C REACTIVE PROTEIN IN DIFFERENTIAL DIAGNOSIS OF PLEURAL EFFUSION

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Abstract
Present study has included 95 Pleural Effusion patients. Pleural fluid were collected from them and classified as Transudate and Exudate according to the standard criteria. Pleural Fluid C-Reactive Protein (CRP) concentrations indicated towards diagnosis and severity of exudates. CRP in pleural fluid is a helpful tool in diagnosis and monitoring of pleural effusion patients.

Keywords: Pleural effusion, Exudate, CRP

INTRODUCTION
Pleural effusion is defined as abnormal accumulation of pleural fluid in pleural space (more than 10-20 ml). The condition arises when production of pleural fluid is excessive or when pleural fluid resorption is less. Commonly pleural effusion arises as secondary manifestations or as a complication resulting from any primary diseases [1]. Diagnosis and treatment of pleural effusion becomes a major challenge since its causative role in many diseases. The abnormal fluid may be transudate, exudate, benign or malignant. This dilemma still exists, since treatment differs in different outcomes [2]. Further, many false negative reports have been submitted regarding cytological examination of pleural fluid [3]. C Reactive Protein (CRP) is considered as a sensitive but non-specific marker of systemic inflammation. CRP production is activated by a number of cytokines like interleukin-6 releasing at inflammatory regions [4]. Increased (S) CRP levels have been identified in many lung diseases like pneumonia, thromboembolisms and malignancies [5]. However, a very few studies are available regarding variations of CRP values in differential diagnosis of pleural fluid in pleural effusion. Present study is undertaken to evaluate the CRP levels in differential diagnosis of pleural effusion at our hospital, so that CRP estimation in pleural fluid can indicate towards the diagnosis in pleural effusion.

Materials and methods:
Study design: The present hospital based, cross sectional study was conducted in the Department of Biochemistry, Calcutta National Medical College, Kolkata, West Bengal from November 2018 to April 2019.

Selection of case group- The study group includes 95 adults (age group between 25 – 55 years) patients (55 male and 40 female) admitted with provisional diagnosis of pleural effusion.

All patients were subjected to
(a) History of illness and clinical examinations.
(b) (S) Lactate Dehydrogenase (LDH) and CRP estimations.
(c) Liver and renal function tests.
(d) Chest X-ray (Anteroposterior and lateral view).
(e) Tuberculin skin test, in case of suspected tubercular pleuricy.
(f) Diagnostic thoracocentesis- Collection and processing of pleural fluid (aprx 300-500 ml) which is subjected to following examinations.
   i) Physical examinations.
Biochemical examinations include protein levels, TC, DC, Adenosine Deaminase (ADA) for suspected tubercular effusions.

Bacteriological examinations.

Cytological examinations for malignant cells.

Quantitative measurement of pleural fluid CRP.

CT guided biopsy.

Exclusion criteria:

a) Patient receiving radiotherapy or chemotherapy.
b) Empyema patients.
c) Immunocompromised patients.
d) Patient with extremely poor general conditions.
e) Quantity of pleural fluid is inadequate.
f) Congestive heart failure patients.

Classification of pleural fluid into transudate or exudate is based upon Light’s criteria by one or more of the following:

a) Ratio of LDH in pleural fluid and serum is more than 0.6 (exudates).
b) Ratio of total protein in pleural fluid and serum is more than 0.5 (exudates).
c) Pleural effusion LDH level is more than two third of upper limit of lab reference of (S) LDH (exudate).

Different exudate groups included in the present study are Tuberculosis, Malignancy, Parapneumonic and chronic non-specific.

Diagnosis of tuberculous pleurisy was based upon high positivity in tuberculin test, lymphocytic predominance, and elevated ADA level in pleural fluid.

Effusions were considered malignant if malignant cells were found in cytological examination or by pleural biopsy.

For parapneumonic effusion, clinical, biochemical and radiological signs of suspected acute inflammation, positive bacterial culture and neutrophil predominance.

Measurement of CRP: CRP analysis was performed by Autoanalyzer Konelab Prime 600 using an immunoturbidimetric method. The diagnostic reagent used for analysis was GmBH (Hamburg Germany). Normal value < 5 (according to the kit literature)[6].

Statistical methods used: Statistical analysis was done by Independent t test and ANOVA. P value <0.05 was considered as significant.

Data collection and processing for statistical analysis:

To assess the significance of difference between the mean values of CRP between transudate and exudates.

To assess the significance of difference between the mean values of CRP within the different groups of exudates.

Results: Ninety five patients suffering from pleural effusion were participated in the study. Pleural fluid of seventeen patients were diagnosed as transudate, Seventy eight fluids were diagnosed as exudates according to Light’s criteria.

### Table 1- Serum mean CRP levels and significance between transudative and exudative pleural fluid.

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>Transudative pleural fluid(n=17) Mean±SD</th>
<th>Exudative pleural fluid(n=78) Mean±SD</th>
<th>Standard error of mean</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S) CRP</td>
<td>19.50±3.99</td>
<td>46.54±28.41</td>
<td>5.95</td>
<td>15.23-38.84</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 3: ANOVA showing significance between and within the subgroups of exudative fluid.

<table>
<thead>
<tr>
<th></th>
<th>Sum of squares</th>
<th>df</th>
<th>Mean square</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between</td>
<td>71883.86</td>
<td>3</td>
<td>23961.28</td>
<td>1322.81</td>
<td>0.0000</td>
</tr>
<tr>
<td>Within</td>
<td>1594.02</td>
<td>88</td>
<td>18.114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>73477.88</td>
<td>91</td>
<td></td>
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</tbody>
</table>

Discussion:
The cornerstone of etiological diagnosis of pleural effusion depends on whether it is transudate or exudate [7]. If the pleural fluid exceeds 15-20 ml it is considered as pleural effusion. It develops from variations in hydrostatic or colloidal osmotic pressure between pleural and pulmonary capillaries, alterations in vascular permeability of pleura and decreased lymphocytic drainage [8]. CRP is an acute phase protein primarily produced and released by hepatocytes [9].

The present study was aimed to analyse the level of CRP in pleural fluid in pleural effusion. Furthermore, the estimation of CRP was performed in transudate and exudates. The present study included four types of exudates as follows: tubercular, malignant, parapneumonic and chronic non-specific.

The results of the present study have clearly observed that there is a significant difference (p<0.0001) between the mean values of CRP between transudate and exudates. Furthermore, significant difference of mean values of CRP were also observed between the four groups of exudative fluid selected within the groups.

In the present study, 17.8% of total patients were found to have transudate, 12.6% have malignancy, 31.57% were tuberculosis, 27.36% were parapneumonic and 10.52% were non-specific.

In comparison, one study with exudative pleural effusion, the tuberculosis accounts for 67.5%, malignant effusion 25%, chronic non-specific 11%, and parapneumonic 7.5% [10]. Few authors documented majority as exudative effusion as tuberculosis (58.3%), followed by malignancy (16.7%)[11]. Another study focused that the tuberculosis was 55.8%, and malignancy was 44.2% [12].

In agreement with our results shows that the significant difference of CRP between transudate and exudates, Alexandrasis et al found the similar trend [13]. Present study was also agreed with Ahmed et al [14]. Furthermore, Rezaeetala B et al and Yousuf et al had documented the similar type of results [15,16]. The later study also evidenced the higher level of CRP in exudative effusion, than that of transudative effusion [16].

The results of the present study had also shown the significant difference of mean CRP levels (P<0.0001) between the exudative fluids of different origin.

Yilmaz et al [17] suggested that the pleural fluid CRP can be used as differential diagnosis of exudative pleural fluid. They worked among the subgroups of parapneumonic, tuberculosis and malignant effusion.

Accommodated evidences suggested that the most common cause of transudative pleural effusion was heart failure or a low blood protein count whereas CRP has been raised in inflammartory conditions [13,15,18]. Classification of transudate and exudates in pleural effusion is mainly based on Light’s criteria [19]. However, as the exudative group may be observed in many diseases, in order to achieve a particular diagnosis, some more tests have performed like ADA in blood, cytological examination or bacterial culture.

Antibiotic therapy in parapneumonic effusion and diuretics may misdiagnose the conditions. CRP can be analysed in pleural fluid after withdrawal of diuretics [20]. Recently many studies have focused on pleural fluid CRP in pleural effusions [21,22,23]. The present study tried to evaluate the CRP levels in different subtypes of exudative pleural effusion. Vidriales et al indicated the CRP levels were highly raised in inflammatory conditions than others [21]. They also documented that pleural to serum CRP ratio was significantly increased in exudative effusions. Furthermore, they found the high ratio in parapneumonic and tubercular effusions than malignant effusion. Turay et al [17] observed that the serum CRP levels are generally increased in infective
conditions, but usually they do not consistent in all bacteriaemic process. In tubercular effusions, the CRP levels were lower than parapneumonic effusions but as an indicator of inflammation, they are higher than those found in transudative effusions. Vidriales et al [21] observed the CRP levels were twice as high in tuberculosis than in malignancy.

In conclusion, pleural fluid CRP levels may be an useful marker of exudative pleural effusion, it reflects the extent of inflammation, therefore indicating towards diagnosis.

Reference: