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PLEURAL FLUID CRP LEVELS: A KEY DIAGNOSTIC STEP TOWARDS ETIOLOGICAL DIAGNOSIS OF EXUDATIVE PLEURAL EFFUSION

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Abstract

Background and Objectives: Exudative pleural effusion is a common clinical problem with various underlying causes. This study aimed to assess the diagnostic utility of pleural fluid C-reactive protein (CRP) in differentiating between the etiologies of exudative pleural effusions, specifically focusing on tuberculous, malignant, and parapneumonic effusions.

Material and Methods: We enrolled 60 patients with exudative pleural effusion diagnosed through clinico-radiological criteria. Sociodemographic and hematological variables were evaluated across the three etiological groups. Additionally, pleural fluid parameters, including CRP, were measured. The study participants were categorized into groups based on the etiology of their effusions as malignant, parapneumonic and tubercular effusions.

Results: Tuberculous effusion was the most common etiology in our study, followed by malignant and parapneumonic effusions. Malignant effusions were more prevalent in older age groups and among males. Hematological variables did not show significant differences between the groups. Total leukocyte counts were higher in parapneumonic effusions. Smoking history was more prevalent among patients with malignant effusions. Co-morbid conditions like hypertension and diabetes did not correlate significantly with effusion etiology. Pleural fluid LDH, ADA, and CRP were elevated in tuberculous effusions compared to malignant effusions.

Conclusion: Pleural fluid CRP levels were notably higher in parapneumonic effusions compared to both tuberculous and malignant effusions. Additionally, CRP demonstrated a significant role in distinguishing between parapneumonic and malignant effusions, as well as between tuberculous and malignant effusions. These findings suggest that pleural fluid CRP can serve as a valuable diagnostic

marker in the etiological differentiation of exudative pleural effusions, aiding clinicians in prompt and accurate decision-making for patient care.

Keywords: C-Reactive Protein, Pleural Effusion, Exudates, Transudates, Leukocytes.

INTRODUCTION

Pleural effusion arises from an imbalance between pleural fluid generation and absorption. A crucial initial step in pleural effusion management is categorizing it as either transudative or exudative. Exudative pleural effusion necessitates the fulfillment of at least one of Light's criteria, including a pleural fluid protein-to-serum protein ratio greater than 0.5, pleural fluid lactate dehydrogenase (LDH)-to-serum LDH ratio exceeding 0.6, or pleural fluid LDH surpassing two-thirds of the upper limit of normal serum LDH [1, 2].

Exudative pleural effusion arises due to local factors influencing pleural fluid dynamics. When an effusion is exudative, it mandates an extensive diagnostic exploration to pinpoint the local causative factors. In India, prevalent etiologies of exudative pleural effusion encompass tuberculosis (TB), parapneumonic effusion, malignancy, and empyema [3, 4].

Currently, the evaluation of exudative pleural effusions encompasses pleural fluid cell counts, differentials, glucose levels, adenosine deaminase (ADA) levels, Mycobacterium tuberculosis (MTb) GeneXpert analysis, fluid culture, and cytology. Regrettably, these tests often exhibit suboptimal sensitivity and specificity. Although pleural fluid cultures offer definitive evidence of parapneumonic effusion and empyema, their positivity rate stands at 60%, and they entail time-consuming procedures. Pleural fluid cytology, too, demonstrates a notably high rate of false negatives. Consequently, researchers are exploring novel biomarkers to establish an efficient, cost-effective, and swift method for distinguishing among exudative pleural effusions [5-11].

C-reactive protein (CRP), an acute-phase protein primarily synthesized by hepatocytes in response to various stimuli such as bacterial infections, inflammation, malignancy, and pulmonary embolism, holds significant clinical utility. CRP level measurement serves as a valuable screening test for organ diseases, a severity indicator, and a therapy response metric. Pleural fluid CRP is likely to mirror serum CRP levels, as pleural fluid CRP may result from increased diffusion from the blood, arising from capillary leakage due to inflammation [12-14].

Numerous international studies have explored the role of pleural fluid CRP in diagnosing exudative pleural effusions [4,5,10,11]. However, in India, where the spectrum of common exudative effusion causes differs from developed countries, only a limited number of studies with small sample sizes are available [3]. Against this backdrop, our study was conducted to assess the diagnostic efficacy of pleural fluid CRP as a biomarker for distinguishing the etiologies of exudative pleural effusions.

The aim of this study is to investigate the significance of pleural fluid C-reactive protein (CRP) in facilitating the etiological diagnosis of exudative pleural effusion. The specific objectives encompass establishing a robust correlation between the underlying causes of exudative pleural effusion, categorized into tuberculous, malignant, parapneumonic, or other etiologies, utilizing pleural fluid CRP levels as a key parameter. Additionally, this research seeks to assess the diagnostic efficacy of pleural fluid CRP in effectively discriminating between various etiological categories of exudative pleural effusions.

MATERIAL & METHODS

This cross-sectional observational study was conducted at SSG Hospital, Vadodara, India. After getting permission from The Institutional Ethics Committee for Human Research- PG Research (IECHR-PGR) to carry out this study, around 60 patients were enrolled in the study. According to

available data 5-6 admissions of exudative pleural effusion were there in SSGH. Since period of study was from February 2020 to November 2020 (10 months), we have taken sample size of 60 patients.
In this study, the inclusion criteria comprised patients newly diagnosed with pleural effusion aged over 18 years who were admitted to the hospital following Light's criteria [2]. Conversely, cases with transudative effusion, cardiac failure, liver disease, respiratory failure under treatment (including Anti-Tuberculosis Treatment or any other therapy), renal disease, and pregnant or lactating women were excluded. Additionally, individuals with exudative effusion due to other causes were also excluded from participation in the study.

Patients underwent clinical history assessment, physical examination, chest X-ray (P/A view), and chest ultrasound. Routine blood investigations, including complete blood count, serum glucose, serum creatinine, HIV screening, serum protein, serum LDH, sputum for acid-fast bacilli (AFB), and culture examination, were performed. Thoracocentesis was conducted aseptically, and pleural fluid analysis included assessment of appearance, white blood cell (WBC) count, differential cell count, ADA level, sugar level, protein level, LDH level, GeneXpert for MTb, fluid culture, and cytological examination. Pleural fluid CRP was measured using the quantitative turbidometric immunoassay.

In this study, patients meeting the inclusion criteria had their pleural fluid CRP levels analyzed. Exudative pleural effusion cases were categorized into three groups:

Parapneumonic Effusion: Diagnosed based on clinical, biochemical, and radiological signs of acute inflammation, along with a predominance of neutrophils, gram-reactive organisms, or positive bacterial cultures in pleural fluid. Otherwise, they were placed in an 'other' category.

Tuberculous Effusion: Identified by lymphocytic predominance in pleural fluid, pleural fluid ADA level >40 units, and positive sputum for TB or pleural fluid AFB. Pleural biopsy showing granulomas served as a diagnostic criterion.
Malignant Effusion: Confirmed by positive pleural fluid cytology for malignant cells or biopsy-proven lesions.

Exudative effusions with causes other than these categories were categorized as 'other causes,' including various medical conditions such as connective tissue disorders, pancreatitis, viral, fungal, or parasitic effusions, sarcoidosis, and pulmonary embolism.

In the data analysis phase, categorical variables were presented as counts and percentages, while continuous variables were expressed as mean ± SD and median values. Quantitative variables were compared using an ANOVA test for the three groups, followed by Bonferroni correction for post hoc comparisons. Qualitative variables underwent analysis using either the Chi-Square test or Fisher's Exact test. Data entry was performed using Microsoft Excel, and the final analysis was conducted utilizing Statistical Package for Social Sciences (SPSS) software version 21.0. Statistical significance was determined with a threshold of $p < 0.05$, denoting significance.

RESULTS

The findings of this study are presented in tables 1-5.

Table 1: Clinico-demographic parameters in study population

Age(years)	Frequency	Percentage
31-40	7	11.67%
41-50	17	28.33%
51-60	24	40.00%
>60	12	20.00%
Mean ± SD	53.32 ± 9.9	
Median(25th-75th percentile)	53.5(47-59.25)	

Range	32-78	
Gender		
Female	21	35.00%
Male	39	65.00%
Chief complaints		
Breathlessness	41	68.33%
Chest pain	20	33.33%
Cough	39	65.00%
Fever	26	43.33%
Hemoptysis	3	5.00%
Smoking history		
No	20	33.33%
Yes	40	66.67%
Total	60	100.00%

Table 2: Laboratory parameters in study population

Laboratory parameters	Mean ± SD	Median (25th-75th percentile)	Range
Hemoglobin(gm/dL)	10.55 ± 1.73	10.5 (9.2-11.875)	6.8-14.2
Total count(mm^3)	10970.83 ± 4849.26	9800 (7800-11475)	4000-32000
Platelet count($X10^5/mm^3$)	3.12 ± 1.21	3 (2.245-4)	1.18-6
ESR(mm/hr)	75.32 ± 26.91	80 (56-92.5)	18-120
Serum protein(g/dL)	4.72 ± 0.75	4.7(4.075-5.2)	3.4-6.1
Serum LDH(IU/L)	223.27 ± 68.32	204.5(180-251)	112-400

Table 3: Comparison of Laboratory parameters between malignant, parapneumonic and tubercular PE

Laboratory parameters	Malignant PE (n=14)	Parapneumonic PE (n=10)	Tubercular PE (n=36)	Total	P value
Hemoglobin (gm/dL)	9.39 ± 1.37	11.73 ± 1.71	10.67 ± 1.63	10.55 ± 1.73	< 0.05
Total count(mm^3)	10707.14 ± 2478.05	19075 ± 6211.69	8822.22 ± 1973.84	10970.83 ± 4849.26	< 0.05
Platelet count($X10^5/mm^3$)	2.55 ± 0.91	3.94 ± 1.51	3.12 ± 1.13	3.12 ± 1.21	< 0.05
ESR(mm/hr)	80.93 ± 31.07	75.8 ± 22.75	73 ± 26.67	75.32 ± 26.91	< 0.05
Serum protein(g/dL)	4.69 ± 0.75	5.22 ± 0.85	4.58 ± 0.67	4.72 ± 0.75	0.054
Serum LDH(IU/L)	199.43 ± 38.47	324.3 ± 77.81	204.47 ± 47.49	223.27 ± 68.32	< 0.05

Table 4: Comparison of Pleural fluid analysis between malignant, parapneumonic and tubercular PE

Parameters	Malignant PE (n=14)	Parapneumonic PE (n=10)	Tubercular PE (n=36)	Total	P value
Pleural fluid gram stain					
Absent	14 (100%)	6 (60%)	36 (100%)	56 (93.33%)	0.0004
Present	0 (0%)	4 (40%)	0 (0%)	4 (6.67%)	
Pleural fluid culture sensitivity					
Absent	14 (100%)	4 (40%)	36 (100%)	54 (90%)	<.0001
Present	0 (0%)	6 (60%)	0 (0%)	6 (10%)	
Pleural fluid cytology					

Lymphocytic	0 (0%)	0 (0%)	36 (100%)	36 (60%)	<.0001
Mesothelial	14 (100%)	0 (0%)	0 (0%)	14 (23.33%)	
Polymorphonuclear	0 (0%)	10 (100%)	0 (0%)	10 (16.67%)	
Pleural fluid sugar(mg/dL)					
Mean ± SD	79 ± 16.01	41.8±19	52.64 ± 13.6	56.98± 18.33	<.0001
Median(25th-75th percentile)	78(72-91)	55	53(42-62)	56	
Range	40-100	30-57	28-88	28-100	
Pleural fluid protein(g/dL)					
Mean ± SD	3.27 ± 0.52	3.9 ± 0.7	3.66 ± 0.41	3.61 ± 0.52	0.008
Median(25th-75th percentile)	3.05(2.925-3.425)	4.05(3.35-4.275)	3.7(3.5-3.925)	3.7(3.2-4)	
Range	2.8-4.5	2.8-4.8	2.5-4.2	2.5-4.8	
Pleural fluid LDH(IU/L)					
Mean ± SD	251.25 ± 6.29	390 ± 10	207 ± 10.13	273 ± 78.11	<.0001
Median(25th-75th percentile)	250(248.75-252.5)	390(385-395)	205(199.5-212.5)	250(215-320)	
Range	245-260	380-400	198-220	198-400	
Pleural fluid ADA					
Mean ± SD	19.07 ± 5.25	24.8 ± 7.67	53.11 ± 9.12	40.45 ± 17.67	<.0001
Median(25th-75th percentile)	19.5(15.75-20)	25(22.75-27.75)	54(48-59.25)	45(22.75-55)	
Range	Dec-32	Dec-38	23-68	Dec-68	

Table 5: Comparison of pleural fluid CRP(mg/L) between malignant, parapneumonic and tubercular PE.

Pleural fluid CRP(mg/L)	Malignant PE	Parapneumonic PE	Tubercular PE	Total	P value	Test performed
Mean ± SD	24.44 ± 6.16	120.17.56 ± 19.20	56.1 ± 14.01	57.46 ± 31.99	<.0001 ME vs PE:<.0001 ME vs TB:<.0001 PE vs TB:<.0001	ANOVA;F value=62.366
Median(25th-75th percentile)	22.2(19.525-29.75)	114.55(95.775-128.625)	59.5(46.2-67.8)	54.45(31.65-70.2)		
Range	16.2-35.4	90.8-150.9	23.5-85.9	16.2-150.9		

DISCUSSION

In our study, a total of 60 subjects were enrolled, comprising 39 males and 21 females, with a mean age of 53.32 ± 9.9 years. This demographic profile closely resembled that of a study conducted by Ahemad et al., and Wafaa et al. [13-14]. Importantly, our analysis revealed no

statistically significant differences in age and gender distribution among the studied groups, highlighting the consistency of these demographic factors across the referenced studies.

In our analysis of symptomatology and the characteristics of pleural effusion, our study revealed that among the 60 patients with exudative effusion, the most prevalent symptom was breathlessness, reported by the majority (68.33%) of patients, followed closely by cough (65.00%), fever (43.33%), and chest pain (33.33%). A smaller proportion, 5.00%, reported experiencing haemoptysis. These findings align with those of a study conducted by Gabhale et al. [15], highlighting the consistency of symptom presentation in both studies.

In our study, the assessment of smoking's significance revealed that among the 60 cases of exudative effusions, 40 individuals had a history of smoking. Interestingly, our findings indicated a higher prevalence of smoking history among patients with malignant effusion, followed by those with tuberculous effusion and parapneumonic effusion. However, it's noteworthy that our analysis did not yield statistically significant differences among these study groups, as depicted in Figure 16. These observations closely parallel the findings reported by Waffa et al. [13]. Consequently, when considered individually, smoking history did not emerge as a reliable indicator for distinguishing between different types of pleural effusions.

Upon analyzing the hematological variables in our study, it was discerned that no statistically significant differences were observed in variables such as total WBC count, hemoglobin levels, platelet count, and ESR among the study subjects. These results are consistent with findings reported by Qiayoying et al. [16], indicating a similarity in the hematological profiles of the study populations across both studies.

Gabhale et al. [15] reported lower serum protein levels in tuberculous and malignant effusions, attributing this finding to the chronic nature of these conditions. However, in our study, we did not observe a significant difference in serum protein levels between these groups. The serum LDH levels in parapneumonic pleural effusion were notably higher compared to both tubercular and malignant PE. Interestingly, serum LDH levels were comparable between tubercular PE and malignant PE. These findings contrast with those of Sabah Ahmed Hussein et al. [17].

In our study, Parapneumonic effusions exhibited a predominance of neutrophils due to their acute onset, aligning with the expected initial response to acute inflammation. As inflammation progressed, a shift toward a lymphocytic predominance was observed, as evident in our tubercular effusion. This pattern is consistent with the findings emphasized by San Jose et al. [18], who underscored the significance of cell predominance in pleural fluid cytology. Similarly, Perlat et al. [19] reported analogous results in their study.

In our study, pleural fluid sugar levels were notably lower in parapneumonic PE compared to malignant PE and tuberculous PE. Additionally, pleural fluid protein levels were higher in parapneumonic PE and tubercular PE when compared to malignant PE. These findings are consistent with previous studies [20].
Furthermore, our study revealed significantly elevated pleural fluid LDH levels in parapneumonic PE in comparison to both malignant PE and tubercular PE. Manuel Vives et al. [21] also reported similar findings in their study.

In our study, we observed that pleural fluid ADA levels in tubercular PE were significantly elevated compared to parapneumonic PE and malignant PE. However, there was no significant difference in pleural fluid ADA levels between parapneumonic PE and malignant PE. These findings are consistent with studies conducted by Nusrath et al. [22] and Motoki S. [23].

Our study revealed that pleural fluid C-reactive protein (CRP) levels in parapneumonic PE were substantially higher at 120.17 ± 19.2, compared to tubercular PE (56.1 ± 14.01, p value < 0.0001) and malignant PE (24.44 ± 6.16, p value < 0.0001). Conversely, pleural fluid CRP levels were significantly lower in malignant PE compared to tubercular PE (p value < 0.0001) and parapneumonic PE (p value < 0.0001). These findings are in line with studies conducted by San Jose et al. [24], Perlat et al. [19], Gabhale et al. [15], and Amores et al. [12].

CONCLUSION

Pleural fluid CRP levels can serve as an additional diagnostic tool in distinguishing exudative effusions. It notably distinguishes parapneumonic effusion and empyema from tuberculous and malignant effusions. However, our study did not find pleural fluid CRP to be significantly helpful in differentiating between malignant and tuberculous effusions. Our findings underscore that pleural fluid CRP is a rapid and cost-effective method for distinguishing parapneumonic effusion and empyema from other exudative effusions.

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