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ORIGINAL ARTICLE

Research on the coagulation function changes in non small cell lung cancer patients and analysis of their correlation with metastasis and survival

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Summary

Purpose: *To investigate the relationship between coagulation function and prognosis of non-small cell lung cancer (NSCLC) patients.*

Methods: *539 patients who were admitted to our hospital for the first time from December 2008 to December 2013 and pathologically diagnosed as NSCLC were enrolled in this study (study group), while 80 healthy persons served as controls (control group). Morning fasting venous blood samples were collected for coagulation function indexes, such as prothrombin time (PT), prothrombin time activity (PTA), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen (Fib), D-dimer (D-D) and platelet count (PLT) and the coagulation function and survival rate were compared.*

Results: *All coagulation function indexes (PT, PTA, INR, APTT, Fib, D-D and PLT) in the study group patients were significantly different compared with the control group. PTA and APTT in the control group were longer compared with the study group, and PT in the study group was significantly longer compared with control group. No obvious correlation between age and the coagulation function indexes was found. Gender correlated significantly to PT, PTA, INR and APTT. Fib and PLT levels in stage I-II NSCLC patients were significantly higher than those in stage III-IV NSCLC patients. Fib level increased, PT and INR were prolonged and PTA declined significantly and patient survival rate was significantly reduced.*

Conclusion: *Most NSCLC patients have abnormal coagulation function, and each coagulation index may be used to judge the prognosis as well as survival of such patients.*

Key words: *coagulation function, NSCLC, prognosis, survival*

Introduction

NSCLC is a life-threatening illness and the most common cause of death, compared with all other types of lung cancer [1]. NSCLC patients account for a larger proportion of all other types of lung cancer [1]. In most cases, NSCLC cannot be detected in the early phases [2]. There is an obvious relationship between the lymph node metastasis, TNM staging and the coagulation function where hypercoagulability and hyperfibrinolysis occur generally. In addition to lung cancer, other malignant tumors may also cause abnormal coagulation function from mild to severe [3].

This study investigated the relationship between coagulation function and prognosis in NSCLC patients. We believe that the results of the present study can be used as reference for preventing hypercoagulable state in patients suffering from lung cancer, and to also improve the prognosis and reduce the mortality to a certain extent.

Methods

General information

539 patients who were admitted to our hospital for

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the first time from December 2008 to December 2013 and pathologically diagnosed as NSCLC were enrolled in this study. There were 350 males and 189 females aged 21-82 years (median 58). For this study the data collected were age, gender, presence of lymph node metastasis, TNM staging and coagulation function. Blood coagulation function indexes included PT, PTA, INR, APTT, Fib, D-D and PLT. Eighty healthy individuals served as controls. The inclusion criteria were patients admitted to our hospital for the first time and pathologically diagnosed as NSCLC. Exclusion criteria: (i) patients younger than 18; (ii) patients who were treated within 12 months prior to the beginning of the study; (iii) patients who were not available for interviews and visits during one year after the study. During the follow-up period, general conditions and patients' laboratory test results were collected through phone interviews.

Study instrumentation and indexes values

Morning fasting venous blood samples were collected for coagulation function index analysis. Instruments used in this experiment included CA-40 automatic coagulation process analysis equipment and auxiliary reagents, Beckman Coulter fully automatic hematology analyzer and auxiliary reagents for PLT. The normal reference value of each coagulation function index was as follows: PT (9-12s), PTA (80-160%), INR (08-1.2), APTT (28-41s), Fib (2.00-4.40 g/l), D-D (0-1.00 mg/l) and PLT (100-300 *10^9/l).

Statistics

SPSS19.0 was used for statistical analysis. Chi-square test was used for enumeration data, and multivariate Cox hazards regression analysis was used to assess survival. Kaplan-Meier curves were generated

Table 1. Comparison of differences in the coagulation function indexes between the study and control group

Coagulation function indexes	*Study group*		*Control group*	
	Median	*Range*	*Median*	*Range*
PTA（%）	97	31-140	116	105-137
PT（s）	12.1	9.7-27.8	9.9	8.5-10.7
INR	1.06	0.87-2.13	0.92	0.81-0.96
Fib（g/l）	3.98	2.09-10.13	2.16	1.89-3.70
APTT（s）	31.9	20.8-54.9	32.3	29.6-31.8
D-D（mg/l）	0.3	0.1-8.4	0.2	0.1-0.3
PCT（*10^9/l）	269	126-677	208	116-253

For abbreviations see text

Table 2. Relationship between coagulation function indexes and clinical data of NSCLC patients

Clinical data	*Coagulation function index*					
	PT (s)	*PTA (%)*	*INR*	*APTT (s)*	*Fib (g/l)*	*D-D (mg/l)*
Age, years						
>65	11.6	98	1.07	30.6	4.20	0.1
<65	11.0	97	1.05	31.3	4.21	0.1
p value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Gender						
Male	11.5	96	1.06	33.9	4.28	0.1
Female	11.1	99	1.07	31.0	4.00	0.3
p value	<0.05	<0.05	<0.05	<0.05	<0.05	>0.05
TNM stage						
I-II	11.5	99	1.07	39.2	3.96	0.2
III-IV	11.3	96	1.04	30.8	4.31	0.2
p value	>0.05	>0.05	<0.05	<0.05	<0.05	>0.05
Lymph node metastasis						
N0	11.0	106	1.06	33.6	3.76	0.2
N1-N3	11.3	98	1.03	30.9	4.19	0.3
p value	>0.05	>0.05	>0.05	<0.05	<0.05	<0.05

For abbreviations see text

for survival analysis and log-rank test was used to explore differences between groups. P <0.05 meant that the difference was statistically significant.

Results

Comparison of differences in the coagulation function indexes between study and control group

All coagulation function indexes (PT, PTA, INR, APTT, Fib, D-D and PLT) in the study group were significantly different compared with the control group. PTA and APTT in the control group were longer than those in the study group, and PT in the study group was significantly longer than that in the control group. INR, Fib, D-D and PCT levels in the study group were obviously higher than those in the control group, with statistical significance (p<0.05) (Table 1).

Relationship between coagulation function index and clinical data of NSCLC

Data, including age, gender, TNM staging, and lymph node metastasis were assessed. No obvious correlation between age and the coagulation function indexes was found. Gender correlated significantly to PT, PTA, INR and APTT (p<0.05). Fib and PLT levels in stage I-II NSCLC patients were significantly higher than those in patients with stage III-IV (p<0.05), but there was no significant correlation with PT, PTA and INR. For patients with lymph node metastasis, Fib and D-D levels of N1-N3 nodal stage were significantly higher compared with N0 patients (p<0.05), but there was no significant correlation with PT, PTA, INR and PLT (Table 2).

Relationship between coagulation function index and survival

Fib level increased, PT and INR were prolonged and PTA declined significantly with significant reduction of survival (p<0.05) (Table 3, Figures 1, 2 and 3).

Multivariate analysis of survival of NSCLC patients

Multivariate Cox regression analysis revealed that only the high or low INR levels were independent risk factors affecting prognosis and survival (p<0.05) (Table 4).

Table 3. Relationship between coagulation function indexes and survival of NSCLC patients

Coagulation function		*Median*	*95% CI*		x^2
			Low limit	*High limit*	
PTA	<median	20	14.791	23.199	7.779
	>median	22	13.148	30.001	
PT	<median	25	19.001	35.007	4.672
	>median	17	14.793	21.796	
INR	<median	29	21.137	35.653	11.853
	>median	18	14.912	19.176	
APTT	<median	22	14.899	28.253	1.577
	>median	21	15.976	22.198	
Fib	<median	35	28.914	41.176	30.002
	>median	16	11.794	16.159	
D-D	<median	19	14.116	21.769	2.531
	>median	16	9.412	20.001	
PLT	<median	23	17.159	28.067	2.151
	>median	19	15.017	22.098	
Gender	<median	20	15.119	20.768	1.319
	>median	30	21.012	34.019	
Age	<median	21	15.139	23.146	2.412
	>median	18	11.615	19.018	
TNM staging	<median	40	29.018	41.049	102.3
	>median	15	13.016	16.163	
Lymph node metastasis	<median	47	36.073	59.083	82.49
	>median	15	36.073	59.083	82.49

For abbreviations see text

Table 4. Multivariate analysis of survival of NSCLC patients

Coagulation function	*B*	*SD*	*Wald*	*DOF*	*Test value*	*HR*
TNM staging	1.839	0.612	7.332	1	0.008	7.003
INR	0.499	0.198	5.614	1	0.020	1.712

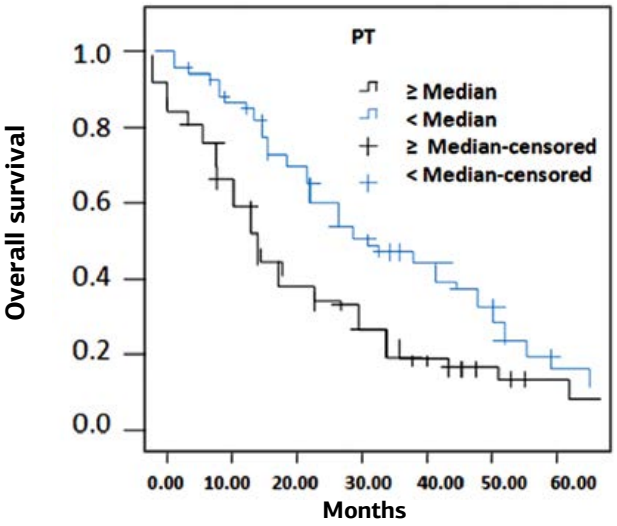

Figure 1. Overall survival in patients with NSCLC according to PT levels (p=0.028).

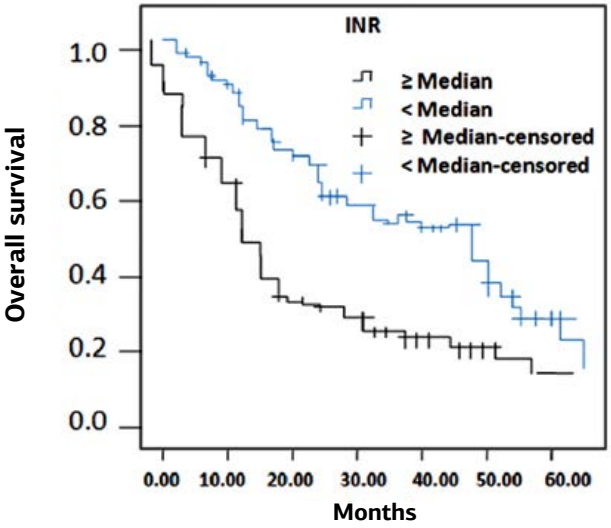

Figure 2. Overall survival in patients with NSCLC according to INR levels (p=0.001).

Discussion

Patients with malignant tumors often suffer from different degrees of abnormal coagulation. It has been reported that as many as 94% of cancer patients suffer from one or more abnormal coagulation functions. This situation is worst in patients with advanced tumors with systemic multiple metastases [4]. Patients with lung cancer often suffer from thrombosis, and the hypercoagulable state, hyperfibrinolysis and disease progression may promote further advancement of the tumor [5]. There is a limited number of reports about the coagulation function changes in NSCLC patients, but relevant research has argued that the correlation between further progression of NSCLC and coagulation function changes are generally related to the following reasons [6]: the molecular weight of fib is larger in all plasma components, while the higher levels of fib in NSCLC patients could increase the risk of high blood coagulation. Under the effect of prothrombin and other molecules, fib can combine with platelets to form thrombus, thus further protecting the tumor cells from the blows of the immune system and enhancing the establishment and the in-depth infiltration and metastasis [7]. There are studies showing that the

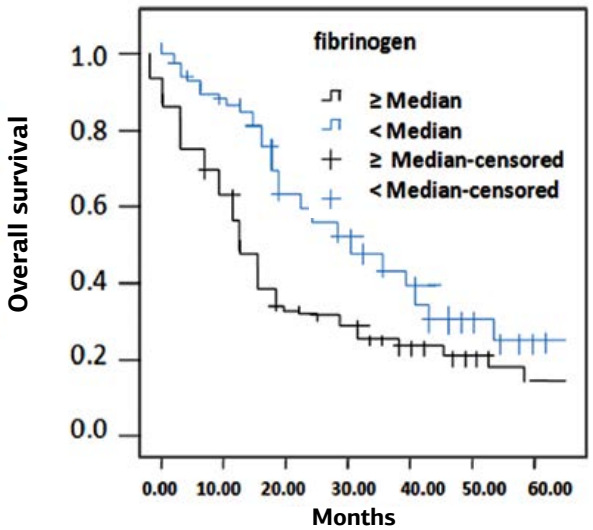

Figure 3. Overall survival in patients with NSCLC according to fibrinogen levels (p=0.001).

loss of blood coagulation factors in the process of thrombosis prolongs PT and APTT [8] and cancer cells in NSCLC patients may generate molecules such as the tumor necrosis factor (TNF) which can promote thrombosis [9]. On the other hand, it can also increase the interaction between coagulation and anti-coagulation factors, resulting in abnor-

mal indexes of coagulation [10]. Based on the high blood coagulation and hyperfibrinolysis, endothelial cells promote the progression of disease to more advanced stages and multiple metastases [11].

The results of this study suggested that there were obvious differences in the coagulation indexes between the study and control group. D-D level in the study group increased more significantly compared to that of the control group. There were significant differences in the lymph node metastasis, Fib and APTT in TNM staging in NSCLC patients, and at the same time, the multivariate analysis of survival confirmed that INR level was an independent risk factor affecting the prognosis of NSCLC.

There are several studies reporting on the activation of coagulation function in patients with malignant tumors, which leads to thrombosis [12]. It is more likely for patients to suffer of thrombosis or hemorrhage, which negatively affects their survival [13]. In the case of over consumption or low generation of anti-coagulation factors, and higher generation or low consumption of coagulation factors, the hypercoagulable state of blood may lead to thrombosis [14]. The coagulation system plays an important role in stopping the bleeding and promoting wound healing [15]. Among cancer patients, the imbalance between anti-coagulation and coagulation molecules makes NSCLC patients candidates for thrombosis. Previous studies showed that there are two types of coagulants: the cancer cell pro-coagulant (CP) and tissue factor (TF) [16]. In the process of blood coagulation in NSCLC patients, TF acts as an important factor for activation of coagulation, but normal cells do not express TF. However, a small amount of TF is secreted in some cases, e.g. inflammatory stimuli. CP is a protein produced and secreted by malignant tumor cells. CP can directly stimulate TF and lead to the aggregation of coagulation factors, blood hypercoagulable state or embolism [17].

We conclude that the imbalance between coagulation and anticoagulation factors in NSCLC patients led to the infiltration and spread of cancer cells. Nevertheless, it is unclear whether the abnormal blood coagulation can promote lymph node metastasis or hematogeneous metastasis in NSCLC patients. Also, it is still unclear whether the anticoagulant therapy may improve the effect of treatment [18]. Cancer cells in NSCLC patients can secrete fib, and fib combines with fibroblast growth factors and promotes the growth of tumor cells. It is known that the megakaryocyte in the marrow hematopoietic system can promote platelet proliferation, and the aggregation of a large number of platelets produced by cancer cells facilitates cancer metastasis [19].

The abnormal coagulation in NSCLC patients is mainly characterized by the imbalance in hypercoagulability and fibrinolysis, which increases the risk of thrombosis. Blood coagulation in NSCLC patients in early disease stage should be detected and analyzed as soon as possible [20], and early detection can improve the prognosis and increase survival.

Conflict of interests

The authors declare no confict of interests.

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