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ORIGINAL ARTICLE

Cytokeratin 7 and thyroid transcription factor - 1 levels in patients with lung cancer complicated with superior vena cava syndrome and their correlation with clinicopathological characteristics

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Summary

Purpose: *This study aimed to detect the levels of cytokeratin 7 (CK7) and thyroid transcription factor -1(TTF-1) in serum of patients with non-small cell lung cancer (NSCLC) complicated with superior vena cava syndrome (SVCS), and to explore their prognosis and relationship and correlation with pathological characteristics.*

Methods: *68 patients with NSCLC complicated with SVCS treated in Shaoxing Second Hospital from July 2014 to May 2018 comprised the experimental group, 60 healthy persons comprised the control group, and 60 patients with lung cancer comprised the lung cancer group. The levels of CK7 and TTF-1 in the three groups were determined by enzyme-linked immunosorbent assay (ELISA), and the differences were compared. The relationship between the expression levels of CK7 and TTF-1 and clinicopathological characteristics of patients, the correlation between CK7 and TTF-1 in lung cancer patients complicated with SVCS, and their 3-year survival rate were analyzed.*

Results: *CK7 and TTF-1 levels in the experimental group were significantly higher than those in the control group ($p<0.05$). The levels in the lung cancer group were significantly higher than those in the control group ($p<0.05$). In the experimental group, the expression of CK7 and TTF-1 was not related to gender, age, weight, histological classification and tumor size ($p>0.05$)). CK7 expression was positively correlated with TTF-1 expression in lung cancer patients ($p<0.001$). The 3-year survival rate in the CK7 and TTF-1 high expression group was significantly lower than that in the low expression group ($p<0.05$).*

Conclusion: *The expressions of CK7 and TTF-1 are increased in patients with lung cancer complicated with SVCS, and are related to TNM stage, lymph node metastasis and grade of differentiation. The high expressions of CK7 and TTF-1 in serum of patients are expected to be potential prognostic indicators for lung cancer complicated with SVCS.*

Key words: *lung cancer, superior vena cava syndrome, CK7, TTF-1, clinicopathology, prognosis*

Introduction

Lung cancer, a malignant tumor with high incidence, poses a great threat to the health of patients. Treatment of lung cancer is associated with dismal conditions, of which superior vena cava syndrome (SVCS) is the most common [1]. SVCS, also known as SVC obstruction syndrome, is due to the fact that stenosis of vena cava prevents blood in SVC from refluxing, thus resulting in a series of symptoms such as dyspnea, dizziness, headache, upper limb edema, etc. [2]. Malignant obstruction can be caused by direct invasion of tumor into SVC or by external pressure of adjacent pathological processes involving right lung and lymph node to SVC, leading to blood flow stagnation and throm-

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bosis [3]. Surgical treatment of lung cancer with SVCS has a high mortality and complications, and the median survival is lower than that with radiotherapy and chemotherapy [4]. Among the factors inducing SVCS, 60-85% are thoracic malignant tumors, 50% are NSCLC and 25% are small cell lung cancer (SCLC) [5]. In the United States, the incidence of SVCS is about 15,000 cases per year, being a potential life-threatening disease. However, according to other authors, it is not fatal in most cases [6].

With the deep research of tumor biology, tumor molecular markers have become a research hotspot in assisting the diagnosis of malignant tumors. Cytokeratin 7 (CK7) is a low molecular weight cytokeratin with the anatomic distribution limited to epithelia and tumor. A study has pointed out that CK7 is expressed in most cancer tissues except colon cancer, prostate cancer, kidney cancer, thymic adenocarcinoma, pulmonary and gastrointestinal carcinoid and Merkel cell carcinoma [7], suggesting that it has certain diagnostic value. Another study has shown that thyroid transcription factor 1 (TTF-1) is linked to cancer genes [8]. Many downstream target genes of TTF-1 are reported to be related to the biology of lung cancer [9]. Skovira et al [10] found that TTF-1 may re-encode the proteome secreted by lung cancer cells into an anti-angiogenic state, providing a new basis for long-term observation of good prognosis for TTF-1. The increased expression of TFF-1 is shown to be involved in the occurrence and development of lung adenocarcinoma and is related to its severity and prognosis [11]. There are few reports on

Table 1. General data

Group	*Experimental group (n=68)* *n (%)*	*Control group (n=60)* *n (%)*	*Lung cancer group (n=60)* *n (%)*	x^2	*p*
Gender				0.011	0.995
Male	30 (44.12)	26 (43.33)	26		
Female	38 (55.88)	34 (56.67)	34		
Age (years)				0.037	0.982
>30	28 (41.18)	25 (41.67)	24		
≤30	40 (58.82)	35 (58.33)	36		
Weight (kg)				0.175	0.916
>60	27 (39.71)	22 (36.67)	24		
≤60	41 (60.29)	38 (63.33)	36		
Smoking				0.035	0.983
Yes	31 (45.59)	27 (45.00)	28		
No	37 (54.41)	33 (55.00)	32		
Excessive drinking				0.163	0.922
Yes	22 (32.35)	18 (30.00)	20		
No	46 (67.65)	42 (70.00)	40		
Histological classification				1.830	0.176
Squamous cell carcinoma	33 (48.53)	-	22		
Adenocarcinoma	35 (51.47)	-	38		
Differentiation grade				0.243	0.622
Moderately and highly differentiated	22 (32.35)	-	17		
Poorly differentiated	46 (67.65)	-	43		
TNM stage				0.515	0.473
I+II	28 (41.18)	-	21		
III+IV	40 (58.82)	-	39		
Lymph node metastasis				2.091	0.148
Yes	30 (44.12)	-	19.		
No	38 (55.88)	-	41		
Tumor size (cm)				2.091	0.148
<3	27 (39.71)	-	19.		
≥3	41 (60.29)	-	41		

CK7 and TTF-1 in lung cancer complicated with SVCS in recent years. Therefore, this experiment explored the level changes of CK7 and TTF-1 and their prognostic value in patients with lung cancer complicated with SVCS.

Methods

General data

68 patients with lung cancer complicated with SVCS treated in Shaoxing Second Hospital from July 2014 to May 2018 were selected as the experimental group, including 30 males and 38 females with an age range of 20-56 years and an average age of 43.64±11.63 years. Sixty healthy persons were selected as the control group, including 26 males and 34 females, with an age range of 22-55 years and an average age of 39.86±10.27 years. Another 60 patients with lung cancer were selected as the lung cancer group, including 26 males and 34 females with an age range of 23-54 years and an average age of 38.47±10.92 years.

Inclusion criteria: Patients diagnosed with lung cancer complicated with SVCS by pathological examination; patients cooperating with the medical staff to complete relevant diagnosis and treatment; patients with first onset of SVCS.

Exclusion criteria: patients with pulmonary diseases; patients with incomplete clinical data; patients failing to follow-up.

Patients and their families were informed in advance and signed an informed consent form. There was no significant difference in general data of age, gender, weight, excessive drinking and smoking among the three groups, p>0.05 indicating comparability (Table 1).

Sample collection

Fasting venous blood was collected in the morning, and centrifuged to obtain serum after 30-min standing. The serum was stored at -70°C for later use.

Reagents

CK7 ELISA Kit (Shanghai Caiyou Industry Co., Ltd., item no: 33060M), TTF-1 ELISA Kit (Shanghai Hengfei Biotechnology Co., Ltd., item no: SEG777Hu-1).

Detection of CK7 and TTF-1 levels with ELISA

The concentrations of CK7 and TTF-1 in serum samples were determined by ELISA. Standard wells were set on the ELISA plate, and the standard volume in each standard well was 50 µl with a concentration of 0.15-1.8 µg/L. Then, the blank wells and sample wells were respectively set. Forty µl of diluent was added into the sample wells, and 10 µl of sample was added into the wells, making the sample diluted 5 times, which was then mixed gently. Each reaction well was sealed with a sealing plate membrane and incubated at 37°C for 30 min. After diluting the concentrated material was washed with phosphate-buffered saline (PBS) 20 times with distilled water, the membrane was uncovered, and the liquid in the reaction wells was discarded. Each well was filled with diluted PBS stood for 30 s, and then dried. The step was repeated 5 times. Each reaction well was sealed with sealing membrane again, and incubated at 37°C for 30 min, washed 5 times, and added with 50 µl of each developer A and developer B. Chromogenic reaction was carried out in the dark at 37°C for 15 min. Finally, 50 µl of termination solution was added to terminate the reaction with yellow color appearing in the reaction

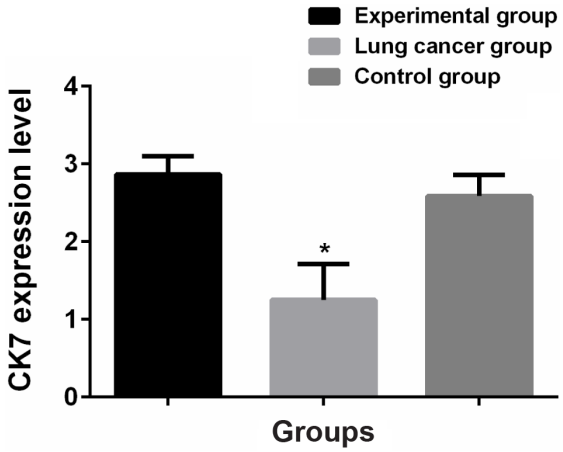

Figure 1. Expression of CK7 in the three groups. ELISA showed that the expression levels of CK7 in the experimental group, the control group and the lung cancer group were 2.87±0.23 ng/ml, 1.25±0.46 ng/ml and 2.59±0.27 ng/ml, respectively. Therefore, the expression of CK7 in the experimental group and the lung cancer group was significantly higher than that in the control group, and the differences were statistically significant (p<0.05). compared with experimental group and control group (*p<0.05).

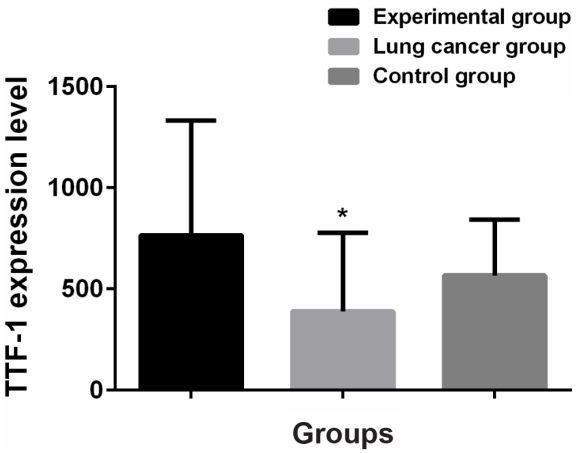

Figure 2. Expression of TTF-1 in the three groups. ELISA showed that the expression levels of TTF-1 in the experimental group, the control group and the lung cancer group were 765.65±565.64 pg/ml, 389.74±388.43 pg/ml and 567.46±274.87 pg/ml, respectively. So the expression of of TTF-1 in the experimental group and the lung cancer group was significantly higher than that in the control group, and the differences were statistically significant (p<0.05). *compared with the experimental group and control group, *p<0.05.

wells. The optical density (OD) value in each reaction well was finally measured using a spectrophotometer at 450 nm with the blank well as the zero reference value.

Statistics

In this study, SPSS20.0 software package (IBM Corp, Armonk, NY, USA) was used to carry out statistical analyses on the experimental data, and the GraphPad Prism 7 software was used to draw the experimental figures. Measurement data were expressed by mean ± standard deviation, and comparison between the two groups was carried out with *t*-test. Chi square test was used for counting data, survival analysis was conducted by Kaplan-Meier method and compared with Log-rank test. P<0.05 indicated a statistically significant difference.

Results

Expressions of CK7 and TTF-1 in the three groups

The expression levels of CK7 in the experimental group, the control group and the lung cancer group were 2.87±0.23 ng/ml, 1.25±0.46 ng/ml and 2.59±0.27 ng/ml, respectively. Therefore, the expression in the experimental group and the lung cancer group was significantly higher than that in the control group, and the differences were statistically significant (p<0.05). The expression levels of TTF-1 in the three groups were 765.65±565.64 pg/ml, 389.74±388.43 pg/ml and 567.46±274.87 pg/ml, respectively. So, the expression in the experimental group and the lung cancer group was significantly higher than that in the control group, and the differences were statistically significant (p<0.05) (Figures 1 and 2).

Relationship between CK7 expression and clinicopathological characteristics

The expression of CK7 was not significantly correlated with gender, age, weight, histological type and tumor size in lung cancer patients with SVCS (p>0.05), but was significantly correlated with the grade of differentiation, lymph node metastasis and TNM stage (p<0.05). The expression level of CK7 in serum of male and female patients with lung cancer and SVCS was 2.86±0.43 ng/ml and 2.88±0.37 ng/ml respectively, and the difference was not statistically significant (*t*=0.206, p=0.837). The expression in patients aged>30 years and ≤30 years was 2.88±0.32 ng/ml and 2.86±0.29

Table 2. Relationship between CK7 expression and clinicopathological characteristics (mean±SD, ng/ml)

Group	*n=68*	*Expression of CK7*	*t*	*p*
Gender			0.206	0.837
Male	30	2.86±0.43		
Female	38	2.88±0.37		
Age (years)			0.268	0.789
>30	28	2.88±0.32		
≤30	40	2.86±0.29		
Weight (kg)			1.114	0.269
>55	27	2.81±0.47		
≤55	41	2.93±0.41		
Histological classification			0.697	0.488
Squamous cell carcinoma	33	2.91±0.43		
Adenocarcinoma	35	2.83±0.51		
Differentiation grade			19.17	<0.001
Moderately and highly differentiated	22	2.04±0.27		
Poorly differentiated	46	3.70±0.36		
TNM stage			17.89	<0.001
I+II	28	2.21±0.31		
III+IV	40	3.50±0.28		
Lymph node metastasis			14.74	<0.001
Yes	30	3.59±0.46		
No	38	2.21±0.31		
Tumor size (cm)			1.429	0.158
<3	27	2.91±0.34		
≥3	41	2.80±0.29		

ng/ml respectively, and the difference was not statistically significant (t=0.268, p=0.789). The expression in patients weighing>55 kg and ≤55 kg was 2.81±0.47 ng/ml and 2.93±0.41 ng/ml respectively, with no significant difference (t=1.114, p=0.269). The expression in squamous cell carcinoma and adenocarcinoma was 2.91±0.43 ng/ml and 2.83±0.51 ng/ml respectively, with no significant difference (t=0.697, p=0.488). The expression in patients with tumor<3 cm and ≥3 cm was 2.91±0.34 ng/ml and 2.80±0.29 ng/ml respectively, with no significant difference (t=1.429, p=0.158). The expression in the moderately and highly differentiated tumors and poorly differentiated tumors was 2.04±0.27 ng/ml and 3.70±0.36 ng/ml, respectively, indicating the expression of CK7 in the moderately and highly differentiated tumors was significantly lower than that in poorly differentiated tumors, and the difference was statistically significant (t=19.17, p<0.001). The expression of CK7 in the serum of stage I+II patients and stage III+IV patients was 2.21±0.31 ng/ml and 3.50±0.28 ng/ml respectively, showing the expression in stage I+II patients was significantly lower than that in stage III+IV patients, and the difference was statistically significant (t=17.89, p<0.001). The expression in the serum of patients with lymph node metastasis and without metastasis was 3.59±0.46 ng/ml and 2.21±0.31 ng/ml respectively, suggesting the expression in serum of patients with lymph node metastasis was significantly higher than that of patients without metastasis, and the difference was statistically significant (t=14.74, p<0.001). (Table 2).

Relationship between TTF-1 expression and clinicopathological characteristics

The expression of TTF-1 was not significantly correlated with gender, age, weight, histological type and tumor size in lung cancer patients with SVCS (p>0.05), but was significantly correlated with grade of differentiation, lymph node metastasis and TNM stage (p<0.05). The expression level of TTF-1 in serum of male and female patients with lung cancer complicated with SVCS was 762.85±538.72 pg/ml and 768.45±529.26 pg/ml respectively, and the difference was not statistically significant (t=0.043, p=0.966). The expression in patients aged>30 years and ≤ 30 years was 735.85±518.86 pg/ml and 795.45±502.37 pg/ml respectively, with no significant difference (t=0.475, p=0.636). The

Table 3. Relationship between TTF-1 expression and clinicopathological characteristics (mean±SD, pg/ml)

Group	*n=68*	*Expression of TTF-1*	*t*	*p*
Gender			0.043	0.966
Male	30	762.85±538.72		
Female	38	768.45±529.26		
Age (years)			0.475	0.636
>30	28	735.85±518.86		
≤30	40	795.45±502.37		
Weight (kg)			0.119	0.906
>55	27	773.54±529.36		
≤55	41	757.76±538.28		
Histological classification			0.032	0.975
Squamous cell carcinoma	33	767.94±582.36		
Adenocarcinoma	35	763.36±592.29		
Differentiation grade			2.135	0.037
Moderately and highly differentiated	22	614.82±539.37		
Poorly differentiated	46	907.48±523.76		
TNM stage			2.268	0.027
I+II	28	619.45±528.37		
III+IV	40	911.85±519.63		
Lymph node metastasis			2.059	0.043
Yes	30	906.85±592.13		
No	38	624.45±536.29		
Tumor size (cm)			0.094	0.925
<3	27	759.52±528.37		
≥3	41	771.78±521.29		

expression in patients weighing>55 kg and ≤55 kg was 773.54±529.36 pg/ml and 795.45±502.37 pg/ml respectively, with no significant difference (t=0.119, p=0.906). The expression in squamous cell carcinoma and adenocarcinoma was 767.94±582.36 pg/ml and 763.36±592.29 pg/ml respectively, with no significant difference (t=0.032, p=0.975). The expression in patients with tumor<3 cm and ≥ 3 cm was 759.52±528.37 pg/ml and 771.78±521.29 pg/ml respectively, without statistically significant difference (t=0.094, p=0.925). The expression in the moderately and highly differentiated and poorly differentiated tumors was 614.82±539.37 pg/ml and 907.48±523.76 pg/ml respectively, indicating the expression of TTF-1 in the moderately and highly differentiated tumors was significantly lower than that in the poorly differentiated tumors, with t=2.135, p=0.037. The expression of TTF-1 in the serum of stage I+II and stage III+IV patients was 619.45±528.37 pg/ml and 911.85±519.63 pg/ml respectively, showing the expression in stage I+II patients was significantly lower than that in stage III+IV patients (t=2.268, p=0.027). The expression in serum of patients with lymph node metastasis and without metastasis were 906.85±592.13 pg/ml and 624.45±536.29 pg/ml respectively, suggesting the expression in serum of patients with lymph node metastasis was significantly higher than that of patients without metastasis, and the difference was statistically significant (t=2.059, p=0.043) (Table 3).

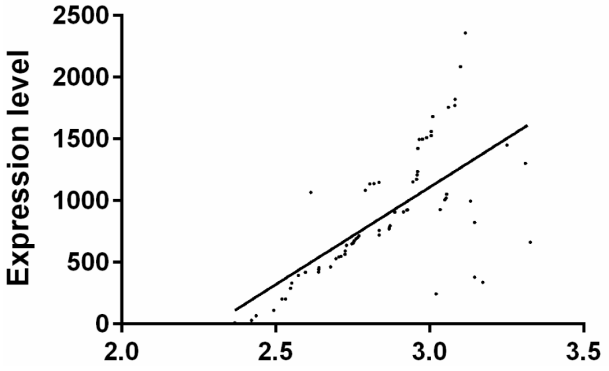

Figure 3. Correlation between CK7 and TTF-1 expressions in patients with lung cancer complicated with SVCS. Partial correlation results showed that the expression of CK7 was positively correlated with TTF-1 expression in the serum of lung cancer patients with SVCS (r=0.676, p<0.001).

Correlation between CK7 and TTF-1 expressions in patients with lung cancer complicated with SVCS

Partial correlation results showed that the expression of CK7 was positively correlated with TTF-1 expression in the serum of lung cancer patients with SVCS (r=0.676. p<0.001) (Figure 3).

Prognostic value of CK7 in patients with lung cancer complicated with SVCS

The survival data in the experimental group were counted. According to the average value (1.44) of CK7 expression, the patients were divided into a low expression group (n=33, CK7<0.59) and a high expression group (n=35, CK7 ≥1.44). The deadline for follow-up was May 2, 2018. The survival rate in the high expression group was 45.71%, and in the low expression group 75.76%. It can be seen that the 3-year survival rate in the CK7 high expression group was significantly lower than that in the low expression group, and the difference was statistically significant (p<0.05) (Figure 4).

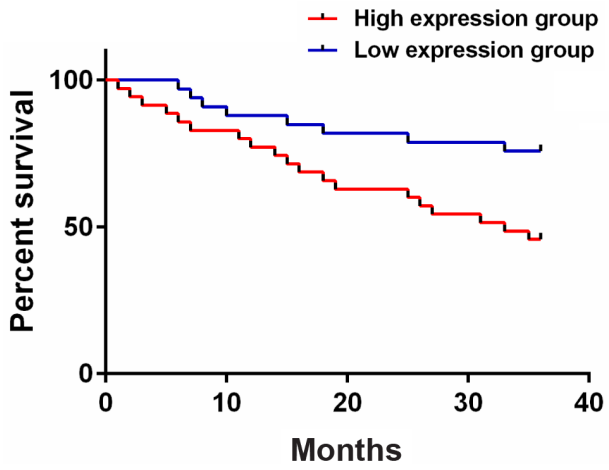

Figure 4. Prognostic value of CK7 and TTF-1 in patients with lung cancer complicated with SVCS. The survival rate in the CK7 high expression group was significantly lower than that in the low expression group, and the difference was statistically significant (p<0.05).

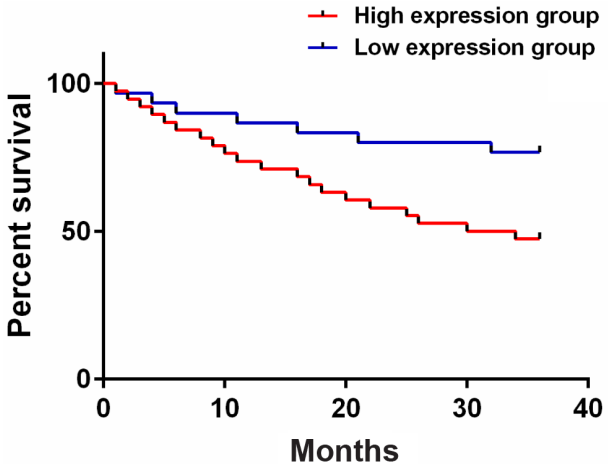

Figure 5. Prognostic value of TTF-1 in patients with lung cancer complicated with SVCS. The survival rate in the TTF-1 high expression group was significantly lower than in the low expression group, and the difference was statistically significant (p<0.05).

Prognostic value of TTF - 1 in patients with lung cancer complicated with SVCS

The survival data in the experimental group were counted. According to the average value (382.83) of CK7 expression, the patients were divided into a low expression group (n=30, CK7<382.83) and a high expression group (n=38, CK7≥382.83). The deadline for follow-up was May 2, 2018. The survival rate in the high expression group was 47.37%, and that in the low expression group 76.67%. It can be seen that the 3-year survival rate in TTF-1 high expression group was significantly lower than that in the low expression group, and the difference was statistically significant (p<0.05) (Figure 5).

Discussion

SVCS is a clinical syndrome caused by venous stenosis due to the compression of SVC, mostly by malignant tumors [12,13]. Moreover, it is a common sequel of mediastinal malignant tumors, which can cause severe respiratory distress of patients [14]. CK7 is a low molecular weight protein, which is abundantly expressed and stably exists in most epithelial tissues. Moreover, it is also expressed in tumor cells [15], many ducts and glandular epithelial cells (mainly gallbladder, hepatic duct and pancreatic duct), female reproductive tract tissues (ovary, endometrium, fallopian tube and cervix), and breast, lung and urinary tract normal tissues [16]. A study found that CK7 level increased during the occurrence of liver cancer and participated in the progression of tumor [17]. The positive expression of CK7 in colon cancer tissues was reported to be 10-27% [18]. Another study showed that CK7 was expressed differently in the squamous epithelium of some squamous cell carcinomas, and found that it was correlated with the prognosis of squamous cell carcinomas in different pathological stages, possessing thus a guiding significance for clinical treatment [19]. TTF-1 is a member of NKX2-1 family and is expressed in normal thyroid, lung, brain and other tissues [20]. Some studies pointed out that TTF-1 was expressed in diffuse subependymal giant cell astrocytomas (SEGAs) and can be used as an auxiliary marker [21,22]. In addition, TTF-1 expression was detected in 92% of lung adenocarcinoma patients, and it can predict the occurrence and metastasis of early lung adenocarcinomas [23]. Goldstein and Thomas mentioned that TTF-1 expression in bronchoalveolar carcinoma reached 92% [24]. However, there are few studies on the clinical and prognosis of CK7 and TTF-1 in patients with lung cancer complicated with SVCS. Therefore, this paper explored the expressions of CK7 and TTF-1 in the serum of patients with this disease and their relationship with clinicopathological characteristics, and analyzed the correlation between CK7 and TTF-1.

In this study, the levels of CK7 and TTF-1 in the sera of normal subjects and patients with lung cancer complicated with SVCS were firstly measured by ELISA. The results showed that the expressions in the experimental group were significantly upregulated than in the control group (p<0.05), indicating that CK7 and TTF-1 were highly expressed in lung cancer complicated with SVCS. Then, the expressions of CK7 and TTF-1 and the clinicopathological characteristics of patients were analyzed, and the results showed that the expressions were not significantly correlated with gender, age, weight, histological type and tumor size in lung cancer patients with SVCS (p>0.05), but were significantly correlated with grade of differentiation, lymph node metastasis and TNM stage (p<0.05). The expressions of TTF-1 and CK7 in the moderately and highly differentiated tumors were significantly lower than those in poorly differentiated tumors, and the difference was statistically significant (t=2.135, p=0.037). The expressions in stage I+II patients were significantly lower than those in stage III+IV patients, and the difference was statistically significant (t=2.268, p=0.027). The expressions in patients with lymph node metastasis were significantly higher than in the patients without metastasis, and the difference was statistically significant (t=2.059, p=0.043). At present, there are few reports on the correlation between the expressions of CK7 and TTF-1 and the clinicopathological characteristics of patients with lung cancer complicated with SVCS. A study pointed out that CK7 and TTF-1 were highly expressed in patients with NSCLC, and were closely related to lymph node metastasis and histological type of patients [25]. Next, the correlation between CK7 and TTF-1 in lung cancer complicated with SVCS was analyzed, and the results showed that CK7 was positively correlated with TTF-1 (r=0.676, p<0.001). Therefore, it is speculated that the clinicopathological characteristics of thyroid cancer are closely related to the expressions of CK7 and TTF-1. Finally, the prognostic value of CK7 and TTF-1 in patients with lung cancer complicated with SVCS was analyzed and showed that the 3-year survival rate in CK7 and TTF-1 high expression group was significantly lower than that in the low expression group (p<0.05). TTF-1 was shown to be a predictive and prognostic indicator in advanced lung adenocarcinoma [26]. Therefore, it is believed that monitoring the expression changes of CK7 and TTF-1 in serum has diagnostic

and prognostic value for the occurrence and development of lung cancer complicated with SVCS.

Due to limited resources and the small number of the patients studied, there may be some contingency in the research results. Therefore, we will take more time and effort to improve the experiment in order to achieve more sound results.

To sum up, the expressions of CK7 and TTF-1 are related to TNM stage, lymph node metastasis and grade of differentiation in lung cancer patients with SVCS. Moreover, the high expressions of CK7 and TTF-1 in the serum of patients are expected to be potential prognostic indicators for lung cancer complicated with SVCS.

Conflict of interests

The authors declare no conflict of interests.

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