JBUON 2019; 24(2): 585-590
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Correlations of coagulation indexes and inflammatory changes with the prognosis of lung cancer complicated with thromboembolic disease

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Summary

Purpose: *To investigate the correlations of coagulation indexes and inflammatory changes with the prognosis of lung cancer (LC) patients complicated with thromboembolic (TE) disease.*

Methods: *A total of 84 LC patients complicated with TE disease admitted to hospital from January 2010 to January 2016 were enrolled in this study and their clinical data were retrospectively analyzed. A 2-year post-treatment follow-up was carried out. According to the prognosis, patients were divided into 2 groups as dead group (n=25) and alive group (n=59). The coagulation indexes and inflammatory factor levels before low-molecular weight heparin (LMWH) treatment and on the 1st, 3rd, and 7th day after treatment were compared between the two groups. Their relations with the prognosis of patients were analyzed using Pearson method.*

Results: *No statistically significant difference was found in the prothrombin time (PT), levels of Fibrinogen (FIB), D-Dimer (D-D), Interleukin-6 (IL-6) and Procalcitonin (PCT), and activated partial thromboplastin time (APTT) before treatment between the two groups (p>0.05). The PT and levels of FIB, D-D, IL-6, and PCT on the 1st, 3rd, and 7th day after treatment were significantly increased in the dead group compared to those in the alive group, while the APTT was remarkably shortened. Moreover, the PT was gradually prolonged and FIB, D-D, IL-6 and PCT levels were increased in the dead group , but the APTT was gradually shortened over time (p<0.05). The poor prognosis of LC patients complicated with TE disease was positively correlated with PT, FIB, D-D, IL-6 and PCT, but negatively correlated with APTT (p<0.05).*

Conclusion: *The poor prognosis of LC complicated with TE disease has positive correlations with PT, FIB, D-D, IL-6 and PCT, and a negative association with APTT, providing a certain reference as a prognostic value in the diagnosis and treatment.*

Key words: *lung cancer, thromboembolic disease, coagulation index, inflammatory factor, correlation*

Introduction

Lung cancer (LC), as the most common malignant tumor in clinical practice, ranks first among malignant tumors in terms of mortality and incidence rates [1]. With the rapid development of the economy and accelerated industrialization in China in recent years, the surrounding environment is getting worse and the pressure of life and work is increasing, leading to gradually increased number of smokers, and further resulting in elevated incidence rate. Besides, the relatively high mortality rate of the disease makes it more harmful to patients [2]. Studies have manifested that the formation of thrombi may be the clinical syndrome advantage of malignancies, so the common complications of malignant tumors include embolism and thrombosis [3]. Venous thromboembolism (VTE)

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Received: 12/09/2018; Accepted: 03/10/2018

occupies an important position in leading causes of cancer-related death and ranks second only to the malignant tumor itself in causes of death of patients with tumors [4]. There are three distinct types of TE diseases in LC as follows: capillary thrombosis, arterial embolism, and venous embolism, mainly including peripheral arterial embolism, superficial venous thrombosis, cerebral thrombosis (CT), pulmonary embolism (PE) and deep venous thrombosis (DVT). In addition, some of the classic exam signs of DVT/PTE include tachycardia, tachypnea and hypotension [5]. Moreover, most LC patients are complicated with various range of diseases such as diabetes and coronary heart disease, resulting in long-term bed rest, which makes patients far more prone to thrombosis. Furthermore, therapies including hormones, blood transfusions, surgery, central venous catheterization, and chemotherapy increase the incidence rate of thrombosis to a certain extent [6]. At the same time, concurrent thrombosis in patients with LC will also affect the therapeutic effect against tumor, reducing the quality of life along with survival expectancy and resulting in poor prognosis. A study revealed that the coagulation parameters and inflammatory factor levels in LC patients complicated with TE disease are closely related to their prognosis [7]. Therefore, herein their correlations were analyzed in order to provide a reference parameter for a prognostic value in the diagnosis and treatment of LC patients complicated with TE disease.

Methods

General data

The clinical data of 84 LC patients complicated with TE disease admitted to our hospital from January 2010 to January 2016 were retrospectively analyzed. The post-treatment follow-up period was 2 years. These patients were divided into 2 groups according to the prognosis as dead group (n=25) and alive group (n=59). There were no statistically significant differences in general data including age, gender, and type of thromboembolism between the groups (p>0.05) (Table 1).

Inclusion and exclusion criteria

Inclusion criteria: 1) Patients meeting the diagnostic criteria for LC and TE [8,9]; 2) Those definitely diagnosed through pathology and color Doppler, magnetic resonance imaging (MRI, or computed tomography; 3) Those with complete clinical data; and 4) Patients and their families who agreed and actively cooperated in this study and signed the written informed consent form.

Exclusion criteria: 1) Patients with thrombosis before the definite diagnosis of LC; 2) Patients without clear pathological diagnosis of LC.

Treatment methods

All patients were treated with oxygen inhalation and strict bed rest. In all patients with DVT, the extremity was elevated at 15°-30° and wet compress with magnesium sulfate was applied for local superficial phlebitis [10]. At admission, patients were intravenously pumped with 2 mL/L Low-Molecular-Weight Heparin (LMWH) sodium [national medicine permission number (NMPN) H32020612, Jiangsu Wanbang Biochemical Pharmaceutical Group Co., Ltd., Xuzhou, China] to maintain the Activated Partial Thromboplastin Time (APTT) at about 2 times higher than the normal value. If the APTT was higher than 35 s, heparin infusion was appropriately reduced by 0.1 mL/L, while it was increased for adjustment when the APTT was lower than 35 s. When the International Normalized Ratio (INR) of plasma prothrombin in patients was 2-3, the administration of LMWH sodium was stopped and then warfarin (NMPN H31022123, Shanghai Xinyi Pharmaceutical Co., Ltd., Shanghai, China) was orally given at a dose of 3.75 mg/d to maintain the INR at 2-3. If the INR was less than 2, the dose of warfarin was increased by 25%. If the INR was greater than 3, the dose of warfarin was reduced by 25%. When

Table 1. Comparisons of baseline data between the two groups

	Dead group (n=25) *n (%)*	*Alive group (n=59)* *n (%)*	t/x^2	*p*
Male/female	14/11	34/25	0.019	0.890
Age (years), range	35-85	36-85	-	-
Mean age (years)	56.58±6.52	56.74±6.68	0.101	0.460
PTE	7 (28.00)	16 (27.12)	0.007	0.934
PTE due to lower extremity VTE	4 (16.00)	10 (16.95)	0.046	0.831
Lower extremity VTE	7 (28.00)	18 (30.51)	0.053	0.818
Upper extremity VTE	1 (4.00)	2 (3.39)	0.120	0.788
Internal jugular VTE	1 (4.00)	2 (3.39)	0.120	0.788
Supraclavicular venous embolism	1 (4.00)	3 (5.08)	0.000	0.990
Cerebral thrombosis	3 (12.00)	6 (10.17)	0.019	0.890
Peripheral artery embolism	1 (4.00)	1 (1.69)	0.000	0.992

For abbreviations see text

the INR was normal, treatment with warfarin was maintained for PTE for 6-12 months. LC patients complicated with DVT were intravenously injected with urokinase (NMPN H10920040, Nanjing Nanda Pharmaceutical Co., Ltd., Nanjing, China) at a dose of 20,000-40,000 units/d and the dose was appropriately adjusted according to the condition of patients. For those complicated with CT, in addition to routine anticoagulant therapy, concurrent therapy with Herba Erigernotis was administered to promote the blood circulation and remove blood stasis, mannitol was given to reduce intracranial pressure, and aspirin (NMPN H20065051, Shenyang Original Pharmacolabo, Shenyang, China) was given to prevent platelet aggregation.

Observation indexes

1) Detection of inflammatory indexes: Fasting venous blood (5 mL) samples were collected from patients in the morning before treatment and on the 1st, 3rd, and 7th day after treatment, followed by centrifugation at the centrifugal radius of 10.5 cm and AT A speed of 3000 r/min for 10 min using a centrifuge (Ortho BioVue, Johnson & Johnson (Shanghai, China) Medical Equipment Co., Ltd.). Then, the supernatant was collected and stored in a refrigerator at -75°C. The serum procalcitonin (PCT) level was measured via double-antibody sandwich immuno-luminescence assay. Enzyme-linked immunosorbent assay was applied to determine the serum interleukin-6 (IL-6) level. The kits were purchased from Diagreat (Beijing, China) and the operation was performed strictly according to the instructions. 2) Measurement of coagulation indexes: The plasma D-Dimer (D-D) was detected by automatic immunoturbidimetry and the APTT, prothrombin time (PT), and plasma fibrinogen (FIB) of patients were measured before and after anesthesia using a fully automatic coagulation analyzer (sta-r evolution, asnières-sur-seine, France).

Statistics

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used to sort and analyze the above data. Quantitative data were expressed as mean±SD and subjected to t-test. Numerical data were expressed as percents (%) and subjected to x^2 test. Pearson's correlation coefficient was employed to analyze the correlations of coagulation indexes and inflammatory changes with prognosis. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of PT before and after treatment between the two groups

Before treatment, the difference in PT was not statistically significant between the two groups (p>0.05). However, the PT in the dead group was clearly longer than that in the alive group on 1st, 3rd and 7th day after treatment. Moreover, the PT was gradually prolonged with time in the dead group (p<0.05) (Table 2).

Table 2. Comparison of PT before and after treatment between the two groups (mean±SD)

	Before treatment	*1st d*	*3rd d*	*7th d*	*F*	*p*
Alive group (n=59)	11.52±0.87	11.64±0.59	11.61±1.64	11.87±1.36	0.879	0.256
Dead group (n=25)	11.46±0.85	12.97±1.01	13.68±2.14	14.85±2.15	8.924	<0.001
t	0.283	7.154	4.623	7.780		
p	0.389	<0.001	<0.001	<0.001		

d: day

Table 3. Comparison of APTT before and after treatment between the two groups (mean±SD)

	Before treatment	*1st d*	*3rd d*	*7th d*	*F*	*p*
Alive group (n=59)	36.79±3.74	36.56±3.66	36.47±3.54	36.84±3.61	0.842	0.301
Dead group (n=25)	36.84±3.67	35.02±2.89	34.10±2.74	32.05±2.15	8.910	<0.001
t	0.055	1.831	2.926	6.094		
p	0.478	0.036	0.002	<0.001		

d: day

Table 4. Comparison of FIB levels before and after treatment between the two groups (mean±SD)

	Before treatment	*1st d*	*3rd d*	*7th d*	*F*	*p*
Alive group (n=59)	3.41±1.02	3.48±1.05	3.57±1.08	3.54±1.11	0.614	0.548
Dead group (n=25)	3.39±1.04	4.28±1.21	5.34±1.36	6.85±1.58	9.215	<0.001
t	0.079	2.943	6.099	10.473		
p	0.469	0.002	<0.001	<0.001		

d: day

Table 5. Comparison of D-D levels before and after treatment between the two groups (mean±SD)

	Before treatment	*1st d*	*3rd d*	*7th d*	*F*	*p*
Alive group (n=59)	1.04±0.53	1.08±0.51	1.07±0.53	1.15±0.46	0.754	0.478
Dead group (n=25)	1.01±0.48	1.54±0.64	1.77±0.68	2.35±0.57	8.910	<0.001
t	0.238	3.362	4.874	9.777		
p	0.406	0.001	<0.001	<0.001		

d: day

Table 6. Comparison of IL-6 levels before and after treatment between the two groups (mean±SD)

	Before treatment	*1st d*	*3rd d*	*7th d*	*F*	*p*
Alive group (n=59)	49.56±6.87	50.15±7.21	50.10±7.16	53.47±7.10	0.587	0.582
Dead group (n=25)	49.42±6.94	68.94±8.25	85.69±7.12	94.71±7.69	7.885	<0.001
t	0.083	10.096	20.262	22.979		
p	0.467	<0.001	<0.001	<0.001		

d: day

Table 7. Comparison of PCT levels before and after treatment between the two groups (mean±SD)

	Before treatment	*1st d*	*3rd d*	*7th d*	*F*	*p*
Alive group (n=59)	0.57±0.12	0.78±0.15	0.69±0.32	1.24±0.67	0.456	0.697
Dead group (n=25)	0.54±0.09	1.39±0.21	4.68±0.98	6.89±1.34	9.216	<0.001
t	0.101	14.401	26.049	24.261		
p	0.137	<0.001	<0.001	<0.001		

d: day

Table 8. Correlation analyses of coagulation parameters and inflammatory changes with the prognosis in LC patients complicated with TE

	r	*p*
PT	0.684	0.015
APTT	-0.217	0.017
FIB	0.374	0.023
D-D	0.869	<0.01
IL-6	0.781	0.005
PCT	0.537	0.014

For abbreviations see text

Comparison of APTT before and after treatment between the two groups

No statistically significant difference was found in APTT between the groups before treatment (p>0.05), whereas the dead group had significantly shorter APTT on 1st, 3rd and 7th day after treatment compared to alive group. Besides, the APTT was gradually shortened over time in dead group (p<0.05) (Table 3).

Comparison of FIB levels before and after treatment between the two groups

There was no statistically significant difference in FIB levels between the two groups before treatment (p>0.05). The FIB levels in the dead group were significantly higher than that in the alive group on 1st, 3rd and 7th day after treatment and gradually elevated over time (p<0.05) (Table 4).

Comparison of D-D levels before and after treatment between the two groups

No evident difference was detected in D-D levels between the two groups before treatment (p>0.05), whereas the dead group had significantly increased D-D levels on the 1st, 3rd and 7th day after treatment compared to the alive group. Besides, the D-D level was gradually increased over time in the dead group (p<0.05) (Table 5).

Comparison of IL-6 levels before and after treatment between the two groups

Before treatment, the difference in IL-6 level was not evident between the two groups (p>0.05). However, the IL-6 level in the dead group was remarkably elevated compared to that in the alive group on the 1st, 3rd and 7th day after treatment. Moreover, the IL-6 level was gradually increased over time in the dead group (p<0.05) (Table 6).

Comparison of PCT levels before and after treatment between two groups

There was no statistically significant difference in PCT levels between two groups before treatment

(p>0.05). The PCT levels in the dead group were significantly higher than those in the alive group on 1st, 3rd and 7th day after treatment, and gradually elevated with time (p<0.05) (Table 7).

Correlation analyses of coagulation parameters and inflammatory changes with the prognosis in lung cancer patients complicated with thromboembolic disease

Poor prognosis of LC patients complicated with TE was positively associated with PT, FIB, DD, IL-6 and PCT, and negatively correlated with APTT (p<0.05) (Table 8).

Discussion

Most LC patients complicated with TE disease have the sign of coagulation disorder and blood coagulation system is an enzymatic process, in which the coagulation factors of the body endogenously or exogenously participate [11]. PT and APTT can accurately reflect the activity and content of coagulation factors in the coagulation system. The results showed that after surgery, the APTT was shortened, the PT was prolonged, and the consumption of various coagulation factors was relatively evident, leading the body of patients to a hypercoagulable state. The endogenous pathway in patients is activated by the exogenous initiation of tissue factors, and the contact of negatively charged foreign bodies with blood surface [12]. This may be due to the production of massive foreign bodies and tissue factors caused by the damage of the vascular endothelium under the action of external stress during the treatment [13]. Besides, various inflammatory factors in the body may also promote the production of tissue factor, further facilitating the formation of thrombin and decomposing FIB to form a succinct fibrin polymer, which aggravates thrombosis and affects prognosis [14]. D-D and FIB are specific indicators reflecting the hypercoagulable state and hyper-fibrinolysis of the body. D-D is a kind of characteristic metabolite formed through the decomposition of fibrin by plasmin and can reflect the dissolution and formation of fibrin, and thrombus in the body [15]. FIB is a fibrin polymer produced by the liver, which is high in the blood and relatively has a strong cross-linking network function. It is able to cross-link various blood cells to lead to the formation of blood clots and activate platelets by binding to glycoprotein [16]. In this study, the D-D and FIB levels were remarkably increased in dead group after treatment, suggesting that after treatment, the coagulation system is activated via response to external stress , resulting in the formation of a large number of thrombi and the increase in the production of D-D and FIB, and further aggravating the embolism, which is positively related to poor prognosis.

Due to the influences of external physical and chemical factors, metabolites, toxins, and pathogen components, a large number of inflammatory transmitters are released in LC patients complicated with TE, excessively activating mononuclear macrophages in surrounding tissues and thus promoting alveolar endothelial cells and epithelial cells to synthesize and secrete numerous inflammatory factors. IL-6, as a pro-inflammatory factor, can induce the inflammatory chemotaxis in the body. The accumulation of massive neutrophils in the inflammation sites leads to the production of numerous nitric oxide, reactive oxygen species, and free radicals, increases vascular permeability, and inhibits the repair of vascular endothelium [17]. In addition, it is positively correlated with the severity of infection and thrombosis in patients, has certain specificity and sensitivity for the diagnosis of bacterial infection, and can guide the application of antibiotics in patients with LC. Moreover, it has a certain predictive value for the prognosis of patients [18]. Furthermore, the synergistic effect, overlapping function, and diversity of cytokines related to inflammatory response jointly reflect the body's response to inflammatory stimuli and tumors, so it is not feasible to predict the prognosis of patients through individual inflammatory factors [19]. However, the over-activated "inflammation-coagulation" network and coagulation function are induced by peripheral inflammatory transmitters in LC patients complicated with TE disease with poor prognosis, resulting in inhibition of the anticoagulant activity in the body and also resulting in the chemotaxis, migration and uncontrolled release of inflammatory mediators, thereby further aggravating the disorder of coagulation function, and exacerbating the inflammatory response in return [20]. Therefore, poor prognosis is positively associated with the inflammatory response.

In conclusion, the poor prognosis of lung cancer complicated with thromboembolic disease is positively correlated with PT, FIB, D-D, IL-6 and PCT and negatively related to APTT, providing a certain reference for the prognostic value in the diagnosis and treatment of disease.

Conflict of interests

The authors declare no conflict of interests.

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