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Risk factors for disseminated intravascular coagulation in patients with lung cancer

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Keywords
Antithrombin; disseminated intravascular coagulation (DIC); lung cancer; squamous cell carcinoma; thrombomodulin.

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Abstract

Background: The mortality rate from disseminated intravascular coagulation (DIC) is higher in patients with lung cancer than in non-lung cancer patients. Moreover, the prevalence of DIC varies among the pathologic types of lung cancer. This study analyzed the relationship between coagulation factors and the pathologic types of lung cancer.

Methods: Twenty-six patients with progressive, inoperable stage IIB or higher lung cancer (20 men, 6 women; mean age 71 years; 11 Adeno, 10 squamous cell carcinoma, and 5 small cell carcinoma) and five healthy volunteers without respiratory disease (3 men, 2 women; mean age 72 years) were enrolled in the study. Blood samples were collected at lung cancer diagnosis, before treatment.

Results: White blood cell count, platelet count, serum C-reactive protein, fibrin/fibrinogen degradation products, fibrinogen, thrombin-antithrombin complex, and D-dimer levels differed significantly between lung cancer patients and the control group, but not among the pathologic types of lung cancer. Thrombomodulin levels were significantly higher in patients with Adeno and squamous cell carcinoma than in those with small cell carcinoma ($P < 0.05$ and $P < 0.01$, respectively). Antithrombin levels were significantly lower in patients with squamous cell carcinoma than in those with Adeno ($P < 0.05$).

Conclusion: Coagulation disorders may develop secondary to chronic inflammation in patients with progressive lung cancer. DIC in lung cancer may be attributed to changes in anticoagulation factors, such as thrombomodulin and antithrombin, but not in other coagulation factors.

Introduction

Lung cancer and other solid tumors are known risk factors for disseminated intravascular coagulation (DIC), and the mortality rate among lung cancer patients who develop DIC is very high.[1–3] Several publications have reported the relationship between better prognosis and increased thrombomodulin expression in lung cancer, and have suggested that thrombomodulin might inhibit the development of DIC.[4–6] However, the relationship between thrombomodulin and DIC in lung cancer patients has not been evaluated in previous studies.

In our previous study on the relationship between blood coagulation factors and DIC in patients with lung cancer, we found that serum C-reactive protein (CRP) level and prothrombin time-international normalized ratio (PT-INR) at the onset of DIC were lower in survivors than in non-survivors.[7] These two factors were more sensitive indices than the DIC score.[7,8] When the effects of thrombomodulin-α therapy for DIC in patients with lung cancer were analyzed, the required dose of thrombomodulin-α was higher in survivors than in non-survivors.[7] The percentage of patients with DIC was also significantly lower in squamous cell carcinoma (SCC; 1.57%) than in Adeno (4.23%) and small cell lung carcinoma (SCLC; 10.26%).[7] Other pathologic studies have shown that thrombomodulin expression was higher in SCC than in Adeno or other types of lung cancer.[4,9] These

studies suggested that the risk of DIC varies among the pathologic types of lung cancer.

According to the abovementioned studies, certain blood coagulation factors, such as PT-INR or thrombomodulin, may contribute to the development of DIC in patients with lung cancer and the expression of these coagulation factors may differ among pathologic types of lung cancer, leading to differences in the propensity to develop DIC. This study analyzed the relationship between blood coagulation factors and pathologic types of lung cancer, with the aim of preventing DIC in lung cancer.

Methods

Study design

This prospective study enrolled patients who were diagnosed with but had not yet received treatment for progressive inoperable stage IIB or higher lung cancer at our hospital between August 2015 and 2017. The study objective was explained to the patients and written informed consent was obtained upon disclosure of their diagnosis and stage. We also obtained written informed consent from healthy volunteers. The ethics committee of the Dokkyo Medical University Koshigaya Hospital (No. 1440) approved the study.

In addition to data on the baseline levels of blood coagulation factors, data on baseline white blood cell (WBC) count and serum CRP at the time of lung cancer diagnosis were obtained. The relationship between these blood factors and the pathologic types of lung cancer was analyzed.

Subjects

Subjects comprised 26 patients (20 men, 6 women; mean age, 71 ± 6.3 years) diagnosed with lung cancer according to the criteria specified by the National Comprehensive Cancer Network[10,11] and five healthy volunteers without respiratory disease and malignant tumors (3 men, 2 women; mean age, 72 ± 4 years) as controls (Table 1). The pathologic types of lung cancer were Adeno in 11, SCLC in 5, and SCC in 10 subjects. The stage of lung cancer was IIB in 2, IIIA in 8, IIIB in 5, and IV in 11 subjects.

Measurement of blood coagulation and fibrinolysis factors

Fibrin/fibrinogen degradation products (FDP) were measured by using latex immunoturbidimetric assay. Fibrinogen and prothrombin time (PT) were measured by using a blood coagulation procedure and PT-INR was calculated. Protein C activity and the level of activated factor VIII was measured using the automatic hemostasis analyzer ACL TOP (Instrumentation Laboratory, Bedford, MA, USA). Thrombomodulin and thrombin-antithrombin complex (TAT) were measured by enzyme immunoassay using the Emax Microplate Reader (Molecular Devices LLC, San Jose, CA, USA). Von Willebrand factor (vWF) antigen was measured by latex agglutination assay using the automatic analyzer JCA-BM 1650 (JEOL Ltd., Tokyo, Japan). Plasminogen was measured with the chromogenic synthetic substrate method by using the automatic analyzer JCA-BM 1650 (JEOL Ltd.). D-dimer was measured by latex immunoturbidimetric assay. Antithrombin was measured with the chromogenic synthetic substrate method. Tissue plasminogen activator and plasminogen activator inhibitor-1 (tPA/PAI-1) complex was measured with latex photometric immunoassay using the automatic analyzer, STACIA (Instrumentation Laboratory).

Table 1 Background patient characteristics

Characteristic	Patients (%)	Controls (%)
Subject	26	5
Mean age (years)	71.0 ± 6.3	72.0 ± 4.0
Male/female	20/6	3/2
Smoking		
Smoker	12 (46.2)	0 (0.0)
Ex-smoker	11 (42.3)	0 (0.0)
Never-smoker	3 (11.5)	5 (100)
Lung cancer group		
Adeno	11 (42.3)	
SCC	10 (38.5)	
SCLC	5 (19.2)	
Stage		
II B	2 (7.7)	
III A	8 (30.8)	
III B	5 (19.2)	
IV	11 (42.3)	

Adeno, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung carcinoma.

Statistical analysis

All statistical analyses were performed using Excel (Microsoft Corporation, Washington, DC, USA) and JMP (SAS Institute Inc., Cary, NC, USA) software. Differences between two independent samples were examined by the chi-square or Wilcoxon's signed-rank tests, as appropriate. Differences of $P < 0.05$ were considered statistically significant. No significant difference was shown as NS.

Results

Relationship between laboratory data and pathologic types of lung cancer

The background patient characteristics are shown in Table 1. Chi-square tests revealed no significant differences between the patients with lung cancer and healthy

controls, with the exception of smoking. WBC count and serum CRP level were analyzed in each of the pathologic type groups at the time of lung cancer diagnosis and staging and in the controls (Fig 1). No significant differences were noted among the four groups in terms of the WBC count (Adeno $7.30 \pm 1.43 \times 10^3/\mu L$; SCC $7.60 \pm 2.13 \times 10^3/\mu L$; SCLC $9.52 \pm 5.74 \times 10^3/\mu L$; controls $5.68 \pm 1.17 \times 10^3/\mu L$) (Fig 1a). However, the WBC count was significantly higher in all patients with lung cancer ($7.84 \pm 2.90 \times 10^3/\mu L$; $P < 0.05$) and non-small cell lung cancer (NSCLC) ($7.44 \pm 1.76 \times 10^3/\mu L$; $P < 0.05$) than in the control group.

The serum CRP level was significantly higher in patients with Adeno (2.21 ± 3.46 mg/dL; $P < 0.05$) and SCC (1.85 ± 1.87 mg/dL; $P < 0.05$) than in the control group (0.14 ± 0.19 mg/dL), but not when compared to patients with SCLC (1.00 ± 1.78 mg/dL, NS) (Fig 1b). The serum CRP level was significantly higher in all patients with lung cancer (1.84 ± 2.60 mg/dL; $P < 0.05$) and NSCLC (2.04 ± 2.76 mg/dL; $P < 0.05$) than in the control group.

Relationship between blood coagulation factors used in the disseminated intravascular coagulation score and pathologic types of lung cancer

Platelet count, FDP, fibrinogen, and PT-INR were determined for the pathologic type groups at the time of lung cancer diagnosis and staging and for the controls (Fig 2). The platelet count was significantly higher in patients with Adeno ($29.8 \pm 10.5 \times 10^4/\mu L$; $P < 0.05$) and SCC ($32.8 \pm 12.1 \times 10^4/\mu L$; $P < 0.05$) compared to the control group ($19.2 \pm 3.5 \times 10^4/\mu L$), but not in patients with SCLC ($29.1 \pm 15.3 \times 10^4/\mu L$, NS) (Fig 2a). The platelet count was significantly higher in all patients with lung cancer ($30.8 \pm 11.7 \times 10^4/\mu L$; $P < 0.05$) and NSCLC ($31.2 \pm 11.1 \times 10^4/\mu L$; $P < 0.05$) than in the control group.

The FDP level was significantly higher in patients with Adeno (10.3 ± 11.2 μg/mL; $P < 0.05$) and SCC (5.89 ± 5.54 μg/mL; $P < 0.05$) than in the control group (2.50 ± 0.51 μg/mL), but not when compared to patients with SCLC (4.72 ± 1.88 μg/mL, NS) (Fig 2b). The FDP level was significantly higher in all patients with lung cancer (7.55 ± 8.25 μg/mL; $P < 0.05$) and NSCLC (8.22 ± 9.05 μg/mL; $P < 0.05$) than in the control group.

The fibrinogen level was significantly higher in patients with Adeno (533 ± 173 mg/dL; $P < 0.05$) and SCC (521 ± 155 mg/dL; $P < 0.05$) than in the control group (314 ± 79 mg/dL), but not when compared to patients with SCLC (477 ± 150 mg/dL, NS) (Fig 2c). The fibrinogen level was significantly higher in all patients with lung cancer (518 ± 157 mg/dL; $P < 0.05$) and NSCLC (528 ± 160 mg/dL; $P < 0.05$) than in the control group.

The difference in PT-INR values was significant between patients with SCC and the control (1.03 ± 0.06 vs. 0.95 ± 0.06, respectively; $P < 0.05$), but not with the other groups (Adeno 0.98 ± 0.08, SCLC 1.00 ± 0.08) (Fig 2d). Moreover, there were no significant intergroup differences in the PT-INR values in all patients with lung cancer (1.00 ± 0.08) and NSCLC (1.00 ± 0.08).

Relationship of thrombomodulin and activated protein C with pathologic types of lung cancer

Thrombomodulin and activated protein C were determined for the pathologic type groups at the time of lung cancer diagnosis and staging and for the controls (Fig 3). Thrombomodulin levels were significantly higher in patients with Adeno (2.94 ± 0.53 FU/ml; $P < 0.05$), SCC (3.93 ± 2.80 FU/mL;

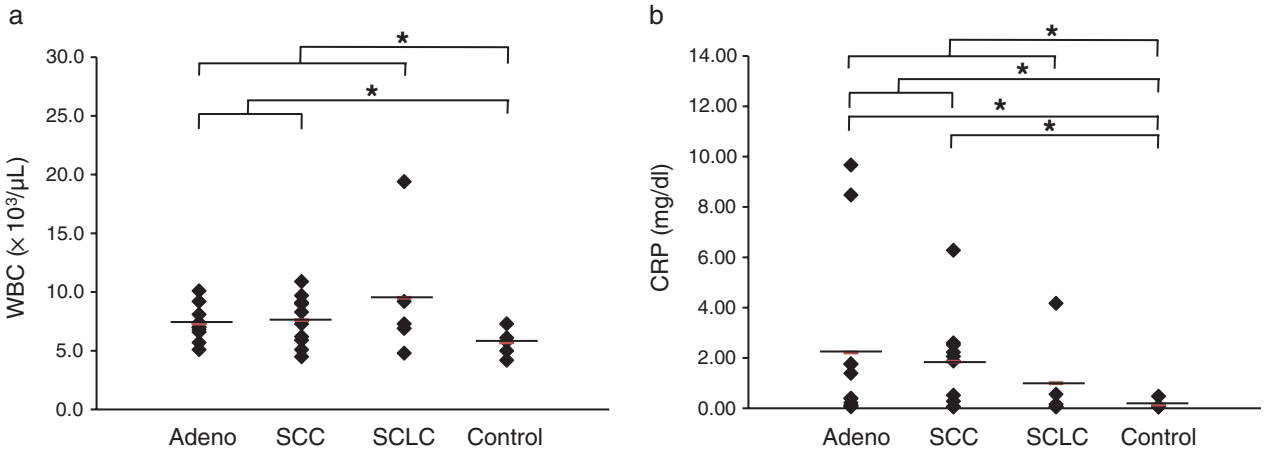

Figure 1 (**a**) White blood cell (WBC) count and (**b**) serum C reactive protein (CRP) level differ significantly between lung cancer patients and controls, but not among the pathologic types of lung cancer. *$P < 0.05$. Adeno, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung carcinoma.

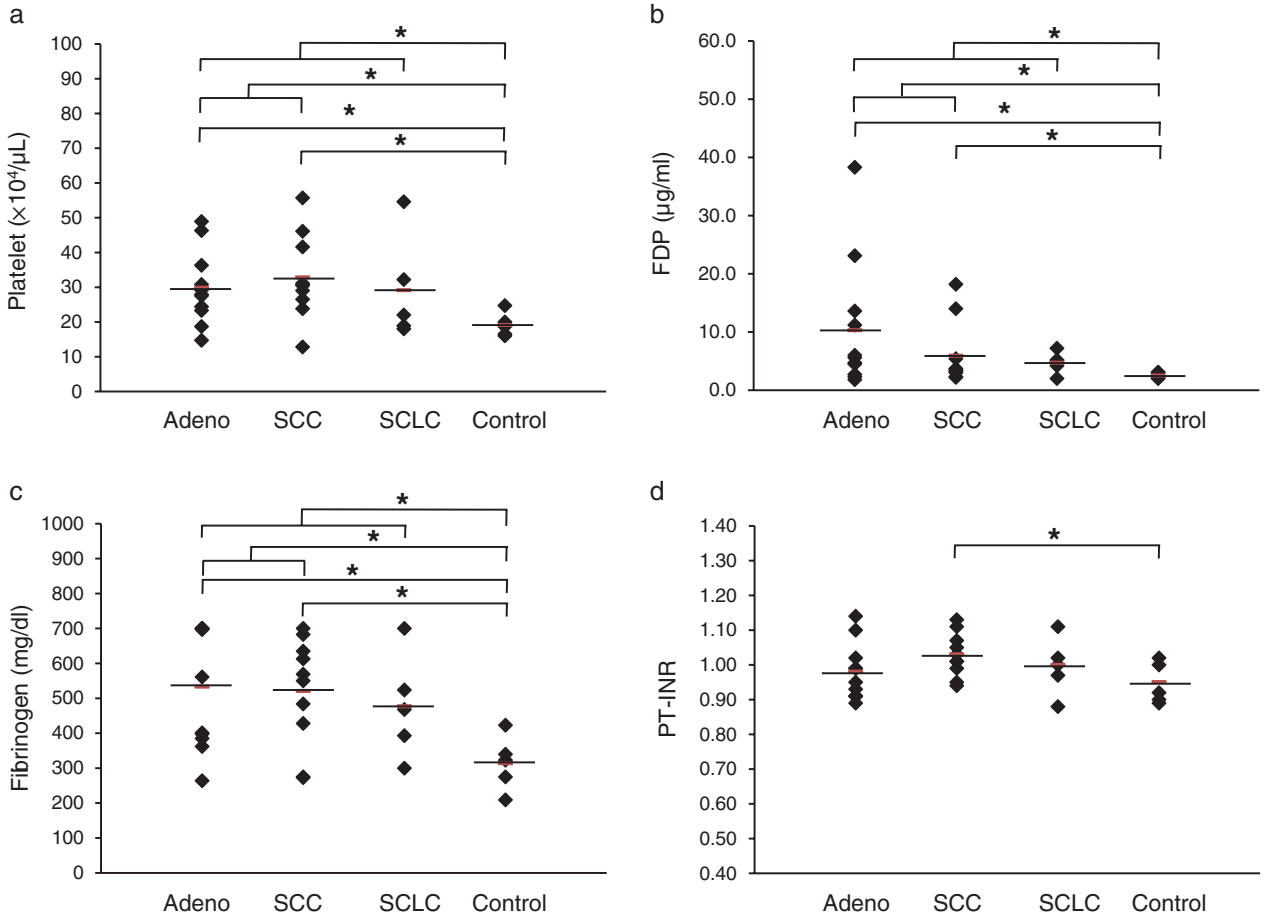

Figure 2 (**a**) Platelet count, (**b**) fibrin/fibrinogen degradation products (FDP), and (**c**) fibrinogen are significantly different between lung cancer patients and the control, but not among the pathologic types of lung cancer. (**d**) There were no significant differences in prothrombin time-international normalized ratio (PT-INR). *$P < 0.05$. Adeno, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung carcinoma.

$P < 0.01$), and NSCLC (3.41 ± 1.98 FU/mL; $P < 0.01$) than in those with SCLC (2.24 ± 0.21 FU/mL) (Fig 3a). The thrombomodulin level was significantly higher in patients with NSCLC compared to the control (2.30 ± 0.71 FU/mL; $P < 0.05$), but not when compared to all patients with lung cancer (3.18 ± 1.84 FU/mL, NS).

The were no significant intergroup differences in the level of activated protein C (Adeno 107.7 ± 25.7%, SCC 95.9 ± 22.4%, SCLC 99.2 ± 20.9%, and control, 108.4 ± 17.0%) or between all patients with lung cancer (101.5 ± 23.4%) and NSCLC (102.1 ± 24.4%) (Fig 3b).

Relationship of other blood coagulation factors as activated factor VIII, vWF antigen, and TAT with pathologic types of lung cancer

Those levels of activated factor VIII, vWF antigen, and TAT, are shown in Figure 2. There were no significant intergroup differences in activated factor VIII levels among patients with Adeno (129 ± 33%), SCC (115 ± 16%), SCLC (135 ± 50%), and in the control (116 ± 18%) or between all patients with lung cancer (125 ± 31%) and those with NSCLC (122 ± 26%) (Fig 4a).

There were no significant intergroup differences in the vWF antigen level among patients with Adeno (178 ± 54%), SCC (167 ± 70%), SCLC (202 ± 85%), and in the control (130 ± 33%) or between all patients with lung cancer (179 ± 65%) and those with NSCLC (173 ± 61%) (Fig 4b).

The TAT level was significantly higher in patients with lung cancer (Adeno 3.43 ± 1.77 ng/mL, $P < 0.05$; SCC 7.32 ± 6.78 ng/mL, $P < 0.05$; and SCLC 3.54 ± 0.90 ng/mL, $P < 0.05$) than in the control group (1.52 ± 0.43 ng/mL) (Fig 4c). The TAT level was also significantly higher in all patients with lung cancer (4.95 ± 4.65 ng/mL; $P < 0.01$) and in those with NSCLC (5.28 ± 5.12 ng/mL; $P < 0.05$) than in the control.

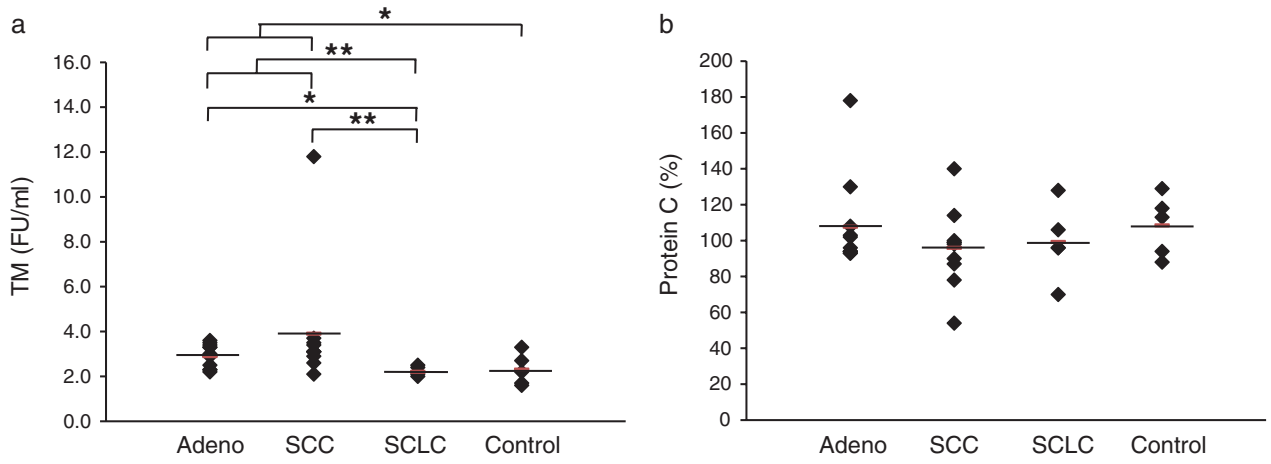

Figure 3 (**a**) Thrombomodulin (TM) levels are significantly higher in adenocarcinoma (Adeno) and squamous cell carcinoma (SCC) than in small cell lung carcinoma (SCLC). (**b**) No significant differences in activated protein C levels were noted among the pathologic types of lung cancer. *$P < 0.05$; **$P < 0.01$. Adeno, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung carcinoma.

Relationship between blood fibrinolysis factors and pathologic types of lung cancer

Those levels of plasminogen and D-dimer are shown in Figure 5. There were no significant intergroup differences in plasminogen level among patients with Adeno (114 ± 14%), SCC (112 ± 16%), SCLC (100 ± 23%), and the control (108 ± 8%) or between all patients with lung cancer (111 ± 17%) and NSCLC (113 ± 15%) (Fig 5a).

The difference in D-dimer values was only significant between patients with Adeno and the control (3.70 ± 4.21 μg/mL vs. 0.67 ± 0.08 μg/mL; $P < 0.05$), and not with the other groups (SCC 2.08 ± 2.56 μg/mL, SCLC 1.63 ± 0.80 μg/mL) (Fig 5b). Moreover, the D-dimer values were significantly higher in all patients with lung cancer (2.68 ± 3.22 μg/mL; $P < 0.05$) and NSCLC (2.93 ± 3.54 μg/mL; $P < 0.05$) than in the control.

Relationship of anticoagulation and/or fibrinolysis factors with pathologic types of lung cancer

Those levels of antithrombin and tPA/PAI-1 complex were determined for the pathologic type groups at the time of lung cancer diagnosis and staging and the controls (Fig 6). The antithrombin level was significantly lower in patients with SCC than in those with Adeno (95.7 ± 11.7% vs. 111.4 ± 15.4%; $P < 0.05$), but no significant differences were observed in the other groups (SCLC 104.4 ± 7.1%, control 99.2 ± 13.6%) (Fig 6a). The antithrombin level was not significantly different between all patients with lung cancer (104.0 ± 14.3%) and NSCLC (103.9 ± 15.7%).

There were no significant intergroup differences in tPA/PAI-1 complex level among patients with Adeno (21.2 ± 10.9 ng/mL), SCC (20.4 ± 4.8 ng/mL), SCLC (26.0 ± 13.5 ng/mL), and the control (29.6 ± 12.9 ng/mL) or between all patients with lung cancer (21.8 ± 9.4 ng/mL) and NSCLC (20.8 ± 8.3 ng/mL) (Fig 6b).

Discussion

This study demonstrates that patients with lung cancer had higher WBC count, CRP level, and blood coagulation and fibrinolysis parameters, including platelet count, FDP, fibrinogen, thrombomodulin, TAT, and D-dimer, compared to healthy volunteers. Comparison of the pathologic types showed significantly higher thrombomodulin levels in Adeno and SCC than in SCLC and a significantly lower antithrombin level in SCC than in Adeno.

Interleukin (IL-6) is known to induce CRP 6, and IL-6 and CRP levels are reported to be higher in individuals with lung cancer than in those with benign respiratory disease.[11] One mechanism could be the fact that lung cancer cells produce IL-6.[12,13] Changes in IL-6 levels have been used to estimate the effect of lung cancer treatment.[14,15] In this case, the chronic inflammation is caused by lung cancer itself. Conversely, in bacterial infection, macrophage stimulation by bacteria triggers the secretion of IL-6, resulting in an elevated CRP level. Thus, the risk of DIC is higher in lung cancer, as in bacterial infection, because chronic inflammation via IL-6 is similar to that induced by bacterial infection.

In this study, most of the coagulation and fibrinolysis factors showed abnormal levels in patients with lung cancer compared to the control. These disorders of coagulation

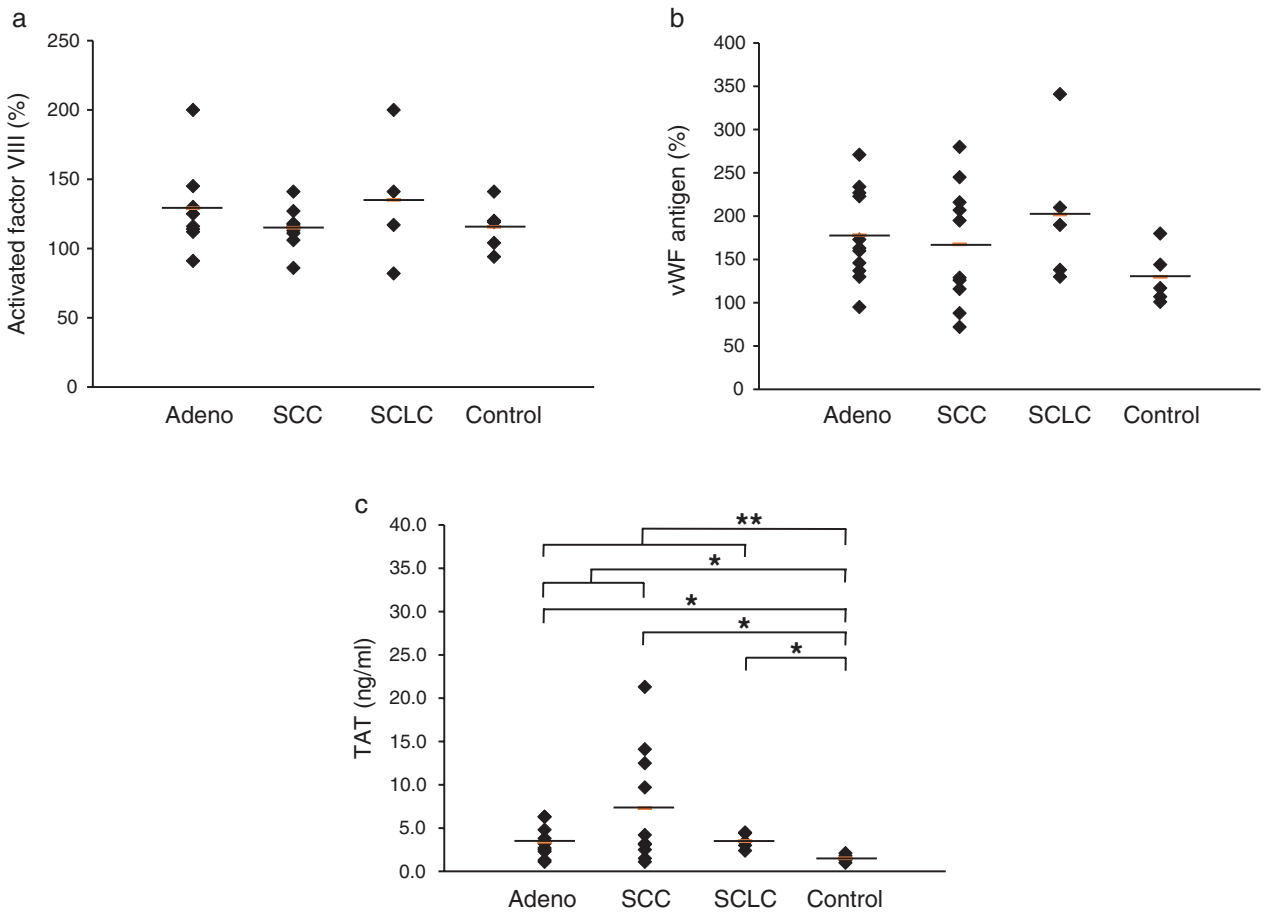

Figure 4 Comparison between lung cancer patients and controls shows no significant differences in levels of (**a**) activated factor VIII and (**b**) von Willebrand factor (vWF) antigen, but a significant difference was observed in the (**c**) thrombin-antithrombin complex (TAT) level. **P* < 0.05; ***P* < 0.01. Adeno, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung carcinoma.

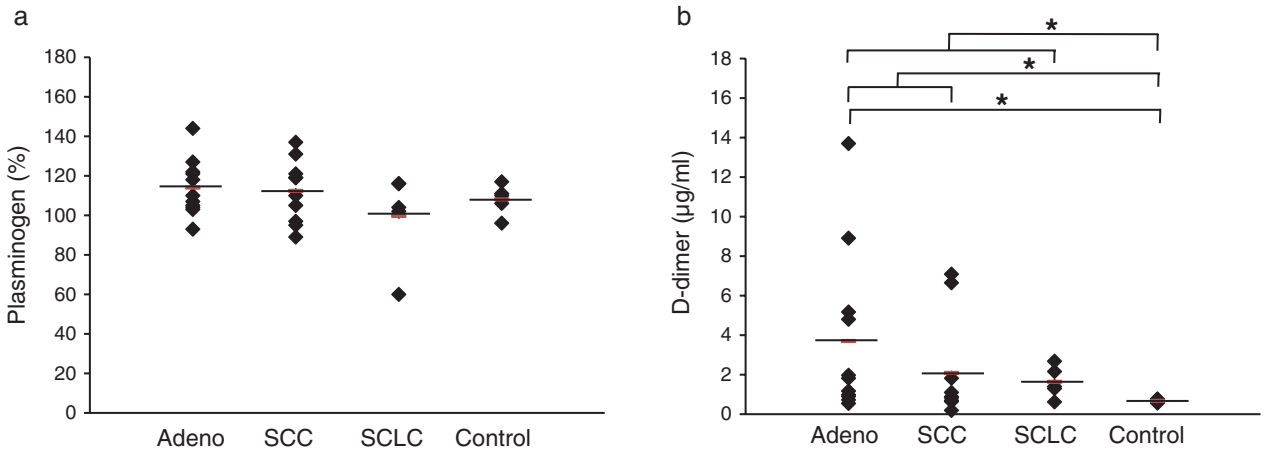

Figure 5 Comparison between lung cancer patients and the control group showing that (**a**) plasminogen does not significantly differ, but the (**b**) D-dimer is significantly different. **P* < 0.05. Adeno, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung carcinoma.

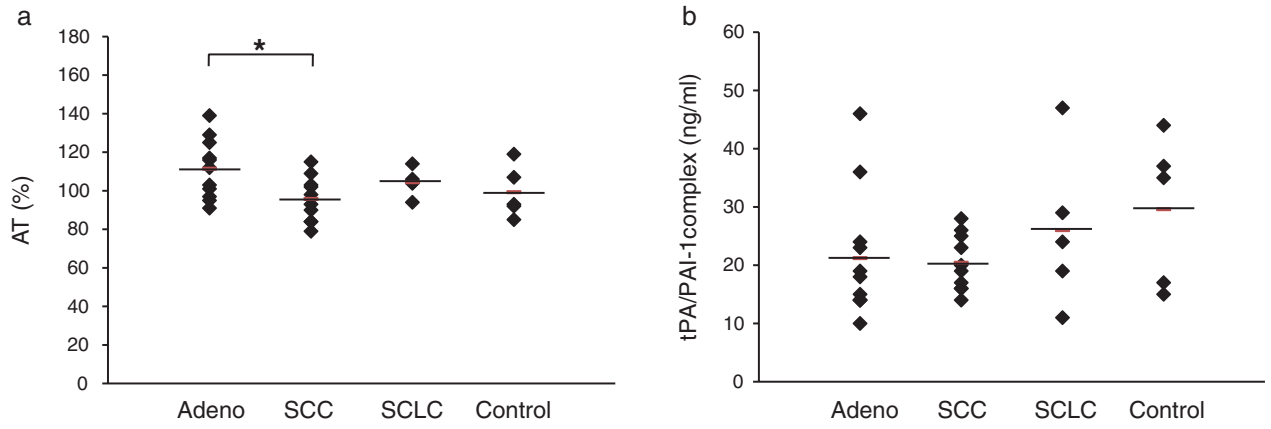

Figure 6 (**a**) The antithrombin (AT) level in adenocarcinoma (Adeno) is significantly higher than that in squamous cell carcinoma (SCC). (**b**) The tissue plasminogen activator/plasminogen activator inhibitor-1 (tPA/PAI-1) complex is not significantly different among the pathologic types of lung cancer. *$P < 0.05$. Adeno, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung carcinoma.

leading to DIC in lung cancer might be attributed to the fact that chronic inflammation increases thrombin production, which is reflected in TAT levels. Another mechanism for increased thrombin production in lung cancer could be activation of the X factor by elevated cancer procoagulant level, which may affect the coagulation system[16] however, we did not evaluate cancer procoagulant in this study. Nevertheless, elevated thrombin levels from chronic inflammation in lung cancer increases fibrinogen and fibrin levels, which promotes the production of FDP and D-dimer. Therefore, patients with lung cancer are at risk of developing DIC. In this study, however, differences in coagulation disorders were not observed among the pathologic types of lung cancer.

Thrombomodulin and antithrombin, both anticoagulant factors in the coagulation pathway, were increased in patients with Adeno and SCC. Pathological studies have shown that thrombomodulin expression is higher in SCC than in Adeno or other types of lung cancer.[4,9] The thrombomodulin level may be affected by the production of the lung cancer cells. In our study, the thrombomodulin level in SCC was significantly higher than in SCLC. In our previous study, the rates of DIC among patients with lung cancer were 1.57% for SCC, 4.23% for Adeno, and 10.26% for SCLC, and a negative correlation between the thrombomodulin level and the rate of DIC was demonstrated according to the type of lung cancer.[17] Furthermore, the percentage of lung cancer patients with thrombomodulin-positive was higher in those with stage IV metastatic cancer than in those with stage I–IIIB localized Adeno. In addition, thrombomodulin expression is reported to be higher in mesothelioma than in Adeno[18,19] and has been shown to influence the prognosis of lung cancer, with thrombomodulin-negative lung cancer yielding a poorer prognosis than thrombomodulin-positive lung cancer of the same stage.[4,5,20] Therefore, pathologic examination of thrombomodulin expression may help to assess the prognosis of patients with lung cancer. The presence of thrombomodulin suppresses lung cancer cell growth[21] and has been associated with pulmonary toxicity secondary to early phase radiation for lung cancer.[22] Therefore, thrombomodulin has several effects in lung cancer. Thrombomodulin binds to thrombin, thereby downregulating the procoagulant activity of thrombin. This thrombin-thrombomodulin complex activates protein C, which normalizes the coagulation system. Therefore, we expected that protein C levels, similar to the thrombomodulin levels, would be different among the various types of lung cancer. However, the protein C levels did not show significant differences among the types of lung cancer in this study. In addition, the mechanism for the higher thrombomodulin level in SCC remains unclear.

The higher thrombomodulin levels in SCC and Adeno observed in this study support our former study, in which the prevalence of DIC in patients with lung cancer was lower in SCC and Adeno.[7] The risk of DIC can be predicted from the thrombomodulin level in patients with lung cancer. When a patient with lung cancer develops DIC, the best treatment may be to administer human recombinant thrombomodulin-α.

Patients with progressive lung cancer were observed to have coagulation disorders, which can likely be attributed to the elevation of CRP secondary to chronic inflammation. However, no differences in coagulation and fibrinolysis factors were observed among the pathologic types of lung cancer. On the other hand, the thrombomodulin level, which is an anticoagulation factor, was higher in SCC and Adeno. Furthermore, the risk of DIC in lung cancer may depend on the level of thrombomodulin, but not on other coagulation and fibrinolysis factors. Our results suggest that

evaluation of the thrombomodulin level could predict the risk of DIC and that human recombinant thrombomodulin-α might be an effective treatment for DIC in lung cancer.

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Disclosure

No authors report any conflict of interest.

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