

## The diagnostic role of pentraxin-3 in the differential diagnosis of pleural effusions

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Received: 17.10.2017 • Accepted/Published Online: 26.07.2018 • Final Version: 12.12.2018

**Background/aim:** Discrimination of pleural effusion etiology is not always easy in clinical practice. Pentraxin-3 (PTX-3) is a new acute-phase protein. The aim of this study was to investigate the role of PTX-3 in the differential diagnosis of pleural effusions.

**Materials and methods:** This prospective study enrolled all consecutive patients from two tertiary hospitals who underwent diagnostic or therapeutic thoracentesis. In a cohort of 149 subjects with pleural effusion, including transudates and malignant (MPE), tuberculous (TPE), and parapneumonic effusion (PPE), serum and pleural effusion PTX-3 concentration measurements were performed using ELISA. Serum and pleural effusion protein, lactate dehydrogenase, C-reactive protein (CRP), and adenosine deaminase levels were also assessed.

**Results:** Of these patients, 34 had transudates, 29 had PPE, 63 had MPE, and 23 had TPE. There was a weak correlation between pleural effusion PTX-3 level and serum CRP ( $P < 0.01$ ). There was a significant difference in pleural PTX-3 levels between the exudative effusion groups ( $P < 0.01$ ). The median pleural effusion PTX-3 was significantly higher in patients with PPE (11.2 ng/mL, 2–17.8) than MPE (4.7 ng/mL, 1.8–13.9) and TPE (3.1 ng/mL, 2.0–4.1). At a cut-off point of 5.89 ng/mL, PTX-3 had the best discriminatory power for PPE versus other exudative effusions (sensitivity: 86.2%, specificity: 87.7%). The exudative effusion group had a significantly different pleural effusion/serum PTX-3 ratio ( $P = 0.03$ ).

**Conclusion:** PTX-3 concentration in pleural effusion was elevated without a significant correlation with serum PTX-3 in PPE. These results may suggest that PTX-3 is a local acute-phase reactant and may allow discrimination of PPE from other exudative effusions.

**Key words:** Pleural effusion, pentraxin-3, transudates, malignant pleural effusion, tuberculous pleural effusion, parapneumonic effusion.

### 1. Introduction

Pleural diseases are very common pulmonary conditions, the main causes of which are primary lung diseases, systemic diseases, functional organ failure, medication, and primary pleural pathologies (1). Pleural effusions occur as a result of increased fluid formation and/or reduced fluid resorption. Definite physiopathology of pleural effusion accumulation depends on the underlying etiology. Pleural effusions may be secondary to increased pulmonary hydrostatic pressure, reduced plasma oncotic pressure, increased permeability of the pleura or lymphatic obstruction, and, rarely, thoracic duct injury. Heart failure, malignancy, pneumonia, tuberculosis, and pulmonary embolism are the leading causes of pleural effusions (2).

Pleural effusion analysis can usually identify the cause of effusion, and thoracentesis should be performed

in all patients with pleural effusion of unknown origin whose width measures more than 1 cm on chest X-ray or ultrasound, excluding patients with heart failure (3).

Biochemical, microbiologic, and cytologic analyses of pleural effusion are the fundamental studies to determine the etiology of the effusion but it is not easy to find the main cause every time (4). Therefore, several biomarkers have been suggested to help differential diagnosis. Procalcitonin, amyloid A, and C-reactive protein (CRP) are well known acute-phase proteins and the results of these studies have lately been proposed to use for differentiation of infectious diseases from other origins of pleural effusion (5). Pentraxin-3 (PTX-3) has also been called tumor necrosis factor-stimulated gene 14. It is a member of the pentraxin superfamily (6,7). The secreted human PTX-3 is a 45-kDa glycoprotein with a 162-amino acid N-terminal

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extension and 202-amino acid C-terminal pentraxin domain. PTX-3 is a long pentraxin but the structure of its pentraxin domain is similar to that of pentraxin domains found in classic short pentraxins. CRP is one of the most important short pentraxins. All of the short pentraxins are produced in the liver (6–8). However, PTX-3 is secreted by different cells (alveolar epithelium, neutrophils, macrophages, endothelial cells, myeloid-derived dendritic cells, ovarian granulosa cells, renal mesangial cells, adipocytes, smooth muscle cells, synovial cells, fibroblasts, and glial cells) (9). PTX-3 is stimulated and secreted after proinflammatory stimuli (10). PTX-3 is an acute-phase biomarker in humans and increases rapidly in blood during inflammation (6,7). Although the diagnostic role and prognostic significance of pleural fluid PTX-3 levels were stressed in two former studies, these points deserve further clarification (11,12).

In this study we aimed to determine the clinical significance and diagnostic role of serum and pleural fluid PTX-3 levels in patients with pleural effusion secondary to various different etiologic conditions.

## 2. Materials and methods

### 2.1. Subjects

This prospective study enrolled all consecutive patients from two tertiary chest disease clinics who underwent diagnostic or therapeutic thoracentesis between January 2012 and November 2015. Thoracentesis and laboratory tests were conducted by the authors at their clinics. The samples taken for PTX-3 evaluation were centrifuged and stored at  $-80^{\circ}\text{C}$  in two clinics until the day of operation. PTX-3 measurement was performed in the biochemistry laboratory of Ankara University. Tests other than PTX-3 measurement were performed immediately after thoracentesis. This study included patients with pleural effusion of transudate character, malignant pleural effusion (MPE), parapneumonic effusion (PPE), and tuberculosis-associated pleural effusion (TPE).

The inclusion criteria included an age of over 18 years and known pleural effusion etiology. The exclusion criteria included pleural effusion of unknown etiology, i.e. patients whose disease could not be definitively diagnosed on the basis of biochemical tests, microbiologic analyses, cytology, and pathology examination of pleural biopsy specimens.

### 2.2. Diagnostic criteria

Pleural effusion was diagnosed using chest X-rays, computerized tomography (CT) of the chest, and thoracic ultrasonography. Pleural effusion samples were aspirated using a fine needle (21 G) and a 50-mL syringe, and blood samples were drawn simultaneously. The fluid sample was divided and placed in sterile tubes. Glucose, albumin, total protein, lactate dehydrogenase (LDH), and adenosine

deaminase (ADA) levels were measured and recorded in simultaneously taken pleural effusion and serum samples. The macroscopic features of the pleural effusion and its pH level, Gram staining, bacterial culture, and cytology results were recorded. Serum CRP level was also measured.

Pleural fluid secondary to heart failure was diagnosed in patients with bilateral pleural effusion on the basis of typical heart failure symptoms (dyspnea, ankle edema, fatigue)  $\pm$  concomitant signs (increased jugular venous pressure, pulmonary rales, and peripheral edema) and a left ventricular ejection fraction of less than 50% in transthoracic echocardiography (13).

Exudative fluids were defined and confirmed according to Light's criteria (14). PPE was defined as the acute onset of symptoms suggestive of a lower respiratory tract infection and a new infiltrate on chest X-ray (14). PPE was analyzed in three groups: empyema, noncomplicated PPE, and complicated PPE. Complicated PPE was described as acidic pleural fluid (pH  $<7.20$ ) and suspected infection or positive Gram stain or positive bacteria culture, and empyema was described as complicated PPE with pus view in a fluid (15). A TPE was identified if mycobacterial cultures of pleural effusion were positive or granulomatous inflammation was detected on pleural biopsy samples. A pleural effusion was classified as malignant if malignant cells were detected in pleural effusion or pleural biopsy samples.

### 2.3. PTX-3 analysis

Venous blood samples and pleural fluid taken during the daytime were put into biochemistry tubes. The samples were then centrifuged at 1500 rpm for 15 min to separate the sera at room temperature. The samples were then divided into aliquots using a sterile plastic transfer pipette, which were put into sterile plastic containers and stored at  $-80^{\circ}\text{C}$  until required for biochemical analysis. When an adequate number of samples was collected, all stored samples were transferred to the laboratory and simultaneously thawed. According to the manufacturer's instructions, serum and pleural fluid PTX-3 measurement was performed using an enzyme-linked immunosorbent assay (ELISA) kit (Quantikine ELISA-Human Pentraxin 3; R&D Systems Europe, Ltd., UK) by an operator who was blinded to each individual's lung disease or treatment group. All samples were studied twice.

### 2.4. Statistical evaluation

The descriptive statistics for categorical variables are expressed as frequency (percentage) and median (range) or mean  $\pm$  standard deviation for continuous variables, depending on the normality of distribution. Depending on the normality of data distribution, independent group comparisons were performed with ANOVA or Kruskal-Wallis tests. The chi-square test and Fisher's exact test were used for categorical variables. The correlation between pleural effusion PTX-3 level and other pleural fluid

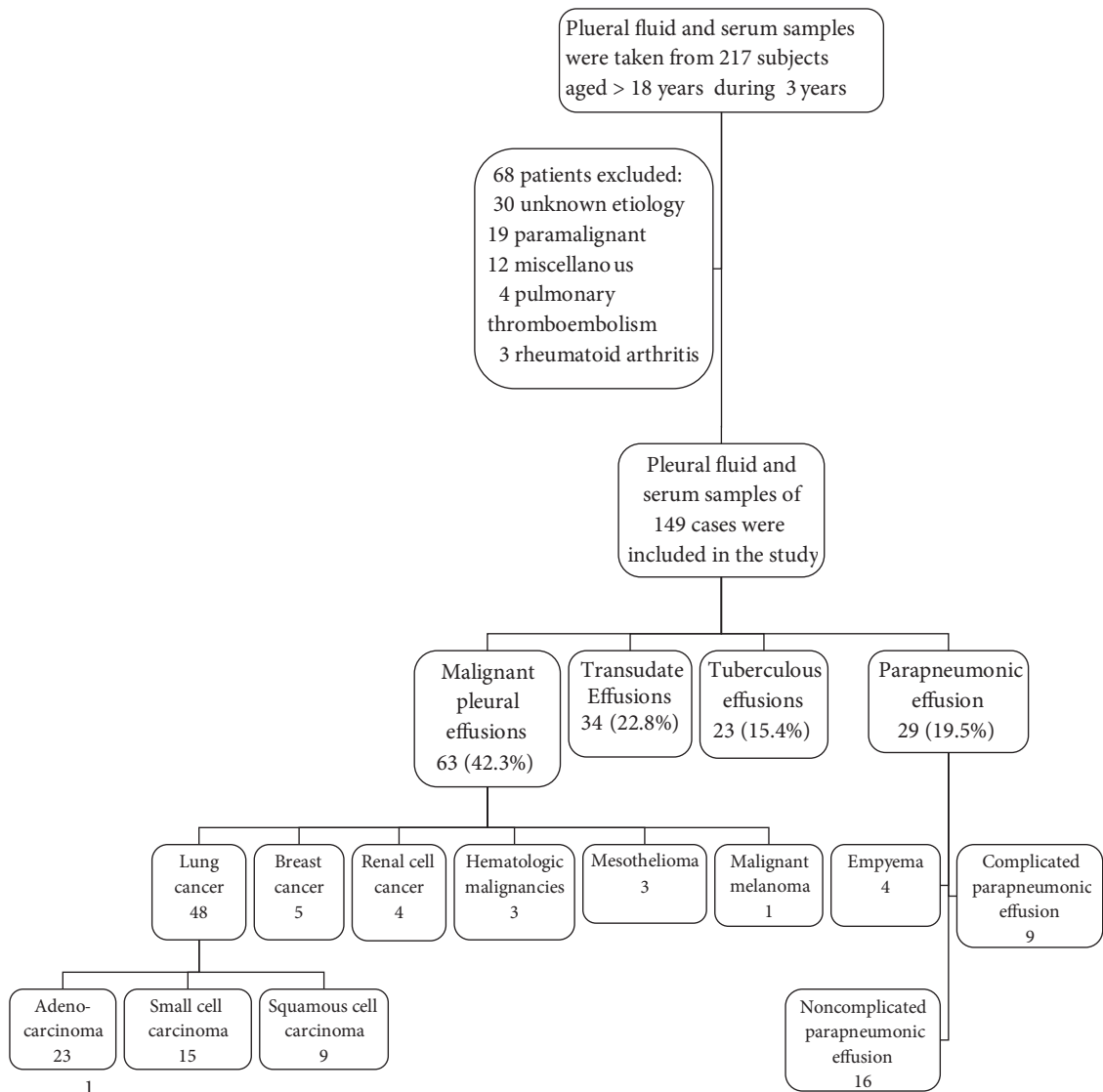
markers was measured using Spearman's rank correlation. A receiver-operating characteristic test was used to determine optimal cut-off values for pleural effusion PTX-3 to predict PPE. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios (LRs) with their respective 95% confidence intervals (CIs) were calculated according to standard formulae.  $P < 0.05$  was considered statistically significant. SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

**3. Results**

During the 3-year study period, a total of 217 patients underwent thoracentesis and their pleural effusion samples were analyzed. Sixty-eight patients were excluded from

the study: 30 patients with pleural effusion were excluded because of having unknown pleural effusion etiology, 19 were included in the paramalignant fluid group due to absence of malignant cells in pleural effusion despite the patients having a malignancy, 12 cases were classified as 'miscellaneous' because they had more than one etiologic condition, 4 had pulmonary thromboembolism, and 3 patients with rheumatic arthritis had numbers too low to conduct statistical analyses (Figure 1).

The study group included 149 subjects (97 males and 52 females) with a mean age of  $66.67 \pm 11.47$  years. Of these, 34 (22.8%) had transudates due to heart failure, 29 (19.5%) had PPE, 63 (42.3%) had MPE, and 23 (15.4%) had TPE. Sixty-three patients with MPE had effusions secondary to lung cancer ( $n = 48$ ), breast cancer ( $n = 5$ ),



**Figure 1.** Flow chart of the study showing the inclusion and exclusion criteria.

renal cell cancer (n = 4), hematologic malignancies (n = 3), mesothelioma (n = 3), and malignant melanoma (n = 1). Primary lung tumors responsible for pleural effusion were adenocarcinoma (n = 23), small cell carcinoma (n = 15), and squamous cell carcinoma (n = 9).

Among the patients with PPE, 4 had empyema, 9 had complicated parapneumonic PE, and 16 had noncomplicated parapneumonic PE. Although there was no correlation between pleural fluid etiology and the patient age, sex, and body mass index (BMI), the rate of cumulative smoking history of patients with MPE was significantly higher than in the other exudative effusion groups (P = 0.03) (Table 1).

Table 2 shows the comparison of pleural effusion PTX-3, ADA, and serum PTX-3 and CRP levels between the different etiological groups of pleural effusion. There was a statistically significant but weak correlation between pleural effusion PTX-3 level and serum CRP level (r = 0.425, P < 0.01).

The median pleural effusion PTX-3 level of the whole study group was 4.8 ng/mL (range: 1.0–17.8 ng/mL) and the median PTX-3 level of the exudative fluid group was 5.4 ng/mL (range: 2.0–17.8 ng/mL). The PTX-3 level in exudative pleural effusion samples significantly differed by pleural effusion etiology (P < 0.01). The median pleural effusion PTX-3 was significantly higher in patients with PPE (11.2 ng/mL; range: 2–17.8 ng/mL) than MPE (4.7 ng/mL; range: 1.8–13.9 ng/mL) and TPE (3.1 ng/mL; range: 2.0–4.1 ng/mL) (Figure 2). Pleural effusion PTX-3 levels' diagnostic accuracy for identifying PPE was measured using area under the receiver-operating characteristic curve analysis (area under the curve of 0.88). At a cut-off point of 5.89 ng/mL, PTX-3 had the best discriminatory power for PPE versus other exudative effusions (sensitivity: 86.2%, specificity: 87.7%) (Figure 3). The negative predictive value of PTX-3 for PPE was found as 89%. There were no significant differences between the pleural effusion PTX-3 levels of empyema and complicated parapneumonic PE

cases and noncomplicated parapneumonic PE cases (13.4 ng/mL and 10.2 ng/mL, respectively; P > 0.05). Pleural effusion PTX-3 level was not significantly correlated with serum PTX-3 level. Serum PTX-3 level had no significant correlation to exudative pleural effusion etiology. The pleural effusion/serum ratios of PTX-3, protein, and LDH levels were also calculated. The exudative effusion group had a significantly different pleural effusion/serum PTX-3 ratio (P = 0.03), whereas no significant difference was found for the other parameters (Table 2).

**4. Discussion**

PTX-3 plays a key role in the early stages of inflammation (16–21). Based on this information, pleural effusion and serum PTX-3 levels were studied in pleural effusion of different etiologies. The pleural fluid PTX-3 level was higher in the whole exudative pleural fluid than the transudative fluid. An etiology-based comparison of the serum and pleural effusion PTX-3 levels revealed that the PTX-3 level was significantly higher in PPE compared with other exudative effusion groups. The results of our study were comparable with those of the other studies that investigated PTX-3 levels and correlations in exudative pleural effusions (11,12).

The present study showed that serum PTX-3 levels of exudative pleural effusion were not significantly different, with the exception of the PPE. There was a significant difference between serum CRP levels but no significant difference between serum PTX-3 levels. These results suggest that PTX-3 is an inflammatory acute-phase biomarker produced at the site of infection; different from CRP, it may be a better biomarker in pointing to local inflammation. CRP, rather than PTX-3, is primarily produced in the liver after stimulation of IL-6 and TNF-α. However, PTX-3 is produced by a variety of cells and tissues, especially dendritic cells and macrophages, in response to inflammatory cytokines (21–23). Higher levels of CRP in pleural fluid may simply reflect higher systemic

**Table 1.** Comparison of the general characteristics of the study population based on pleural effusion etiology.

	Transudate n = 34	Exudates n = 115			P
		MPE n = 63	PPE n = 29	TPE n = 23	
Age, years	71.4 ± 13.5	71.3 ± 10.7	66.2 ± 12.7	67.1 ± 7.2	NS
BMI, kg/m <sup>2</sup>	27.3 ± 4.5	24.4 ± 8.4	25.3 ± 10.3	23.1 ± 4.4	NS
Cumulative smoking, pack-years	12.3 ± 10.4	35.2 ± 20.3	25.4 ± 12.2	20.24 ± 10.8	0.03

Values are presented as mean ± SD.

MPE, Malignant pleural effusion; PPE, parapneumonic pleural effusion; TPE, tuberculous pleural effusion.

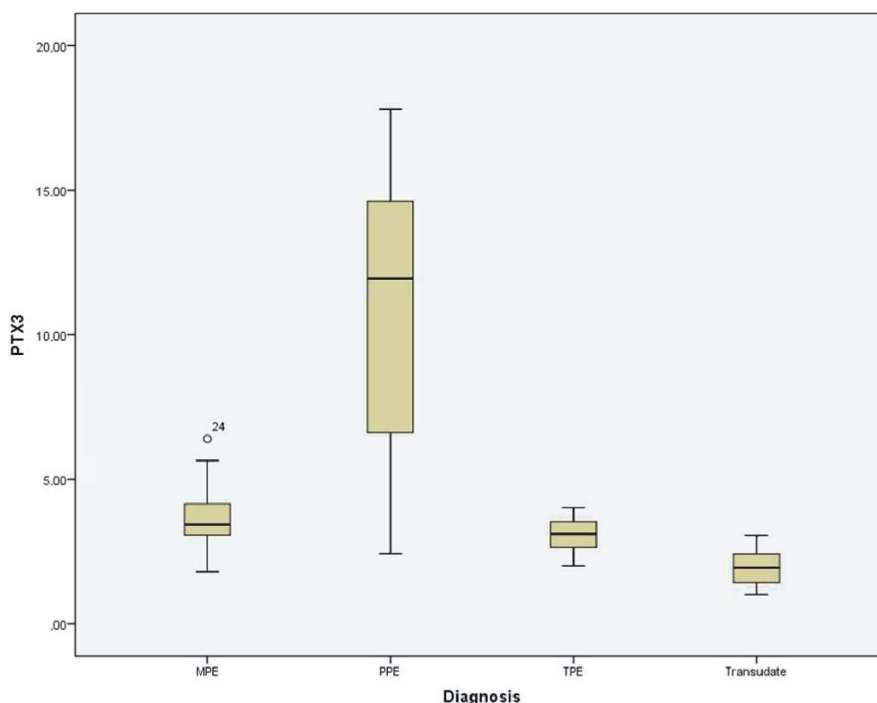
**Table 2.** Comparison of serum and pleural fluid findings based on pleural fluid etiology.

	Transudate n = 34	Exudates n=115			P
		MPE n = 63	PPE n = 29	TPE n = 23	
Pleural effusion PTX-3 level, ng/mL	1.9 (1.01–3.06)	4.7 (1.8–13.9)	11.2 (2.0–17.8)	3.1 (2.0–4.1)	< 0.01
Serum PTX-3 level, ng/mL	2.7 (1.1–4.65)	3.2 (1.13–5.6)	4.3 (1.5–8.3)	3.5 (1.3–6.3)	NS
CRP, mg/L	5.3 ± 2.2	18.6 ± 11.3	75.6 ± 34.2	62.4 ± 51.2	< 0.01
ADA (PE), IU/L	10.4 ± 0.5	28.2 ± 6.6	20.3 ± 4.7	45.6 ± 7.3	0.04
Pleural effusion/serum rates					
PTX-3 rate	1.2 (0.3–1.5)	2.9 (0.6–3.5)	3.9 (0.2–4.6)	2.3 (0.3–1.6)	0.03
Protein rate	0.3 (0.2–0.5)	0.7 (0.5–1.0)	0.7 (0.6–1.1)	0.9 (0.5–1.3)	NS
LDH rate	0.4 (0.3–0.6)	0.8 (0.6–1.1)	0.9 (0.5–1.0)	0.8 (0.6–1.2)	NS

Values are presented as median (range) or mean ± SD.

PTX-3, Pentraxin-3; MPE, malignant pleural effusion; PPE, parapneumonic pleural effusion; TPE, tuberculous pleural effusion; CRP, C-reactive protein; LDH, lactate dehydrogenase; ADA, adenosine deaminase; PTX-3 rate, pleural effusion PTX-3 level/serum PTX-3 level; protein rate, pleural effusion protein level/serum protein level; LDH rate, pleural effusion LDH level/serum LDH level.

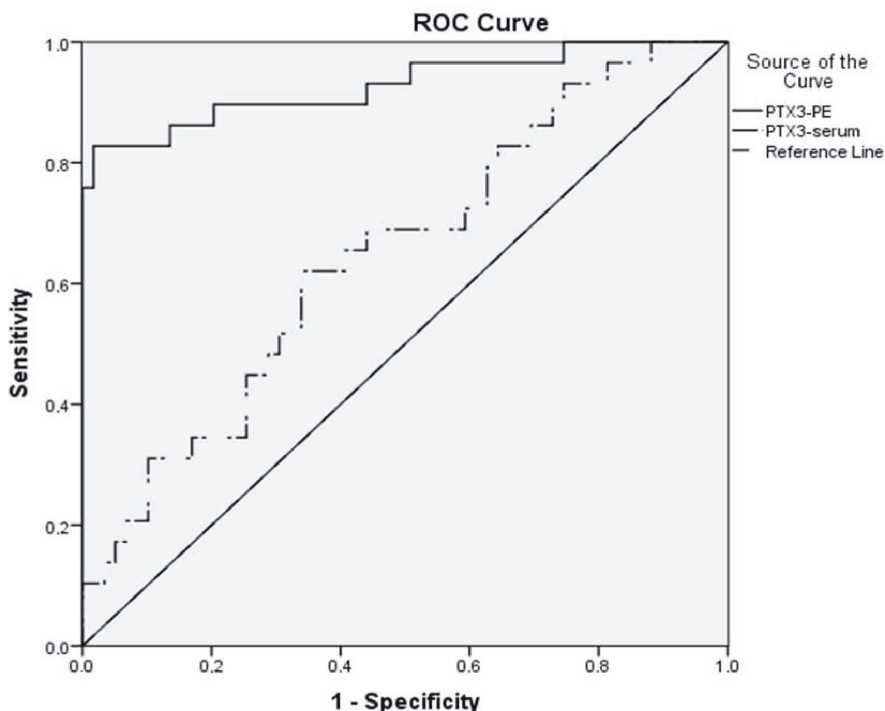
P-value shows difference between exudative effusions.



**Figure 2.** Box-plot graphics showing pentraxin-3 (PTX-3) concentrations in pleural fluids associated with different etiologies (MPE, malignant pleural effusions; PPE, parapneumonic effusions; TPE, tuberculous pleural effusions).

levels because CRP is primarily produced in the liver and may arrive in the pleural space from plasma diffusion (24). This may suggest that CRP is unlikely to reflect local inflammation, but rather the spread of systemic

inflammation (25). Another reason why PTX-3 may be a better indicator of local inflammation is the fact that lung epithelial cells, endothelial cells, and leukocytes are important sources of PTX-3 production when stimulated



**Figure 3.** The receiver-operating characteristics (ROC) curves drawn to differentiate pleural effusion and serum pentraxin-3 (PTX-3) concentrations of the parapneumonic effusion (PPE) group from other etiologies of exudative pleural fluid.

(20,21). The level of PTX-3 was elevated in patients with acute lung injury and acute respiratory distress syndrome (22).

We found no significant differences between the MPE, TPE, and PPE groups with regard to pleural effusion protein, glucose, and LDH levels. Moreover, the pleural effusion to serum protein and LDH ratios, which are components of Light's criteria, were not different among the exudative effusion groups, whereas the PTX-3 ratio was significantly greater in the PPE group. This suggests that the PTX-3 effusion/serum ratio may be of value in differential diagnosis, and other biochemical tests have no role in the differential diagnosis of exudative effusions.

Several studies suggested that PTX-3 was a promising biomarker for acute inflammation processes (16,18,19,21). Alveolar PTX-3 was an early marker of microbiologically confirmed pneumonia with better diagnostic accuracy than other biomarkers. Mauri et al. reported that PTX-3 levels in BAL fluid might have a superior diagnostic accuracy for pneumonia than other current biomarkers and clinical markers in critically ill intubated patients (23).

In experimental pneumonia, PTX-3 has been shown to identify various microorganisms (i.e. bacteria, viruses, and fungi) and to improve their clearance, primarily by control

of neutrophil recruitment (20). Serum PTX-3 levels correlate with clinical severity of many infectious diseases in humans (24). For example, serum PTX-3 is raised in the severe forms of community-acquired and ventilator-associated pneumonia (25,26). PTX-3 measurement promotes discrimination of PPE from other exudative effusions (24).

There are some limitations of this study. First, its modest sample size prevented us from performing more precise statistical analyses and evaluating the subgroups of MPE and PPE groups. No specific test was used to assess the correlation between PTX-3 level and disease severity. Testing for other inflammatory markers and making statistical comparisons might have strengthened our results.

In conclusion, pentraxin-3 could be a favorable acute-phase inflammatory mediator to differentiate PPE from other causes of pleural fluids. Pentraxin-3 is a promising biomarker involved in the local recognition of inflammation. In PPE, an increased pleural fluid PTX-3 level without a significant increase in serum PTX-3 level may reflect a more severe local inflammation than those occurring in MPE or TPE.

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