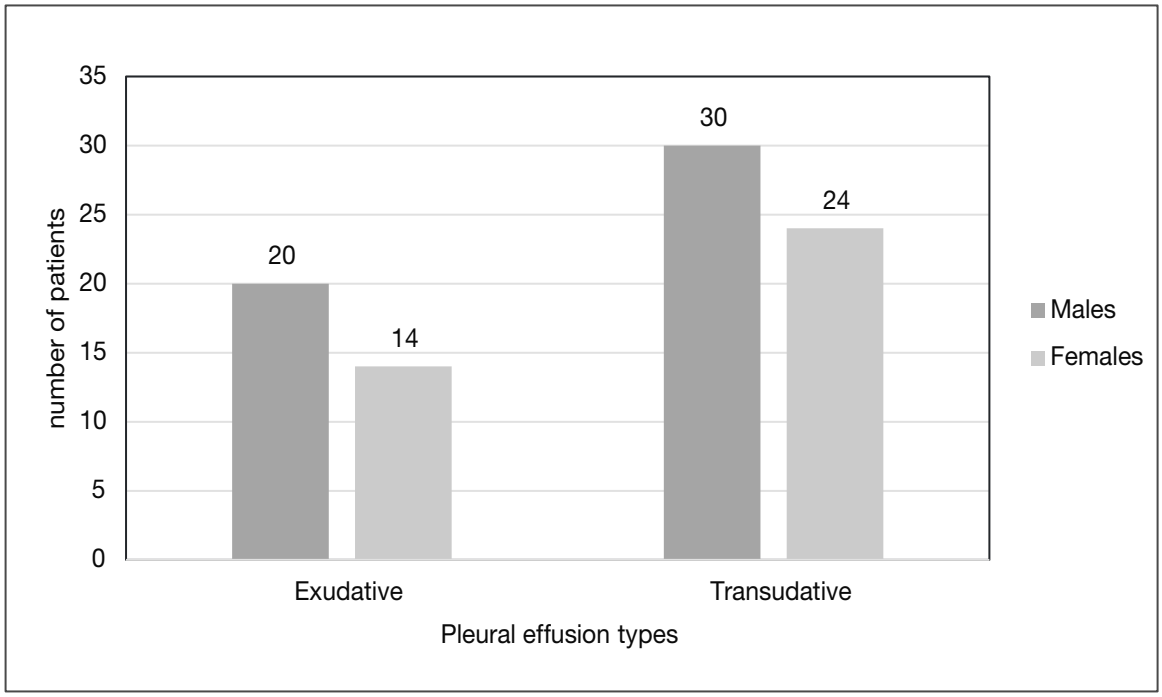

Figure 1. Gender Distribution Among Patients with Exudative and Transudative Pleural Effusion

very useful, simple, and inexpensive diagnostic tool in clinical practice.

Traditionally, Light's criteria based on pleural fluid, serum protein and lactate dehydrogenase (LDH) concentrations have been used to make this separation.[10] Yet, in specific clinical contexts including diuretic patients, Light's criteria can be insufficient. In such situations, other biomarkers such as C-reactive protein (CRP) have also drawn attention due to their value for diagnosis.

We noted in our study that the pleural fluid CRP levels were notably high in exudative patients (mean 12.7 ± 35.4 mg/dL) when compared to those in transudative patients (mean 3.4 ± 4.1 mg/dL). Further, CRP positivity was noted in 94.4% (51/54) of exudative, but only 32.3% (11/34) of transudative cases, with a highly significant difference ($p < 0.001$). A work by Muralidharan et al. (2023) illustrated that pleural fluid (PF) and serum CRP concentrations significantly differ with various etiologies of pleural effusion. The greatest CRP concentrations were found to be in parapneumonic effusions, with tuberculous and malignancy effusions having a lesser value, the lowest concentration was seen in transudative effusions.[11] These findings support the hypothesis that pleural CRP is an accurate marker of exudative pleural disease, probably reflecting the underlying inflammatory or infectious processes that are most often encountered in such effusions.[12]

The observations of a previous study by Li et al. (2019) indicated that serum CRP can leak into the pleural space and thus pleural CRP may act as a pleural infection marker. Serum and pleural CRP have been explored for the diagnosis of parapneumonic effusions and the differentiation of uncomplicated from complicated cases.[13] Similarly, a retrospective study by Izhakian et al. (2016) assessed the diagnostic performance of pleural fluid CRP in differentiating parapneumonic effusions from others. In their cohort of 244 patients, CRP was notably elevated in parapneumonic effusions (mean 5.38 mg/dL) than in those secondary to heart failure, malignancy, or lung transplant. Using a cut-off value of ≥1.38 mg/dL,

Table 2. Distribution of CRP Positivity in Pleural Effusions

CRP Status	Exudative (n=54)	Transudative (n=34)	p-value
Positive	51	11	<0.001
Negative	3	23	

CRP had 84.2% sensitivity and 71.5% specificity for parapneumonic effusions. The results confirm pleural CRP as a valuable biomarker for distinguishing infectious from non-infectious effusions.[14]

Another comparative study by TURAY et al. (2000) also identified that pleural CRP concentration was significantly higher in exudative compared to transudative effusions. They observed in their study that within the exudates, the highest CRP levels (mean 89 mg/L) were seen in parapneumonic effusions. A CRP cut-off >30 mg/L was 93.7% sensitive and 76.5% specific for the diagnosis of parapneumonic effusions. CRP was helpful in distinguishing both the nature and etiology of pleural effusion.[15]

Moreover, CRP levels could also have a correlation with disease severity and might even be used as a prognostic marker. Certain studies indicate that CRP can help in assessing the response to treatment, particularly in infectious effusions such as empyema or tuberculosis, where reduction in CRP levels might reflect resolution of inflammation. A study by Ansar et al. (2016) also showed that C-reactive protein (CRP) increases rapidly in the setting of infection or injury. It is a useful marker for the diagnosis and monitoring of inflammatory disease. Case reports indicate a relation between CRP levels and clinical presentation, positioning it as both diagnostic and prognostic.[16]

Despite its strengths, CRP also has some limitations. It is a non-specific marker and can be raised in systemic inflammatory processes, autoimmune disorders, or malignancy irrespective of pleural involvement. Mouliou et al. (2023) also found in their study that CRP is a probable biomarker in a vast number of diseases ranging from cardiovascular to respiratory, autoimmune, to malignant diseases Thus, its interpretation always has to be placed in the context of the entire clinical scenario, imaging features, microbiology, and cytology.[17]

The present study supports the diagnostic utility of pleural fluid CRP for distinguishing between exudative and transudative effusions. Raised CRP is strongly correlated with exudative causes, particularly infectious and malignant etiologies. In combination with Light's criteria and clinical judgment, CRP improves diagnostic reliability and aids in timely and proper therapeutic decisions. Considering its low cost, widespread availability, CRP must be made a routine test in the initial workup of pleural effusions, especially in resource-poor countries.

Conclusion

This research illustrates that pleural fluid CRP concentrations were markedly elevated in exudative effusions as opposed to transudative effusions, and especially in the context of infectious or malignant causes. The high sensitivity and diagnostic accuracy of CRP, particularly when used together with Light's criteria, render it a useful tool in the assessment of pleural effusions. With its ease of performance, cost-effectiveness, and accessibility, pleural CRP must become a part of standard diagnostic algorithms, particularly in resource poor environments. Future studies are encouraged to determine standardized cutoff levels and evaluate its prognostic value in different pleural conditions.

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