Section: General Medicine

Original Research Article

ROLE OF PLEURAL FLUID C REACTIVE PROTEIN AND RATIO OF PLEURAL FLUID CRP: SERUM CRP IN DIFFERENTIATING THE TRANSUDATIVE AND EXUDATIVE EFFUSION AND ITS ETIOLOGICAL DIAGNOSIS

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Abstract

Background: Pleural effusion is an important debilitating disorder that occurs because of various pathological conditions. This study aimed to determine the diagnostic value and role of pleural fluid CRP and the ratio of pleural fluid CRP: Serum CRP in etiological diagnosis of pleural effusion. **Materials and Methods:** This cross-sectional study was conducted at the Department of General Medicine, Government Madurai Medical College, Madurai, for 1 year on 100 patients with pleural effusion. Patients aged >18 years and newly diagnosed cases of pleural effusion were included. A detailed history and meticulous clinical examination were frequently recorded. **Result:** In our study, 80% were exudates, and 20% were transudates. Approximately 47.5% had para-pneumonic effusion, 37.5% had tuberculosis pleural effusion, and 15% had malignant pleural effusion. Comparison of various factors between exudate and transudate, ESR, Serum LDH, PF protein, PF sugar, protein ratio, PF LDH, LDH ratio, PF ADA, PF CRP, Serum CRP and Pleural/Serum CRP ratio showed statistically significant differences between them. ESR, Serum LDH, PF protein, protein ratio, PF LDH, LDH ratio, PF ADA, PF CRP, Serum CRP and Pleural/Serum CRP ratio were higher in exudate than in transudate. In contrast, the PF sugar content was higher in transudates. PE. Pleural/serum CRP is higher in parapneumonic PE, followed by malignant PE, tuberculous PE, and transudate PE. **Conclusion:** Our study showed that PF CRP and Serum CRP levels showed significant differences between the different causes of pleural effusion. It is higher in parapneumonic PE, followed by tuberculous PE, malignant PE, and transudate PE.

INTRODUCTION

Pleurae paired with thoracic cavity linings surround each lung and form a potential space called the pleural cavity. Pleural fluid is crucial for the diagnosis of respiratory disease. It is produced by parietal circulation and reabsorbed by the lymphatic system through the stomata in the parietal pleura. In a healthy human, the pleural space typically contains a small amount of fluid and low protein concentration.[1] Pleural fluid was filtered at the parietal pleural level, with lymphatics providing 75% drainage. Pleural effusion and fluid accumulation between the parietal and visceral pleura are major causes of pulmonary mortality and morbidity. It is differentiated as a transudate or exudate based on modified Light's criteria.[2,3]

Transudates are caused by conditions that alter hydrostatic pressure in the pleural space, such as heart failure, liver cirrhosis, and hypoalbuminaemia. Pulmonary infections, malignancies, inflammation, and benign asbestos cause exudates.[4] Less common causes include pulmonary embolism, drug-induced exudates, post-radiotherapy, oesophageal rupture, and ovarian hyperstimulation syndrome.[5]

Commonly performed tests on pleural fluid to determine aetiology include measurement of fluid pH, fluid protein, Albumin and LDH, Fluid triglyceride, fluid cell count differential, fluid glucose, fluid gram stain and culture, and fluid cytology.[6] The prognosis is based on the cause of the pleural effusion. Benign effusions can be cured; however, if the cause is a malignancy, the prognosis is very poor. Another feature of pleural effusions is recurrence, which is observed in benign disorders such as lupus, anaemia, and rheumatoid arthritis. If pleural effusion is not drained, it will result in dyspnoea and empyema.

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There have been multiple investigations into the utility of CRP in diagnosing exudative pleural effusion internationally.[7-9] But, in India, where the prevalent causes of exudative effusion diverge from those in developed countries, only a few studies are available with limited sample sizes.[4]

This study aimed to determine the diagnostic value and role of pleural fluid CRP and the ratio of pleural fluid CRP: Serum CRP in etiological diagnosis of pleural effusion.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of General Medicine, Government Madurai Medical College, Madurai, from April 2022 to March 2023 on 100 patients with pleural effusion. Participants were informed of the purpose of the study, and only those who agreed to participate were obtained after obtaining informed consent.

Inclusion Criteria

Patients aged >18 years newly diagnosed with pleural effusion were included.

Exclusion Criteria

Exclusion criteria were chronic liver disease and IL6 Antagonist use.

Upon admission, eligible patients were screened for enrolment in the study. The study team frequently recorded a detailed history and performed meticulous clinical examinations. Patients who satisfied the inclusion criteria were recruited for the study after obtaining informed consent. Baseline investigations were performed and clinical parameters were recorded serially.

Data were evaluated, including pleural fluid analysis (glucose, proteins, and LDH), pleural fluid CRP, pleural fluid cytology and culture, complete blood count, renal function test, liver function test, serum proteins and LDH, and chest CT.

Statistical Analysis

The data were entered in an MS Office Excel sheet and analysed using SPSS version 16. Continuous data with normal distribution are expressed as the mean with standard deviation. Categorical data are expressed as frequencies with percentages. Fisher's exact test was used to compare frequencies between the groups. The unpaired t-test was used to compare the mean values between the two groups. One-way ANOVA was used to compare the variance between more than two groups. An ROC curve was constructed to derive the cutoff values for various parameters in predicting malignant and parapneumonic effusions. Statistical significance was set at $p < 0.05$.

RESULTS

In our study, 80% were exudates, and 20% were transudates. Approximately 77% were males and 23% were females. Approximately 14% are in 21-30 years, 34% are in 31-40 years, 37% are in 41-50 years, 12% are in 51-60 years, and 3% are in 61-70 years of age. There was no significant difference in age between the exudative and transudative pleural effusions.

Approximately 47.5% had para-pnuemonic effusion, 37.5% had tuberculous pleural effusion, and 15% had malignant pleural effusion as the cause of the exudative pleural effusion [Table 1].

The majority of patients (85%) had a cough and two-thirds (69%) had sputum. Fever and weight loss were less common (50% and 37%, respectively), and hemoptysis was the rarest symptom (13%). Symptoms varied across effusion types, with parapneumonic effusions showing high prevalence of cough (97.4%), sputum (92.1%), and fever (65.8%). [Table 2].

Transudative pleural effusion displayed the lowest mean values for ESR, serum LDH, serum protein, PF protein, PF glucose, protein ratio, PF LDH, LDH ratio, PF ADA, PF CRP, and pleural/serum CRP ratio. Tuberculosis pleural effusion had the highest mean values for ESR, serum LDH, PF ADA, and PF CRP. Para-pneumonic pleural effusion had the highest mean values for PF protein, PF LDH, and PF CRP. Cytology showed lymphocytes in 90% of tuberculosis pleural effusion cases, PMN in 94.7% of para-pneumonic pleural effusion cases, and malignant cells in 100% of malignant pleural effusion cases. [Table 4].

Exudates and transudates exhibited significant differences in various parameters, including ESR, serum LDH, PF protein, PF sugar, protein ratio, PF LDH, LDH ratio, PF ADA, PF CRP, serum CRP, and pleural/serum CRP ratio. Age and serum protein levels showed no significant differences between the two groups. Exudates had higher values for these parameters, while transudates had higher PF sugar levels. ESR was higher in patients with tuberculous, parapneumonic, and malignant PE. The mean age was slightly lower in exudative PE compared to transudative PE, but this difference was not statistically significant. Several laboratory markers showed significant differences between the two groups, with exudates exhibiting higher values for ESR, serum LDH, PF protein, PF sugar, PF LDH, PF ADA, PF CRP, and serum CRP. The protein, LDH, and CRP ratios were also significantly different between the two groups. UL-LDH was absent in all patients with transudative PE. [Table 5].

Serum LDH, PF protein, PF LDH, protein ratio, and LDH ratio did not show significant differences between the different causes of exudative pleural effusion. PF sugar, PF ADA, PF CRP, serum CRP, and Pleural/Serum CRP ratio showed significant differences between different causes of exudative pleural effusion. The following parameters did not show statistically significant differences: serum lactate dehydrogenase (LDH) levels, pleural fluid protein concentration, pleural fluid LDH, protein ratio, and LDH ratio. [Table 6].

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Table 1: Demographic data of the study

		Number of cases	Percentage of cases
Cases	Exudate	80	80
	Transudate	20	20
Sex	Male	77	77
	Female	23	23
Age group (years)	21-30	14	14
	31-40	34	34
	41-50	37	37
	51-60	12	12
	61-70	3	3
Type of symptom	Cough	85	85
	Sputum	69	69
	Hemoptysis	13	13
	Fever	50	50
	Loss of weight	37	37
Cause of exudative PE	Tuberculosis	30	37.5
	Parapneumonic effusion	38	47.5
	Malignancy	12	15

Table 2: Symptom analysis of different effusions

		No of cases	% of cases
Parapneumonic effusion	Cough	37	97.4
	Sputum	35	92.1
	Hemoptysis	2	5.3
	Fever	25	65.8
	Loss of weight	2	5.3
Tuberculosis pleural effusion	Cough	28	93.3
	Sputum	28	93.3
	Hemoptysis	10	33.3
	Fever	24	80
	Loss of weight	25	83.3
Malignant pleural effusion	Cough	11	91.7
	Sputum	4	33.3
	Hemoptysis	1	8.3
	Fever	1	8.3
	Loss of weight	10	83.3
Transudate pleural effusion	Cough	9	45
	Sputum	2	10
	Hemoptysis	0	0
	Fever	0	0
	Loss of weight	0	0

Table 3: Distribution of sex and cytology of various effusions

		Tuberculosis pleural effusion	Para pneumonic pleural effusion	Malignant pleural effusion
Sex	Male	26 (86.7%)	29 (76.3%)	6 (50%)
	Female	4 (13.3%)	9 (23.7%)	6 (50%)
Cytology	Lymphocyte	27 (90%)	1 (2.6%)	0
	PMN	1 (3.3%)	36 (94.7%)	0
	Normal	2 (6.7%)	0	0
	Malignant cells	0	1 (2.6%)	12 (100%)

Table 4: Mean lab parameters of various effusion

Parameter	Transudative pleural effusion	Tuberculosis pleural effusion	Para pneumonic pleural effusion	Malignant pleural effusion
ESR (mm/hr)	14.3 ± 3.5	52.4 ± 15.3	38.7 ± 8.5	13.2±1.9
Serum LDH (IU/L)	80.9 ± 33	156.6 ± 37.4	155 ± 37.6	163 ± 45.8
Serum protein (g/dL)	5.25 ± 0.6	5.2 ± 0.5	5.6 ± 0.4	5.5±0.45
PF protein (g/dL)	1.3 ± 0.5	3.81 ± 0.48	4.05 ± 0.5	3.87 ± 0.5
PF sugar (mg/dL)	73.2 ± 17.7	49.3 ± 7.7	47.6 ± 10	65.5 ± 16.2
Protein ratio	0.23 ± 0.1	0.73 ± 0.06	0.75 ± 0.18	0.75 ± 0.22
PF LDH (IU/L)	25.4 ± 12.6	185.2 ± 52.2	188 ± 98.5	191 ± 78.6
LDH ratio	0.31 ± 0.08	1.27 ± 0.59	1.16 ± 0.32	1.03 ± 0.22
PF ADA (IU/L)	11.4 ± 3.5	62.1 ± 14	18.4 ± 6.5	12.3 ± 2.67
PF CRP (mg/L)	9.1 ± 3.3	50 ± 13.7	92.7 ± 27.6	11 ± 2.14
Serum CRP (mg/dL)	20.4 ± 4.8	72 ± 14.8	97.8 ± 24.8	12.9 ± 2.2
Pleural/serum CRP ratio	0.45 ± 0.14	0.68 ± 0.08	0.93 ± 0.08	0.85 ± 0.17

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Table 5: Comparison of the mean value of various parameters between exudative and transudative pleural effusion

Parameter	Exudative PE (n=80)	Transudative PE (n=20)	P-value
Age in years	42.3 ± 9.8	45.6 ± 7.3	0.161 (NS)
ESR (mm/hr)	40 ± 17	14.3 ± 3.5	<0.0001
Serum LDH (IU/L)	157 ± 38.4	80.9 ± 33	<0.0001
Serum protein (g/dL)	5.4 ± 0.48	5.2 ± 0.62	0.106(NS)
PF protein (g/dL)	3.93 ± 0.5	1.22 ± 0.5	<0.0001
PF sugar (mg/dL)	50.9 ± 11.9	73.2 ± 17.7	<0.0001
Protein ratio	0.74 ± 0.15	0.23 ± 0.1	<0.0001
PF LDH (IU/L)	187.6 ± 80.1	25.4 ± 12.6	<0.0001
LDH ratio	1.18 ± 0.43	0.31 ± 0.09	<0.0001
PF ADA (IU/L)	33.9 ± 24.1	11.5 ± 3.5	<0.0001
PF CRP (mg/L)	64.5 ± 36.3	9.1 ± 3.3	<0.0001
Serum CRP (mg/dL)	75.4 ± 34.7	20.4 ± 4.8	<0.0001
Pleural/serum CRP ratio	0.83 ± 0.15	0.45 ± 0.14	<0.0001
UL-LDH absent	0	20 (100%)	<0.00001
UL-LDH present	80 (100%	0	

Table 6: Comparison of various parameter values between the different causes of exudative pleural effusion

Parameter	Tuberculosis PE (n=30)	Para pneumonic PE (n=38)	Malignant PE (n=12)	P value
Serum LDH	156 ± 37.3	155 ± 37.6	163 ± 45.8	0.839 (NS)
PF protein	3.81 ± 0.48	4.05 ± 0.5	3.87 ± 0.49	0.142 (NS)
PL LDH	185 ± 52	188 ± 98	191 ± 78.6	0.972 (NS)
Protein ratio	0.72 ± 0.07	0.75 ± 0.18	0.75 ± 0.22	0.689 (NS)
LDH ratio	1.27 ± 0.59	1.16 ± 0.32	1.03 ± 0.22	0.272 (NS)

Table 7: Comparison of parameters and post-hoc comparison between the different causes of exudative pleural effusion

Parameter	Tuberculosis PE (n=30)	Para pneumonic PE (n=38)	Malignant PE (n=12)	P value
ESR (mm/hr)	52.4 ± 15.3	38.7 ± 8.5	13.2 ± 1.9	<0.0001
Post hoc comparison	Group Vs Group	Mean difference	95% Confidence interval	P value
	TB Vs PP	13.7	7.1 to 20.3	<0.0001
	TB Vs ME	39.2	29.9 to 48.5	<0.0001
	ME Vs PP	25.5	16.5 to 34.5	<0.0001
PF sugar (mg/dL)	49.3 ± 7.6	47.6 ± 10	65.5 ± 16.2	<0.0001
Post hoc comparison	Group Vs Group	Mean difference	95% Confidence interval	P value
	TB Vs PP	1.65	-4.5 to 7.85	0.999 (NS)
	TB Vs ME	16.2	7.48 to 24.8	<0.0001
	ME Vs PP	17.8	9.4 to 26.2	<0.0001
PF ADA (IU/L)	62.1 ± 14	18.4 ± 6.5	12.3 ± 2.7	<0.0001
Post hoc comparison	Group Vs Group	Mean difference	95% Confidence interval	P value
	TB Vs PP	43.6	37.7 to 49.4	<0.0001
	TB Vs ME	49.7	41.6 to 57.9	<0.0001
	ME Vs PP	6.1	-14 to 1.7	0.183 (NS)
PF CRP (mg/L)	50 ± 14	92.7 ± 27.6	11.01 ± 2.1	<0.0001
Post hoc comparison	Group Vs Group	Mean difference	95% Confidence interval	P value
	TB Vs PP	42.7	30.1 to 55.2	<0.0001
	TB Vs ME	39	21.5 to 56.5	<0.0001
	ME Vs PP	81.7	64.7 to 98.6	<0.0001
Serum CRP (mg/L)	72 ± 14.8	97.8 ± 24.8	12.9 ± 2.23	<0.0001
Post hoc comparison	Group Vs Group	Mean difference	95% Confidence interval	P value
	TB Vs PP	25.7	14.1 to 37.4	<0.0001
	TB Vs ME	59.1	42.7 to 75.3	<0.0001
	ME Vs PP	84.9	69.1 to 100.7	<0.0001
Pleural/serum CRP ratio	0.68 ± 0.08	0.93 ± 0.08	0.85 ± 0.17	<0.0001
Post hoc comparison	Group Vs Group	Mean difference	95% Confidence interval	P value
	TB Vs PP	0.24	0.18 to 0.31	<0.0001
	TB Vs ME	0.17	0.08 to 0.25	<0.0001
	ME Vs PP	0.07	-16 to 0.007	0.084 (NS)

Table 8: Description of ROC statistics for various lab parameters measurements in predicting the malignant pleural effusion and para pneumonic pleural effusion

Variable	Malignant pleural effusion		Para pneumonic pleural effusion	
	Area under curve	P value	Area under curve	P value
Pleural/serum CRP ratio	0.648	0.098 (NS)	0.928	<0.00001
PF ADA	0.205	0.001	0.439	0.305 (NS)
PF CRP	0.17	<0.00001	0.961	<0.00001
Protein ratio	0.561	0.501 (NS)	0.66	0.006
LDH ratio	0.525	0.779 (NS)	0.678	0.003

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Table 9: Comparison of various CRP parameters for type of pleural effusion

Parameter	Tuberculosis PE (n=30)	Para pneumonic PE (n=38)	Malignant PE (n=12)	Transudate PE (n=20)	P value
PF CRP	50 ± 13.7	92.7 ± 27.6	11 ± 2.1	9.1 ± 3.4	<0.0001
Serum CRP	72 ± 14.8	97.8 ± 24.8	12.9 ± 2.2	20.4 ± 4.8	<0.0001
Pleural/serum CRP ratio	0.68 ± 0.08	0.93 ± 0.08	0.85 ± 0.17	0.45 ± 0.14	<0.0001

Elevated levels of PF ADA and PF CRP are significant predictors of malignant pleural effusion, while elevated PF CRP and pleural/serum CRP ratio are indicative of parapneumonic pleural effusion. Among the different causes of pleural effusion, PF CRP and serum CRP levels exhibited significant differences, with parapneumonic PE displaying the highest levels, followed by malignant and tuberculous PE. ESR levels were markedly higher in TB pleural effusions compared to parapneumonic and malignant pleural effusions. Levels of pleural fluid sugar and pleural fluid adenosine deaminase were significantly lower in TB pleural effusions compared to parapneumonic and malignant effusions. Additionally, pleural fluid C-reactive protein levels were significantly elevated in parapneumonic pleural effusions compared to TB and malignant effusions. Similar patterns were observed for serum CRP levels and pleural/serum CRP ratios.

PF CRP, serum CRP, and pleural/serum CRP levels showed significant differences among the various causes of pleural effusion. PF CRP and serum CRP levels were highest in parapneumonic PE, followed by tuberculous PE and malignant PE. Pleural/serum CRP levels were highest in parapneumonic PE, followed by malignant PE and tuberculous PE. These findings suggest that PF CRP, serum CRP, and pleural/serum CRP levels may be useful biomarkers for differentiating between different causes of pleural effusion.

DISCUSSION

This study included 100 patients with exudative effusion, and Light's criteria was used to differentiate transudative from exudative effusion. Exudative pleural effusion is commonly observed in various respiratory disorders, and its classification is primarily dependent on the analysis of pleural fluid, which includes routine and specialised tests for biochemistry, cytology, and histopathology.[9] Exudative pleural effusion occurs because of local factors that influence the production and resorption of pleural fluid.[10] When pleural effusion is identified as exudative, thorough diagnostic assessments are required to ascertain the underlying cause. In India, the predominant causes of exudative pleural effusion include tuberculosis (TB), parapneumonic effusion, malignancy, and empyema.[4]

The current study demonstrated the presence of exudates in 80% of patients, whereas 20% were diagnosed with transudates. Parapneumonic effusion was reported in 47.5% of patients, and 37.5% had tuberculous pleural effusion. In our study, male patients were the most affected (77%), and the age group between 41-50 was a common category for exudates and transudates. Similar study findings were also reported by Qu et al., where 87 male patients were reported with exudative effusion due to TB (80%), and parapneumonic and malignant effusion was seen in 8% and 7% of patients, respectively.[9] In another study conducted by Antonangelo et al., among 326 patients showed that pleural effusion was due to TB, which was the most common cause of exudative effusion in 55.8% of patients.[11]

Our study revealed a notable distinction between exudate and transudate in terms of ESR, LDH, PF protein, PF sugar, protein ratio, PF LDH, LDH ratio, PF Adenosine Deaminase (ADA), PF CRP, Serum CRP, and Pleural/Serum CRP ratio. This finding was also consistent with Watanabe et al,[5] where pleural fluid pepsin was found at elevated levels in patients with empyema and parapneumonic effusion. Qu et al,[9] reported a strong association between the combined analysis of pleural C-reactive protein (p-CRP) with CRP and the successful and precise differential diagnosis of EPE, attributed to its elevated sensitivity and specificity. In contrast, despite being recognised as a highly sensitive marker for bacterial infection diagnosis, neither serum procalcitonin (s-PCT) nor pleural procalcitonin (p-PCT) demonstrated correlations with the differential diagnosis of EPE. In contrast, Radhakrishnan et al.4 also reported similar observations, where pleural fluid ADA levels were significantly higher in TB effusion groups, which was not similar to our study.

Our study observed a significant difference between PF CRP, protein ratio, and LDH ratio, which was also similar to the findings of Makwana et al,[2] where pleural fluid protein, pleural fluid LDH, and pleural fluid cells were significantly different among the exudative group. However, pleural fluid neutrophils were predominantly observed in the TB and malignant effusion groups, which was comparatively less in our study.

The findings of our study correlate with those of Izhakain et al., who reported that parapneumonic effusion had higher pleural fluid CRP levels than other exudative effusions at a cutoff value of >1.38 mg/dL.6 In addition, the study reported by Porcel et al. also showed similar results for parapneumonic effusions with elevated CRP levels >10 mg/dL.[8]

CONCLUSION

Our study showed that PF CRP and Serum CRP levels differed significantly among the different causes of pleural effusion. It is higher in parapneumonic PE, followed by tuberculous PE,

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malignant PE, and transudate PE. Pleural/serum CRP is higher in parapneumonic PE, followed by malignant PE, tuberculous PE, and transudate PE. Hence, these factors may be considered to differentiate between different causes of pleural effusion.

Limitations

The interpretation of this study necessitates consideration of certain limitations. Notably, the predominance of tuberculous cases in our study group reflects the elevated prevalence of TB in our specific geographic region. Consequently, to enhance the robustness of our findings and establish a more comprehensive understanding of the aetiology of exudative pleural effusions, a future multicentre longitudinal study with an expanded sample size encompassing a substantial representation of patients with parapneumonic, empyema, and malignant effusions is needed.

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