Diagnostic value analysis of combined detection of Trx, CYFRA21-1 and SCCA in lung cancer

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Abstract. The expression levels of thioredoxin (Trx), cytokeratin fragment 21-1 (CYFRA21-1) and serum squamous cell carcinoma antigen (SCCA) in patients with lung cancer and the diagnostic value of combined detection were investigated. Sixty-five patients with lung cancer in Weihai Municipal Hospital from January 2014 to June 2017 were retrospectively selected as the observation group, while 60 healthy subjects receiving physical examination were selected as the control group. The expression levels of serum Trx, CYFRA21-1 and SCCA were detected. The sensitivity and specificity of single detection and combined detection of these indexes were compared. Moreover, the diagnostic values of single detection and combined detection were analyzed using the receiver operating characteristic (ROC) curve. The levels of CYFRA21-1 and SCCA were the highest in squamous carcinoma (P<0.05). The level of Trx was the highest in small cell lung cancer compared with those in squamous carcinoma and adenocarcinoma (P<0.05). The levels of serum Trx, CYFRA21-1 and SCCA in lung cancer patients in clinical stage III-IV were obviously higher than those in patients in clinical stage I-II (P<0.001). The positive rate of Trx was the highest in small cell lung cancer, and the positive rates of CYFRA21-1 and SCCA were the highest in squamous carcinoma compared with other cancers (P<0.05). The area under the ROC curve of combined detection of the three indexes was the largest. The optimal cut-off value of combined detection of the three indexes in lung cancer was 9.952 with the sensitivity of 86.2% and specificity of 75.0%. The detection of serum Trx, CYFRA21-1 and SCCA is of great significance in the diagnosis, progression and pathological type of lung cancer, and combined detection can improve both specificity and sensitivity, which is more conducive to the positive rate of diagnosis of lung cancer.

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Introduction

Lung cancer has top ranking in the malignant tumors in the world, and there are approximately 1,820,000 incidence cases and approximately 386,000 deaths (more male deaths than female deaths) every year (1). Lung cancer is mainly caused by the surrounding environment, which is related to air pollution, smoking, heredity, chronic lung diseases and occupational factors. In the early stage of lung cancer, there is no obvious specificity, but most patients with lung cancer, at diagnosis, have lost the optimal opportunity for treatment due to the rapid progression and high malignant degree of lung cancer (2). If changes in some tumor markers can be detected in the early stage of lung cancer, 'early detection and early treatment' can be realized, which is an important measure to reduce the mortality rate of lung cancer (3). Therefore, it is extremely important to search for lung cancer markers with high sensitivity and specificity.

Lung cancer markers mainly include hormones, enzymes, alpha-fetoprotein, cell surface membrane antigens and some cytokines (4). Thioredoxin (Trx) is a dimeric selenium-enzyme and a member of the pyridine nucleotide-disulfide oxidoreductase family, which is closely related to the condition of patients with lung cancer. Previous studies have demonstrated that Trx plays an important role in the development of cancer cells, and it is expected to be a new target for diagnosis, treatment and prognosis of tumor (5). Cytokeratin fragment 21-1 (CYFRA21-1) is a cytokeratin released into the blood in case of necrosis or lysis of tumor cells, its sensitivity and concentration increase with the progression of cancer cells. Therefore, CYFRA21-1 is considered as one of the best tumor markers for detecting lung cancer (6). Serum squamous cell carcinoma antigen (SCCA) is a tumor-associated antigen, and its levels in serum and specificity are higher in lung cancer patients (7). No lung cancer marker with good specificity and sensitivity has been found yet. Therefore, the combined detection of multiple tumor markers can complement one another and make up for deficiencies, thus providing an important auxiliary basis for the diagnosis and progression of lung cancer (8). In this study, the diagnostic value of combined detection of serum Trx, CYFRA21-1 and SCCA in lung cancer was investigated.

Table I. Clinical data of patients [n (%)].

Groups	Observation group (n=65)	Control group (n=60)	χ^2/t value	P-value
Sex			1.346	0.285
Male	36 (55.38)	27 (45.00)		
Female	29 (44.62)	33 (55.00)		
Age			2.187	0.108
≥55	41 (63.08)	29 (48.33)		
<55	24 (36.92)	31 (51.67)		
Smoking			0.157	0.593
Yes	38 (58.46)	32 (53.33)		
No	27 (41.54)	28 (46.67)		
Drinking			0.936	0.285
Yes	37 (56.92)	28 (46.67)		
No	28 (43.08)	32 (53.33)		
Body mass index (kg/m^2)	21.3±3.9	29.6±4.3	1.433	0.154

Materials and methods

Clinical data. A total of 65 patients with lung cancer in Weihai Municipal Hospital (Weihai, China) from January 2014 to June 2017 were selected as the observation group, including 36 males and 29 females with an average age of 55.1±9.6 years. There were 30 cases of squamous carcinoma, 20 cases of adenocarcinoma and 15 cases of small cell lung cancer. Another 60 healthy subjects receiving physical examination were selected as the control group, including 36 males and 24 females with an average age of 52.1±7.2 years.

Inclusion and exclusion criteria. Inclusion criteria: Patients clinically diagnosed with lung cancer, patients aged ≥18 years, patients who had not undergone systematic treatment, and patients without other hereditary diseases. Exclusion criteria: Patients with diseases of the respiratory system, patients with cardiovascular or cerebrovascular diseases, handicapped patients, patients infected with the human immunodeficiency virus (HIV), or patients who had taken antibiotics in the prior three months. This study was approved by the Ethics Committee of Weihai Municipal Hospital. Subjects of the study were informed, agreed to participate in the clinical study and signed the informed consent.

Methods. After 5 ml fasting venous blood was drawn from patients and healthy volunteers, it was centrifuged at 2,100 x g for 15 min at 4˚C using a low-temperature high-speed centrifuge to collect the serum. The levels of serum CYFRA21-1 and SCCA were detected via chemiluminescence using the full-automatic chemiluminescence immune analyzer (MKY) and corresponding reagents. The level of Trx in cells was detected via enzyme-linked immunosorbent assay (ELISA) with human thioredoxin, Trx ELISA Kit (Cusabio, Wuhan, China) using a microplate reader (LB942; Berthold, Bad Wildbad, Germany) and corresponding reagents. The activity of Trx reductase was analyzed. Samples were collected and instruments were used strictly according to the manufacturer's instructions.

Evaluation criteria. The positive evaluation criteria for the three tumor markers are as follows: SCCA >15 μg/l, CYFRA21-1 >50 μg/l, and the optical density (OD) value of Trx samples ≥ cut-off value indicated positive.

Statistical analysis. Statistical Product and Service Solutions (SPSS) 17.0 (supported by Beijing Xinmei Jiahong Technology Co., Ltd., Beijing, China) was used for the analysis of all data in this experiment. Measurement data were expressed as mean ± SD. t-test was used for the comparison between the two groups, and multi-factor analysis of variance was used for the comparison among the groups and the post hoc test was Dunnett's test. Enumeration data were expressed as rate (%), and Chi-square test was adopted. The diagnostic values were analyzed using the ROC curve. P<0.05 was considered to indicate a statistically significant difference.

Results

Analysis of clinical data of patients. Analysis of sex, age, smoking or not, drinking or not and body mass index in the observation and control groups revealed that there were no statistically significant differences in the groups (P>0.05) (Table I).

Determination of serum Trx, CYFRA21-1 and SCCA in the observation and control groups. The expression levels of serum Trx, CYFRA21-1 and SCCA in the observation group were, respectively, 47.6±10.7, 76.6±10.4 and 45.3±6.9 μg/l, which were higher than those in the control group (13.1±8.9, 3.5±2.8 and 7.8±3.2 μg/l)(P<0.01) (Fig. 1).

Diagnostic value analysis of single and combined detection of Trx, CYFRA21-1 and SCCA. The area under the receiver

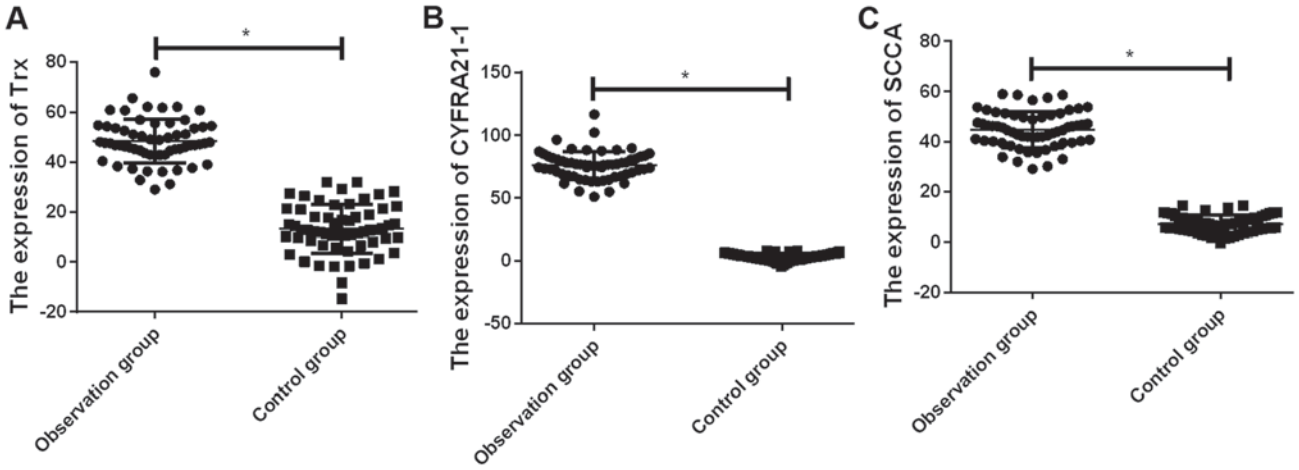

Figure 1. Trx, CYFRA21-1 and SCCA expression levels. (A) The expression level of Trx in the observation group is significantly higher than that in the control group, and there is a statistically significant difference (*P<0.05). (B) The expression level of CYFRA21-1 in the observation group is significantly higher than that in the control group, and there is a statistically significant difference (*P<0.05). (C) The expression level of SCCA in the observation group is obviously higher than that in the control group, displaying a statistically significant difference (*P<0.05).

Table II. ROC curve analysis of single and combined detection of Trx, CYFRA21-1 and SCCA.

Index	Area under curve	OR	95%CI	P-value	Sensitivity (%)	Specificity (%)
Trx	0.674	0.048	0.580-0.768	0.001	58.5	73.3
CYFRA21-1	0.829	0.037	0.757-0.901	0.001	70.8	85.0
SCCA	0.684	0.048	0.590-0.779	0.001	64.6	76.0
Combined detection	0.851	0.035	0.782-0.919	0.001	86.2	75.0

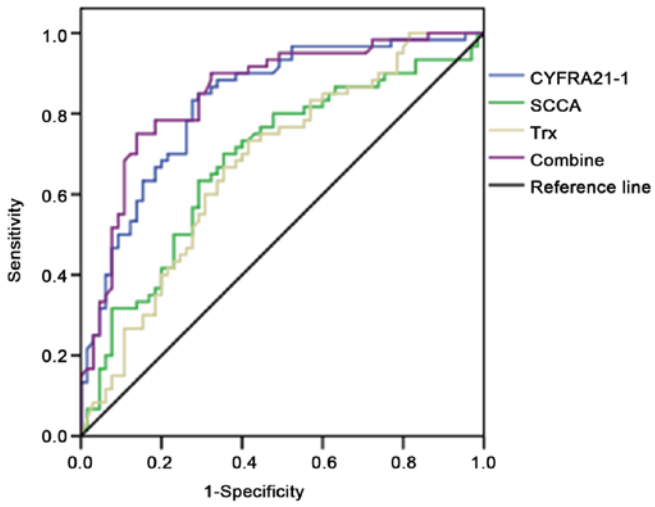

Figure 2. ROC curve analysis. The area under the curve of combined detection of the three indexes is the largest, followed by CYFRA21-1, SCCA and Trx, showing statistically significant differences (P<0.05).

operating characteristic (ROC) curve of combined detection of the three indexes was the largest, followed by CYFRA21-1, SCCA and Trx. The value of combined detection of the three indexes was higher than that of single detection, and the sensitivity of combined detection of the three indexes was obviously higher than that of single detection, displaying statistically significant differences (P<0.05). The combined detection of the three indexes in lung cancer was the best with the sensitivity of 86.2% and specificity of 75.0% (Table II and Fig. 2).

Comparison of serum Trx, CYFRA21-1 and SCCA levels in different pathological types of lung cancer. The levels of CYFRA21-1 and SCCA were the highest in squamous carcinoma, and there were statistically significant differences compared with those in adenocarcinoma and small cell lung cancer (P<0.05). The level of Trx was the highest in small cell lung cancer, and it had statistically significant differences compared with those in squamous carcinoma and adenocarcinoma (P<0.05) (Table III).

Comparison of serum Trx, CYFRA21-1 and SCCA levels in different clinical stages of lung cancer. The levels of serum Trx, CYFRA21-1 and SCCA in lung cancer patients in clinical stage III-IV were obviously higher than those in patients in clinical stage I-II, displaying statistically significant differences (P<0.001). There were no statistically significant differences in levels of Trx, CYFRA21-1 and SCCA in patients with lymph node metastasis and distant metastasis (P>0.05) (Table IV).

Comparison of positive rates of Trx, CYFRA21-1 and SCCA in different pathological types of lung cancer. The positive rate of Trx was the highest in small cell lung cancer, and the positive rates of CYFRA21-1 and SCCA were the highest in

Table III. Comparison of serum Trx, CYFRA21-1 and SCCA levels in different pathological types of lung cancer.

Pathological types	n	Trx (μg/l)	CYFRA21-1 (μg/l)	SCCA (μg/l)
Squamous carcinoma	30	22.6±21.1	95.9±23.9[b]	101.8±29.8[b]
Adenocarcinoma	20	18.6±10.8	39.9±10.6	17.6±10.2
Small cell lung cancer	15	56.9±8.7[a]	30.5±10.6	17.5±8.9
F value		12.77	10.32	14.64
P-value		0.001	0.001	0.001

[a]P<0.01 vs. squamous carcinoma and adenocarcinoma, and [b]P<0.01 vs. adenocarcinoma and small cell lung cancer.

Table IV. Comparison of serum Trx, CYFRA21-1 and SCCA levels in different clinical stages of lung cancer.

Groups	n	Trx	CYFRA21-1	SCCA
Stage I-II	20	17.9±5.7	16.5±4.9	14.3±5.6
Stage III-IV	45	30.9±6.1	28.6±8.4	25.5±6.3
t value		8.086	5.989	6.835
P-value		0.001	0.001	0.001
Lymph node metastasis	28	26.3±5.3	21.6±2.5	24.8±4.3
Distant metastasis	25	24.5±4.2	20.4±5.6	25.6±5.9
t value		1.359	1.026	0.568
P-value		0.180	0.310	0.572

Table V. Comparison of positive rates of Trx, CYFRA21-1 and SCCA in different pathological types of lung cancer [n (%)].

Pathological types	n	Trx	CYFRA21-1	SCCA
Squamous carcinoma	30	16 (53.33)	24 (80.00)[b]	26 (86.67)[c]
Adenocarcinoma	25	13 (52.00)	9 (36.00)	10 (40.00)
Small cell lung cancer	10	9 (90.00)[a]	4 (40.00)	6 (60.00)
χ^2 value		4.851	12.147	13.099
P-value		0.050	0.002	0.001

[a]P<0.05 vs. squamous carcinoma and adenocarcinoma, [b]P<0.05 vs. adenocarcinoma and small cell lung cancer, and [c]P<0.05 vs. small cell lung cancer and adenocarcinoma.

squamous carcinoma, showing statistically significant differences compared with other cancers (P<0.05) (Table V).

Discussion

The incidence and mortality rates of lung cancer have shown increasing trends in recent years, seriously threatening people's health. However, it is noteworthy that there are generally no obvious symptoms in the early stage of lung cancer, and it is hard for patients to notice. At the same time, rich blood supply in lung tissues provides favourable conditions for the metastasis of cancer cells, so that patients are often in the late stage once there are obvious clinical symptoms, leading to difficult treatment, which is also an important cause of the high mortality rate of lung cancer (9). Therefore, the early diagnosis and treatment of lung cancer are of great importance. In the diagnosis of lung cancer, tissue biopsy serves as a golden standard in clinic, but it is only applied when symptoms develop and patients need to be diagnosed, and cannot be used in the early screening of lung cancer due to trauma (10). Therefore, the value of tumor markers in the diagnosis of early lung cancer has gained extensive attention.

The oxidative active amino acid composition of Trx is Cys-Gly-Pys-Cys, and Trx can catalyze the redox reaction and also maintain intracellular homeostasis, regulate apoptosis and resist oxidative stress response under biological functions (11). A number of studies have demonstrated that the expression of Trx is increased in a variety of malignant tumors, such as gastric, breast, liver, lung, rectal and cervical cancers (7,12), indicating that Trx is closely related to malignant tumors. It was found in related studies that Trx can inhibit apoptosis of tumor cells, promote cell proliferation and disturb normal

cell cycle (13). CYFRA21-1 is a cytokeratin existing in cells of epithelium-derived malignant tumors. A large amount of soluble CYFRA21-1 enters the blood circulation in case of lysis or death of tumor cells (14). Moreover, studies have revealed that the expression level of serum CYFRA21-1 in patients with lung cancer is remarkably higher than that in healthy individuals, so it can be used in the identification of malignant lesions in the lung (15). SCCA is a tissue antigen, which is mainly used in the diagnosis of squamous carcinoma, including squamous carcinoma in the head and neck, lung and trachea, esophagus, cervix, anal canal, genitourinary tract and brain, monitoring of condition and prognosis and therapeutic evaluation (16).

In this study, it was found that the expression levels of serum Trx, CYFRA21-1 and SCCA in the observation group were higher than those in the control group ($P<0.01$), and there were significant differences between the two groups, indicating that the tumor markers (Trx, CYFRA21-1 and SCCA) have important value in the clinical diagnosis of lung cancer. The above results are basically consistent with those in related results, and the more severe the disease is, the higher the levels of tumor markers are (17), suggesting that the levels of serum Trx, CYFRA21-1 and SCCA can provide a certain reference basis for the diagnosis of lung cancer. In this study, the levels of CYFRA21-1 and SCCA were the highest in squamous carcinoma, and there were statistically significant differences compared with those in adenocarcinoma and small cell lung cancer ($P<0.05$). The level of Trx was the highest in small cell lung cancer, and it had statistically significant differences compared with those in squamous carcinoma and adenocarcinoma ($P<0.05$), suggesting that CYFRA21-1 and SCCA are superior in detecting squamous carcinoma to adenocarcinoma and small cell lung cancer, and Trx is more valuable in detecting small cell lung cancer. SCCA is a good marker for the diagnosis of squamous carcinoma, which can monitor the disease development and evaluate the prognosis. Trx, CYFRA21-1 and SCCA are of important significance in guiding the diagnosis and treatment of lung squamous carcinoma. The three indexes can improve the diagnostic accuracy rate of lung cancer and help provide diagnostic information, so as to perform the targeted treatment, improve the therapeutic efficiency and prolong the life of patients, which are basically consistent with results in related studies (18). In this study, the levels of serum Trx, CYFRA21-1 and SCCA in lung cancer patients in clinical stage III-IV were obviously higher than those in patients in clinical stage I-II, indicating that Trx, CYFRA21-1 and SCCA are related to the progression of lung cancer, and they can be used to monitor metastasis and recurrence of malignant tumor in clinic. The concentration of serum tumor markers is positively correlated with the tumor size, which is also consistent with related literature reports (19). Results of this study manifested that despite high specificity of single detection of Trx, CYFRA21-1 and SCCA, the sensitivity is unsatisfactory, failing to meet the clinical requirements. Therefore, lung cancer should not be diagnosed using only one single index at present, but multiple indexes should be combined for joint diagnosis, thus improving the accuracy. The sensitivity of combined detection of the three indexes is improved, and the sensitivity, specificity and accuracy are 86.8, 80.4 and 89.6%, respectively. It can be seen that both sensitivity and specificity are significantly improved compared with single detection, thus benefiting the early screening of lung cancer patients, performing the treatment as early as possible improves the prognosis, which is consistent with the report of Jiang *et al* (20). Combined detection plays an important role in the diagnosis of lung cancer, which can be used in the early screening of patients with lung cancer. The ROC curve can reflect the specificity, sensitivity and accuracy of detection indexes objectively and accurately. The closer the area under the curve is to 0.5, the lower the diagnostic accuracy will be, and the closer it is to 1.0, the higher the diagnostic accuracy will be. In this study, the area under the ROC curve of combined detection of the three indexes was the largest, followed by CYFRA21-1, SCCA and Trx. The area under the curve was <0.9 in single detection of the three indexes and 0.906 in combined detection, and the combined detection of the three indexes in lung cancer was optimal with the sensitivity of 86.2% and specificity of 75.0%, proving that both accuracy and efficiency of combined detection are superior to those of single detection of any index, which are consistent with results of Zhang *et al* (21). The above results suggest that the combined detection is able to improve the diagnostic rate.

The combined detection of the three indexes can improve the accuracy and can also be used in the early screening and early treatment of lung cancer and the improvement of prognosis. However, there are still some false-negative and false-positive cases in the combined detection of the three indexes in the diagnosis of lung cancer, indicating that lung cancer still cannot be diagnosed only using one means, but imaging and pathological methods should be combined for comprehensive evaluation, thereby avoiding misdiagnosis and improving diagnostic accuracy. The sample size in this study was small, and there was a certain selection bias, so further study is still necessary for verification.

In conclusion, the detection of serum Trx, CYFRA21-1 and SCCA is of great significance in the diagnosis, progression and pathological type of lung cancer, and combined detection can improve both specificity and sensitivity, which is more conducive to the positive rate of diagnosis of lung cancer.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

TQ, JZ, NX and BL collected and analyzed the general data of patients. ML and ALiu performed ELISA. ALi and HT evaluated the tumor markers. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Weihai Municipal Hospital (Weihai, China). Signed informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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