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Original Article

The Role of Pleural Fluid Procalcitonin in the Differential Diagnosis of Parapneumonic Pleural Effusions and its Relation with Pleural Fluid Ultrasound

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Keywords: Parapneumonic pleural effusion; procalcitonin; thorax ultrasonography.

ABSTRACT

Objective: Procalcitonin (PCT) is a highly specific marker for the detection of infectious diseases. In recent years, studies on this marker have been conducted in patients with pleural fluid. Our aim in this study is to investigate the role of pleural fluid procalcitonin level in distinguishing parapneumonic pleural effusion (PPE) from other causes of exudative pleural effusion and its relationship with thorax ultrasonography (USG).

Methods: A total of 128 exudative pleural effusion patients were included in this study. The patients were divided into two groups as PPE and non-PPE. Demographic findings, comorbidities, radiographic images in chest radiography and thorax USG, hemogram and CRP results, albumin, protein, lactate dehydrogenase (LDH) and glucose levels in pleural fluid and pleural fluid cell count were recorded. Pleural fluid PCT levels, serum PCT levels and thoracic USG images of PPE and non-PPE groups were compared statistically with each other. P-value <0.05 was considered statistically significant.

Results: Of the 128 patients, 71 (55%) were diagnosed with PPE and 57 (45%) were diagnosed with non-PPE causes. There was no significant difference in the level of pleural fluid PCT and serum PCT levels between the PPE and non-PPE groups (p=0.31 and p=0.21, respectively). No statistically significant difference was found between the anechoic fluids and the complex pleural effusion without septum in the PPE and non-PPE groups (p=0.079 and p=0.147, respectively). However, complex septated fluids were higher in PPE group and this difference was statistically significant (p=0.003).

Conclusion: It was found that the pleural fluid PCT and serum PCT measurements in the PPE did not have a diagnostic value. Pleural fluid PCT/serum PCT ratio were not significantly different between the two groups. In addition, there was no correlation between thoracic USG images and PCT levels.

INTRODUCTION

Pleural effusions are pathologies that are frequently encountered in daily practice and develop as a result of many different diseases. Among the most common causes of pleural effusion we encountered may be listed as congestive heart failure (CHF), pneumonia, malignancy and tuberculous pleural effusion (TPE).[1] However, the incidence of TPE shows epidemiological differences according to countries/regions. The most common cause of exudative fluids is parapneumonic pleural effusion (PPE) and are detected in 35–40% of the patients who are followed with a diagnosis of pneumonia.[1]

The first procedure to be performed in a patient with pleural effusion is thoracentesis. Results of biochemical analysis of the pleural fluid as for lactate dehydrogenase (LDH), pH, protein, albumin, glucose values, cell count, and its cytological examination, microbiological staining and culture help to achieve differential diagnosis. In addition to clinical and radiological findings, pleural fluid analysis also helps in diagnosing PPE. None of the available examinations are sufficiently specific to diagnose pleural effusion. Therefore, new biomarkers have been emphasized recently in the diagnosis of PPE. Recently, the use of procalcitonin (PCT) for this purpose has been come up in many studies. When the studies on the pleural fluid PCT level are examined, it

is seen that there are few relevant studies in the literature which indicate its low or high diagnostic sensitivity.[2]

Depending on the etiology, PPE can be seen in different forms, varying from simple effusion that is treated only with antibiotic therapy to complicated empyema requiring surgery. The decision for treatment method is based on radiological findings, biochemical parameters of the pleural fluid, and microbiological analysis.

Another examination that can help in the imaging of the pleural fluid is thoracic ultrasonography (USG). Ultrasonography has found an increasing use in the discipline of chest diseases in recent years. Ultrasonographic imaging is one of the best methods for imaging pleural fluids. Even small amounts of pleural fluid can be detected by thoracic USG.[3]

The present study aims to investigate the effectiveness of PCT level measured in pleural fluid in the diagnosis of PPE, its potential use in differentiation from other causes of exudative pleural effusion and its relationship with thoracic USG image.

MATERIALS AND METHODS

Study population

Inpatient or outpatients who were treated in our clinic between October 2016 and July 2018 with a diagnosis of pleural effusion were prospectively included in the study. The study was performed in accordance with the Declaration of Helsinki's Good Clinical Practice guidelines and approved by the Kartal Dr. Lütfi Kırdar Training and Research Hospital Clinical Researches Ethics Committee.

Demographic information, concomitant diseases, radiographic findings on chest radiograms and thoracic USG, hemogram and C-reactive protein (CRP) findings, albumin, protein, LDH and glucose levels, cell counts in pleural fluid were recorded. Results of bacterial growth in pleural fluid, and blood culture media, and pleural cytology were also recorded.

Patients with pleural fluid detected on chest x-ray or thoracic computed tomography were included in this study. Patients clinically and radiologically thought to have pleural fluid due to heart failure were excluded from the study. Patients without any contraindications for thoracentesis were included in this study and consent forms were obtained from these patients for the procedure.

Procedures

In our patients, GE Logic7 USG device and convex probe (3.5 MHz) were used. Patients were divided into four groups as anechoic, complex septated, and complex nonseptated echogenic fluids according to thoracic USG images of pleural fluid. When evaluating pleural effusions according to thoracic USG, the pleural fluids seen in one probe area were classified as small, in two probe areas as moderate and in more than two probe areas as massive amounts of fluid.

Assessment tools

A patient with pleural effusion was evaluated in three groups according to fluid level seen on posteroanterior (PA) chest x-ray:

1. Pleural fluid enough to wipe the costophrenic sinus; small amount of liquid
2. Pleural fluid that reaches the level of hilus but does not exceed the e level of the hilus; moderate amount of liquid
3. Pleural fluid exceeding the level of hilus; massive amount of pleural fluid

In pleural fluids, differentiation between exudate, and transudate was based on Light criteria; pleural fluid/serum protein ≥0.5, pleural fluid LDH level more than 2/3 of the laboratory upper limit, pleural fluid/serum LDH ≥0.6.[1] After differentiation between exudate, and transudate was made, patients with exudative fluid were included in this study. The patients were divided into two groups as PPE and non-PPE (malignant pleural effusion –MPE, and TPE). The diagnosis of MPE was made based on pleural fluid cytology and/or detection of malignant cells in pleural biopsy; the diagnosis of PPE was made by the presence of pneumonia and accompanying pleural effusion, and detection of microorganism in gram staining and/or its growth in culture. The diagnosis of TPE was made by detecting calcified granulomatous inflammation in pleural biopsy.

PCT in serum and pleural fluid was analyzed in the Roche HITACHI Cobas e 601 (Tokyo, Japan) device with the ECLIA (electrochemiluminescence immunoassay) method using the Elecsys BRAHMS PCT (Mannheim, Germany; lot no 27885702) kit.

Statistical Analysis

SPSS 17.0 program was used in statistical analysis. Student's t-test was used to compare the PCT level between both groups. In the classification of categorical data, chi-square test was used. P-values less than 0.05 were considered statistically significant.

RESULTS

Four of the 132 patients included in this study were excluded from this study because pleural fluid had characteristics of transudate. Patients were divided into two groups as PPE and non-PPE exudative pleural effusions according to the etiology of pleural fluid.

Pleural effusions in 71 (55%) patients were determined as PPE, in 57 (45%) patients effusions were due to non-PPE etiologies (51 MPE, 6 TPE). The average age was 64.6 years for the PPE group and 59.8 years for the non-PPE group, and there was no significant difference between the two groups concerning average age (p=0.063). There was no significant difference between the groups in terms of gen-

Table 1. Levels of the some biochemical markers and procalcitonin in pleural fluid and serum

	PPE (n=71)	Non-PPE (n=57)	p
	Mean±SD	Mean±SD	
Pleural fluid procalcitonin (ng/mL)	0.90±2.93	0.47±1.45	0.31
Serum procalcitonin (ng/mL)	1.30±4.51	0.56±1.88	0.21
Pleural fluid procalcitonin/ serum procalcitonin	1.15±1.74	1.06±0.35	0.72
Pleural fluid albumin (g/dL)	2.03±0.76	2.30±0.71	0.043
Pleural fluid protein (g/dL)	3.9±1.38	4.25±1.28	0.27
Pleural fluid lactate dehydrogenase (U/L)	1197±4040	410.07±545	0.14
Pleural fluid glucose (mg/dL)	125.7±78.26	130.94±71.2	0.69

PPE: Parapneumonic pleural effusion; SD: Standard deviation.

der (F/M ratio was 30/41 for PPE and 27/30 for non-PPE group) (p=0.760).

When the groups were evaluated concerning concomitant disease, 111 patients had, and 17 patients had not any concomitant disease. As expected, the number of patients without additional disease in the non-PPE group was very low. Only three of 17 patients without comorbidities were found in the non-PPE group (p=0.038).

PCT values of pleural fluids and sera of the patients were examined. The mean values of serum and pleural fluid PCT by groups are given in Table 1.

There was no significant difference in pleural fluid between the two groups in terms of serum and pleural fluid PCT levels (p=0.31 for pleural fluid-PCT and p=0.21 for serum-PCT). The ratio of pleural fluid PCT level to serum PCT level was not statistically significant between the groups (p=0.72) (Table 1).

Protein, albumin, glucose and LDH levels were measured in pleural fluid (Table 1). There was no significant difference between the two groups concerning glucose, LDH and protein levels in pleural fluid (p=0.69 for glucose, p=0.14 for LDH and p=0.27 for protein). Albumin level was higher in the non-PPE group compared to the PPE group, and this difference was found to be statistically significant (p=0.043).

Hemogram and CRP levels were evaluated in all patients. Serum leukocyte count was 10540±4300/mm^3 in PPE cases and 8100±3070/mm^3 in non-PPE cases (p<0.001). Serum CRP value was calculated as 110.10±95.06 mg/L in PPE cases and 63.64±56.92 mg/L in non-PPE cases (p=0.001). Serum neutrophil percentages were 73.5±11.4 and 70.11±11.5, respectively (p=0.094).

PA chest radiography and thoracic USG were used to evaluate the radiology of the pleural fluid. In the PPE group, a small amount of pleural fluid was detected in seven cases, a moderate amount in 54 cases, and massive amounts of pleural fluid in 10 cases, in the non-PPE group, a small amount of pleural fluid was detected in five cases, a moderate amount in 41 cases and a massive amount of pleural fluid in 11 cases. Levels of pleural effusion on PA chest X-ray levels were not significantly different between groups (p=0.710). In addition, free or loculated fluid was evaluated on PA chest radiograms. According to this evaluation, statistically significantly greater amounts of loculated fluids were detected in the PPE group (p=0.016) (Table 2).

According to thoracic USG, a small amount of pleural fluid was detected in six, a moderate amount in 55 cases, and a massive amount of pleural fluid in 10 cases in the PPE group, while in the non-PPE group a small amount of pleural fluid was detected in five, a moderate amount in 41 cases and massive pleural fluid in 11 cases. The pleural fluid levels detected in thoracic USG examination were similar to those observed in the PA chest radiograms without any statistically significant intergroup difference (p=0.710). At the same time, thoracic USG examination was divided into four groups according to the appearance of pleural fluid. In our study where echogenic pleural effusion was not seen in any patient, the distribution by groups is given in Table 3. Accordingly, in PPE and non-PPE groups, there was no significant difference between anechoic and complex nonseptate effusions (p=0.079, p=0.147). However, it was observed that complex septated pleural effusions were more

Table 2. Appearance of the pleural effusion in posteroanterior chest-Xray in both groups

	PPE (n=71)	Non-PPE (n=57)	p
Free fluid	59	55	
Loculated fluid	12	2	0.016

PPE: Parapneumonic pleural effusion.

Table 3. Characteristic features of the pleural effusion detected thoracic USG examination in both groups

	PPE (n=71)	Non-PPE (n=57)	p
Anechoic	26	34	0.079
Complex nonseptated	24	18	0.147
Complex septated	21	5	0.003

PPE: Parapneumonic pleural effusion.

frequently detected in the PPE group with a statistically significant intergroup difference (p=0.003).

The number of cells and polymorphonuclear leukocyte (PMNL) ratio from the pleural fluid samples of the patients were evaluated. The average number of cells was 776.83/mm^3 in the PPE group and 426.05/mm^3 in the non-PPE group. The average PMNL ratio was 69.79% in the PPE group and 53.74% in the non-PPE group. Mean number of cells and PMNL ratio were significantly higher in the PPE group than the non-PPE group (p=0.038 for cell number and p=0.009 for PMNL ratio).

There was no difference between the groups as for pleural fluid culture positivity rate. In one patient from the PPE group, *S. aerus* was grown in the pleural fluid culture, while in the non-PPE group; *M. tuberculosis* was grown in the pleural fluid culture in one patient.

DISCUSSION

There was no significant difference between PPE and non-PPE groups in terms of serum, and pleural fluid PCT levels. The ratio of pleural fluid PCT level to serum PCT level was not significantly different between both groups. In addition, no correlation was found between thoracic USG images and PCT levels.

Considering the few numbers of studies evaluating PCT measurements in pleural fluid, one of the first studies on this subject was conducted by Topolcan et al.[4] in 2007. As a result of this study, in which many biomarkers were discussed in pleural fluid, mean pleural effusion PCT value (0.67 ng/mL) in patients hospitalized due to pneumonia was statistically significantly higher than those with pleural transudate (0.006 ng/mL), MPE (0.14 ng/mL) and pleural effusions with viral etiology (0.07 ng/mL). However, the researchers did not specify any cut-off values. Inclusion of transudative pleural effusions in this study may be considered as a factor in the detection of significantly higher levels of PCT in pleural fluids of patients followed up with pneumonia.

In our study, cases in the PPE group were not categorized according to causative agents of pneumonia as bacterial or viral PPE. Another study on this subject was done by Porcel et al.[2] and 308 patients with pleural effusion. Patients with diagnosis of transudative pleural effusion (n=40), TPE, (n=50), MPE (n=40), PPE (n=128 including 68 complicated and 60 uncomplicated PPE), empyema (n=30) and 20 patients with non-diagnostic exudative fluid were included in this study. There was no significant difference between the groups in terms of pleural fluid PCT levels and it was reported that pleural fluid PCT value was not useful in distinguishing infectious pleural fluids from non-infectious pleural fluids. In another study, pleural fluid and serum PCT levels were measured in a total of 82 patients with pleural effusions who were divided into two groups as PPE and non-PPE (7 MPE, 12 TPE and 18 transudates).[5] The findings obtained in this study showed that both pleural fluid and serum PCT levels were higher in the PPE group than in the non-PPE group.

In a similar study by Doğan et al.,[6] 65 patients with exudative pleural fluid were included in this study. In this study, PCT levels in pleural fluid and serum were compared in the patients diagnosed as PPE, and higher pleural fluid PCT levels (average values of PCT: 0.03 ng/mL vs 1.03 ng/mL) and serum PCT levels (average values of PCT: 0.05 ng/mL vs 0.90 ng/mL) were detected in the PPE group (p<0.001). In addition, significant cut-off levels for pleural fluid, and serum PCT values were determined (0.0285 ng and 0.105 ng/mL, respectively). In this study, it was stated that the reason for the detection of higher levels of pleural fluid PCT levels in the PPE group may be related to the presence of intense inflammation in the fluid in the pleural space, loculated fluid, or thickening of the pleura. In the same study, higher leukocyte counts, fever and CRP values (p<0.05) were detected in the PPE group.[6]

In our study, in the PPE group significantly higher leukocyte counts were detected (p<0.001). Although a higher percentage of neutrophils was observed in the PPE group, any statistically significant intergroup difference could not be noted. In our study, significantly higher serum CRP values were measured in the PPE group (mean values for CRP in PPE, and non-PPE groups were 110.10 mg/L, and 63.64 mg/L, respectively), (p=0.001).

In a study by San José et al.,[7] 233 patients, including 28 PPE, 57 MPE, 49 TPE, 53 patients with transudative effusions and 46 undiagnosed patients with exudative pleural fluids were enrolled. In all patients, pleural fluid PCT level was measured and although pleural fluid PCT level (0.15 ng/mL) was found higher in PPE group than other groups, no significant difference was found among PPE, transudate and MPE groups.

In another study conducted in patients with pleural effusions, 24 PPE (n=24), TPE (n=11), MPE (26) and transudative effusions (n=28) were included in this study and the usability of pleural fluid PCT level in the diagnosis of PPE was investigated. As a result of the study, the mean pleural fluid PCT level in the group with PPE patients was 0.11 ng/mL; There was no significant difference between MPE (0.16 ng/mL), TPE (0.13 ng/mL) and transudate (0.08 ng/mL) groups.[8] As a result, pleural fluid PCT value was found to be higher in the PPE group compared to other groups in half of the studies concerning the effectiveness of pleural fluid PCT value, while in another half of the studies a significant difference could not be detected between groups. In our study, no significant difference was observed between the two groups in terms of pleural fluid PCT levels. In our study, although the pleural fluid PCT level was higher in the PPE group, the higher standard deviation was considered to be a possible reason for the difference between PPE and non-PPE groups.

In similar studies investigating the PPE PCT level, the presence of additional disease was also addressed. In the study conducted by Doğan et al.,[6] any significant difference was not reported between the PPE and non-PPE groups concerning the presence of additional diseases. In another study, the presence of comorbid disease was significantly

more frequent in the MPE group compared to the PPE group (p<0.001).[8] In our study, when the groups were evaluated in terms of additional disease, as expected, the number of patients without additional disease in the non-PPE group was found to be very low. Only 3 of 17 patients without comorbidities were in the non-PPE group (p=0.038).

In our study, PPE and non-PPE groups were compared concerning PA chest radiography and thoracic USG images. There was no significant difference in the amount of fluid as detected in the PA chest X-ray and thoracic USG examinations, but increase in the amount of loculated fluids in the PPE group was statistically significant (p=0.016). The appearance of the pleural fluid was also evaluated with thoracic USG. Echogenic pleural effusion was not found in any patient. In PPE and non-PPE groups, there was no significant difference between the presence of anechoic and complex nonseptated pleural effusions (p=0.079 and p=0.147). However, complex septated effusions were more common in the PPE group with a statistically significant intergroup difference (p=0.003).

In our study, pleural fluid culture positivity was detected in two patients, one in each group, while bacterial growth was seen in the blood cultures of 4 (0.13%) of 32 patients, and the groups could not be compared in terms of pleural fluid culture and blood culture results due to relatively small number of patients.

In the light of the available information, it is accepted that PCT levels above 0.5 ng/mL are related to infectious causes. However, there is no acceptable cut-off value of PCT for pleural effusions. In the study conducted by Doğan et al.,[6] the cut-off value for pleural fluid PCT level was given as 0.0285 ng/mL (with 96.9% specificity and 57.5% sensitivity). In our study, since there was no difference between the PPE group and the non-PPE group in terms of pleural fluid PCT value, the Receiver Operating Characteristic (ROC) analysis could not be performed and a cut-off value could not be determined.

In conclusion, in our study, the diagnostic value of pleural fluid PCT and serum PCT in PPEs could not be demonstrated. In our study, the majority of the patients in the PPE group had simple uncomplicated PPEs, besides the low rate of detection of bacteriological factors in the PPE group (bacterial growth was detected in only one patient), the single-center design of this study and the inability to make a discrimination between bacterial and viral factors in the PPE group were significant limitations of our study. In addition, lack of a gold standard method for the diagnosis of PPE, occasionally potential of MPEs become complicated, possible antibiotic use before thoracentesis, and the unequal distribution of additional diseases among the groups may also be considered as limiting factors of our study.

Ethics Committee Approval

Approved by the local ethics committee (date: 12.08.2016, no: 2016/514/89/3).

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: B.M.S.; Design: S.Ş.C., N.G.K.; Supervision: S.Ş.C., N.G.K.; Fundings: B.A.; Materials: B.A.; Data: H.K., B.A.; Analysis: A.F., B.A.; Literature search: B.A., N.G.K.; Writing: B.A.; Critical revision: S.Ş.C., N.G.K.

Conflict of Interest

None declared.

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Parapnömonik Plevral Efüzyonlarda Plevral Sıvı Prokalsitonin Düzeyinin Ayırıcı Tanıdaki Yeri ve Plevral Sıvının Ultrason Görüntüsü İle İlişkisi

Amaç: Prokalsitonin (PCT) enfeksiyon hastalıklarının tayininde kullanılan özgüllüğü oldukça yüksek bir belirteçtir. Plevral sıvısı olan hastalarda son yıllarda bu belirteç ile ilgili çalışmalar yürütülmüştür. Bu çalışmada amacımız, plevral sıvı PCT düzeyinin parapnömonik plevral efüzyon (PPE) tanısındaki rolünü, diğer eksudatif plevral efüzyon nedenlerinden ayrımında kullanılabilirliğini ve toraks ultrasonografi (USG) görüntüsü ile ilişkisini araştırmaktır.

Gereç ve Yöntem: Çalışmaya toplam 128 eksudatif plevral sıvılı hasta dahil edildi. Hastalar PPE (n=71) ve PPE dışı (n=57) olmak üzere iki gruba ayrıldı. Hastaların demografik bilgileri, ek hastalıkları, akciğer grafisindeki ve toraks USG'deki radyolojik bulguları, hemogram ve C-reaktif protein (CRP) bulguları, plevral sıvıda albümin, protein, laktat dehidrogenaz (LDH) ve glukoz seviyeleri, plevral sıvı hücre sayımı kaydedildi. PPE ve PPE dışı grupların plevral sıvı PCT düzeyleri, serum PCT düzeyleri ile toraks USG bulguları istatistiksel olarak birbirleri ile karşılaştırıldı. İstatistiksel analizler için SPSS 17.0 programı kullanıldı. P değerinin <0.05 olması istatistiksel olarak anlamlı kabul edildi.

Bulgular: Yüz yirmi sekiz hastanın 71'i (%55) PPE ve 57'si (%45) PPE dışı nedenlere bağlı tanı aldı. Plevra sıvısında PCT düzeyi ve serum PCT düzeyi bakımından PPE ve PPE dışı gruplar arasında anlamlı fark yoktu (sıvı PCT için p=0.31 ve serum PCT için p=0.21). Toraks USG görüntülerine göre dört gruba ayrılan hastalarda PPE ve PPE dışı gruplarda anekoik sıvılar ile kompleks septasız sıvılarda gruplar arasında istatistiksel olarak anlamlı bir fark saptanmadı (sırasıyla, p=0.079 ve p=0.147). Ancak kompleks septalı sıvılar PPE grubunda daha fazla bulundu ve aralarındaki bu fark istatistiksel olarak anlamlıydı (p=0.003).

Sonuç: Sonuç olarak, çalışmamızda PPE'lerde, plevral sıvı PCT ve serum PCT ölçümünün tanısal değeri olmadığı saptandı. Her iki grupta plevra sıvı PCT düzeyinin, serum PCT düzeyine oranı da tanısal önem taşımıyordu. Ayrıca toraks USG görüntüleri ile PCT düzeyleri arasında korelasyon saptanmadı.

Anahtar Sözcükler: Parapnömonik plevral efüzyon; prokalsitonin; toraks ultrasonografi.