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Original Research Article

USE OF PLEURAL FLUID C-REACTIVE PROTEIN LEVEL AS A DIAGNOSTIC MARKER FOR PLEURAL EFFUSIONS

Sidhant Narang[1], Rutuja Prabhudesai[2], Hafiz Deshmukh[3], Ashish Deshmukh[4], Sunil Jadhav[5], Shivprasad Kasat[6]

[1]*Resident, Department of Pulmonary Medicine, MGM Medical College & Hospital, Chhatrapati Sambhajinagar, Maharashtra, India.*
[2]*Consultant Pulmonologist, Rutuja Respiratory and Occupational Centre, Ponda, Goa, India.*
[3]*Associate Professor, Department of Pulmonary Medicine, MGM Medical College & Hospital, Chhatrapati Sambhajinagar, Maharashtra, India.*
[4]*Professor and Head, Department of Pulmonary Medicine, MGM Medical College & Hospital, Chhatrapati Sambhajinagar, Maharashtra, India.*
[5]*Professor, Department of Pulmonary Medicine, MGM Medical College & Hospital, Chhatrapati Sambhajinagar, Maharashtra, India.*
[6]*Assitant Professor Department of Pulmonary Medicine, MGM Medical College & Hospital, Chhatrapati Sambhajinagar, Maharashtra, India.*

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Corresponding Author:
Dr. Sidhant Narang,
Resident, Department of Pulmonary Medicine, MGM Medical College & Hospital, Chhatrapati Sambhajinagar, Maharashtra, India.
Email: sidhant1955@gmail.com

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ABSTRACT

Background: Pleural effusion, the abnormal accumulation of fluid in the pleural space, presents a significant diagnostic challenge due to its diverse aetiology, ranging from benign conditions like heart failure to life-threatening malignancies and infections such as tuberculosis (TB). While Light's criteria are the standard for differentiating transudates from exudates, they possess limitations, particularly in cases with overlapping biochemical features. This study is aimed to evaluate the diagnostic utility of pleural fluid C-reactive protein (CRP) levels in differentiating transudative from exudative effusions and further stratifying exudates into parapneumonic, tuberculous, and malignant aetiologies.

Materials and Methods: A cross-sectional observational study was conducted at a tertiary care centre in Aurangabad, India, involving 80 patients. Pleural fluid was analysed for routine biochemistry, cytology, and CRP levels. Effusions were classified based on Light's criteria and final clinical diagnosis.

Results: Of the 80 patients, 88.75% had exudative effusions (predominantly tuberculous) and 11.25% had transudative effusions. Pleural fluid CRP levels were significantly higher in exudative effusions compared to transudates. Among exudates, infectious aetiologies (parapneumonic and tuberculous) exhibited markedly elevated CRP levels (range: 25.48–302.4 mg/dL), whereas malignant effusions showed significantly lower levels (range: 1.02–17.63 mg/dL).

Conclusion: Pleural fluid CRP is a valuable, cost-effective biomarker. Levels >30–45 mg/dL strongly suggest an infectious aetiology , while levels <20 mg/dL support a diagnosis of malignancy or transudate, aiding in rapid differential diagnosis.

Keywords: Pleural Fluid, C reactive protein.

INTRODUCTION

Pleural effusion is a prevalent medical condition affecting millions globally. In the United States alone, approximately 1.5 million people suffer from pleural effusion annually.[1,2] The epidemiology varies significantly by region; while congestive heart failure and malignancy are leading causes in developed nations, tuberculosis remains the predominant cause in developing countries like India. Studies from central and southern India have reported that tuberculosis accounts for 56% to 72.4% of pleural effusion cases, highlighting the necessity for

diagnostic tools tailored to this high-burden context.[3-5]

Pathophysiology and Anatomy

The pleural space is a potential gap between the visceral pleura (covering the lungs) and the parietal pleura (lining the chest cavity). Under normal physiological conditions, a small amount of fluid (5–10 ml) facilitates lung movement. Fluid turnover is regulated by hydrostatic and oncotic pressure gradients according to Starling's law.

Pleural effusions occur when this equilibrium is disrupted. They are broadly classified into:

- Transudates: Caused by systemic imbalances in hydrostatic or oncotic pressures (e.g., congestive heart failure, cirrhosis, nephrotic syndrome).
- Exudates: Caused by localized pleural disease, inflammation, infection, or malignancy, leading to increased vascular permeability or impaired lymphatic drainage.

Diagnostic Challenges: Accurate differentiation between transudative and exudative effusions is the first step in management. The "Light's criteria" is the gold standard for this differentiation.[6,7] According to these criteria, an effusion is an exudate if it meets one of the following:

1. Pleural fluid protein to serum protein ratio > 0.5.
2. Pleural fluid LDH to serum LDH ratio > 0.6.
3. Pleural fluid LDH > 2/3 the upper limit of normal serum LDH.

However, Light's criteria have limitations. Approximately 20% of patients with heart failure may meet exudative criteria after diuretic therapy, leading to misclassification.[8] Furthermore, distinguishing between different types of exudates—specifically separating malignant effusions from infectious ones (tuberculous or parapneumonic)—remains challenging when biochemical findings are ambiguous.[9]

The Role of C-Reactive Protein (CRP)

C-reactive protein (CRP) is an acute-phase reactant synthesized by the liver in response to inflammatory cytokines, particularly Interleukin-6 (IL-6).[10] While serum CRP is a well-known marker of systemic inflammation, pleural fluid CRP has emerged as a potential biomarker for local pleural inflammation.

Research suggests that CRP levels in pleural fluid are significantly elevated in infectious etiologies (empyema, parapneumonic effusions) due to intense local inflammation, whereas levels remain relatively low in malignancies and transudates.[12] This study explores the sensitivity, specificity, and diagnostic thresholds of pleural fluid CRP to validate its utility in clinical practice.

Aims

The primary aim of this research was to differentiate between transudative and exudative pleural effusions using pleural fluid CRP levels.

Objectives

The specific objectives of the study were to determine:

1. The predictive value of CRP in parapneumonic pleural effusions.
2. The predictive value of CRP in malignant pleural effusions.
3. The predictive value of CRP in tubercular pleural effusions.

MATERIALS AND METHODS

Study Design and Setting: This was a cross-sectional, observational study conducted at the Department of Respiratory Medicine in a tertiary care center in Aurangabad, Maharashtra. The study was time-bound, conducted from May 2023 to December 2024.

Study Population: The study included 80 patients presenting with pleural effusion.

Inclusion Criteria

Patients over 18 years of age with confirmed pleural effusion.

Exclusion Criteria

Pregnant women, patients refusing consent, or patients unwilling to undergo pleural tapping.

Methodology: The diagnostic evaluation begins with imaging, utilizing a Chest X-ray (PA view) and chest Ultrasonography (USG) to confirm the quantity and loculation of the fluid, followed by diagnostic or therapeutic thoracentesis.

The collected pleural fluid then undergoes a comprehensive analysis: routine biochemistry measures Protein, LDH, and Sugar to apply Light's Criteria; microbiological testing includes Gram stain, culture and sensitivity, and CBNAAT; and pathological examination involves cytology, cytoblock, and Adenosine Deaminase (ADA) levels, alongside biomarker analysis for Pleural Fluid C-Reactive Protein (CRP). Finally, in cases where malignancy is suspected, a pleural or lung biopsy is performed for histopathological assessment.

Statistical Analysis

Data was managed using Microsoft Excel and analyzed using SPSS version 24.0. Quantitative data were expressed as mean and standard deviation (SD), while qualitative data were expressed as percentages. The unpaired t-test and Fisher's exact test were used to determine statistical significance, with a p-value of <0.05 considered significant.

RESULTS

Demographic Profile: The study population (N=80) showed a male predominance.72.5% were male and 27.5% were female. Among those with exudative effusions, 63.75% were male. There was a statistically significant association between age and the type of effusion (p=0.0398). The 11–30 year age group exclusively presented with exudative effusions (likely TB), while transudative effusions were more common in the older population (51–80 years). There was a statistically significant association between age and the type of effusion (p=0.0398). The 11–30 year age group exclusively presented with exudative effusions (likely TB), while transudative effusions

were more common in the older population (51–80 years).

Table 1: Gender of the patient Vs Type of pleural effusion

Sex	Type			Fisher exact test P-value*
	Exudate	Transudate	Sex Total	
Male	51 (63.75%)	7 (8.75%)	58(72.50%)	1
Female	20 (25.00%)	2 (2.50%)	22(27.50%)	
Type Total	71 (88.75%)	9 (11.25%)	80(100.00%)	

Table 2: Age of patients Vs Type of pleural effusions

Age (In years)	Type			Fisher Exact test P-value*
	Exudate	Transudate	Sex Total	
11-30 years	26 (32.50%)	0 (0.00%)	26 (32.50%)	0.0398
31-50 years	22 (27.50%)	3 (3.75%)	25 (31.50%)	
51-80 years	23 (28.75%)	6 (7.50%)	29 (36.25%)	
Type Total	71 (88.75%)	9 (11.25%)	80 (100.00%)	

2. Clinical Presentation and Comorbidities

- Laterality: Right-sided effusions were the most common (43.75%), followed closely by left-sided (40%). Bilateral effusions were observed in 13.75% of cases and were significantly associated with transudative causes (p=0.0132).
- Comorbidities: Hypertension (16.25%) and Diabetes Mellitus (7.5%) were the most common comorbidities. Chronic Kidney Disease (CKD) was exclusively associated with transudative effusions.

Table 3: Comorbidities of patients with pleural effusions

Comorbidities with type	Exudate	Transudate
DM	4 (5.00%)	2 (2.50%)
WPD	2 (2.50%)	1 (1.25%)
HTN	11 (13.75%)	2 (2.50%)
IHD	2 (2.50%)	0 (0.00%)
CKD	0 (0.00%)	1 (1.25%)

3. Etiological Classification

Based on Light's criteria and clinical diagnosis, the patients were classified as follows:

Exudative Effusions (88.75%):

- Tubercular: 63.75% (N=51).
- Parapneumonic: 13.75% (N=11).
- Malignant: 11.25% (N=9).

Transudative Effusions (11.25%):

- Congestive Cardiac Failure (CCF): 8.75% (N=7).
- Chronic Kidney Disease (CKD): 2.50% (N=2).

Among the 9 malignant cases, Adenocarcinoma of the lung was the most common subtype (3.75%), followed by Squamous cell carcinoma and non-small cell carcinoma.

Table 4: Type vs Diagnosis of patients with pleural effusions

Type	Diagnosis	Count (%)
Exudative pleural effusion	Malignancy	9 (11.25%)
	Parapneumonic	11 (13.75%)
	Tubercular	51 (63.75%)
Exudative pleural effusion		71 (88.75%)
Transudative pleural effusions	CCF	7 (8.75%)
	CKD	2 (2.50%)
Transudative pleural effusions Total		9 (11.25%)

4. CRP Analysis

The core finding of the study was the distinct variation in pleural fluid CRP levels across different aetiologies. The data revealed a clear demarcation between infectious exudates and other types.

Table 5: Pleural Fluid CRP Levels by Diagnosis

Type	Diagnosis	C-Reactive Protein [CRP] (mg/dL) (Min-Max)
Exudative pleural effusion	Malignancy	1.02-17.63
	Parapneumonic	31.68-232.77
	Tubercular	25.48-302.4
Exudative pleural effusion total		1.02-302.4
Transudative pleural effusions	CCF	6.33-19.6
	CKD	6.88-9.37
Transudative pleural effusion total range		6.33-19.6

Key Observations from CRP Data:

- Infectious vs. Non-Infectious: Both Tubercular and Parapneumonic effusions showed high CRP levels, often exceeding 30 mg/dL.
- Malignancy vs. Infection: Despite being exudates, malignant effusions had CRP levels comparable to transudates (mostly <20 mg/dL). This provides a crucial differentiation point between malignant and infectious causes.
- Transudates: Consistently showed low CRP levels (<20 mg/dL).

DISCUSSION

Pleural effusion is a prevalent and often complex condition where distinguishing the aetiology is critical for appropriate management. This study underscores the utility of pleural fluid C-reactive protein (CRP) as a robust biomarker for differentiating between transudative and exudative effusions, and more importantly, for stratifying exudative effusions into infectious and non-infectious causes.

Demographic and Epidemiological Trends:

The demographic data revealed a significant male predominance (72.5%) in the study population, particularly in exudative effusions (63.75%). This trend mirrors global literature, such as Turay et al., who also reported a higher prevalence of pleural effusions in men.[13] This male preponderance is often attributed to higher rates of smoking and occupational exposure, which are risk factors for conditions like parapneumonic effusions.

A striking association was found between age and aetiology (p=0.0398). Young adults (11–30 years) exclusively presented with exudative effusions, primarily of tubercular origin. This is consistent with findings by Kapisyzi et al,[15] and Pachon et al,[16] reflecting the high burden of tuberculosis in younger populations in endemic regions like India. Conversely, the older demographic (51–80 years) exhibited a mix of exudative and transudative aetiologies, aligning with the increased incidence of malignancy and heart failure in the elderly, as noted by Porcel et al.[17]

Etiological Patterns and Laterality: The study reaffirmed that tuberculosis remains the leading cause of pleural effusion in this setting (63.75%), followed by parapneumonic (13.75%) and malignant (11.25%) causes. This distribution is typical for developing countries but contrasts with Western data where malignancy and heart failure predominate. Laterality also provided diagnostic clues: unilateral effusions were largely exudative (TB or parapneumonic), while bilateral effusions were significantly associated with transudative causes (p=0.0132), consistent with systemic fluid overload conditions like CHF and CKD.

Diagnostic Utility of CRP Levels: The most significant contribution of this study is the validation of pleural fluid CRP levels as a discriminatory tool.

Distinguishing Infectious from Non-Infectious Exudates

1. The study demonstrated that infectious effusions (tubercular and parapneumonic) are characterized by markedly elevated CRP levels.

- Parapneumonic Effusions: CRP levels ranged from 31.68 to 232.77mg/dL. This strongly supports the findings of Gabhale et al., who identified CRP >90.8mg/L (approx. 9 mg/dL) as highly sensitive for parapneumonic effusions {23}, and Porcel et al., who suggested a cut-off of >45mg/L.[17]
- Tubercular Effusions: Similarly, tubercular effusions showed elevated CRP levels (25.48–302.4mg/dL). This confirms observations by Chierakul et al,[24] and Pachon et al,[16] that CRP levels >30mg/L are indicative of tuberculosis. The high CRP reflects the intense local inflammatory response driven by these infections.

2. Identifying Malignancy in Exudates A critical diagnostic dilemma often lies in distinguishing malignant effusions from other exudates. This study found that malignant effusions, despite being exudates, exhibited significantly lower CRP levels (1.02–17.63mg/dL).

- This aligns with Garcia-Pachon and Llorca, who reported that CRP levels <20mg/L strongly favor malignancy with high specificity.[25]
- The data suggests that a low CRP value in an exudative effusion is a strong negative predictor for infection and should prompt an immediate search for malignancy.

3. Transudates vs. Exudates Transudative effusions consistently showed low CRP levels (6.33–19.6mg/dL), distinct from the high levels seen in infectious exudates. This reinforces the utility of CRP in confirming transudative processes when Light's criteria might be borderline, as supported by Turay et al.[13]

Limitations and Future Scope: The study had a relatively small sample size (n=80) and was conducted in a single center, which may limit the generalizability of the findings. The high prevalence of TB in the study population reflects regional epidemiology. Future multi-centric studies with larger cohorts are recommended to establish standardized cut-off values using ROC analysis and to further validate CRP's prognostic value.

Summary of Clinical Implications: The study supports the integration of pleural fluid CRP into routine diagnostic panels. A CRP level >30–45mg/dL should raise a high suspicion of infection (TB or bacterial), whereas a level <20mg/dL in an exudative effusion strongly points towards malignancy. This simple, cost-effective test can significantly expedite diagnosis and treatment, particularly in resource-limited settings.

CONCLUSION

Pleural fluid CRP is a reliable, accessible, and cost-effective biomarker that significantly enhances the diagnostic workup of pleural effusions.

1. Differentiation: It effectively differentiates infectious exudates (high CRP) from malignant exudates and transudates (low CRP).

2. Thresholds:

- > 30–45 mg/dL: Strongly suggestive of infectious etiology (Tuberculosis or Parapneumonic).
- < 20 mg/dL: Strongly suggestive of malignancy (in exudates) or congestive heart failure (in transudates).

3. Clinical Utility: In cases where traditional biochemical markers are ambiguous, pleural CRP can serve as a decisive tool. A low CRP in an exudative effusion should trigger a search for malignancy, while a high CRP supports empirical treatment for infection, particularly in high-TB burden settings.

Future research should focus on multi-centric studies with larger sample sizes to establish standardized global cut-off values and explore the integration of CRP with other biomarkers like ADA and Procalcitonin for even greater diagnostic precision.

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