Determining the Etiological Factors in Pleural Fluid by CRP, Albumin and Procalcitonin Levels

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ABSTRACT

Aim: The Light criteria with a specificity of 72% and a sensitivity of 100% have led to further research into the detection of more specific diagnostic methods for transudate exudate separation. In this study, we aimed to evaluate whether pleural fluid and serum CRP, procalcitonin, on the other hand CRP / Albumin and Procalcitonin / Albumin ratios may be suggested as an alternative to Light criteria in the differential diagnosis of pleural effusions.

Material and Method: In this study, the pleural effusions of 121 patients who were aged ≥18 years were evaluated. The study was planned as a prospective cohort type study.

Results: Effusions were divided into two sub-groups as transudate (n:37) and exudate (n:84); and malignant (n:30) and non-malignant (n:91). Serum procalcitonin level of 0.035 was having a sensitivity of 0.726 and specificity of 0.964; on the other hand, pleural fluid procalcitonin level of 0.035 was having a sensitivity of 0.690 and specificity of 0.919. For serum procalcitonin /albumin ratio, 0.0104 value was having a sensitivity of 0.774 and specificity of 0.757 while for pleural fluid procalcitonin /albumin ratio of 0.019 value was having a sensitivity of 0.667 and specificity of 0.649.

Conclusion: Serum and pleural fluid procalcitonin levels and procalcitonin/ albumin ratio were having a significant role in differentiating transudate and exudate. However, procalcitonin, CRP or any other ratios obtained from these parameters were not useful in diagnosis of malignant effusions.

Keywords: Pleural fluid, C-Reactive Protein, Albumin, Procalcitonin.

Introduction

Pleura is the serous membrane that covers the mediastinum, diaphragm, lung parenchyma and the inner surface of the rib cage. There is a small amount of fluid in the potential space between the pleural leaves that allows the pleural surfaces to slide easily over each other during respiratory movements [1]. Increase in the amount of this liquid due to pulmonary, pleural or systemic diseases
result in increased pleural effusion. In evaluation of the etiology of pleural effusion, fluid obtained by thoracentesis should be examined with biochemical, bacteriological, and cytological tests. In the 1970s, Light et al established some criteria for practical application in differentiation of pleural fluids as exudate and transudate [2]. Since the sensitivity and specificity of the light criterions were 100% and 72%, some new parameters are required to increase the diagnostic value of these tests. C-reaction protein (CRP) is an acute phase reactant mainly produced by liver. Procalcitonin is an essential marker in the diagnosis of especially bacterial infections [3]. Pleural fluid CRP and procalcitonin levels are studied in especially infectious causes of pleural effusions [4,5,6,7]. In this study, we aimed to evaluate whether pleural fluid and serum CRP, procalcitonin, on the other hand CRP / Albumin and Procalcitonin / Albumin ratios may be suggested as an alternative to Light criteria in the differential diagnosis of pleural effusions.

**Material and Method**

This study was performed in İzmir Metropolitan Municipality Hospital and Okmeydanı Training and Research Hospital between 01.02.2019 and 30.09.2019. Ethical approval was obtained from the local ethics committee. In this study, the pleural effusions of 121 patients who were aged ≥18 years were evaluated. Informed consent was obtained from all participants. Thoracentesis were performed under local anesthesia and pleural fluid samples were immediately analyzed for total protein, glucose, and lactate dehydrogenase and total and differential cell counts, and cytological examination. Pleural fluid was collected in a serum-separating tube for CRP measurement and in a tube containing EDTA for procalcitonin measurement. Samples were centrifuged at 1200xg for 5 min at 4 °C, and the supernatants were stored at –30 °C until they were assayed. Concurrently, venous blood samples were obtained and analyzed for total protein, albumin, lactate dehydrogenase, CRP and procalcitonin levels.

Effusions were divided into two sub-groups as transudate and exudate regarding the Light’s criteria; and malignant and non-malignant. Serum and pleural fluid parameters were analyzed in differentiation of transudate and exudate, or malign and non-malign effusions.

**Statistical Analyses**

Statistical analyses were performed using SPSS version 21.0 software package (SPSS Inc, Chicago IL, United States). The distribution of data was analyzed with Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean ± SD. Categorical data are reported as number (frequency). Student’s t-test and chi square test were performed to compare the data. ROC curves were constructed to evaluate the role of serum and pleural fluid CRP and procalcitonin levels and pleural fluid /serum CRP ratio, pleural fluid /serum procalcitonin ratio, pleural fluid CRP/albumin ratio, pleural fluid procalcitonin /albumin ratio, serum CRP/albumin ratio, serum procalcitonin /albumin ratio in differentiation of transudate and exudate, or malign and non-malign effusions. A p-value < 0.05 was considered statistically significant.

**Results**

In a total of 121 patients (90 male and 31 female) were included in the study. Among pleural effusions obtained from these patients, 37 were transudate and 84 were exudate. The mean age of the patients with transudate was significantly older than that of the patients with exudate (p:0.001) (Table 1).

| Age (years) | Transudate (n:37) | Exudate (n:84) | p     |
|------------|------------------|----------------|-------|
|            | 59.13 ±9.74      | 51.45 ±9.05    | 0.001 |
| Gender (Male/Female) | 29/8            | 61/23          | 0.652 |

Laboratory data obtained from the serum and pleural effusions of the study participants are compared between patients having exudate or transudate and summarized in Table 2.
### Table 2. Comparison of laboratory data between patients having transudate or exudate

|                               | Transudate (n:37) | Exudate (n:84) | p    |
|-------------------------------|-------------------|----------------|------|
| Pleural fluid total protein (mg/dl) | 2.10 ±0.98        | 3.75 ± 0.71    | 0.001|
| Serum total protein (mg/dl)   | 6.37 ± 0.57       | 6.72± 0.55     | 0.002|
| Pleural fluid LDH (U/l)       | 79.13±20.68       | 125.83±29.85   | 0.001|
| Serum LDH (U/l)               | 207.10±35.67      | 198.20±38.75   | 0.22 |
| Pleural fluid albumin (g/dl)  | 1.31 ± 0.45       | 1.89 ± 0.56    | 0.001|
| Serum albumin (g/dl)          | 2.76 ± 0.87       | 3.06± 0.56     | 0.027|
| Pleural fluid - serum albumin gradient (g/dl) | -1.45 ± 0.65     | -1.17 ± 0.41   | 0.002|
| Pleural fluid CRP (mg/dl)     | 2.06 ±1.95        | 3.85 ±2.23     | 0.002|
| Serum CRP (mg/dl)             | 3.34± 2.28        | 4.22± 3.12     | 0.121|
| Pleural fluid Procalcitonin (ng/dl) | 0.02 ±0.01      | 0.66±1.15      | 0.001|
| Serum Procalcitonin (ng/dl)   | 0.02± 0.01        | 0.52 ± 0.93    | 0.001|

Among those pleural effusions analyzed, 30 were malignant and 91 were non-malignant. Some ratios are calculated from those laboratory data and compared between patients having transudate and exudate or malignant and non-malignant effusions (Tables 3 and 4). Serum and pleural fluid procalcitonin/albumin ratio were significantly different between patients having transudate or exudate and on the other hand, serum and pleural fluid CRP/albumin ratio, and serum and pleural fluid procalcitonin /albumin ratio were all significantly different between patients having malignant or non-malignant pleural effusions.

### Table 3. Comparison of different ratios obtained from laboratory tests between patients having transudate or exudate

|                               | Transudate (n:37) | Exudate (n:84) | p    |
|-------------------------------|-------------------|----------------|------|
| Pleural fluid /serum total protein ratio | 0.32±0.13        | 0.56± 0.10     | 0.001|
| Pleural fluid /serum LDH ratio  | 0.38±0.07         | 0.64±0.15      | 0.001|
| Pleural fluid /serum albumin ratio | 0.50±0.17        | 0.61±0.12      | 0.002|
| Pleural fluid /serum CRP ratio  | 0.57±0.19         | 0.78±0.38      | 0.001|
| Pleural fluid /serum Procalcitonin ratio | 1.25 ±1.12       | 1.45±1.24      | 0.381|
| Serum CRP/Albumin ratio        | 1.53±1.44         | 1.42±1.13      | 0.654|
| Pleural fluid CRP/Albumin ratio | 1.54±1.23         | 2.21±1.58      | 0.142|
| Serum Procalcitonin /Albumin ratio | 0.010 ±0.004     | 0.18 ± 0.13    | 0.001|
| Pleural fluid Procalcitonin /Albumin ratio | 0.018 ±0.012     | 0.38 ± 0.26    | 0.001|

### Table 4. Comparison of different ratios obtained from laboratory tests between patients having malignant or non-malignant effusions

|                               | Malign effusions (n:30) | Non-malign effusions (n:91) | p    |
|-------------------------------|-------------------------|-----------------------------|------|
| Pleural fluid /serum total protein ratio | 0.61±0.08              | 0.44±0.15                   | 0.001|
| Pleural fluid /serum LDH ratio  | 0.71 ± 0.05            | 0.51±0.18                   | 0.001|
| Pleural fluid /serum albumin ratio | 0.62±0.08              | 0.56±0.16                   | 0.023|
| Pleural fluid /serum CRP ratio  | 0.55±0.12              | 0.77±0.38                   | 0.001|
| Pleural fluid /serum Procalcitonin ratio | 1.40±0.74              | 1.39±0.87                   | 0.963|
| Serum CRP/Albumin ratio        | 1.05 ± 0.43            | 1.59±0.97                   | 0.001|
| Pleural fluid CRP/Albumin ratio | 0.97± 0.49             | 2.34± 1.52                  | 0.001|
| Serum Procalcitonin /Albumin ratio | 0.02± 0.018           | 0.16±0.12                   | 0.001|
| Pleural fluid Procalcitonin /Albumin ratio | 0.034± 0.029          | 0.34 ± 0.24                 | 0.001|
Receiver operating characteristic (ROC) curves were drawn for serum and pleural effusion CRP and procalcitonin levels in differentiation of transudate and exudate (Figure 1). Areas under the curve for serum CRP, serum procalcitonin, pleural fluid CRP and pleural fluid procalcitonin levels were: 0.570, 0.849, 0.648 and 0.831, respectively. Some cut-off values for serum and pleural fluid procalcitonin levels are summarized in Table 5. Serum procalcitonin level of 0.035 was having a sensitivity of 0.726 and specificity of 0.964; on the other hand pleural fluid procalcitonin level of 0.035 was having a sensitivity of 0.690 and specificity of 0.919.

For pleural fluid /serum CRP ratio was 0.630 and for pleural fluid /serum procalcitonin ratio, it was 0.542, for pleural fluid CRP/albumin ratio it was 0.528, for serum CRP/albumin ratio it was 0.525, for pleural fluid procalcitonin /albumin ratio it was 0.748 (0.693-0.834) and for serum procalcitonin /albumin ratio it was 0.797 (0.717-0.878).

Some cut-off values were calculated for the sensitivity and specificity of serum and pleural fluid procalcitonin /albumin ratios (Table 6). For serum procalcitonin /albumin ratio, 0.0104 value was having a sensitivity of 0.774 and specificity of 0.757 while for pleural fluid procalcitonin /albumin ratio of 0.019 value was having a sensitivity of 0.667 and specificity of 0.649.

Table 5. Some cut-off values calculated for the sensitivity and specificity of serum and pleural fluid procalcitonin levels in differentiation of transudate and exudate

|               | Sensitivity | Specificity |
|---------------|-------------|-------------|
| Serum         |             |             |
| Procalcitonin | 0.83        | 0.703       |
| 0.025         | 0.726       | 0.964       |
| 0.035         | 0.690       | 0.964       |
| 0.045         |             |             |
| Pleural fluid procalcitonin | 0.869 | 0.405 |
| 0.015         | 0.810       | 0.676       |
| 0.025         | 0.690       | 0.919       |
| 0.035         |             |             |

ROC curves were drawn for serum and pleural effusion CRP and procalcitonin levels in differentiation of malignant and non-malignant effusions (Figure 2). Areas under the curve for serum CRP, serum procalcitonin, pleural fluid CRP and pleural fluid procalcitonin were, 0.459, 0.726, 0.528 and 0.525, respectively.

Figure 2: ROC curves for CRP and procalcitonin levels in differentiation of malignant and non-malignant effusions

|               | Sensitivity | Specificity |
|---------------|-------------|-------------|
| Serum         |             |             |
| Procalcitonin /albumin ratio | 0.798 | 0.649 |
| 0.0910        | 0.774       | 0.757       |
| 0.0104        | 0.762       | 0.865       |
| 0.0109        |             |             |
| Pleural fluid procalcitonin /albumin ratio | 0.714 | 0.595 |
| 0.017         | 0.667       | 0.649       |
| 0.019         | 0.655       | 0.730       |
| 0.022         |             |             |
Pleural fluid /serum CRP ratio was 0.306 and for pleural fluid /serum procalcitonin ratio it was 0.466, for serum CRP/albumin ratio it was 0.328, for serum CRP/albumin ratio it was 0.434, for pleural fluid procalcitonin /albumin ratio it was 0.463 and for serum procalcitonin /albumin ratio it was 0.483. Since in any of the parameters area under the curve could not reach the value of 0.50, we did not compute the sensitivity and specificity values.

Discussion
In this study we analyzed the prognostic value of serum and pleural fluid CRP and procalcitonin levels and some ratios obtained from analyses of serum and pleural fluid laboratory data in differentiation of transudate or exudate and malignant or non-malignant pleural effusions. We determined that, especially serum and pleural fluid procalcitonin levels and procalcitonin /albumin ratios were having significant diagnostic value in differentiation of exudate and transudate; however any of the ratios were not having any significant diagnostic value in diagnosis of malignant effusions. To the best of our knowledge, this is the first study in literature evaluating the diagnostic role of those ratios in pleural effusions. Procalcitonin is a peptide precursor for calcitonine that is secreted from extra-thyroidal organs. In recent years, the diagnostic value of procalcitonin in describing infectious causes of pleural effusions has been studied. Wang et al reported that elevated procalcitonin levels in pleural fluid are associated with the empyema or para-pneumonic effusions [8]. Recently, Watanebe et al also reported that pleural fluid CRP and procalcitonin levels were useful in diagnosing infectious causes of pleural effusions [9]. Koshla et al reported that, procalcitonin was a novel biomarker for diagnosing infectious pleural effusion [10]. Yeo et al reported that, pleural fluid CRP levels were significantly different between transudate and exudate; but not the pleural fluid procalcitonin levels [11]. In this study we determined that, in differentiation of transudate and exudate; both serum and pleural effusion procalcitonin levels were useful as well as the procalcitonin/albumin ratio.

Identification of malignant pleural effusions is highly important to start the treatment immediately. Lee et al reported that both serum and pleural fluid procalcitonin levels were higher in differentiating para-pneumonic pulmonary effusions from tuberculosis pleurisy and malignant effusion [12]. Botana-Rial et al reported that pleural effusion CRP or procalcitonin levels were not useful for discriminating between benign and malignant pleural effusions [13]. Ji et al reported an optimal discrimination by combining pleural CRP, pleural carcinoembryonic antigen and serum procalcitonin may be performed in differentiation of malignant and non-malignant pleural effusions [14]. However we did not determine any significant role of serum or pleural fluid procalcitonin or CRP levels or different ratios obtained from those parameters in diagnosing malignant pleural effusions.

In some previous studies, serum and/or pleural fluid CRP levels were defined to be important in differentiating infectious pleural effusions from other etiologies [15,16,17]. However, we did not determine any significant role of CRP or CRP based ratios in defining transudate or exudate and malignant effusions. Ji et al reported that combination of prealbumin and CRP was having incrementally discriminating values for malignant effusions [18]. Pleural fluid CRP levels were reported to have a significant role in differentiating malign or benign pleural effusions [19]. However we did not determine any significant role of CRP or CRP based ratios in differentiation of transudate or exudate and malignant pleural effusions.

There are some limitations of this study that should be mentioned. The first is the less number of patients analyzed. Secondly, we did not analyze the serum or pleural fluid tumor marker levels which may be useful in differentiation of malignant effusions.

In conclusion, serum and pleural fluid procalcitonin levels and procalcitonin/albumin ratio were having a significant role in differentiating transudate and exudate. However, procalcitonin, CRP or any other ratios obtained from these parameters were not useful in diagnosis of malignant effusions. Further, larger prospective studies are warranted to determine the role of procalcitonin in differentiating transudate and exudate.

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