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The Association of D-Dimer Levels with Other Prognostic Factors in Patients with Lung Cancer

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Aim: To determine the factors related with coagulation disorders, deep venous thrombosis and thromboembolic events that are significant causes of morbidity and mortality in patients with lung cancer.

Materials and Methods: D-dimer (DD) levels at the time of diagnosis were determined in patients diagnosed with lung cancer and these cases were monitored prospectively for thromboembolic events and survival.

Results: DD levels significantly increased and were associated with length of survival in lung cancer patients. Age, histopathological type, extent of the disease (stage), DD, performance status (ECOG), and thromboembolism were found to effect survival. DD, thromboembolism, ECOG, and histopathological type were found to be independent risk factors.

Conclusions: Survival time is significantly shorter in the cases with thromboembolism. DD levels can be monitored and thromboembolism can be investigated when high DD levels are detected. Mortality and morbidity can significantly be reduced through initiation of anticoagulant treatment (low molecular weight heparin and warfarin) in the early period. DD can be considered as an inexpensive, simple test to be used in the diagnosis, treatment, and follow-up process of lung cancer patients.

Key Words: D-dimer, lung cancer

Akciğer Kanserli Hastaların D-Dimer Düzeylerinin Diğer Prognostik Faktörler ile Olan İlişkisi

Amaç: Akciğer kanserli hastalarda önemli bir morbidite ve mortalite nedeni olan koagülasyon bozuklukları, derin ven trombozları ve tromboembolik olaylar ile ilişkili faktörlerin belirlenmesi ve prognozla ilişkilerinin saptanmasıdır.

Yöntem ve Gereç: Akciğer kanserli olguların tanı anındaki koagülasyon faktörlerinin belirlenmesi, olguların prospektif olarak izlenerek gelişen tromboembolik olayların saptanması ve hastaların sağkalımlarının belirlenmesidir.

Bulgular: Akciğer kanserli olgularda D-dimer (DD) düzeylerinde belirgin yükseklik saptanmış ve sağkalım ile ilişkili bulunmuştur. Yaş, histopatolojik tip, hastalığın yaygınlığı (evre), DD, performans durumu (ECOG), tromboemboli, sağkalım üzerine etkili değişkenler olarak saptanmıştır. Bunlardan DD, tromboemboli gelişimi, ECOG ve histopatolojik tip bağımsız risk faktörü olarak belirlenmiştir.

Sonuç: Tromboemboli saptanan olgularda sağkalım önemli derecede kısadır. DD düzeyleri takip edilerek yükseklik tespit edildiğinde tromboemboli açısından araştırılabilir. Erken dönemde antikoagülan tedavi (düşük moleküler ağırlıklı heparin ve warfarin) uygulanmasıyla mortalite ve morbidite önemli derecede azaltılabilir. DD akciğer kanserli hastaların tanı, tedavi ve takip aşamasında kullanılabilecek ucuz, kullanımı kolay bir test olarak değerlendirilmiştir.

Anahtar Sözcükler: D-dimer, akciğer kanseri

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Introduction

Coagulation or fibrinolytic system activation is present in lung cancer patients at clinical or subclinical level. There is a complex interaction, which has an important role in the course of the disease, between pathogenetic mechanisms of thrombosis, tumor cells, homeostatic systems, and patient characteristics. Patients with deep venous thrombosis (DVT) or subclinical hypercoagulopathy usually have worse prognosis. Activation of the coagulation system not only plays a role in the local and systemic dissemination of the disease, but also has a significant impact on mortality and survival rate by leading to thromboembolic events (1).

Determination of coagulation and fibrinolytic system markers may be important in the evaluation of their relationship with disease stage, performance status of the patients, and survival as well as in the selection of treatment that will be administered to the patient. Currently, similar treatment methods are used in several subgroups of lung cancer patients. Although these treatment methods can provide substantial benefits for survival and quality of life in early stages, these benefits become significantly less in later stages. When adverse event profile and costs and benefits of these treatment alternatives are evaluated, there appears a need for different treatment regimes in some patients.

Measurement of DD levels can be performed by inexpensive and simple methods in most health-care institutions. Fibrin, which is degraded by activated plasmin following the activation of the fibrinolytic system, is the main ingredient in thrombus. Fibrin degradation products including DD are formed by the degradation of cross-linked fibrin. It is formed in all conditions where coagulation and fibrinolytic systems are activated. It is known to be increased in certain medical conditions such as pulmonary embolism, DVT, solid tumors, leukemias, chronic liver diseases, serious infections, trauma, recent surgery, disseminated intravascular coagulation (DIC), pregnancy, preeclampsia, vasculitis, sickle-cell anemia, myocardial infarction, and unstable angina pectoris (2,3,4,5).

Plasma concentration of DD is increased either due to increased production or decreased excretion (6). Since 2% to 3% of plasma fibrinogen is transformed into fibrin in healthy individuals, very low amount of DD can be detected in plasma (7). Its half-life is about 8 h, and its clearance from the plasma is accomplished via the urinary and the reticuloendothelial system. In contrast to other markers of homeostasis, DD is a relatively more convenient and more stable marker to measure, thus can be utilized in routine clinical practice as well as in epidemiologic studies. It can be detected in blood and plasma using specific monoclonal antibodies that are developed against epitopes located on DD. Despite being a fibrinogen degradation product, DD also increases plasma fibrinogen levels by increasing its hepatic synthesis (8).

Coagulation and fibrinolytic systems have previously been investigated in lung cancer patients, and correlations between D-dimer (DD) levels and several variables such as tumor stage and types have been demonstrated (2,9).

Goal of this study is to determine the high risk patient groups and implement early treatment interventions. More aggressive treatment methods can be utilized in patients with early stage disease when there is evidence of hypercoagulation. Palliative treatment alternatives may be considered instead of chemotherapy in late stage disease, thus reducing drug-related costs and increasing quality of life in these patients.

D-dimer, being a simple and inexpensive test, can be preferred as a screening tool. Other treatment alternatives such as heparin, low molecular weight heparin, and warfarin can be initiated in those patients, who do not have any contraindications, in an earlier period including the time interval before confirmation of histopathological diagnosis.

Materials and Methods

Information about the study was provided to all patients (and/or their families) with a confirmed histopathological diagnosis of lung cancer and those who gave informed consent were included in the study. Follow-up forms were prepared for each patient.

A total of 70 patients (65 men, 5 women) were included. Their mean age was 62.4 ± 10.9 years and median age was 63.0 ± 10.97 (Range: 21-83) years. Demographic information, physical examination findings, biochemical laboratory test results, imaging studies including thoracic, abdominal and cranial computerized tomography and bone scintigraphy, bronchoscopy findings and histopathological evaluation results of biopsy, BAL (bronchoalveolar lavage) and sputum material were recorded on follow-up forms.

Two whole blood samples of 5 ml each were obtained from every patient and plasma and serum were separated and stored at -80 °C. At the end of 3-year follow-up period, laboratory measurements, which are explained below, were performed on plasma and serum samples.

Date of histopathological diagnosis was recorded as the time of diagnosis in all patients and they were followed up in 2-month intervals through their oncology follow-up cards and addresses to record their exact date of death.

Staging of lung cancer was performed according to systems introduced by WHO/IASLC (World Health

Organization/International Association for Study of Lung Cancer) in 1999 and by "American Joint Committee on Cancer" and "Union Internationale Contre le Cancer" in 1997. Performance status was evaluated by ECOG (Eastern Cooperative Oncology Group) score.

Inclusion criteria

Patients who are recently diagnosed with lung cancer (in last year), patients who are not on regular anticoagulant or antiaggregant treatment (patients using acetyl salicylate not exceeding a dose of 75 mg/week were included in the study), patients who do not have a personal or family history of thrombophilia, patients who do not have a previous history of chemotherapy, radiotherapy or surgery due to malignancy, patients in any stages of lung cancer, patients with ECOG scores of 1-2-3.

Exclusion criteria

Patients who do not provide consent to be included in the study or those who withdraw their consent at any stage of the study, patients with ECOG score of 4, patients who are on regular anticoagulant and antiaggregant treatment, patients with a family history of coagulopathy, patients with a previous history of thromboembolism, patients with inadequate follow-up data.

Laboratory Measurements

D-dimer (DD) was measured by enzyme-linked immunosorbent assay (ELISA) method using IMUCLONE D-dimer ELISA kit (American Diagnostica Inc. - Cat. No 602). Specific monoclonal antibodies that bind to epitopes located on DD are utilized in nearly all laboratory methods measuring DD levels. These epitopes are not found on fibrin, fibrinogen, and non-cross-linked fibrin. Although many techniques can be used in DD measurement, ELISA is considered as the "gold standard". ELISA method has a high sensitivity for DD (greater than 99%) and can detect DD concentrations of as low as 30-80 ng/dl.

Statistical Analysis

Data were recorded using Microsoft Excel program. Statistical analysis was performed using SPSS/PC version 10.0. Survival means of the study groups were computed by Kaplan-Meier analysis. Survival time was assessed in months. Subgroup comparisons were made by log rank method. P values of less than 0.05 were considered statistically significant.

Relationships between factors that may have effects on prognosis were assessed by Cox regression analysis. P values of less than 0.05 in Cox regression analysis were considered statistically significant.

Kruskal-Walls test was used in multiple comparisons of the groups. Mann Whitney U-test and t-test were used in between-group comparisons. Pearson and Spearman correlation analyses were also performed to assess associations between study variables.

Results

A total of 70 patients consisting of 5 women (7.1%) and 65 men (92.9%) were followed up for 12 to 28 months throughout the study period. Five men were alive at the end of the study, and 65 patients were deceased.

Mean age of the patients with small cell lung cancer (SCLC) (all were in extensive stage) was 52 ± 9.8 years. There was a 22-year-old Stage IB case among non-small cell lung cancer (NSCLC) patients. Mean age was 64 ± 1.4 (Range: 33-65) years in Stage II cases (n = 2), 52 ± 9.1 (Range: 44-62) years in Stage IIIA cases (n = 3), 64.9 ± 8.1 (52-80) years in Stage IIIB cases (n = 24), and 62.7 ± 10.6 (43-83) years in Stage IV cases (n = 40). Clinical characteristics of the patients are summarized in Table 1.

Table 1. Clinical characteristics of the patients.

Characteristic	Number of patients	%
Sex (Female/Male)	5/65	7.1/92.9
Histopathology		
SCLC	7	10
SqCLC	16	22.9
NSCLC-U	14	20
Adenocarcinoma	30	42.9
ULC	2	2.9
ECOG		
1	8	11.4
2	46	65.7
3	16	22.9
Treatment		
Chemotherapy (N/Y)	2/68	3/97
Radiotherapy (N/Y)	36/34	51/49
Surgery (N/Y)	63/7	90/10
Thromboembolic event	7	10

Abbreviations: SCLC: Small Cell Lung Cancer, NSCLC-U: Non-Small Cell Lung Cancer-undifferentiated, SqCLC: Squamous Cell Lung Cancer, ULC: Undifferentiated Lung Cancer, N: No, Y: Yes

Mean survival time was 11.47 ± 1.1 and 9.47 ± 1.99 months in men and women, respectively. Median survival time was 11.77 ± 1.82 and 9.40 ± 3.65 months in men and women, respectively. Sex did not have any statistically significant effect on survival (P > 0.05). Mean survival time was 1.75 ± 0.33 months and median survival time was 1.77 ± 0.4 months in SCLC. Mean survival time was 11.17 ± 1.01 months and median survival time was 11.77 ± 1.18 months in NSCLC. There was a statistically significant difference between SCLC and NSCLC in terms of survival time (P < 0.001) (Figure 1).

One-year survival rates were 0% for SCLC and 47.61% for NSCLC. Two-year survival rates were 0% for SCLC and 11.86% for NSCLC.

Mean survival time was 14.35 ± 2.53 months and median survival time was 13.77 ± 1.32 months in SqCLC cases; mean survival time was 10.28 ± 1.66 months and median survival time was 10.15 ± 1.34 months in adenocarcinoma cases; mean survival time was 9.8 ± 7.63 months in ULC cases; mean survival time was 10.28 ± 1.66 months and median survival time was 9.30 ± 3.18 months in NSCLC-U cases (Figure 1).

Significant difference was detected between all NSCLC and SCLC cases in terms of survival time (P < 0.005). Survival times of SqCLC cases were significantly different compared to adenocarcinoma cases (P < 0.01) and NSCLC-I cases (P < 0.05). No significant difference was found between NSCLC and adenocarcinoma cases in terms of survival time (P < 0.05).

All SCLC cases were in extensive stage (10% of the study population). Thirty patients with NSCLC were in Stage IV (47.1%), 24 (34.3%) were in Stage IIIB, 3 (4.3%) were in Stage IIIA, 2 (2.9%) were in Stage II, and 1 (1.4%) was in Stage I (Table 2).

In NSCLC cases, while survival was significantly different in Stage IIIA compared to Stage IIIB (P < 0.001) and Stage IV (P < 0.05), no significant difference was found between late Stage IV and IIIB (log Rank = 0.187, P > 1.74). Statistical comparison could not be performed between Stage I and II patients and other groups due to very few numbers of cases (Figure 2).

Mean DD level was 4110 ± 3732 ng/ml and median value was 842 ± 3121 ng/ml. DD level was significantly higher in late stage disease (Table 3).

DD level was less than 500 ng/dl in 4.3% of the patients, between 500 and 1000 ng/dl in 5.7%, and ≥1000 ng/dl in 94.3%. Survival analysis could not be performed between normal and high level patients since none of our patients had a normal DD level (<400 ng/dl).

Median survival time was 5.60 ± 2.45 months and 12.6 ± 0.61 months in patients with a DD level greater and less than 2850 ng/dl, respectively (P = 0.002).

DD levels were significantly higher in SCLC cases compared to NSCLC cases (Figures 3 and 4) (P = 0.024). No significant difference was found between SCLC cases and ULC cases (Figure 3).

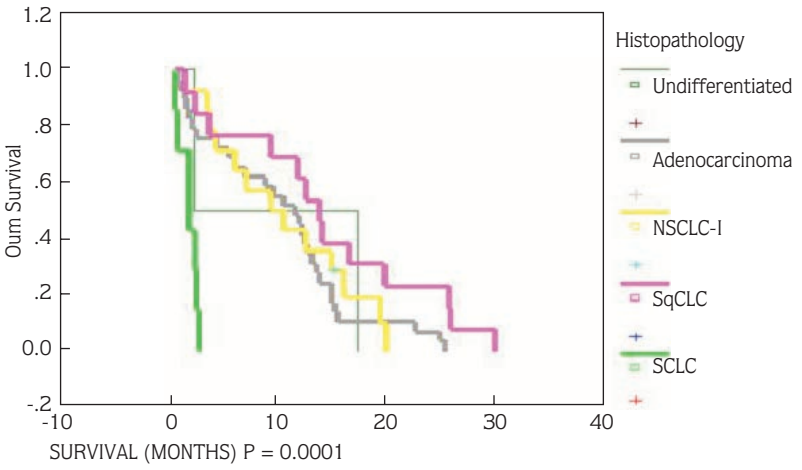

Figure 1. Survival times for different histopathological subgroups (SCLC: Small Cell Lung Cancer, NSCLC-I: Non-Small Cell Lung Cancer-undifferentiated, SqCLC: Squamous Cell Lung Cancer, ULC: Undifferentiated Lung Cancer).

Table 2. Demographic and histopathological characteristics of the patients according to stage of disease.

Characteristic	Stage I-II-IIIA (n)	%	Stage IIIB-IV (n)	%
Age				
<65 years	6	100	35	54.6
≥65 years	0	0	29	45.4
Sex				
Male	6	100	59	92.1
Female	0	0	5	7.9
Histopathology				
SCLC	0/0*	0	7/7**	100
SqCLC	2/16	12.5	14/16	87.5
NSCLC-I	1/14	7.1	13/14	92.8
Adenocarcinoma	3/30	10	27/30	90
ULC	0/0	0	2/2	100

Abbreviations: SCLC: Small Cell Lung Cancer, NSCLC-I: Non-Small Cell Lung Cancer-undifferentiated, SqCLC: Squamous Cell Lung Cancer, ULC: Undifferentiated Lung Cancer. *Limited disease; **Extensive disease

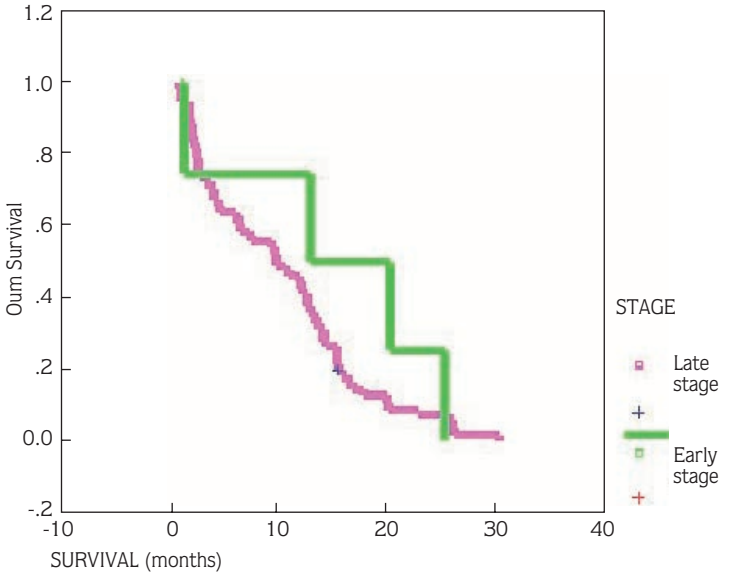

Figure 2. Comparison of survival time in early and late stage disease.

No significant difference was found in DD levels of NSCLC subgroups except ULC cases in which DD levels were significantly higher (P = 0.002).

Compared to early stage cases, DD level was significant different in late stage cases (P = 0.025) (Figure 5).

DD levels were significantly correlated with survival (P = 0.012) and histopathological type (P = 0.002).

High levels of DD was found to be an independent risk factor in monovariate regression analysis (RR = 1, 95% CI 1-1, P = 0.013) and in multivariate regression analyses (RR = 1, 95% CI 1-1, P = 0.014).

Table 3. Comparison of DD levels between early and late stage disease and patients with or without thromboembolism.

	DD (ng/gl)	P value
Early stage (I,II,IIIa) Median ± SD	3957 ± 2942 (982-8114)	0.025
Late stage (IVa) Median ± SD	4125 ± 3165 (302-11442)	
Thromboembolism present	5676 ± 2791	0.162
Thromboembolism absent	3936 ± 3133	

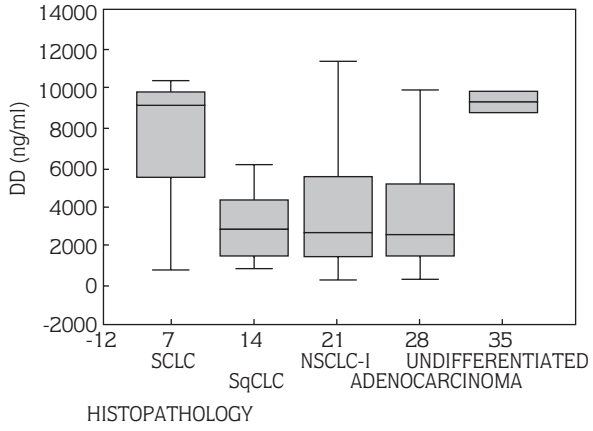

Figure 3. Comparison of DD levels in different histopathological subgroups (P = 0.002).

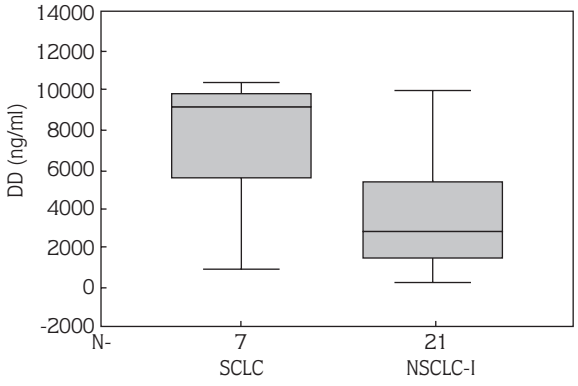

Figure 4. Comparison of DD levels in SCLC and NSCLC cases (P = 0.024).

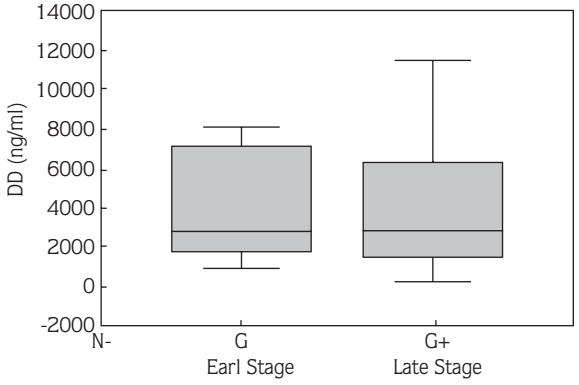

Figure 5. Comparison of DD levels in early and late stage disease (P = 0.025).

A total of 7 (10%) thromboembolic events were noted in our study: 2 femoral artery thromboses, 1 portal vein thrombosis, 1 brachiocephalic vein thromboses, and 3 pulmonary emboli. According to histopathological types, 5 of these events were in adenocarcinoma cases, 1 in SCLC cases and 1 in SqCLC cases. Venous Doppler Ultrasonography study for the detection DVT was done in 2 pulmonary emboli cases and revealed normal findings.

Portal thrombosis was detected in the follow-up abdominal computerized tomography of an asymptomatic patient. All thromboembolic events have been discovered after treatment of the patients and not in the early period of diagnosis.

While platelet counts were within normal limits in patients with arterial thrombus, they were increased over normal limits in patients with portal and brachiocephalic vein thrombus. Platelet counts were at lower and upper limits of normal in patients with pulmonary emboli. Among the patients in whom thromboembolic events have occurred, 5 of them (71.4%) had received chemotherapy, 2 of them (28.6%) (femoral artery thrombus, pulmonary emboli) had received both chemotherapy and radiotherapy. None of the patients, in whom thromboembolic events have occurred, had surgical treatment.

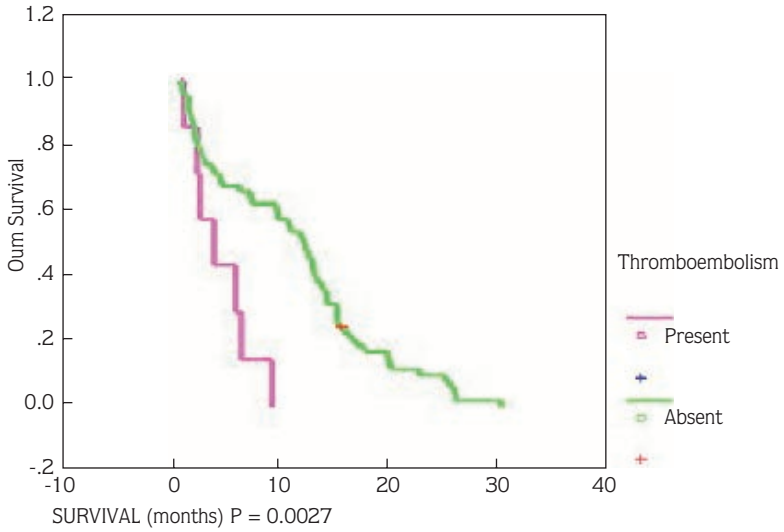

Figure 6. Comparison of survival time in cases with and without thromboembolism.

Median survival time was 9.40 ± 3.65 months in patients with thromboembolic events, and 11.77 ± 1.10 months in patients without a thromboembolic event, and this difference was statistically significant (P = 0.042) (Figure 6).

Thromboembolism was found to be an independent risk factor for decreased survival in monovariate regression analysis (RR = 0.289, 95% CI 0.122-0.685, P = 0.005) and multivariate regression analyses (RR = 2.446, 95% CI 0.945-6.33, P = 0.065).

Comparison of DD levels between patients with or without thromboembolism is shown at Table 3.

Discussion

In lung cancer, exhibiting an increasing incidence in recent years, thromboembolic events are the leading cause of cancer-related deaths in this patient population. Despite advances in treatment approaches, no significant increase in survival rates or improvement in patients' quality of life is observed.

Determining the high-risk patient groups early and classification of patients accordingly may help tailoring treatment modifications. More aggressive treatment methods can be implemented in early stage patients who demonstrate a hypercoagulative state. Application of palliative treatments instead of chemotherapy in late stage disease may reduce drug-related costs and improve patient comfort.

Coagulation and fibrinolytic system constitutes an important component of the prognosis of lung cancer. This system plays significant roles in various processes from the early period of tumor formation until the patient's death (1). Even though it may not be clinically manifest in most cancer cases, subclinical coagulation system activation is often present and this phenomenon can be demonstrated by various markers (4,5). Measurement of DD levels can be sufficient to detect coagulation and fibrinolytic system activation. In the light of the above-mentioned features, DD levels might be used as a beneficial test in defining present disease status, planning further investigations, and selecting proper treatment. Similar approach can also be applied to other malignant disorders.

The relationship between cancer and the coagulation system has first been described by Trousseau. Trousseau has explained this phenomenon in 1865; shortly before he was diagnosed with gastric cancer. One out of 7 patients hospitalized with the diagnosis of cancer dies due to pulmonary emboli. There is localized cancer and/or limited metastasis in 60% of these patients. Frequency of thromboembolic events in lung cancer patients varies between 6% and 8%. Still, true rates for thromboembolic events are unknown owing to lack of information in clinical trials and difficulties in performing full diagnostic work-up in every patient (11).

Trousseau has demonstrated that systemic activation of coagulation and fibrinolytic system is involved in almost every cancer case. He has stated that prothrombin time (PT) and activated partial thromboplastin time (aPTT) may be prolonged or reduced, and that there is an increase in thrombin production markers such as activated coagulation factors (e.g. fibrinogen, TAT, or F 1+2). Later on, clinical (evident by thromboembolic events) or subclinical activation of coagulation and fibrinolytic system has been demonstrated in numerous studies conducted in different cancer types. It has been established in these studies that survival rate is worse in these patients and activation of the coagulation and fibrinolytic system significantly contributes to tumor spread through various mechanisms.

The relationship between coagulation and fibrinolytic system markers and survival has also been investigated. Activation of the coagulation and fibrinolytic system in cancer patients can be assessed by the measurement of DD levels. High DD levels are found to be correlated with late stage disease and short survival. DD levels show an increase following chemotherapy and surgery. Although diverse results have been obtained in various studies performed in lung cancer subgroups, DD level correlation with poor outcome is more marked in adenocarcinoma (9,12). Hypercoagulability and fibrinolytic system markers are directly correlated with tumor stage and high levels of tumor markers (2). DD levels tend to rise in several tumor types including lung cancers (1). Survival rates are relatively poor in patients with high DD levels (12).This relationship is more pronounced especially in adenocarcinoma cases. Compared to early stage (stage I, II, III) disease, DD levels are significantly higher in late stage (stage IV) disease (10,13). Similarly, there was a significant difference between Stage IIIB and IV patients in our study.

In our study, mean and median DD level was 4110 ± 3732 ng/ml and 842 ± 3121 ng/ml, respectively. It was less than 500 ng/ml in only 4.3%, between 500 and 1000 ng/dl in 5.7%, and greater than or equal to 1000 ng/dl in 94.3% of our patients.

Tagucci et al. have examined their cases in 2 categories: those with DD levels less than 150 ng/ml and those with DD levels greater than or equal to 150 ng/ml (13). However, DD level was found to be greater than 150 ng/dl in all of our lung cancers cases.

High DD levels have previously been correlated with late stage disease and short survival (9). In our study, DD levels were correlated with survival ($P = 0.012$) and histopathological type ($P = 0.002$) as well.

Unsal et al. have reported that mean survival time was 154 days (95% CI: 122-188 days) in patients with high DD levels, and 308 days (95% CI: 227-409 days) in cases with low DD levels ($P < 0.01$) (10). In our study, median survival time was 5.60 ± 2.45 months in patients with DD levels greater than 2850 ng/dl, and 12.6 ± 0.61 months in patients with DD levels less than 2850 ng/dl ($P = 0.002$). Thus, high DD levels were associated with a significantly shorter survival time. High DD levels were determined to be an independent risk factor in both monovariate ($P = 0.013$) and multivariate ($P = 0.014$) regression analyses.

Incidence of thromboembolic events in lung cancer patients varies between 6% and 8% (11). Thromboembolic events have been detected in 7 (10%) of our patients. Median survival time was 9.40 ± 3.65 months and 11.77 ± 1.10 months in patients with and without thromboembolism, respectively. The difference between these groups was statistically significant ($P = 0.042$). Thromboembolism has been found to be an independent risk factor for shorter survival in both monovariate ($P = 0.005$) and multivariate regression ($P = 0.065$) analyses.

Incidence of thromboembolic events was noted as 10% in this study, whereas it has was reported between 6% and 8% worldwide (11). This figure may be lower than expected since thromboembolic events are frequently missed and underdiagnosed in patients with malignancies. Especially, signs of pulmonary embolism may be difficult to differentiate from the symptoms of lung cancer. Mortality and morbidity may significantly be reduced by monitorisation of coagulation markers and administration of low molecular weight heparin in the early disease period.

In conclusion, there are many prognostic factors in lung cancer patients. Coagulation and fibrinolytic system activation have an important role among these factors. Survival was shorter in cases with coagulation/fibrinolytic system activation even if this phenomenon may not be clinically evident. Survival is substantially shortened in cases with thromboembolic complications. Mortality and morbidity may significantly be reduced by early detection

of coagulation markers and administration of low molecular weight heparin in these patients.

DD levels were significantly high and correlated with short survival in our lung cancer patients. DD levels were higher than 500 ng/dl in 95.7% of the cases. Significant difference was noted in SCLC cases of late stage and extensive disease. DD level has been determined as an independent risk factor for increased mortality in lung cancer patients. DD level can be used as an inexpensive screening tool in lung cancer patients in order to determine the high risk patients for thromboembolic event and initiate early treatment modalities.

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