# Thrombin-Antithrombin III Complex, Proinflammatory Cytokines, and Fibrinolytic Indices for Assessing the Severity of Inflammation in Pleural Effusions

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**Abstract.** This study investigated coagulation-related variables, proinflammatory cytokines, and fibrinolytic indices to assess the severity of inflammation in patients with pleural effusions. Tuberculous pleural fluids revealed significantly higher concentrations of tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and plasminogen activator inhibitor type I (PAI-1) than did malignant and pneumonic pleural fluids. Among the coagulation-related variables, thrombin-antithrombin III complex (TAT) exhibited the largest difference in mean values between pleural fluids and blood samples (125.4 ± 45.1 vs 14.3 ± 20.3 ng/ml, $p < 0.05$). Inflammatory parameters were more closely associated with TAT than tissue type plasminogen activator (tPA), PAI-1, and D-dimers. TAT levels in the severe inflammation group (153.8 ± 45.6 ng/ml) were significantly above those in the mild inflammation group (105.6 ± 38.5 ng/ml, $p < 0.05$); however, no significant differences were observed in PAI-1 and D-dimers levels between the two groups. In conclusion, TNF-$\alpha$ and PAI-1 are important indicators in patients with tuberculous pleural effusions, and measurement of TAT is useful for assessing the severity of inflammation in pleural fluids.

## Introduction

Pleural effusion is a common complication of a variety of diseases. Pleural effusion is a result of disruption in pleural homeostasis and the subsequent occurence of increased pleural permeability. The coagulation system and proinflammatory cytokines contribute to the inflammatory process of pleural diseases. Fibrin deposition is a characteristic feature of pleural inflammation [1].

Pleural injury leads to the activation of parallel pathways of coagulation and fibrinolysis. An imbalance between procoagulant and fibrinolytic activities is responsible for pleural fibrin deposition [2]. Fibrin turnover in the pleural space is greatly affected by the fibrinolytic activity of plasmin. Production of plasmin depends on the interaction of plasminogen activators (PA) and plasminogen activator inhibitors (PAI) [3,4].

Most studies have focused on the diagnosis of pleural effusions. This study investigated the relationships between inflammatory parameters and several indicators, including coagulation-related variables, cytokines, and fibrinolytic indices, to find which indicators accurately reflect the severity of inflammation in patients with pleural effusions. This study also investigated the differences in biological markers among tuberculous, malignant, and pneumonic effusions.

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## Materials and Methods

Stored pleural fluid samples from 94 patients with pleural effusions (61 males and 33 females, median age 51 yr, range 28-75 yr) were investigated. Coagulation, fibrinolytic indices, and inflammatory parameters were measured. Patient selection was based on the following scheme: (a) patients with new onset of pleural effusion, (b) exudative pleural fluids, (c) samples collected prior to treatment, and (d) pleural fluids harvested simultaneously with blood specimens. The study was approved by the Institutional Review Board of Inha University Hospital, and informed consent was obtained from all subjects.

Patients with pulmonary tuberculosis (n = 49), primary lung cancer (n = 28), and bacterial pneumonia (n = 17) were enrolled. Diagnosis was determined by biopsy, cytology, culture, biochemical data, and radiographic findings. Pleural exudates were established by the criteria of Light et al [5].

Subjects with a past history of pleural inflammation (n = 4) and liver diseases (n = 2) were excluded from the study. Patients with lung abscess, empyema, and bronchiectasis were also excluded (n = 5). When several thoracenteses were performed on a single patient, only the results of the first tap were evaluated to avoid duplication of patients.

Pleural fluids (30 ml) were obtained using a standard thoracentesis technique within 24 hr after hospitalization, and venous blood (7 ml) was drawn into evacuated tubes. Pleural fluid and blood samples were immersed into ice and immediately centrifuged at 1,500 x g for 15 min. Aliquots of supernatants were stored at -80°C until further analysis.

Several parameters were measured: procoagulant parameters (TAT and fibrinogen), fibrinolytic indices (D-dimers, tissue type PA [tPA], and PAI type I [PAI-1]), inflammatory parameters (high-sensitivity C-reactive protein [hsCRP], lactate dehydrogenase [LD], glucose, total protein, pH, neutrophils, and mesothelial cells), and proinflammatory cytokines (tumor necrosis factor-α (TNF-α)].

Proinflammatory cytokines and fibrinolytic indices were measured using commercially available enzyme immunoassay kits: tPA and PAI-1 (Diagnostica Stago, Asnieres sur Seine, France), TNF-α (R & D System, Minneapolis, MN), and TAT (Enzygnost TAT micro, Dade Behring, Marburg, Germany) [2,6]. D-dimers levels were assayed by an immuno-turbidimetric method using Sta-Liatest D-Di (Diagnostica Stago) [7,8].

Total leukocytes and their differentials in blood were measured with an automatic counter (ADVIA120, Siemens, Forchheim, Germany), and inflammatory cells in pleural fluids were calculated by a manual method after the slides were stained. Total protein, glucose, LD, and hsCRP levels were tested using a chemical analyzer (Hitachi 7600, Hitachi, Tokyo, Japan). The pH of pleural fluids was determined using a digital pH meter (pH 310, Oakton Instruments, Vernon Hills, IL), calibrated with pH 7 and pH 4 buffer solutions.

Patients were classified into 3 groups according to the etiology of pleural effusions: malignant, tuberculous, and pneumonic groups. Subject populations were also categorized into 2 groups based on the biochemical aspects of the pleural effusions, as described previously [6]: severe group (n = 30; LD >1,000 U/L, glucose <40 mg/dl, pH <7.0) and mild group (n = 64; LD ≤1,000 U/L, glucose ≥40 mg/dl, pH ≥7.0).

Data analysis was conducted using non-parametric tests. Specific comparisons of variables between two groups were performed by the Mann-Whitney U test, and paired data were computed by a Wilcoxon signed-ranked test. To compare the data among three independent groups, Kruskal Wallis one-way analysis of variance was used. Correlations between variables were determined by the Spearman test. All p values <0.05 were considered statistically significant.

## Results

Mean values of coagulation, fibrinolytic indices, and inflammatory parameters are listed in Table 1. Most of the parameters showed significantly higher values in pleural fluids than blood samples. TAT concentrations in pleural fluids were 8.7-fold higher than those in blood (125.4 ± 45.1 vs 14.3 ± 20.3 ng/ml, p <0.05), whereas the ratios of pleural fluids to blood samples in D-dimers, tPA, and PAI-1 were 2.2, 3.1, and 5.0, respectively.

In pleural fluids, the PAI-1 activity was 4.5 times above the tPA activity (229.5 ± 204.2 μg/L vs 51.3 ± 68.2 ng/ml); however, in blood the PAI-1 activity was 2.7 times as high as the tPA activity (45.1 ± 83.2 μg/L vs 16.5 ± 17.2 ng/ml). Mean value of TNF-α was 35.2 ± 92.1 pg/ml in pleural fluids, which was 6.2-fold higher than that in blood (5.6 ± 7.4 pg/ml) (Table 1).

Pleural fluid hsCRP, neutrophil counts, and total protein concentrations were significantly correlated with TAT (r = 0.31, 0.23, and 0.33; p <0.05, respectively) but were not correlated with tPA, D-dimers, and PAI-1. Pleural fluid D-dimers and tPA concentrations revealed positive correlations with only LD activity (r = 0.23, p <0.05; r = 0.21, p <0.05, respectively). PAI-1 had significant relationships with mesothelial cell counts (r = 0.28, p <0.05) and glucose levels (r = -0.22, p <0.05) in pleural fluids (Table 2).

As shown in Table 3, pleural fluid TAT levels in the severe inflammation group were 153.8 ± 45.6 ng/ml, which exceeded the values in the mild inflammation group (105.6 ± 38.5 ng/ml, p <0.05). However, no significant differences were observed in the concentrations of tPA, PAI-1, and D-dimers between the two groups.

Pleural fluid and blood levels of parameters according to the etiology of pleural effusions are

Table 1. Blood and pleural fluid levels of hemostatic or inflammatory parameters in patients with pleural effusions (mean ± SD; median; range).

| Parameters | Blood samples[a] (n = 94) | Pleural fluids (n = 94) | Pleural fluid/blood ratio (95% confidence intervals) |
|---|---|---|---|
| Proinflammatory cytokine | | | |
| Tumor necrosis factor-α (pg/ml) | 5.6 ± 7.4 (4.7); 6.2-17.3 | 35.2 ± 92.1 (28.5);[b] 7.4-210.5 | 6.2 (1.6-9.3) |
| Procoagulant activity | | | |
| Thrombin-antithrombin III complex (ng/ml) | 14.3 ± 20.3 (12.8); 2.9-58.2 | 125.4 ± 45.1 (120.9);[b] 39.2-227.8 | 8.7 (4.7-14.5) |
| Fibrinogen (mg/dl) | 491.7 ± 189.4 (503); 91-935 | 80.6 ± 41.2 (59);[b] 23-246 | 0.2 (0.1-0.5) |
| Fibrinolytic indices | | | |
| D-dimers (μg/ml) | 4.3 ± 3.1 (3.7); 0.9-12.6 | 8.7 ± 3.2 (8.2);[b] 1.7-14.8 | 2.2 (1.2-4.3) |
| Tissue type plasminogen activator (ng/ml) | 16.5 ± 17.2 (7.2); 2.1-30.6 | 51.3 ± 68.2 (25.4);[b] 3.2-109.4 | 3.1 (2.4-7.9) |
| Plasminogen activator inhibitor type I (μg/L) | 45.1 ± 83.2 (43.0); 10.9-490.5 | 229.5 ± 204.2 (194.3);[b] 12.6-850.2 | 5.0 (1.2-6.7) |
| Inflammatory parameters | | | |
| High sensitivity C-reactive protein (mg/dl) | 1.24 ± 2.79 (1.2); 0.6-5.9 | 3.21 ± 3.14 (2.4);[b] 1.2-14.3 | 2.5 (0.7-8.3) |
| Neutrophils (/μl) | 6,413.6 ± 3,825.4 (5,709); 2,128-19,714 | 520.8 ± 427.3 (405);[b] 205-2,719 | 0.1 (0.09-0.17) |
| Mesothelial cells (/μl) | NA | 249.3 ± 475.6 (169); 17-2,407 | NA |
| Lactate dehydrogenase (U/L) | 386.1 ± 118.9 (365); 229-584 | 1,640.8 ± 2,075.2 (920);[b] 243-5,618 | 4.3 (1.0-9.5) |
| Glucose (mg/dl) | 108.3 ± 35.1 (105); 75-282 | 78.2 ± 39.2 (81);[b] 29-132 | 0.7 (0.3-1.6) |
| Total protein (g/dl) | 6.1 ± 0.9 (6.7); 4.6-7.9 | 4.5 ± 1.3 (4.3);[b] 0.7-6.1 | 0.7 (0.2-2.4) |
| pH | NA | 7.31 ± 0.28 (7.4); 5.9-7.5 | NA |

NA = not assayed.
[a]Specification of blood samples: plasma (thrombin-antithrombin III complex, fibrinogen, D-dimers, tissue type plasminogen activator, plasminogen activator inhibitor type I); serum (tumor necrosis factor−α, high sensitivity C-reactive protein, lactate dehydrogenase, glucose, total protein); and blood (neutrophils). [b]Statistically significant ($p < 0.05$) vs blood samples, computed by Wilcoxon signed-ranked test.

Table 2. Correlation coefficients of coagulation and fibrinolytic indices versus inflammatory parameters in pleural effusions.

| Parameters in pleural fluids | Correlation coefficients (r) with inflammatory parameters (pleural fluids; n = 94) | | | |
|---|---|---|---|---|
| | Tissue type plasminogen activator (ng/ml) | Thrombin-antithrombin II complex (ng/ml) | D-dimers (μg/ml) | Plasminogen activator inhibitor type I (μg/L) |
| High sensitivity C-reactive protein (mg/dl) | 0.12 | 0.31[a] | 0.13 | 0.12 |
| Neutrophils (/μl) | 0.10 | 0.23[a] | 0.09 | 0.10 |
| Mesothelial cells (/μl) | - 0.11 | 0.30[a] | - 0.11 | 0.28[a] |
| Lactate dehydrogenase (U/L) | 0.21[a] | 0.24[a] | 0.23[a] | 0.11 |
| Glucose (mg/dl) | 0.09 | - 0.10 | 0.10 | - 0.22[a] |
| Total protein (g/dl) | - 0.13 | 0.33[a] | - 0.12 | 0.13 |
| pH | 0.09 | 0.11 | 0.03 | - 0.08 |

[a] Significant ($p < 0.05$), by Spearman correlation test.

Table 3. Coagulation and fibrinolytic indices in relation to the severity of inflammation in pleural effusions.

| Parameters in pleural fluids | Mild group (n = 64) | Severe group (n = 30) |
|---|---|---|
| **Inflammatory parameters** | | |
| Lactate dehydrogenase (U/L) | 573.9 ± 214.2 (645); 243-975 | 2,709.5 ± 1,813.2 (1,820);a 1,014-5,618 |
| Glucose (mg/dl) | 87.4 ± 38.6 (85); 52-132 | 36.4 ± 5.9 (38);a 29-38 |
| pH | 7.37 ± 0.29 (7.4); 7.2-7.5 | 6.75 ± 0.31 (6.5);a 5.9-6.8 |
| **Coagulation and fibrinolytic indices** | | |
| Tissue type plasminogen activator (ng/ml) | 43.1 ± 56.2 (23.8); 3.2-85.1 | 60.3 ± 64.2 (29.5); 14.5-109.4 |
| Plasminogen activator inhibitor type I (μg/L) | 207.3 ± 152.7 (190.3); 12.6-587.2 | 268.0 ± 261.4 (214.3); 24.9-850.2 |
| Thrombin-antithrombin III complex (ng/ml) | 105.6 ± 38.5 (109.7); 39.2-118.5 | 153.8 ± 45.6 (162.9);a 84.1-227.8 |
| D-dimers (μg/ml) | 8.2 ± 2.5 (8.9); 3.5-14.8 | 7.4 ± 2.3 (7.6); 1.7-9.0 |

Data are expressed as mean ± SD (median) and range.  [a] $p < 0.05$ vs mild group, computed by Mann-Whitney U test.

Table 4. Pleural fluid and blood levels of proinflammatory cytokines, TAT, hsCRP, and fibrinolytic indices according to effusion etiology.

| Parameters | Malignancy  (n = 28) | Tuberculosis (n = 49) | Pneumonia (n = 17) |
|---|---|---|---|
| **Pleural fluids** | | | |
| Tumor necrosis factor-α (pg/ml) | 28.3 ± 36.4 (30.5); 7.4-87.3 | 51.7 ± 47.6 (53.1);a 16.9-210.5 | 34.9 ± 35.2 (32.8); 14.1-120.7 |
| Thrombin-antithrombin III complex (ng/ml) | 109.6 ± 41.7 (112.6); 43.1-170.5 | 138.4 ± 43.9 (141.2); 39.2-227.8 | 121.5 ± 48.3 (109.3) 47.9-162.1 |
| D-dimers (μg/ml) | 9.2 ± 3.7 (9.1); 1.7-10.6 | 8.4 ± 3.2 (8.0); 3.5-12.3 | 8.1 ± 3.5 (8.5); 2.1-14.8 |
| Tissue type plasminogen activator (ng/ml) | 62.1 ± 42.7 (65.3); 4.5-109.4 | 46.7 ± 51.3 (48.1); 3.2-94.2 | 54.1 ± 60.1 (50.6); 6.8-83.6 |
| Plasminogen activator inhibitor type I (μg/L) | 176.2 ± 194.1 (159.4); 12.6-471.5 | 349.2 ± 205.6 (351.2);a 39.1-850.2 | 145.1 ± 192.8 (141.7); 20.7-541.0 |
| High sensitivity C-reactive protein (mg/dl) | 2.81 ± 2.59 (2.5); 1.4-8.6 | 3.19 ± 2.61 (2.7); 1.2-14.3 | 3.52 ± 2.84 (3.1); 1.7-9.5 |
| **Blood samples** | | | |
| Tumor necrosis factor-α (pg/ml) | 4.1 ± 5.9 (3.7); 7.3-15.2 | 6.8 ± 6.4 (6.5); 6.2-17.3 | 5.9 ± 5.3 (5.1); 8.1-14.6 |
| Thrombin-antithrombin III complex (ng/ml) | 12.0 ± 16.9 (12.8); 5.3-40.2 | 11.3 ± 18.5 (10.9); 2.9-49.1 | 23.9 ± 19.2 (29.4);a 8.4-58.2 |
| D-dimers (μg/ml) | 3.5 ± 2.7 (3.4); 0.9-9.8 | 4.1 ± 2.9 (4.3); 1.2-10.3 | 4.8 ± 3.2 (4.5); 1.7-12.6 |
| Tissue type plasminogen activator (ng/ml) | 15.1 ± 13.9 (14.9); 2.1-25.4 | 18.3 ± 15.7 (19.7); 3.7-30.6 | 14.0 ± 12.6 (15.3); 4.9-27.1 |
| Plasminogen activator inhibitor type I (μg/L) | 37.1 ± 50.8 (35.6); 10.9-310.2 | 46.1 ± 57.6 (43.5); 15.6-490.5 | 54.3 ± 70.3 (55.9); 19.3-451.4 |
| High sensitivity C-reactive protein (mg/dl) | 1.04 ± 1.86 (1.1); 0.8-5.1 | 1.58 ± 1.92 (1.4); 0.9-4.3 | 1.17 ± 2.05 (1.2); 0.6-5.9 |

Data are expressed as mean ± SD (median) and range.  [a] $p < 0.05$, determined by Kruskal Wallis one-way analysis of variance.

summarized in Table 4. Pleural concentrations of TNF-α and PAI-1 in the tuberculous group averaged 51.7 ± 47.6 pg/ml and 349.2 ± 205.6 μg/L, which were significantly higher than those in the malignant and pneumonic groups (28.3 ± 36.4 pg/ml and 176.2 ± 194.1 μg/L; 34.9 ± 35.2 pg/ml and 145.1 ± 192.8 μg/L; p <0.05, respectively). In blood samples, TAT levels were significantly increased in the pneumonic group compared to the malignant and tuberculous groups (23.9 ± 19.2 ng/ml vs 12.0 ± 16.9 and 11.3 ± 18.5 ng/ml, p <0.05).

## Discussion

This study investigated differences between pleural fluid and blood levels of a variety of hemostatic and inflammatory parameters and also examined the relationships of several procoagulant and fibrinolytic indices vs a number of inflammatory markers. The results show that TAT has implications for evaluating the severity of inflammation in pleural effusions.

In our study, proinflammatory cytokine and fibrinolytic indices were significantly higher in pleural fluids than in blood. In particular, TAT showed a prominent difference in mean values between the two specimens. It appears that the high pleural fluid/blood ratio is attributable to active production of the variables in pleura, but not to passive diffusion by increased vascular permeability.

Pleural fluid TAT concentrations correlated with most inflammatory parameters, but the D-dimers, tPA, and PAI-1 correlated with only one or two profiles. Inflammatory parameters were more closely associated with TAT than D-dimers, tPA, and PAI-1. These results suggest that TAT has an important relationship to inflammatory parameters and that the relationship is more comprehensive in TAT than in fibrinolytic indices. Physiological balance in the coagulation system is maintained by natural anticoagulants, such as antithrombin III, protein C, and protein S. Antithrombin III plays a major role by joining itself to thrombin, thereby forming a TAT complex and blocking thrombin activity, which is responsible for pleural fibrin deposition [9]. These properties of TAT, which comprise pro-coagulation and coagulation-inhibition, may account for the extensive linkage of TAT to inflammatory parameters.

Idell et al [10] reported that fibrinolytic activity is markedly disturbed in inflammatory pleural diseases. In our study, the PAI-1/tPA ratio was significantly higher in pleural fluids than in blood samples, and the D-dimers levels were relatively low compared to tPA activity in pleural fluids. These results imply that anti-fibrinolytic activity is stronger than fibrinolytic activity in pleural fluids. Reduced D-dimers production seems to be due to the simultaneous activation of PAI-1 in parallel with tPA activity.

Mesothelium contains both procoagulant and fibrinolytic activities [11]. Secretion of PAI-1 by mesothelial cells is associated with proinflammatory cytokines, particularly TNF-α [12]. In the current study, mesothelial cells significantly correlated with PAI-1 activity in pleural fluids, but not with tPA activity. Among the laboratory parameters analyzed in our study, TNF-α showed the second largest difference between pleural fluids and blood, although not as large as TAT. These results agree with the results of previous studies, which demonstrated that the release of TNF-α is markedly elevated in exudative pleural effusions [13,14]. On the basis of these findings, mesothelium may play a role in respect to anti-fibrinolytic activity during the inflammatory process, presumably in conjunction with elevated TNF-α.

Pleural fluid analysis provides an accurate estimation of the stage of pleural inflammation. Several biochemical indices, such as low pleural fluid pH (<7.0-7.2), low glucose levels (40-60 mg/dl), and high LD activity (>1,000 IU/L), have been used to differentiate complicated and uncomplicated forms of pleural effusion [15,16]. In this study, the severity of pleural inflammation was evaluated by strict criteria.

Pleural PAI-1 levels were slightly higher in the severe group than in the mild group, but the D-dimers levels were lower in the severe group than in the mild group, although the differences did not reach statistical significance. Among coagulation and fibrinolysis parameters, only TAT exhibited a significant difference between the two groups. Based on D-dimers production, it appears

that fibrinolysis is more intensely impaired and consequent fibrin deposition more easily occurs in the severe inflammation group. TAT may be more susceptible to the intensity of pleural inflammation than PAI-1, tPA, and D-dimers. These observations suggest that TAT can be considered as an indicator for the severity of pleural inflammation.

Daniil et al [17] found that CRP is a significant parameter in discriminating parapneumonic effusions from tuberculous and malignant effusions. Similarly, several investigators reported that pleural fluid CRP concentrations have a strongly positive predictive value for the diagnosis of parapneumonic effusions [18]. In contrast, in our study there were no significant differences in pleural fluid and blood levels of hsCRP among the tuberculous, malignant, and pneumonic effusions. These discrepancies may reflect the differences in clinical status and inflammatory intensity of subject populations in the various studies.

In this study, pleural fluid TNF-$\alpha$ and PAI-1 levels were significantly higher in the tuberculous group than in the malignant and pneumonic groups, but no significant differences were noted in tPA activity among the corresponding groups. It appears that a considerable difference exists in the regulation of biological parameters according to the etiology of pleural effusions. Considering the relationships between proinflammatory cytokines and intrapleural fibrinolysis [13,19], increased TNF-$\alpha$ in tuberculous effusions may lead to an imbalance of tPA and PAI-1, which subsequently induces fibrin deposition and the development of pleural thickening in patients with tuberculosis.

In conclusion, pleural fluid TAT levels exhibited significant changes in relation to the intensity of inflammation and correlated with most inflammatory parameters, suggesting that measurement of TAT is useful for assessing the severity of inflammation in pleural fluids. TNF-$\alpha$ and PAI-1 can be important indicators in patients with tuberculous pleural effusions.

## Acknowledgement

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