

Prognostic value of plasma D-dimer levels in lung carcinoma

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ABSTRACT

Aims and backgrounds. Plasma concentrations of several proteases of the coagulation system have been shown to predict prognosis in malignancy. The study was aimed to investigate the prognostic value of plasma D-dimer concentrations and some other coagulation factors in lung cancer.

Methods. Between 2004 and 2008, 100 newly diagnosed lung cancer patients and 25 healthy individuals serving as the control group were evaluated. The patients had no history of coagulation system disorders or anticoagulant therapy. Plasma D-dimer concentrations, prothrombin time, activated partial thromboplastin time, international normalized ratio and blood counts of the patients were obtained. Patient age, lung cancer stage, tumor histology, therapy modalities (surgery, chemotherapy and radiotherapy), therapy outcomes and survival durations of the patients were determined.

Results. The median age of the patients (86 males/14 females) was 67 years, and 15% had stage 2, 26% had stage 3A, 24% had stage 3B, and 35% had stage 4 disease. Histologic subtypes were non-small cell carcinoma (87%) and small cell carcinoma (13%). The median D-dimer level of the patients was 1250 ng/dl, which was significantly higher than that of the control group. Survival duration was significantly higher in patients with low D-dimer levels ($P < 0.05$). D-dimer plasma levels predicted survival independently of the clinical stage of disease, histologic tumor type and performance status of the patient (HR = 5.1; 95% confidence interval, 1.015-1.19, $P = 0.013$). Plasma D-dimer level was significantly higher in metastatic disease ($P < 0.01$).

Conclusions. The results suggest that D-dimer plasma levels might be useful to predict the clinical outcome and survival of patients with lung cancer.

Introduction

The close association between cancer and the hemostatic system has been known since Trousseau's study in the early decades of the 19th century. Although the exact mechanism is not clear, it has been shown that coagulation and/or the fibrinolytic system is activated either directly or indirectly in many types of malignancies, including lung, colon, prostate, cervix, ovarian and breast cancer. Activation mainly occurs in two different ways, either leading to coagulation via thrombin formation or activation of the fibrinolytic system via plasminogen activators¹⁻³.

It has been shown that activation of coagulation and the fibrinolytic system is associated with tumor growth and dissemination, inflammatory cell response regulation, tumor angiogenesis, and demarcation line formation in cancer patients³.

D-dimer is the smallest degradation product generated by the proteolytic activation of plasmin, and is a sensitive indicator of fibrinolytic activity³. Activation of coagulation and the fibrinolytic system has been associated with disease stage and prognosis in various types of malignancies³⁻⁵. Some studies have suggested that D-dimer might be

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valuable in determining the prognosis of the disease and evaluating the treatment response in lung cancer⁵⁻⁷.

In the present study, we investigated the association of plasma D-dimer levels and coagulation factors such as prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), and thrombocyte count with the stage and histological type of the disease, as well as with response to therapy and survival in untreated lung cancer patients.

Material and methods

In the study, 100 newly diagnosed, treatment-naive lung cancer patients ≥ 18 years of age were prospectively evaluated. The control group consisted of 25 healthy individuals without comorbidity.

The diagnosis of lung cancer was based on the analysis of biopsy or cytologic specimens obtained by bronchoscopic examination, transthoracic biopsy or surgery. Histological tumor type was determined according to the WHO International histological classification of tumors (World Health Organization Classification)⁸.

Patients were staged according to the TNM classification, based on their conventional radiographs, thoracic and cerebral computed tomography scans, upper abdominal ultrasounds, whole body bone scintigraphs and fiberoptic bronchoscopic examinations⁹.

Prior to treatment, the functional status of the patients was evaluated with the Eastern Cooperative Oncology Group (ECOG) performance scale¹⁰. All the cases had an ECOG performance status between 0 and 2, with an expected survival time of more than three months, and none of the patients had systemic disease that would pose an obstacle for the therapy.

The patients were followed for two years, and the therapies applied (surgical therapy, chemotherapy, radiotherapy, symptomatic therapies), therapy responses and survival durations were recorded. The patients who failed to attend the follow-up visits were telephoned; in case of death, the survivals of the dead patients were calculated according to their definite death dates obtained from the Mernis computerized patient record system.

Patients who were regularly receiving anticoagulant and antiagregant therapy, who had a history of thromboembolism or familial coagulopathy, and patients with concomitant active infection, malnutrition and secondary tumors were not included in the study. The study was approved by the scientific council of the hospital, and written informed consent was obtained from each patient before the study procedures.

Venous blood samples were collected once before the treatment. They were centrifuged and the plasma was separated. D-dimer levels, PT, APTT, and INR values were measured. Thrombocyte count was performed using an automatic hemocounter (ABX Pentra DX 120, Horiba Ltd, UK).

D-dimer level was measured in the plasma, via enzyme-linked fluorescent immunoassay method using a mini-Vidas device (BioMerieux SA). A D-dimer level < 500 ng/dl was considered normal.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 16.0. The Kaplan-Meier method was used for survival analyses, and multivariate Cox regression analysis was used to evaluate independent variables that determined survival. Variables were tested by the Kolmogorov-Smirnov test. Evenly distributed variables were tested by the Pearson correlation, and oddly distributed variables were tested by the Spearman correlation test. $P < 0.05$ was considered statistically significant.

Results

Eighty-six of the 100 patients included in the study were males and 14 were females. The median age of the patients was 67 years (range, 38-74). Thirteen of the cases had small cell lung cancer (SCLC) and 87 cases had non-small cell lung cancer (NSCLC). Twenty five healthy individuals (4 female, 21 males) without comorbidity were admitted to the study as the control group. Their median age was 65 years (range, 35-76).

The general characteristics of the lung cancer patients are shown in Table 1.

Table 1 - Patient characteristics

	n = 100
Median age	67
Male/female	86/14
Histological type	
Non-small cell lung carcinoma	23
Adenocarcinoma	29
Epidermoid carcinoma	33
Combined	2
Small cell lung carcinoma	13
Stage	
IIA	7
IIB	8
IIIA	26
IIIB	24
IV	35
Performance status	
ECOG-0	32
ECOG-1	42
ECOG-2	26
Body weight	
Weight loss $> 10\%$	49
Weight loss $< 10\%$	51
Treatment modalities	
Surgery	10
Chemotherapy (cisplatin-based combination CT)	72
RTR (60 Gy in 30 fractions)	55
Palliative RT (30 Gy in 10 fractions)	21

RTR, radical thoracic radiotherapy.

The applied treatment modalities

Ten of the 15 patients with stage II NSCLC underwent surgery and 6 of them received adjuvant cisplatin-based combination chemotherapy. The remaining 5 patients with stage II NSCLC, who were not suitable for surgery or did not consent to surgery, underwent radical thoracic radiotherapy (RTR) (60 Gy in 30 fractions over 6 weeks).

Whereas 42 of the 50 patients with stage III disease received cisplatin-based chemotherapy and sequential RTR, the remaining 8 patients underwent RTR.

Twelve of 35 patients with stage IV disease received chemotherapy and 11 of them had symptomatic treatment.

The mean follow-up period was 15 months (range, 4-24).

The mean D-dimer and coagulation factor values are shown in Table 2.

The median survival duration of the cases was 12 months (range, 2-42). The general survival curve is shown in Figure 1. There was a significant correlation between survival period and D-dimer levels (ORR = 1.001, $P = 0.001$) (Figure 1).

D-dimer levels in patients with lung cancer were higher than those of the control group, and the difference was statistically significant ($P < 0.01$) (Table 2). However, there was no significant difference between the two groups regarding the other hemostatic parameters ($P > 0.05$).

D-dimer levels according to disease stage are shown in Table 3. When the D-dimer levels were compared according to disease stage in patients with lung cancer, a significant difference was observed between the D-dimer levels of patients with stage IIA and those with stage IV disease ($P = 0.025$). There was no significant difference between the other stage groups in terms of D-dimer levels. D-dimer levels were significantly higher in lung cancer patients than in the control group ($P < 0.01$) (Table 3).

The survival duration was significantly longer in patients with lower D-dimer levels ($P < 0.05$). The mean D-dimer concentration in patients who were still alive at the end of a 2-year follow-up was 768.11 ± 269 ng/dl (95% CI, 199.33-1336.88), whereas the mean D-dimer level of patients who died was 1158.33 ± 122 ng/dl (95% CI, 914.8-1401.87), and the difference between the two groups was significant ($P < 0.02$) (Figure 2).

Table 2 - D-dimer and coagulation factor values in the study groups

	Lung cancer patients (n = 100) Mean ± SD	Control group (n = 25) Mean ± SD
D-dimer (ng/dl)	1076.66 ± 10.41*	248.6 ± 116*
Thrombocyte ($10^3/mm^3$)	377.30 ± 134	258 ± 112**
Prothrombin time (sec)	13.63 ± 1.4	11.6 ± 1.2**
APTT	31.81 ± 3.96	29.2 ± 3.1**
INR	1.15 ± 0.17	0.98 ± 0.11**

* $P < 0.01$, ** $P > 0.05$. APTT, activated partial thromboplastin time; INR, international normalized ratio.

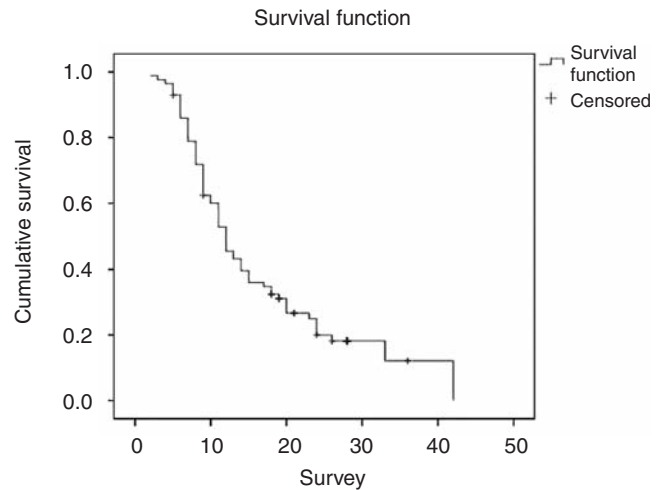


Figure 1 - Survival curve of the patients with lung carcinoma.

Table 3 - D-dimer levels according to disease stage (ng/dl)

Stage	D-dimer		P
	Mean ± SD	Min-max	
IIA	379 ± 128	288-470	$P = 0.025$
IIB	586 ± 152	431-946	$P > 0.05$
IIIA	835 ± 204	237-2897	$P > 0.05$
IIIB	1030.9 ± 850	167-444	$P > 0.05$
IV	1225.4 ± 1268	220-5875	$P = 0.025$
Total	1076.6 ± 1041	167-5875	

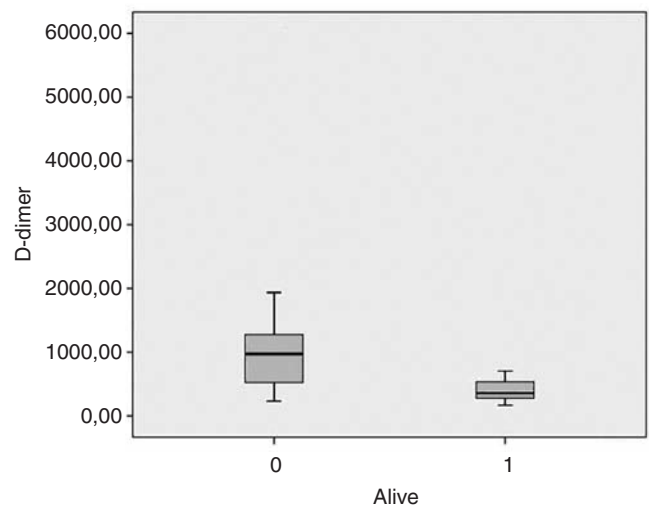


Figure 2 - The difference between the alive (1) and dead (0) patient groups in terms of D-dimer levels (ng/dl) ($P < 0.01$).

The survival of patients with high D-dimer levels was significantly different from that of patients with low D-dimer levels. A high D-dimer plasma level showed a significant correlation with short survival, as the median survival was 9 months for D-Dimer > 500 ng/dl *ver-*

sus a median survival of 15 months for D-dimer <500 ng/dl (95% CI, 2-12 and 95% CI, 4-22, respectively, $P < 0.05$).

Multivariate survival analysis was done using Cox's regression analysis. D-dimer, age, gender, histological tumor type and performance status were analyzed. Only the elevation of plasma D-dimer levels was found to be significantly correlated with shorter survival in regression analysis. The relation was independent of gender differences, histologic tumor type and performance status (hazard ratio for high D-dimer, 5.1; 95% CI, 1.015-1.19, $P = 0.013$).

According to the correlation tests, a significant correlation was found between high D-dimer levels and high PT levels ($r = 0.029$, $P = 0.034$). No significant correlation was determined between D-dimer levels and histologic types of lung cancer. There was a significant correlation between elevated D-dimer levels and the presence of metastasis ($P < 0.01$), but no difference was determined in terms of metastatic sites.

The mean D-dimer level was significantly higher in the patient group with ECOG performance status 2 than in the other groups ($P < 0.05$). The mean D-dimer level was 1108 ± 200 ng/dl (95% CI, 698.9-1517) in the group with ECOG 0, 1043 ± 139.6 ng/dl (95% CI, 763-1323.6) in the group with ECOG 1, and 1436.5 ± 340 ng/dl (95% CI, 2886-5759) in the group with ECOG 2 (Figure 3).

The treatment responses of 81 patients who received chemotherapy and/or radiotherapy without surgical intervention were evaluated according to WHO criteria (Table 4). When the cases were classified according to their response to therapy as regressive disease (0), stable disease (1) and progressive disease (2), D-dimer levels were found to be significantly higher in cases with progression (Figure 4).

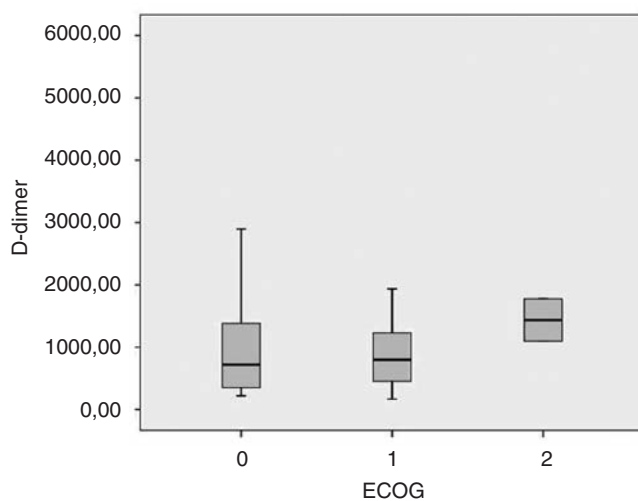


Figure 3 - Comparison between the ECOG groups in terms of D-dimer levels (ECOG 0-1-2).

Table 4 - Therapy responses and D-dimer levels (logrank test, $P = 0.015$)

Therapy response	D-dimer level	No. patients (n = 81)	Median survival (mo)	95% CI
Regression	1041 ± 208.7	28	11	712.8-1569
Stable disease	794.2 ± 86.8	41	9.5	619.2-969.2
Progression	2008 ± 472.3	12	6	969-3048.2

CI, confidence interval.

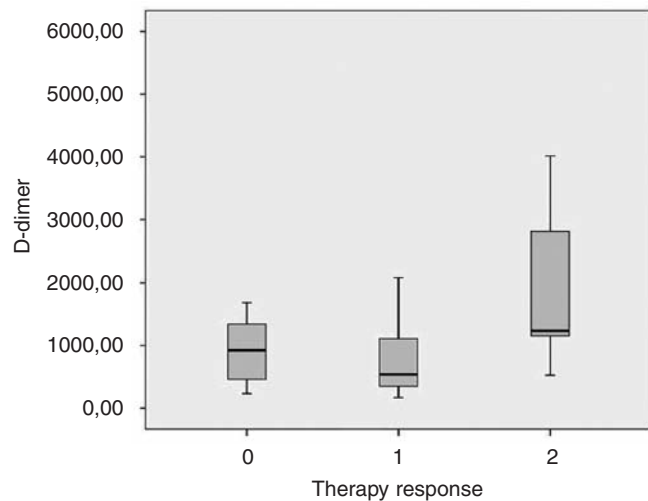


Figure 4 - Comparison of D-dimer levels between different therapy response groups (0-regression, 1-stable response, 2-progression).

Discussion

In the present study, we observed that the elevation in plasma D-dimer levels was associated with various parameters in lung carcinoma. Recent studies have shown that activation of the hemostatic system plays a role in tumor development, dissemination and metastasis^{1-3,5,7}. Thrombin leads to fibrin formation and plays a role in tumor cell growth and angiogenesis. Moreover, fibrin accumulation in the cancer tissue has been shown to act as a protective barrier against inflammatory cells³. Plasminogen activators produce plasmin, which is an active serine protease, and plasmin takes part in tumor invasion and in the penetration of tumor cells into the circulatory system^{2,5-7}.

In lung cancer, fibrin deposits are thought to assist in cell proliferation and neovascularization of the enlarging tumor, whereas capillary fibrin deposition is considered to protect the tumor tissue against immune and chemotherapeutic attacks. However, these complex mechanisms remain unclear¹¹.

The significant relation between D-dimer levels and different histologic types of lung carcinoma has been shown in some publications. The difference has been

attributed to the difference in hemostatic system activation pathways in NSCLC and in SCLC. Studies have shown that body macrophages stimulate the fibrinolytic system by secreting procoagulant substances in NSCLC, whereas the coagulation system is directly stimulated by the factors secreted from the tumor cells in SCLC^{6,12,13}.

In the present study, no significant difference was determined in terms of D-dimer and other coagulation factor values between the three different histological types of lung cancer. In their studies, Unsal *et al.*⁶ and Seitz *et al.*¹⁴ reported no significant difference between NSCLC and SCLC, but Hagedorn *et al.*¹⁵ found higher levels of hemostatic parameters in adenocarcinoma and epidermoid cell carcinoma. Inal *et al.*¹⁶ found that the D-dimer levels of patients with SCLC were higher than those of patients with NSCLC.

Activation of the hemostatic system was reported to be correlated with tumor dissemination, thus, a significant correlation was reported between the hemostatic parameters and tumor stage^{2,17}. Unsal *et al.*⁶ reported that D-dimer levels were significantly higher in patients with distant metastasis independent of the histological type, but no significant difference was found between stage IIIB and stage IV disease. In the present study, a significant correlation, independent of the histological tumor type, was found between the elevated D-dimer concentrations and the presence of metastasis. However, no difference was found between the metastatic sites in terms of D-dimer levels. Considering the stages, a significant difference was present only between the D-dimer levels of patients with stage IIA and stage IV disease, whereas no difference was found between stage II-IB and stage IV. The results of our study showed that D-dimer levels were highest among cases with locally advanced disease and distant metastasis, independent of histological tumor type.

High levels of D-dimer have been found to be associated with a poor prognosis in patients with lung cancer^{5,18,19}. Unsal *et al.*⁶ and Taguchi *et al.*¹⁸ found that a high D-dimer level was an independent determinant of survival.

Pedersen and Milman²⁰ found that thrombocytosis was associated with a poor prognosis, but Unsal *et al.*⁶ did not confirm the association. The present study as well revealed no association between prognosis and thrombocytosis or other coagulation factors (PT, INR, APTT). Multivariate analysis performed to assess the prognostic factors showed that survival duration was shorter in patients with high D-dimer levels and that D-dimer was an independent prognostic factor. Longer survival durations were observed in patients with lower D-dimer levels. Patients who were still alive at the end of a 2-year follow-up had lower D-dimer levels than patients who died during the follow-up period.

Performance status is an independent prognostic factor for lung cancer. In the present study, D-dimer levels

were found to be higher in patients with ECOG 2 performance status. In the study of Altiay *et al.*⁷, no significant correlation was demonstrated between Karnofsky performance status and D-dimer levels⁷.

Some studies have reported that there might be a significant correlation between D-dimer levels and treatment response. It is thought that progression of disease will be aggressive and, in general, treatment responses and expected survival duration will be shorter in patients with high hemostatic activation^{7,21}.

Antonioni *et al.*²¹ investigated the plasma D-dimer levels prior to, during and after chemotherapy and found a decrease in D-dimer levels in those who responded to therapy but an increase in those with progressive disease. Altiay *et al.*⁷ reported a significant correlation between response to chemotherapy and D-dimer levels both in patients with local and advanced disease. In the present study as well, D-dimer levels were found to be lower in patients with regressive or stable disease than in those who showed progression. It was thought that D-dimer levels might be a valuable marker to evaluate treatment response.

It has been shown in some studies that D-dimer levels were significantly increased also in metastatic disease^{5-7,14}. In the present study as well, D-dimer levels were found higher in patients with metastatic disease than in those without metastasis. However, there was no difference between the D-dimer levels regarding metastatic sites.

High levels of D-dimer are associated with disseminated disease, poor therapy response, poor prognosis and shortened survival duration in lung cancer patients. Plasma D-dimer analysis is an inexpensive and easily applicable method that is likely to be a guide in predicting the dissemination and progression of the disease and therapy response in patients with lung cancer. It may also be beneficial in determining the candidates for adjuvant therapy after surgery and in assessing the cases at high recurrence risk after curative therapies.

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