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Clinical and prognostic significance of coagulation assays in lung cancer

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Summary
Activation of coagulation and fibrinolysis is frequently encountered among cancer patients. Such tumors are supposed to be associated with higher risk of invasion, metastases and eventually worse outcome. The aim of this study is to explore the prognostic value of blood coagulation tests for lung cancer patients. The study comprised 110 lung cancer patients. Pretreatment blood coagulation tests including PT, aPTT, PTA, INR, D-dimer, fibrinogen levels and platelet counts were evaluated. The plasma level of all coagulation tests revealed statistically significant difference between patient and control group ($p < 0.001$). There was a significant association between D-Dimer levels and histological subtypes of NSCLC, pointing an elevated plasma D-dimer level in squamous cell cancer ($p = 0.035$). Patients with extensive stage SCLC exhibited evidently higher levels of D-Dimer, INR and PLT ($p = 0.037$, $p = 0.042$, $p = 0.04$, respectively). Prolongation of PT and INR had statistically significant adverse effect on survival ($p = 0.05$ and $p = 0.014$, respectively). Although prolonged aPTT and high levels of D-dimer was associated with worse survival, the difference was not statistically significant ($p = 0.117$, $p = 0.104$). Multivariate analysis revealed INR as the sole independent prognostic variable among coagulation parameters ($p = 0.05$). In conclusion, elevation of PT and INR are associated with decreased survival in lung cancer patients.

Introduction

The relationship between cancer and coagulation is characterized by several mechanisms pointing that tumor biology and coagulation are closely linked processes.[1] It is now well established that clotting activation is frequently encountered in cancer, typically manifesting as a low-grade

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disseminated intravascular coagulation or venous thromboembolism either due to cancer itself or agents used for treatment. Patients with tumors of lung, pancreas and gastrointestinal tract are supposed to be more prone to hypercoagulable state.[2] Thus, clinical consequences of thrombosis can be serious with a negative impact on the course of disease, increasing morbidity and mortality.

Importantly, rather than being merely a trigger of increased thromboembolic events, cancer induced hemostatic activity has been shown to promote tumor growth and cancer cell dissemination.[3] Recent studies have suggested that hemostatic abnormalities observed in cancer patients may lead to recruitment of inflammatory cells, generation of tumor stroma and angiogenesis.[4] For instance, tumors activating coagulation system are supposed to behave more aggressively with higher risk of invasion and metastasis. High levels of circulating biomarkers resembling activated coagulation and fibrinolytic system such as fibrinogen, fibrin (ogen) split products and D-dimer have been associated with decreased survival for several tumor types in previous studies.[5–8] Research activities among lung cancer patients investigating the relationship between activated hemostatic system and prognosis have revealed similar results.[9–12] These findings have emerged studies evaluating the effect of anticoagulants in adjunct with chemotherapy mainly in SCLC patients.[13] Although a survival benefit was observed in that study, sufficient evidence of such an advantage was not provided for cancer patients in general. However, understanding the potential pathways responsible for activated hemostatic/fibrinolytic activity may help indentifying surrogate markers for novel therapeutic targets in the near future.

The aims of the current study are to confirm whether some coagulation abnormalities are more frequently encountered with lung cancer and to delineate the correlation of these coagulation tests with other clinical and laboratory variables.

Patients and methods

This study comprised 110 consecutive patients with histologically or cytologically confirmed non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) treated in outpatient or inpatient clinics of Istanbul University, Institute of Oncology. Patients with bidimensionally measurable disease without history of chemo/radiotherapy in the last six months were included in the study. The pathological diagnosis of lung cancer was established in accordance with the revised World Health Organization classification of lung tumors[14] and staged relying on the revised TNM staging for lung cancer.[15] The pretreatment evaluation included detailed clinical history and physical examination with a series of biochemistry tests, complete blood cell counts and coagulation tests. Those with ECOG performance status $\leq$2 and appropriate blood chemistry tests received chemotherapy on outpatient basis comprising platinum compounds with/without radiotherapy depending on the stage of disease. Follow up programs consisted of clinical, laboratory, radiological assessments performed at 8 weeks intervals during chemotherapy or every 12 weeks for no anticancer treatment. Response to treatment was determinated according to revised RECIST criteria version 1.1.[16] For comparison of coagulation assays, age and sex matched 50 healthy controls were included in the analysis. Institutional review board approval and informed consent was obtained from all patients prior to the commencement of the study.

Biochemical assays

Venous blood samples were collected in tubes containing sodium citrate before initiation of chemotherapy for the measurement of parameters, centrifuged immediately and studied within 2 h. D-dimer values were determined by Microparticle Enzyme Immunoassay (MEIA) using AxSYM analyzer (Abbott Laboratories, Chicago, Illinois, USA) following the manufacturer's instructions. Commercially available reagents provided by the kinetic nephelometric detection system using Diagon Dia-Timer 4 (Diagon Ltd, Budapest, Hungary) were employed for PT, aPTT and Fibrinogen measurement. Prothrombin activity (PTA) reflects calibration of PT. For calibration, sample pool is supposed to have 100% activity. After serial dilutions 50%, 25% and 12.5% activity of sample is obtained, tested again in the device and each value corresponding to a level of activity is plotted in the graphics of PT calibration. The device utilizes these values for generating a log–log axis. Each result positioned to this axis corresponds to an activity of prothrombin measured as percentage.

Statistical analysis

Continuous variables were categorized using median values as cut-off point. Assessment of relationships, comparisons between various clinical/laboratory parameters and coagulation tests including D-dimer, fibrinogen, PT and aPTT were accomplished using Mann–Whitney *U* test and Kruskal–Wallis test for two and three groups, respectively. For comparison of D-dimer values among different histologic subtypes Kruskal Wallis test was performed initially and then Bonferroni correction was applied. Survival was calculated from the date of first contact of patient to death resulting from any cause or to last contact with the patient or any family member. Kaplan–Meier method was used for estimation of survival distribution; differences in survival were assessed by the log-rank statistic. Multivariate survival analysis was performed using the Cox's proportional hazards regression model. A p value <0.05 was considered significant in this purely exploratory analysis. Statistical analysis was carried out using SPSS 16.0 software.

Results

From June 2010 to July 2011, 110 consecutive patients with a pathologically confirmed diagnosis of lung cancer were enrolled into this study. Baseline histopathological characteristics and demographic features of patients are listed in Table 1. Median age at diagnosis was 59-years old, range 35–80 years, where males constituted majority of the group (n = 100, 91%).

Table 1 Patient characteristics.

	%
No. of patients: 110	100
Age, years	
Median (range): 59 (35–80)	
−60	52
60+	48
Gender	
Male	91
Female	9
Histology	
Non-small cell	84
Adeno	30
Squamous	26
Others (unclassified)	28
Small cell	16
Stage of disease	
Non-small cell lung cancer	
Local (stage I + II)	6
Locally advanced (stage III)	33
Metastatic (stage IV)	45
Small cell lung cancer	
Limited	5
Extensive	11
Serum hemoglobin level	
Low (<12 g/dL)	29
Normal (>12 g/dL)	71
Serum WBC count	
Normal (<11,000)	77
Elevated (>11,000)	23
Serum platelet count	
Normal (<350,000)	65
Elevated (>350,000)	35
Erythrocyte sedimentation rate (/h)	
Normal (<40)	45
Elevated (>40)	55
Serum LDH level	
Normal (<450 U/L)	75
Elevated (>450 U/L)	25
Response to chemotherapy	
Responsive (CR* + PR*)	47
Non-responsive (SD* + PD*)	53
Last status	
Alive	72
Dead	28

*CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease.

Comparison of coagulation tests between patients and healthy controls

The plasma level of all coagulation tests including D-dimer, fibrinogen (F), prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR) and platelet counts revealed statistically significant difference between patient and control group ($p < 0.001$ for all variables but for PT; $p = 0.045$) (Table 2).

Coagulation tests and their correlations with other variables

The relationships between clotting tests and other laboratory variables including lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), hemoglobin (Hb) level, white blood cell (WBC) count and clinical characteristics of the patients are summarized in Table 3. There was a statistically significant association between D-Dimer levels and histological subtypes of NSCLC, squamous cell lung cancer patients exhibited higher plasma D-dimer levels when compared with nonsquamous carcinoma patients excluding adenocarcinoma subtype ($p = 0.007$). Extensive stage SCLC was also associated with evidently higher levels of D-Dimer, INR and PLT when compared with limited stage disease (for D-dimer; 200 vs 718 IU/ml $p = 0.037$, for INR; 1.02 vs 1.1 $p = 0.042$, for PLT; 248 000/mm^3 vs 347 000/mm^3, $p = 0.04$). However, a similar association between stages of NSCLC and D-Dimer levels was not demonstrated ($p = 0.554$). Besides there was statistically no significant relationship between age distributions, Hb, LDH levels, WBC counts and coagulation tests. A significant correlation was found between gender and coagulation factor tests such as PT, aPTT and INR ($p = 0.043$, $p = 0.008$ and $p = 0.014$, respectively) but not for fibrinogen and D-dimer, suggesting a higher tendency to activated coagulation cascade among male patients when compared with female subjects. In addition, elevated platelet counts were associated with resistance to chemotherapy (252 000/mm^3 vs 337 000/mm^3, $p = 0.048$), but other factors involved in coagulation pathway did not seem to correlate with response to chemotherapy. Analogously, there was not a significant correlation with any of the coagulation tests and ESR or platelet counts.

Survival analysis

Median follow-up time was 20.3 weeks (range 4.4–72.6 weeks). Median survival for all patients was 57 weeks (95% CI 45.6–68.3 weeks). At the end of observation, 31 patients (28%) were dead due to disease related or unrelated factors.

Evaluation of the effect of clinical and laboratory variables confirmed the acknowledged negative impact of elderly age (above 60 years) and primary resistance to chemotherapy on survival ($p = 0.009$ and $p < 0.001$, respectively) (Table 4). Among the laboratory variables, elevated serum LDH level was associated with worse overall survival (62.1 vs 30.8 weeks for normal and elevated LDH levels, respectively, $p = 0.001$). Evaluation of clotting factors revealed that prolongation of PT and INR had statistically significant adverse effect on survival ($p = 0.05$ and $p = 0.014$, respectively) (Figs. 1 and 2). Although patients with higher levels of D-Dimer, fibrinogen and aPTT had prominently worse outcome when compared with those below the median range, the difference in survival was not statistically significant (6-months survival rates 80.3 vs 68.5%, $p = 0.117$; 81.6 vs 75.1%, $p = 0.186$; 79.3% vs 64.9%, $p = 0.104$, respectively). Multivariate analyses were performed with Cox's proportional hazards regression analyses. Prognostically significant variables with a p value ≤ 0.05 including age, INR, LDH and response to

Table 2 The values of serum coagulation tests in patients with lung cancer and healthy controls.

Coagulation tests	Patients ($n = 110$)		Controls ($n = 50$)		p
	Median	Range	Median	Range	
D-dimer (IU/ml)	360	22–5900	37.8	0–118.5	<0.001
Fibrinogen (mg/dl)	410	131–1705	245	166–463	<0.001
PT (sec)	14.6	9.4–18.8	14.2	10.5–16.8	0.045
aPTT (sec)	27.2	19.8–44.0	31.8	24.6–48.0	<0.001
PTA (%)	81	51.1–276	88.4	69.8–139.9	<0.001
INR	1.10	0.68–2.70	1.01	0.76–1.29	<0.001
Platelet ($\times 10^3/mm^3$)	289	81–710	201	163–254	<0.001

chemotherapy were included in the analysis; PT was excluded due to the high correlation with INR. Consequently, only elevated INR was independently associated with worse survival in addition to elderly age (for age, HR: 0.10, 95% CI 0.013–0.813, $p = 0.031$; for INR, HR: 0.23, 95% CI: 0.05–1.045, $p = 0.05$). 1 year survival rate for patients with high and low INR was 44.8% (±1.1) and 74.1% (±1.1) respectively.

Discussion

A systematic activation of clotting system has been observed in cancer patients which is usually reflected by subclinical abnormalities of conventional coagulation tests.[17,18] Despite numerous studies dealing with the causes of hypercoagulability and thromboembolic complications in

Table 3 Results (median and range) of comparisons between the coagulation tests and various clinical parameters.

Parameters	Coagulation tests[a]						
	D-dimer (IU/ml)	Fibrinogen (mg/dl)	PT (sec)	aPTT (sec)	PTA (%)	INR	PLT ($\times 10^3/mm^3$)
Gender							
Male	363	420	***14.7***	***27.7***	***78.2***	***1.12***	289
Female	227	369	***14.1***	***23.7***	***87.1***	***1.04***	324
	($p = 0.567$)	($p = 0.724$)	***($p = 0.043$)***	***($p = 0.008$)***	***($p = 0.034$)***	***($p = 0.014$)***	($p = 0.524$)
Histology							
Non-small cell							
Adeno	***281***	415	14.4	26.9	81	1.1	287
Squamous	***733***	363	14.6	27.2	79.5	1.09	292
Others	***227***	429	14.9	28.3	75.5	1.15	285
	($p = 0.035$)*	($p = 0.557$)	($p = 0.982$)	($p = 0.641$)	($p = 0.944$)	($p = 0.68$)	($p = 0.457$)
Stage of disease							
Small cell lung cancer							
Limited	***200***	378	14.3	26.5	87.4	***1.02***	***248***
Extensive	***718***	425	14.6	26.3	81.0	***1.1***	***347***
	($p = 0.037$)	($p = 0.648$)	($p = 0.315$)	($p = 0.914$)	($p = 0.073$)	***($p = 0.042$)***	***($p = 0.040$)***
Serum Platelet count							
Normal	313	***337***	***14.5***	27.6	***83***	***1.09***	
Elevated	388	***521***	***14.8***	26.7	***76.3***	***1.13***	–
	($p = 0.065$)	***($p = 0.001$)***	***($p = 0.05$)***	($p = 0.548$)	***($p = 0.024$)***	***($p = 0.018$)***	
ESR							
Normal	226	***329***	***14.1***	27.0	***83.8***	***1.04***	***265***
Elevated	521	***521***	***15.3***	27.4	***74.5***	***1.14***	***357***
	($p = 0.093$)	***($p < 0.001$)***	***($p < 0.001$)***	($p = 0.401$)	***($p < 0.001$)***	***($p = 0.002$)***	***($p = 0.002$)***
Response to chemotherapy							
Responsive	222	377	14.6	26.7	81	1.09	***252***
Non-responsive	511	438	14.4	27.7	81	1.09	***337***
	($p = 0.068$)	($p = 0.396$)	($p = 0.806$)	($p = 0.154$)	($p = 0.947$)	($p = 0.636$)	***($p = 0.048$)***

Bold italics means the values that statistically significant ($p < 0.05$).
**For adeno vs squamous, $p = 0.118$; squamous vs others, $p = 0.007$; adeno vs others $p = 0.455$.
[a] Median values for each parameter.

patients suffering from malignancy, the mechanisms are still not completely understood. There is some evidence that the activation of coagulation and fibrinolytic system by neoplastic cells facilitates invasiveness and metastases.[12] Thus, the extent of such activation has been associated with tumor stage and prognosis in some malignancies such as breast, colorectal and lung cancer.[7,19,20] The purpose of this study was to gain further evidence for prognostic value of routine clotting tests while predicting lung cancer patients' outcome.

So far various markers reflecting activated hemostatic system such as thrombocytosis, hyperfibrinogenemia and elevated D-dimer levels have been demonstrated in different types of cancer involving head and neck, colon, prostate and lung cancer.[21,22] The current study also confirmed the existence of a significant difference between healthy control subjects and lung cancer patients with respect to coagulation tests such as PT, aPTT, INR, D-dimer, fibrinogen levels and platelet counts. In our study D-dimer values were remarkably elevated in patient group when compared with healthy subjects due to activation of both coagulation and fibrinolytic system ($p < 0.001$). Although the mechanism by which coagulation is activated in cancer is multifactorial, tissue factor (TF) is traditionally recognized to play an important role in this process. Increased level of expression of tissue factor by cancer cells and release of TF by platelets, monocytes and stromal cells

Table 4 Univariate analyses.

Characteristic	Overall survival		
	Median (weeks)	6-Month (±SD) (%)	*p* Value
Age (years)			
<60	**57**	**86.3 (5.3)**	**0.009**
>60	**37**	**62.9 (7.6)**	
Gender			
Male	57	71.8 (5.3)	0.415
Female	49	75.0(2.1)	
Histology			
Non-small cell	57	77.1 (5.0)	0.446
Small cell	50.5	75.0 (2.1)	
Non-small cell subtypes			
Adeno	62.1	86.4 (6.4)	0.358
Squamous	37.8	78.3 (8.7)	
Others (unclassified)	NR[#]	65.7 (10.1)	
Stage of disease			
Non-small cell			
Nonmetastatic	62	88.9 (5.3)	0.109
Metastatic	57	65.1 (8.1)	
Small cell lung cancer			
Limited	NR	100	0.103
Extensive	24.4	48.9 (16.6)	
Serum hemoglobin level			
Low	NR	68.0 (8.9)	0.412
Normal	57.0	76.9 (5.7)	
Serum WBC count			
Normal	57.0	72.8 (5.6)	0.829
Elevated	NR	79.8 (9.2)	
Erythrocyte sedimentation rate			
Normal	62	85.7 (6.8)	0.524
Elevated	NR	73.0 (7.8)	
Serum LDH level			
Normal	**62.1**	**86.0 (4.4)**	**0.001**
Elevated	**30.8**	**50.1 (13.6)**	
Response to chemotherapy			
Responsive (PR* and CR*)	**27.0**	**94.5 (3.8)**	**<0.001**
Non-responsive (SD* and PD*)	**NR**	**54.6 (9.6)**	
D-dimer			
Normal (<median value)	62.1	80.3 (6.4)	0.117
Elevated (>median value)	50.5	68.5 (9.5)	
Fibrinogen			
Normal (<median value)	NR	81.6 (6.8)	0.186
Elevated (>median value)	57.0	78.5 (6.4)	
PT			
Normal (<median value)	**NR**	**80.7 (6.6)**	**0.05**
Elevated (>median value)	**30.8**	**58.8 (10.6)**	
aPTT			
Normal (<median value)	NR	79.3 (7.1)	0.104
Elevated (>median value)	30.8	64.9 (9.9)	
INR			
Normal (<median value)	**NR**	**81.7 (6.4)**	**0.014**
Elevated (>median value)	**30.8**	**57.5 (9.6)**	
Platelet			
Normal (<median value)	62.1	69.9 (7.3)	0.763
Elevated (>median value)	57.0	78.5 (6.4)	

Bold values represent statistically significant values ($p < 0.05$).
[#]NR = not reached. *CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease.

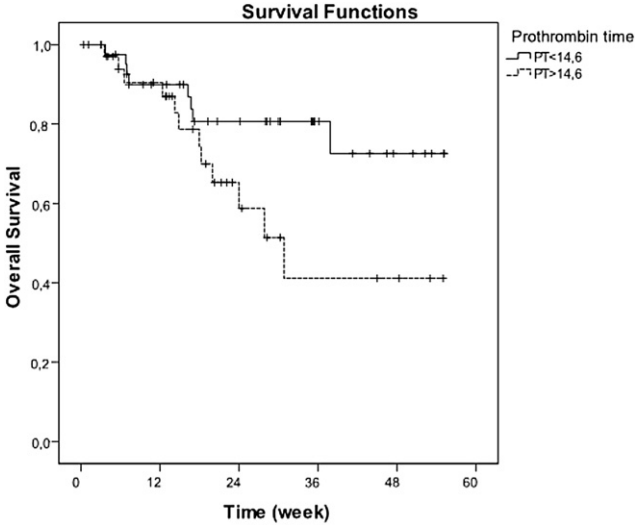

Figure 1 Overall survival curves in patients with lung cancer according to PT levels ($p = 0.05$). <Median value, solid lines; >median value, dashed lines.

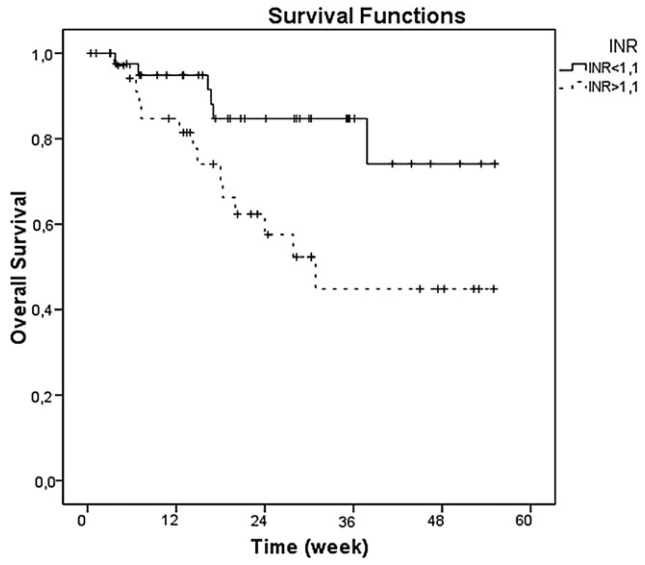

Figure 2 Overall survival curves in patients with lung cancer according to INR levels ($p = 0.014$). <Median value, solid lines; >median value, dashed lines.

contribute as a major source of procoagulant activity.[17,23,24] The coagulation cascade initiated by this transmembrane glycoprotein triggers a number of events which in turn converts prothrombin to thrombin and generates the insoluble fibrin clot. Assuming that fibrinogen level is normal, a prolonged PT signifies a deficiency, depletion of coagulation factors or presence of a specific inhibitor of factors involved in this cascade.[25] Prolongation of PT was strongly associated with poor prognosis in non-small cell lung cancer patients previously but in that report the multivariate model did not confirm the prognostic relevance of any coagulation factor.[26] Our study had also revealed the significance of prolonged PT and INR in univariate analysis but additionally the multivariate analysis of survival emphasized the impact of INR for lung cancer patients. There was also a tendency toward decreased survival for patients with prolonged aPTT but it was not statistically significant (6 months survival rate 79.3% vs 64.9%, $p = 0.104$).

Various studies in this era have demonstrated that increased D-dimer as a marker of coagulation and fibrinolytic activation is a strong predictor of poor prognosis for non-small-cell lung cancer.[27–29] In the current study there was a tendency toward decreased survival for patients with elevated D-dimer levels but it did not reach statistical significance (6 months survival rate 80.3% vs 68.5%, $p = 0.117$). However, in our SCLC patient subgroup extensive stage disease was associated with higher levels of D-dimer.

In clinical practice, prolongation of PT with aPTT due to depletion of coagulation tests is a well-known marker for disseminated intravascular coagulation (DIC). In this state, plasminogen activator inhibitor-1 (PAI-1) and tissue factor (TF) are induced excessively and production of thrombomodulin is restricted to the vascular endothelium.[30] Our findings also support the presence of a low grade DIC in lung cancer patients and its unfavorable effect on survival.

Fibrinogen as one of the major plasma proteins is synthesized in the liver and secreted into the circulation. Although fibrinogen synthesis is significantly upregulated by inflammatory stimulation, the precise mechanism in malignancy has not been elucidated yet. Inflammatory cytokines such as IL-6 secreted from cancer cells are supposed to induce production of fibrinogen from the liver. Thus, hypersecretion of fibrinogen may overcome depletion of coagulation tests by ongoing DIC process.[31] In our study patients with elevated fibrinogen levels had a tendency to decreased survival which did not reach statistical significance. This finding is in concordance with the recent study reporting the correlation of particularly high fibrinogen levels with shorter disease-free survival in colorectal cancer.[32]

Studies conferring evidence of anticoagulation for cancer patients have revealed conflicting results. There is not sufficient data for survival benefit from oral anticoagulants in cancer patients generally; however heparin has provided an advantage for improved survival encouraging administration of novel anticoagulant therapies for both antithrombotic and antitumor effect.[33] Besides, identification of subgroups which will benefit most from anticoagulation is necessary. Our study may suggest a particular subset of patients with poor prognosis as a candidate for anticoagulation. Although high INR is supposed to be associated with hemorrhagic diathesis for patients under oral anticoagulation therapy, it also reflects a depletion of coagulation tests due to increased thrombotic process in our patient group. However further investigation is required before adjusting these assumptions to our daily practices.

The current study confirms that subclinical changes in coagulation-fibrinolytic system are often present in lung cancer. Prolongations of PT and INR have been associated with poor prognosis in univariate analysis and multivariate analyses have revealed the negative impact of elevated INR on survival. Based on these findings, we may advocate the use of coagulation assays particularly PT and INR test in any new lung carcinoma patient to provide a foresight about the outcome and constitute a surrogate marker for treatment with novel anticoagulants in the near future.

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None.

Conflict of interest statement

None.

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