ORIGINAL ARTICLE

Cut-off value of pleural fluid C-reactive protein in etiologic diagnosis of pleural fluid

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Received 6 February 2014; accepted 20 March 2014
Available online 16 April 2014

KEYWORDS
Exudate;
Transudate;
Effusion;
CRP;
Diuretics

Abstract Background: Classification of effusion into transudates or exudates is considered as the corner stone in the etiological diagnosis of pleural effusion.

Objectives: To determine the validity of pleural fluid (high sensitivity-CRP) concentration in etiologic diagnosis of pleural effusion and to obtain a cut-off value of pleural fluid CRP at which we can discriminate between exudative and transudative pleural effusions.

Patients and methods: A study was conducted upon a hundred patients with pleural effusion. All patients were subjected to: history, clinical examination, chest radiography and thoracic ultrasound, tuberculin test and aspiration of pleural fluid. The fluid was sent for biochemical examination including: Protein, L.D.H, A.D.A and CRP levels, cytological examination and bacteriologic examination. Classification of pleural fluid into transudative or exudative is based upon Light’s criteria. Data were compared by independent sample t-test for 2 groups or by a one-way analysis of variance (ANOVA) for more than 2 groups of variables. Simple correlations between variables were examined by calculating Pearson’s product correlation coefficient, Receiver operating characteristic (ROC) curve used to calculate cut off points, area under the curve (AUC), sensitivity and specificity, and 2 tailed \( P < 0.05 \) was considered significant.

Results: There were significant differences between both groups as regards serum, fluid levels and fluid/serum ratio for LDH, total protein and CRP except for CRP fluid/serum ratio. There was a significant correlation between CRP and LDH and total protein fluid levels. Receiver operating characteristic (ROC) curve was used to calculate the sensitivity and specificity of CRP fluid level and also the cut off value of CRP fluid level. Out of the 44 patients with exudative pleural effusion, two cases were diagnosed as cardiac effusion and one case as liver cirrhosis. The three cases were receiving diuretics and the pleural fluid analysis was repeated after withdrawal of the diuretics which turned to be transudative according to Light’s criteria.
Pleural effusion is defined as an accumulation of fluid in the pleural space that exceeds the physiological amount of 10–20 ml, pleural effusion develops either when the formation of pleural fluid is excessive and or when the fluid resorption is disturbed. Pleural effusions may represent as a primary manifestation of many diseases but most often they are observed as 2nd manifestations or complications of other diseases [1].

The following tests are used in etiologic diagnosis of pleural effusion: (Protein in pleural fluid, pleural fluid protein/serum protein ratio, bilirubin ratio, lactate dehydrogenase in pleural fluid, lactate dehydrogenase ratio, cholesterol in pleural fluid, cholesterol ratio, and albumin gradient). All eight tests had similar diagnostic accuracies except for the bilirubin ratio which was less diagnostically accurate [2].

C-reactive protein is an acute phase protein synthesized mainly in hepatocytes in response to tissue inflammation in individuals. Pleural Fluid CRP level was significantly higher in exudates than that in transudative effusion [3].

In a previous study; pleural fluid-C-reactive protein was considered a useful diagnostic tool to differentiate pleural effusion of bacterial origin from others [4].

Aspiration of pleural fluid was done and was sent immediately for the following:

b. Cytological examination.

Tissue biopsy

One of the following was done according to case:

- Ct guided biopsy.
- Abram’s needle pleural biopsy.
- Classification of pleural fluid into transudative or exudative is based upon Light’s criteria which are:
  - Total fluid protein is less than half of that of the total serum protein level in case of transudative pleural effusion.
  - Fluid Lactate Dehydrogenase (LDH) is less than 0.6 of that of the serum LDH in case of transudative pleural effusion.
  - Pleural fluid LDH is less than two thirds the upper limit of the normal of that of the serum level in the case of transudative pleural effusion [2,16].
  - Effusions were considered malignant if malignant cells were found on the cytology examination of pleural fluid or in the pleural biopsy specimens.
  - The diagnosis of tuberculous pleurisy was based upon high tuberculin positivity, lymphocytic pleural fluid, few mesothelial cells, elevated ADA level in pleural fluid or pleural biopsy showing caseating granuloma.
  - Criteria for parapneumonic effusion were; clinical, biochemical and radiological signs of suspected acute inflammation, positive Gram staining, positive culture for bacteria or neutrophil predominance in pleural effusion [1,5].

Data analysis

Data are presented as mean ± SD for continuous variables or frequency (percentage %) for categorical variables. Data were compared by independent sample t-test for 2 groups or by a one-way analysis of variance (ANOVA) for more than 2 groups of variables. Simple correlations between variables were examined by calculating Pearson’s product correlation coefficient. Receiver operating characteristic (ROC) curve used to calculate cut off points, area under the curve (AUC), sensitivity and specificity, and 2 tailed $P < 0.05$ was considered significant.

Analysis of data was performed using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc., Chicago, IL, 2001).
Results

The present study was conducted upon a hundred patients diagnosed as having pleural effusion due to different etiologies. The selected patients were subdivided into two groups according to light’s criteria.

(A) Exudative group: included 41 patients, 27 male patients and 14 female patients with mean age 54.8 ± 11.8 years.
(B) Transudative group: included 59 patients, 33 male patients and 26 female patients with mean age 54.5 ± 10.7 years.

Sex and age distribution of all cases are presented in Table 1.

Comparison between both groups as regards sex was done using chi-square test and there was no significant difference (p = 0.5), also comparison between both groups as regards age was done using independent sample t-test and there was no significant difference between the 2 groups (t = 0.04, p = 0.9). The comparison between groups A and B is presented in Table 2.

Also comparison between groups A and B was done using independent sample t-test regarding the main presenting complaint, associated comorbidities, radiologic findings and side of pleural effusion and there were also no significant differences between the 2 groups (p > 0.5).

The different final diagnoses in the exudative and transudative effusion groups are demonstrated in Figs. 1 and 2.

Comparison was done between both groups as regards the laboratory findings in serum and pleural fluid including LDH, total protein and CRP levels using independent sample t-test, and the results are illustrated in Table 3.

The results of comparison between both groups regarding CRP fluid and serum levels are illustrated in Fig. 3.

Correlation between CRP and LDH and total protein fluid levels was done using the Pearson product of correlation coefficient, there was a significant correlation between CRP and LDH fluid levels (r = 0.725, p = 0.000), also there was a significant correlation between CRP and total protein fluid level (r = 0.65, p = 0.000), the results of correlation are demonstrated in Figs. 4 and 5.

Receiver operating characteristic (ROC) curve was used to calculate the sensitivity and specificity of the CRP fluid level and also the cut off value of the CRP fluid level. The ROC curve and its results are illustrated in Fig. 6.

The pleural fluid and serum levels of CRP in different diagnoses of exudative pleural effusion are demonstrated in Fig. 7.

Out of the 44 patients with exudative pleural effusion, two cases were diagnosed as cardiac effusion and one case as liver cirrhosis. The three cases were receiving diuretics and the pleural fluid analysis was repeated after withdrawal of the diuretics which turned to be transudative according to Light’s criteria. The data of the 3 cases are presented in Table 4.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic distribution of the studied cases.</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Number</td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
</tr>
<tr>
<td>Female</td>
<td>40</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Range</td>
</tr>
<tr>
<td>21–77</td>
<td>54.6 ± 11.09</td>
</tr>
</tbody>
</table>

Sex and age distribution on studied cases, data presented as number and percentage for sex and as range and mean ± SD for age.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison between the 2 groups regarding gender and age.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Exudative effusion patients (n = 44)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>54.7 ± 12.06</td>
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</tbody>
</table>

There were no significant differences between exudate and transudate groups as regards either sex or age.

Figure 1 Final diagnosis of exudative group. Data are presented in %.

Figure 2 Final diagnosis of transudative group. Data are presented as (frequency, %).
Classification of effusion into transudates or exudates is considered as the cornerstone in the etiological diagnosis of pleural effusion. The primary diagnostic step is the identification of an effusion as either a transudative or an exudate [5]. Pleural effusion is defined as an accumulation of fluid in the pleural

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Laboratory investigations of the serum and the pleural fluid.</th>
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<tbody>
<tr>
<td></td>
<td>Exudative effusion patients (n = 44)</td>
</tr>
<tr>
<td>LDH (mg/L)</td>
<td></td>
</tr>
<tr>
<td>Fluid level</td>
<td>784.5 ± 68</td>
</tr>
<tr>
<td>Serum level</td>
<td>3.9</td>
</tr>
<tr>
<td>Fluid/serum ratio</td>
<td>600 ± 364.9</td>
</tr>
<tr>
<td>Protein (mg/L)</td>
<td></td>
</tr>
<tr>
<td>Fluid level</td>
<td>4.7 ± 1.3</td>
</tr>
<tr>
<td>Serum level</td>
<td>7.03 ± 1.3</td>
</tr>
<tr>
<td>Fluid/serum ratio</td>
<td>0.7 ± 0.12</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td></td>
</tr>
<tr>
<td>Fluid level</td>
<td>15.3 ± 7.5</td>
</tr>
<tr>
<td>Serum level</td>
<td>61.8 ± 40.9</td>
</tr>
<tr>
<td>Fluid/serum ratio</td>
<td>0.4 ± 0.3</td>
</tr>
</tbody>
</table>

There were significant differences between both groups as regards serum, fluid levels and fluid/serum ratio for LDH, total protein and CRP except for CRP fluid/serum ratio.

Discussion

Classification of effusion into transudates or exudates is considered as the cornerstone in the etiological diagnosis of pleural effusion. The primary diagnostic step is the identification of an effusion as either a transudative or an exudate [5]. Pleural effusion is defined as an accumulation of fluid in the pleural

![Figure 3](image3.png) **Figure 3** Serum and pleural fluid CRP levels’ differences between both groups.

![Figure 4](image4.png) **Figure 4** Significant correlation between pleural CRP and pleural LDH ($r = 0.725$, $p = 0.000$).

![Figure 5](image5.png) **Figure 5** Significant correlation between pleural CRP and pleural total protein ($r = 0.65$, $p = 0.000$).

![Figure 6](image6.png) **Figure 6** ROC curve and cut off point of CRP. The optimal cut off value of CRP is >8, ROC curve; receiver operating characteristic curve, AUC; area under the curve.
space in excess of 15–20 ml. The etiology for the development of a pleural effusion includes changes in the hydrostatic or colloid-osmotic pressure of pleural and pulmonary capillaries, changes in pleural vascular permeability and impaired lymphatic drainage [6].

CRP is an acute phase protein predominantly produced and secreted by hepatocytes. Other cells including lymphocytes, kupffer’s cells, monocytes and macrophages can also produce CRP [7].

The present study was conducted in the Abbasia Chest Hospital in the period from March 3, 2012 to March 3, 2013. The study was designed to measure the level of CRP in pleural fluid, serum, and fluid to serum ratio in patients of different types of pleural effusion to predict outcome. The study included a hundred patients diagnosed as having pleural effusion due to different etiologies.

The number of patients included in the study within each group of pleural effusion was demonstrated, where there were 4 patients in the malignant group, 2 patients in the tuberculous group, 34 patients in the parapneumonic group and 59 patients in the transudative group.

Our results showed the percentage of pleural effusion due to malignancy was 4%, of TB was 2%, of parapneumonic was 34% and of transudative effusion was 59%.

Another study conducted on 213 patients with pleural effusion had reported that the most common cause of pleural effusion was congestive heart failure 39.4% (84 cases) while malignancy accounted for 27.2% (58 cases) and tuberculosis accounted for 5.2% (11 cases) [8].

On the other hand, Shah et al., (2007), whose study was conducted on 50 patients with exudative pleural effusion reported that tuberculous effusion accounted for 67.5% (27 cases) of all patients, malignant effusion 25% (10 cases), chronic nonspecific effusion 11% (5 cases) and parapneumonic effusion was 7.5% (3 cases) [9]. Another study had reported that the most common cause of exudative pleural effusion was tuberculosis 58.3% (56 cases), followed by malignancy 16.7% (16 cases) [10].

Also, a study conducted on 326 patients with pleural effusion had reported that the most common cause of exudative pleural effusion was tuberculosis 55.8% (182 cases), followed by malignancy 44.2% (144 cases) [11].

In the present study we found a statistically high significant difference between mean LDH level in fluid, serum and fluid to serum ratio among transudative and exudative pleural effusions.

Our results showed a statistically high significant difference between mean protein level in fluid, serum and fluid to serum ratio among transudative and exudative pleural effusions.

In comparing the exudative effusion with the transudative one, we found that; there was a statistically highly significant difference as the mean value of CRP of exudative effusion was 16.1 ± 7.2 and of transudative effusion was 5.7 ± 0.9 (p = 0.0001).

In agreement with our results Alexandrakis et al. (2000) found that fluid CRP level was significantly higher in exudates than that in transudative effusion (p < 0.01) [3]. Also; Rezaeetalab et al. (2011) found that the pleural fluid concentrations of hs CRP were significantly higher in the exudative group than the transudative group with (p < 0.05) [13].

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Case 1 Cardiac effusion</th>
<th>Case 2 Cardiac effusion</th>
<th>Case 3 Liver cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural protein level (mg/L)</td>
<td>Before 3.7</td>
<td>4.3</td>
<td>5.4</td>
</tr>
<tr>
<td>Serum protein level (mg/L)</td>
<td>Before 6.5</td>
<td>6.4</td>
<td>10</td>
</tr>
<tr>
<td>Pleural/serum protein ratio</td>
<td>Before 0.57</td>
<td>0.65</td>
<td>0.54</td>
</tr>
<tr>
<td>Pleural LDH (mg/L)</td>
<td>208</td>
<td>137</td>
<td>142</td>
</tr>
<tr>
<td>Pleural CRP (mg/L)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Laboratory data of the 3 cases with pleural, serum and pleural/serum ratio of protein levels showing exudate before stopping diuretic therapy which turned to be transudate after stopping diuretics according to Light’s criteria; while CRP pleural levels showing transudative effusion levels from the start.
Also; Hoda Abu-Youssef et al. (2010) reported that there was a statistically highly significant difference for mean values of CRP between transudative and exudative pleural fluid effusions ($p < 0.003$) with higher levels in exudative effusion than those of transudative effusion [14].

The present study found that CRP in fluid to serum ratio has no statistical significance between transudative and exudative effusions. In agreement with our results Hoda Abu-Youssef et al., (2010) found that CRP in fluid to serum ratio has no statistical significance between transudative and exudative effusions [14].

In consistence with our results Yilmaz et al. (2000); reported that the ratio of pleural fluid CRP to serum was significantly lower in the transudate group ($P < 0.009$) [15].

The level of hs CRP in pleural fluid in subtypes of exudative effusion showed a statistically significant difference; where the mean level of hs CRP in the tuberculous group was 36.5 ± 0.7 higher than that of the malignant group which was 20 ± 5.4 and more than that of the parapneumonic group which was 13.6 ± 1.9.

Yilmaz et al. (2000), suggested that CRP in pleural fluid can be used in differential diagnosis of exudative pleural effusion subgroups such as parapneumonic, tuberculous and malignant effusion [15].

In agreement with our results Castano and his coworkers (1992) found that fluid CRP level was twice higher in tuberculous than in malignancy [4].

In the present study, the level of fluid CRP was found to be statistically higher in tuberculous compared to parapneumonic effusion.

In agreement with our results Hoda Abu-Youssef et al. (2010) reported that fluid CRP in tuberculous effusion was statistically significantly higher in comparison to that in parapneumonic effusion [14].

While, a previous research reported that pleural fluid CRP level in tuberculous effusion was lower than that in parapneumonic effusion [15].

The difference between the two studies may be due to the fact that the included patients with parapneumonic effusion in the present work were under antibiotics before assessment of CRP level.

Our study found that; there was a statistically significant positive correlation between pleural CRP and pleural (LDH and total protein).

We can discriminate between the transudative and exudative effusions in this study by using pleural fluid CRP level where the exudative effusion can be diagnosed at a value of CRP > 8 mg/L which is considered the optimal cut off value of pleural CRP, with high sensitivity (93.1%) and specificity (100%).

A previous study stated that pleural fluid CRP > 10 mg/L had good sensitivity of 82%, specificity of 87.5% and predictive value of positively 95.5% in the diagnosis of exudate effusions [4].

Yilmaz et al. (2000) reported that in discrimination between exudates and transudates, the highest sensitivity and specificity for pleural fluid CRP were (93.7%) and (76.5%), respectively at pleural fluid CRP levels > 30 mg/dl [15].

While the study of Rezaee et alab and his colleagues (2011) reported that in discrimination between the exudates and transudates, a cutoff value of 5 mg/L for pleural fluid hs CRP showed 94% sensitivity and 96.6% specificity [13].

In our study we found three cases on diuretics therapy were misdiagnosed as exudative effusion by light’s criteria, while they were correctly diagnosed as transudative effusion by pleural fluid CRP;

where the pleural fluid analysis was repeated after withdrawal of the diuretics which turned to be transudative according to Light’s criteria.

In agreement with our results Light (2002); reported that the exudative pleural effusions met at least one of the following criteria, whereas transudative pleural effusions met none:

1. Pleural fluid protein/serum protein ≥ 0.5
2. Pleural fluid LDH/serum LDH > 0.6
3. Pleural fluid LDH more than two-thirds normal upper limit for serum

The above criteria misidentify approximately 15–20% of transudates as exudates, especially those who were receiving diuretic therapy [16]. Also, another research reported that the albumin gradient (the difference between serum and pleural effusion albumin) did not vary in patients with transudates who received diuretics, allowing a correct diagnosis of transudate in 93 (82.4–97.8) % of the cases. However, in patients who were taking diuretics, the classic criteria of protein index correctly defined only 66 (53.4–82.1) % of the cases ($p < 0.05$) [17]. In conclusion; CRP could be a useful diagnostic marker for differentiation between exudative and transudative pleural effusions and also it is more accurate than protein in distinguishing those transudative effusions receiving diuretic therapy which are falsely diagnosed by Light’s criteria to be exudates.

We recommend conducting further studies on a larger number of patients using the cut-off value of this study to confirm its validity.

Conflict of interest

None declared.

References


