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A Correlation Analysis of Postoperative Hypercoagulability and Peripheral Circulating Tumor Cells in Patients with Lung Cancer

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Abstract: *Objective:* To explore the correlation between peripheral circulating tumor cells and hypercoagulability in patients with lung cancer after surgery. *Methods:* From January 2017 to December 2021, 89 patients with lung cancer who were treated in the Affiliated Hospital of Hebei University were selected as the research subjects, and a retrospective analysis was conducted to analyze and observe the D-dimer (DD), fibrinogen (FIB), and platelet (PLT) levels in peripheral blood, as well as detect peripheral CTC. *Results:* There were statistical differences in TMN staging, tumor metastasis, and lymph node metastasis in the clinical data, but there were no statistical differences in gender, smoking history, and pathological classification. After retrospective analysis and comparison of the patients, the DD (mg/ml), FIB (g/L), and PLT ($\times 10^9$/L) levels of the CTC positive group were 3.41 ± 0.58, 3.98 ± 0.87, and 367.26 ± 34.98, respectively; the CTC negative group's DD (mg/ml), FIB (g/L), and PLT ($\times 10^9$/L) levels were 0.89 ± 0.49, 1.06 ± 0.45, and 234.69 ± 35.69, respectively, and the differences were statistically significant. The factors affecting the prognosis of patients included TMN staging and CTC; the number of CTC positives in the death group was significantly higher than that in the survival group, and there was a statistical difference between the groups. Gender, age, smoking history, pathological type, and surgical resection had no effect on the prognosis of patients. Among the enrolled patients, the survival rate was 71.91%. *Conclusion:* CTC-positive patients have a higher probability of hypercoagulability after surgery and are prone to tumor metastasis; thus, CTC can be used as a judgment index for the prognosis of patients.

Keywords: Lung cancer; Hypercoagulable state; Peripheral circulating tumor cells

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1. Case study

Lung cancer is the leading cause of cancer-related death in both, men and women worldwide [1]. According to its pathological classification, it can be divided into two categories: small cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Clinically, non-small cell lung cancer patients account for about 85%, and most of them are diagnosed after the cancer has metastasized or at an advanced stage [2]. Despite significant advancements in the surgical management of lung cancer in recent years and the potentiality to treat locally advanced or distant metastatic tumors using various methods, such as radiotherapy, chemotherapy, targeted therapy [3], and immunotherapy [4], the cure rate of patients is still very low, and their prognosis is poor, thus posing a serious threat to human health [5-7] . In recent years, with the improvement of people's living standards and health awareness, the concept of regular physical examination has gained recognition, thereby increasing the early detection rate and surgical rate of lung

cancer, but postoperative recurrence and metastasis remain the primary causes of high mortality in non-small cell lung cancer patients.

2. Materials and methods

2.1. General information

From January 2017 to December 2021, 89 patients with lung cancer who were treated in the Affiliated Hospital of Hebei University were selected as the research subjects for retrospective analysis. Among them, 41 were CTC positive patients, and 48 were CTC negative patients, in which 64 of them survived, and 25 of them died. The clinical data of the enrolled patients and their follow-up data were complete.

2.2. Methods

An automatic blood coagulation analyzer and its supporting reagents (STAGO, France) were used to detect D-dimer (DD) and fibrinogen (FIB) levels in patients; another reagent (Minray BC-6088) was used to detect the level of platelets (PLT) in patients. CTC detection was based on CellSearch system, and the related reagents, consumables, as well as its detection methods and judgment standards are based on literature [8,9].

The patients were followed up from the day of the surgery via telephone or outpatient follow-up. The end point was either the death of the patient or the deadline for the follow-up (December 2021). The patients were divided into the death group and the survival group based on the end point to analyze the risk factors affecting the prognosis.

2.3. Observation indicators

The levels of DD, FIB, and PLT in peripheral blood, as well as CTC detection were observed and analyzed.

2.4. Statistical analysis

SPSS 19.0 and GraphPad Prism 6.0 were used for data analysis. The experimental data were expressed as mean ± standard deviation ($\bar{x} \pm s$); one-way analysis of variance (one-way ANOVA) was used to compare the means of each group, and SNK-q test was used for pairwise comparison analysis. The difference was considered statistically significant when $p < 0.05$.

3. Results

3.1. Comparing the clinical data of the two groups of patients

There were statistical differences in TMN staging, tumor metastasis, and lymph node metastasis in the clinical data, but there were no statistical differences in gender, smoking history, and pathological type, as shown in **Table 1**.

Table 1. Comparison of clinical data of the two groups of patients

Group		CTC positive group (n = 41)	CTC negative group (n = 48)	X^2	*p*
Gender	Male	21 (51.22)	23 (47.92)	0.0965	0.7561
	Female	20 (48.78)	25 (52.08)		
Age	≥ 60	24 (58.54)	23 (47.92)	1.0007	0.3171
	< 60	17 (41.46)	25 (52.08)		
Smoking history	Yes	21 (51.22)	23 (47.92)	0.0965	0.7561
	No	20 (48.78)	25 (52.08)		
TMN staging	Stage I/II	12 (29.27)	30 (62.50)	9.7988	0.0017
	Stage III	29 (70.73)	18 (37.50)		

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Group		CTC positive group (n = 41)	CTC negative group (n = 48)	X^2	*p*
Pathological type	Lung adenocarcinoma	14 (34.15)	16 (33.33)	0.2299	0.8914
	Lung squamous cell carcinoma	16 (39.02)	17 (35.42)		
	Small cell lung cancer	11 (26.83)	15 (31.25)		
Tumor metastasis	Yes	28 (68.29)	17 (35.42)	9.5611	0.0020
	No	13 (31.71)	31 (64.58)		
Lymph node metastasis	Yes	27 (65.85)	16 (33.33)	9.3648	0.0022
	No	14 (34.15)	32 (66.67)		

3.2. Comparing the coagulation indices between the two groups of patients

After retrospective analysis and comparison of the enrolled patients, the DD (mg/ml), FIB (g/L), and PLT ($\times 10^9$/L) levels of the CTC positive group were 3.41 ± 0.58, 3.98 ± 0.87, and 367.26 ± 34.98, respectively, whereas the DD (mg/ml), FIB (g/L), and PLT ($\times 10^9$/L) levels of the CTC negative group were 0.89 ± 0.49, 1.06 ± 0.45, and 234.69 ± 35.69, respectively; the differences were statistically significantly, as shown in **Table 2**.

Table 2. Comparison of coagulation indices between the two groups of patients

Group	DD (mg/ml)	FIB (g/L)	PLT ($\times 10^9$/L)
CTC positive group (n = 41)	3.41 ± 0.58	3.98 ± 0.87	367.26 ± 34.98
CTC negative group (n = 48)	0.89 ± 0.49	1.06 ± 0.45	234.69 ± 35.69
t	22.2214	20.3027	17.6273
p	0.0000	0.0000	0.0000

3.3. Analyzing the influencing factors for the prognosis of patients with lung cancer postoperatively

The factors affecting the prognosis of patients in this study were TMN staging and CTC. The number of CTC positives in the death group was significantly higher than that in the survival group, and there was a significant difference between the two groups. Gender, age, smoking history, pathological type, and surgical resection had no effect on the prognosis of patients. Among the enrolled patients, the survival rate was 71.91%, as shown in **Table 3**.

Table 3. Analysis of the influencing factors for the prognosis of lung cancer patients after surgery

Group		Death group (n = 25)	Survival group (n = 64)	X^2	*p*
Gender	Male	14 (56.00)	30 (46.88)	0.5988	0.4390
	Female	11 (44.00)	34 (53.12)		
Age	≥ 60	12 (48.00)	35 (54.69)	0.3226	0.5700
	< 60	13 (52.00)	29 (45.31)		
Smoking history	Yes	11 (44.00)	33 (51.56)	0.4113	0.5213
	No	14 (56.00)	31 (48.44)		
TMN staging	Stage I/II	6 (24.00)	36 (56.25)	7.5028	0.0062
	Stage III	19 (76.00)	28 (43.75)		

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Group		Death group (n = 25)	Survival group (n = 64)	X^2	*p*
Pathological type	Lung adenocarcinoma	8 (32.00)	22 (34.38)	0.1334	0.9355
	Lung squamous cell carcinoma	9 (36.00)	24 (37.50)		
	Small cell lung cancer	8 (32.00)	18 (24.12)		
CTC	Positive	18 (72.00)	23 (35.94)	9.4102	0.0022
	Negative	7 (28.00)	41 (64.06)		
Surgical resection	Total lobectomy	11 (44.00)	31 (48.44)	0.1420	0.7063
	Partial lobectomy	14 (56.00)	33 (51.44)		

4. Discussion

In terms of morbidity and mortality, lung cancer ranks first among malignant tumors. Among the cases, 85% of them are non-small cell lung cancer (NSCLC). Although the treatment of NSCLC has made great progress in recent years, the 5-year survival rate of patients is still only about 17%. Surgery is still the preferred treatment for early-stage lung cancer patients. Although postoperative adjuvant chemotherapy can delay tumor recurrence and metastasis, tumor metastasis is still the main cause of death in lung cancer patients. Numerous studies have demonstrated that circulating tumor cells (CTCs) play a key role in the distant metastasis of tumors. CTCs are an independent marker that can predict the survival of patients, and there is a correlation between the number of CTCs and tumor invasion, metastasis, and the time to recurrence [1-7].

Lung cancer is the most common cancer and the leading cause of cancer death in China [2]. According to pathological classification, it can be divided into two categories: SCLC and NSCLC. Clinically, NSCLC patients account for about 85%. Lung cancer is a serious threat to human health as the number of deaths from lung cancer accounts for about 18% of deaths from all cancers each year, and the 5-year survival rate is less than 20%. On the one hand, the early detection and diagnosis of lung cancer pose a challenge. The cure rate of carcinoma in situ is nearly 100%, and the 5-year survival rate of stage I and II lung cancer is about 25% to 73%, but the 5-year survival rate of stage III and IV lung cancer is greatly reduced to 2% to 24%. Traditionally, the diagnosis of lung cancer mainly relies on imaging investigations and histopathological results. However, the former has poor sensitivity for nodules with a diameter of less than 1 cm in the lungs. It is even more difficult to identify CTCs in the blood and micrometastases in other organs, thus often resulting in missed diagnosis of early lung cancer. On the other hand, the recurrence and metastasis of lung cancer after surgery seriously affect the prognosis of patients, which are attributable to minimal residual disease (MRD) [3]. For patients with stage III and above lung cancer, MRD may be derived from residual primary tumor lesions or lymph node metastases after surgery. For patients with early-stage lung cancer recurrence and metastasis after surgery, MRD may be derived from some occult metastases. Most tumor cells are blocked and cleared by the body's immune system, but a small part that is in a static state under the surveillance of the immune system gets activated under the stimulation of certain factors, resulting in the spread and metastasis of malignant tumors [4]. As a non-invasive, real-time, and effective detection method, liquid biopsy is helpful for early diagnosis and prognostic evaluation of patients [6]; it can predict tumor recurrence 1 to 2 years earlier than the progress of radiology [7]. At present, the commonly used CTC detection technology is the FDA-approved CellSearch system, which uses ferromagnetic beads coated with antibodies against epithelial cell surface specific markers, namely epithelial cell adhesion molecule (EpCAM). After initial CTC enrichment, the high expression of CK9, CK18, or CK19 with the low expression of leukocyte surface antigen CD45 based on cell or nuclear morphology, the positive immunofluorescence staining of nuclei, as well as the expression of detectable epithelial cytokeratin (CK)

further promote the identification and enumeration of CTCs [10-15].

Hypercoagulable state is the premise and basis of deep vein thrombosis. DD is the end product of cross-linked fibrin decomposed by plasmin, and its level is an important indicator of hypercoagulable state and abnormal fibrinolytic function. The coagulation factor with the highest content in the plasma is the acute phase reactive protein synthesized by the liver. The level of FIB is closely related to tumor recurrence and metastasis, and it is an important indicator for clinical tumor monitoring. Through the active coagulation factors secreted by tumor cells, platelets will adhere and aggregate. In addition, tumor cells also secrete platelet-derived growth factor, which promotes the rapid growth of tumor cells in the metastatic site. Therefore, the level of PLT is closely related to tumor occurrence, development, and metastasis [16-20].

In conclusion, CTC positive patients have a higher probability of hypercoagulability after surgery and are prone to tumor metastasis; thus, it can be used as a judgment index for the prognosis of patients.

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