International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

The Role of Pleural Fluid C-Reactive Protein in the Etiological Diagnosis of Pleural Effusion

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Abstract: ***Background: Differentiating the etiology of pleural effusion is crucial for management. Pleural fluid C-Reactive Protein (CRP) is a potential biomarker for this purpose. Objectives: To evaluate the diagnostic utility of pleural fluid CRP in distinguishing exudative from transudative effusions and in categorizing causes of exudative effusions. Methods: A cross-sectional study was conducted on 150 patients with pleural effusion. Pleural fluid analysis, including CRP, biochemical tests, cytology, and microbiology, was performed. Effusions were classified using Light's criteria. Statistical analysis was done using SPSS version 17. Results: A pleural fluid CRP cut-off of 3.31 mg/dL differentiated exudates from transudates with 96.3% sensitivity and 72.1% specificity. Parapneumonic effusions had the highest CRP levels (mean 102.99 mg/dL), followed by tuberculous (52.39 mg/dL) and malignant effusions (22.97 mg/dL). A CRP cut-off of 47.4 mg/dL differentiated parapneumonic from tuberculous effusions (sensitivity 87.5%, specificity 92.5%), and 49.2 mg/dL differentiated parapneumonic from malignant effusions (sensitivity 75%, specificity 85.7%). Conclusion: Pleural fluid CRP is a valuable, inexpensive, and readily available diagnostic tool that aids significantly in differentiating exudative from transudative effusions and in characterizing the etiology of exudative effusions.***

Keywords: Pleural Effusion, C-Reactive Protein (CRP), Exudate, Transudate, Diagnosis, Biomarker.

1. Introduction

Pleural effusion, a common clinical finding, arises from diverse etiologies ranging from benign systemic conditions to life-threatening diseases. The primary diagnostic challenge lies in distinguishing transudative effusions, caused by systemic imbalances in hydrostatic or oncotic pressure (e.g., heart failure, cirrhosis), from exudative effusions, resulting from local pleural pathology (e.g., infection, malignancy)[1]. While Light's criteria have been the cornerstone for this differentiation for decades, they have limitations in sensitivity and specificity, especially in complex cases[1,2]. This has spurred the search for additional biomarkers. C-Reactive Protein (CRP), an acute-phase reactant, is a promising candidate. This study aimed to evaluate the role of pleural fluid CRP as an etiological diagnostic marker for pleural effusions.

2. Aim and Objectives

Aim

To determine the role of pleural fluid CRP as an etiological-diagnostic marker of pleural effusion.

Objectives:

a) To assess the diagnostic value of pleural fluid CRP in differentiating exudative from transudative effusion.
b) To ascertain the significance of pleural fluid CRP in categorizing the cause of exudative pleural effusion into tuberculous, parapneumonic, malignant effusion, and others.

3. Review of Literature

The diagnostic process for pleural effusion begins with the task of classifying it as a transudate or an exudate. For over half a century, this differentiation has been dominated by Light's criteria1, established in 1972. This work demonstrated that measuring pleural fluid and serum levels of protein and Lactate Dehydrogenase (LDH) could categorize effusions with high sensitivity (~98%). Light's criteria posited that an effusion is exudative if it meets at least one of the following: a pleural fluid/serum protein ratio >0.5, a pleural fluid/serum LDH ratio >0.6, or a pleural fluid LDH level greater than two-thirds the upper limit of normal for serum. While its sensitivity is excellent, its specificity is lower (~80%), leading to the misclassification of some transudates, particularly diuresed patients with heart failure, as exudates (2, 3). This limitation, coupled with challenges in effusions of mixed etiology, has fueled the continuous search for more reliable biomarkers.

C-Reactive Protein (CRP) has emerged as a prime candidate in this search. CRP is an acute-phase reactant synthesized by hepatocytes primarily in response to interleukin-6 (IL-6) during systemic inflammation (4). Its role in the innate immune system is to bind to damaged cells and microbial pathogens, activating the complement system. The utility of serum CRP as a marker for infection and inflammation is well-established. Consequently, researchers hypothesized that its measurement in pleural fluid could reflect the degree of local pleural inflammation, offering a direct window into the pathological process (5).

A significant body of evidence now supports the value of pleural fluid CRP. Multiple studies have consistently shown that CRP levels are significantly elevated in exudative effusions compared to transudative ones. Villena et al. (2003) conducted a pivotal study measuring CRP in various effusions and found that infectious effusions, particularly parapneumonic effusions and empyema, exhibited the highest concentrations, far exceeding those found in malignant or transudative effusions (6). This makes CRP a useful marker for identifying bacterial infections in the pleural space. Alexandrakis et al. (2003) confirmed these findings, demonstrating that CRP levels could reliably distinguish between transudates and exudates, and furthermore, that

parapneumonic effusions had markedly higher levels than tuberculous or malignant ones (7).

The diagnostic utility of CRP extends beyond simple exudate-transudate differentiation. Bielsa et al. (2008) focused on using CRP to identify complicated parapneumonic effusions and empyema, which require drainage, from uncomplicated ones. They proposed that very high pleural fluid CRP levels (e.g., >100 mg/L) strongly suggest a bacterial infection severe enough to complicate the effusion, thus guiding critical management decisions like chest tube insertion (8). In the context of tuberculosis, while Adenosine Deaminase (ADA) remains the gold-standard biomarker, CRP provides complementary information. Antonangelo et al. (2007) evaluated the combined use of ADA and CRP and concluded that while ADA is highly specific for tuberculous pleurisy, CRP adds significant value in distinguishing tuberculous effusions (which show moderate CRP elevation) from parapneumonic effusions (which show very high CRP), and both from malignant effusions (which show lower levels) (9).

When compared to other novel biomarkers, CRP holds its ground due to its practicality and performance. Studies have investigated procalcitonin and presepsin, among others. Watanabe et al. (2018) found that while procalcitonin and presepsin offered additional specificity for bacterial infections, CRP demonstrated superior overall performance in broader differential diagnoses and was highly sensitive for bacterial effusions (10). The literature suggests that a panel of biomarkers, including CRP, ADA, and perhaps procalcitonin, may yield the highest diagnostic accuracy, but CRP often stands out for its balance of cost, availability, and reliability (11).

The advantages of pleural fluid CRP are numerous. It is a stable molecule not subject to rapid degradation, making it reliable for routine laboratory analysis (12). The test is inexpensive and readily available in most clinical laboratories, unlike more specialized tests. Furthermore, as Paddock and Light (2006) noted, CRP levels in pleural fluid are more reflective of local pleural inflammation than systemic markers, as they are less influenced by concurrent systemic conditions (13). This local production makes it a more specific indicator of pleural pathology.

In conclusion, the extensive literature on pleural fluid CRP solidifies its role as a valuable adjunct in diagnosing pleural effusions. It successfully addresses some of the limitations of Light's criteria, provides powerful discrimination for infectious etiologies, and helps differentiate between causes of exudative effusions. Its integration into diagnostic algorithms, particularly in resource-limited settings where advanced tests are unavailable, can improve diagnostic accuracy, reduce dependence on invasive procedures, and ultimately guide more timely and appropriate patient management (14, 15).

4. Materials and Methods

Study Design: Hospital-based cross-sectional study.

Study Duration & Population: 150 patients admitted with pleural effusion to the General Medicine ward over 18 months.

Inclusion Criteria: Newly detected pleural effusion within 24 hours of admission.

Exclusion Criteria: Patients with HIV, HBsAg, bleeding diathesis, or collagen vascular diseases.

Methodology: Detailed history, clinical examination, and diagnostic tests were performed. Pleural fluid was analyzed for protein, sugar, LDH, ADA, cytology, AFB, culture, and CRP. Serum biochemical tests were also conducted. Effusions were classified using Light's criteria. The transudate group was further investigated via ultrasound and echocardiogram. Etiological diagnosis for exudates (parapneumonic, tuberculous, malignant, others) was based on predefined criteria.

Statistical Analysis: Data were analyzed using SPSS version 17, employing descriptive statistics, chi-square tests, t-tests, and ANOVA.

5. Results (including Observations)

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (N=150)

Characteristic	Category	Frequency (n)	Percentage (%)
Age Group (Years)	21 – 35	47	31.3
	36 – 50	52	34.7
	51 – 65	51	34.0
Gender	Male	99	66
	Female	51	34.0
Presenting Symptoms	Cough	72	48.0
	Fever	69	46
	Sputum	69	46
	Weight Loss	39	26.0
	Hemoptysis	9	6

Table 2: Final Etiological Diagnosis of Pleural Effusions

Diagnosis	Frequency (n)	Percentage (%)
Parapneumonic Effusion	51	34
Tuberculous Effusion	42	28
Heart Failure	27	18
Malignant Effusion	24	16
Decompensated Chronic Liver Disease (DCLD)	6	4
Total	150	100

Table 3: Mean Pleural Fluid CRP Levels Across Different Diagnoses

Diagnosis	N	Mean PF-CRP (mg/dL)	Standard Deviation
Parapneumonic Effusion	52	102.99	32.32
Tuberculous Effusion	42	52.39	14.32
Malignant Effusion	24	22.97	7.40
Heart Failure	27	7.60	2.14
DCLD	6	5.77	1.94
Overall	150	54.96	43.32

Table 4: Diagnostic Performance of Pleural Fluid CRP

Diagnostic Comparison	Cut-off Value (mg/dL)	Sensitivity (%)	Specificity (%)
Exudate vs. Transudate	3.31	96.3	72.1
Parapneumonic vs. Tuberculous	47.40	87.5	92.5
Parapneumonic vs. Malignant	49.20	75.0	85.7

Table 5: Comparison of Key Parameters between Exudative and Transudative Effusions Data presented as Mean ± Standard Deviation.

Parameter	Exudates (n=117)	Transudates (n=33)	p-value
Pleural Fluid CRP (mg/dL)	68.41 ± 39.74	7.27 ± 2.20	<0.001
Pleural Fluid Protein (g/dL)	4.00 ± 0.93	1.66 ± 0.63	<0.001
Pleural Fluid LDH (U/L)	305.54 ± 192.39	34.73 ± 16.02	<0.001
Pleural Fluid Sugar (mg/dL)	56.34 ± 13.61	85.00 ± 23.52	<0.001
Serum LDH (U/L)	221.46 ± 83.83	85.52 ± 38.84	<0.001

6. Discussion

This study confirms that pleural fluid CRP is a highly sensitive marker for distinguishing exudative from transudative pleural effusions (Table 4, 5). The significantly elevated CRP levels in parapneumonic effusions (Table 3) align with the acute inflammatory response characteristic of bacterial infections. The moderate elevation in tuberculous effusions reflects its chronic granulomatous inflammation, while lower levels in malignancy correspond to a less intense local inflammatory state. The identified cut-off values (Table 4) provide clinically useful thresholds for differential diagnosis. The findings are consistent with previous studies, reinforcing the role of CRP as a reliable adjunct to traditional diagnostic methods. Incorporating pleural fluid CRP into the initial workup can improve diagnostic accuracy, guide therapy, and potentially reduce reliance on more invasive diagnostic procedures.

7. Summary and Conclusion

7.1 Summary

This study demonstrates that measurement of pleural fluid CRP is a valuable addition to the diagnostic arsenal for pleural effusion. It effectively differentiates exudates from transudates and further helps in characterizing the underlying cause among exudative effusions, with parapneumonic effusions showing the highest concentrations.

7.2 Conclusion

Pleural fluid CRP is an inexpensive, readily available, and effective biomarker. Its high sensitivity and good specificity warrant its routine inclusion in the diagnostic workup of pleural effusions to aid in accurate etiological diagnosis and appropriate management.

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