RESEARCH ARTICLE

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The Application Value of Serum *HE4* in the Diagnosis of Lung Cancer

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Abstract

Background: To investigate the clinical value of *HE4* detection in the diagnosis of lung cancer and the clinical significance of combined detection with *CEA*, *NSE* and *CYFRA21-1*. **Methods:** 90 cases of lung cancer, 30 cases of pulmonary tuberculosis, 30 cases of pneumonia and 30 cases of health physical examination were selected. The levels of serum *HE4*, *CYFRA21-1*, *CEA* and *NSE* were detected by electrochemiluminescence method. Statistical analysis was performed to observe the sensitivity and specificity. **Results:** The levels of serum *HE4*, *CEA*, *NSE* and *CYFRA21-1* in lung cancer group were significantly higher than those in tuberculosis group and health physical examination group. There was no significant difference in the levels of *HE4*, *CEA* and *NSE* between the lung cancer group and the pneumonia group, the difference of CYFRA21-1 level was statistically significant ($p<0.05$).With health physical examination group as normal controls, the sensitivity and specificity of combined detection of *HE4*, *CEA*, *NSE* and *CYFRA21-1* in the diagnosis of lung cancer were 82.2% and 90.0%,and the area under the curve (AUC) was 0.907, followed by *HE4* (0.867), *CYFRA21-1* (0.787), *CEA* (0.752) and *NSE* (0.747). **Conclusion:** *HE4* can be used as a serological marker for the diagnosis of lung cancer. The combined detection of *HE4*, *CEA*, *NSE* and *CYFRA21-1* can improve the diagnosis of lung cancer. Serum *HE4* levels are highly specific in distinguishing between lung cancer patients and normal population, and are equivalent to *CYFRA21-1*; but they are less specific than *CYFRA21-1* in distinguishing lung cancer patients from pneumonia patients.

Keywords: *HE4- CYFRA21-1- CEA- NSE*- lung cancer

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Introduction

Clinically, the diagnostic value of serum tumor markers has been confirmed, and markers such as carcinoembryonic antigen (*CEA*), neuron-specific enolase (*NSE*), and cytokeratin 19 fragment (*CYFRA21-1*) have been widely used for the diagnosis of lung cancer. Human epididymis secretory protein 4 (*HE4*) is a new tumor marker, highly expressed in ovarian cancer, and extremely low in normal tissues. It is clinically used for early diagnosis of ovarian cancer. In recent years, it has been reported in the literature that *HE4* can also be used for early diagnosis of lung cancer (Mo et al., 2018; Nagy, 2014). This study was to investigate the value of *HE4* detection in the diagnosis of lung cancer and the clinical significance of combined detection with *CEA*, *NSE* and *CYFRA21-1*.

Materials and Methods

Sample collection

From January 2016 to October 2018, there were 90 patients with lung cancer in Weifang People's Hospital, including 56 males and 34 females, aged 46-81 (61.0±12.8) years old, including 29 cases of squamous cell carcinoma, 50 cases of adenocarcinoma,9 cases of small cell lung cancer and 2 cases of large cell lung cancer. All cases were confirmed by pathology, and no surgery, radiotherapy and chemotherapy were performed before blood samples were collected. Another 30 patients with pneumonia in Weifang People's Hospital were selected, including 14 males and 16 females, aged 44-89 (67.0±17.5) years old; 30 health physical examination persons as normal controls, including 15 males and 15 females, aged 45-77 (58.8±10.9) years old. 30 patients with pulmonary tuberculosis in Weifang City Respiratory Hospital were selected, including 17 males and 13 females, aged 30-68 (39.0±8.5) years old.

Detection method

All selected subjects were collected 5 ml of peripheral venous blood on an empty stomach, left at room temperature for about 1 h, centrifuged at 4,000 × g for 5 min, separated serum, and stored in a refrigerator at -80°C for use. *HE4*, *CEA*, *NSE* and *CYFRA21-1* were detected by Roche Cobas e601 electrochemiluminescence immunoassay analyzer. The reagents were supplied by Roche and the reagents were calibrated before the

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experiment.

Statistical analysis

The results of the measurement data were expressed as median (quartile). The Mann-Whitney U rank sum test was used for comparison between groups, the difference was statistically significant at P<0.05. Data comparison and receiver operating characteristic curve (ROC) were statistically analyzed using SPSS 21.0 software. The sensitivity, specificity, and area under the curve (AUC) were calculated from the respective ROC curves.

Results

Serum levels of HE4, CEA, NSE, and CYFRA 21-1 in each group. The results are shown in Table 1.

The levels of serum *HE4*, *CEA*, *NSE* and *CYFRA21-1* in lung cancer group were significantly higher than those in tuberculosis group and health physical examination group (P<0.05).There were no significant differences in *HE4*, *CEA*, and *NSE* levels between the lung cancer group and the pneumonia group (p=0.844, p=0.087, p=0.687), and the *CYFRA21-1* level was statistically significant (p<0.05).

Diagnostic efficiency of HE4, CEA, NSE and CYFRA21-1 for lung cancer

Taking health physical examination group as normal controls, with 76.885 pmol/L as the optimal cut-off value, the sensitivity of *HE4* for diagnosis of lung cancer was 66.7%, and the specificity was 96.7%. With 3.25 ug/L as the optimal cut-off value, the sensitivity of *CEA* for diagnosis of lung cancer was 61.1%, and the specificity was 80.0%. With 11.01 ng/ml as the optimal cut-off value, the sensitivity of NSE for diagnosis of lung cancer was 64.4%, and the specificity was 86.7%. With 3.23 ng/ml as the optimal cut-off value, the sensitivity of *CYFRA21-1* for diagnosis of lung cancer was 58.9%, and the specificity was 86.7%. The sensitivity of combined detection of *HE4*, *CEA*, *NSE*, and CYFRA21-1 for diagnosis of lung cancer was 82.2% and the specificity was 90.0%. *ROC AUC* showed that the combined detection of *HE4*, *CEA*, *NSE* and *CYFRA21-1* had the largest *AUC* (0.907), followed by *HE4* (0.867), *CYFRA21-1* (0.787), *CEA* (0.752) and *NSE* (0.747) See Figure 1.

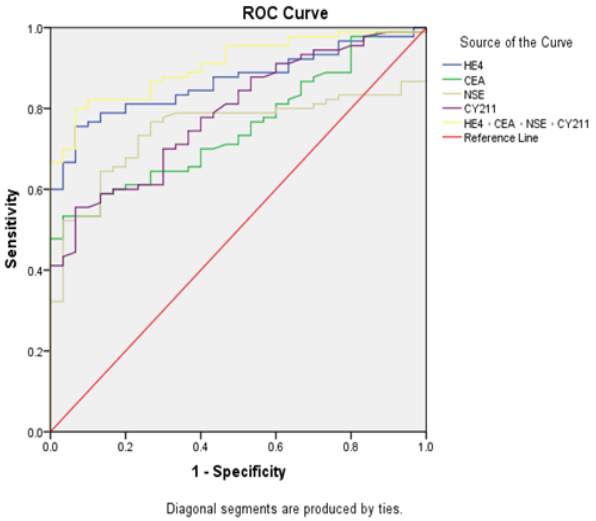

Figure 1. The Diagnostic Efficiency of *HE4* and Other Markers for Lung Cancer, with Health Physical Examination Group as Normal Controls

Discussion

CEA is a complex soluble glycoprotein originally discovered in colon cancer and fetal intestinal tissue. Tumors of various organs can cause elevated levels of serum *CEA*. Serum *CEA* levels have important diagnostic value for lung cancer, especially lung adenocarcinoma. *NSE* is a protease secreted by neurogenic cells, which is markedly elevated in neuroendocrine tumors and small cell lung cancer. *NSE* can be used as a marker for the detection of small cell lung cancer. *NSE* can also be elevated in patients with non-small cell lung cancer, but its sensitivity is low. *CYFRA 21-1* is a soluble fragment of cytokeratin 19 expressed in epithelial-derived malignant cells, and the serum *CYFRA21-1* levels will increase when cells are lysed. *CYFRA 21-1* is the marker for non-small cell lung cancer, and the positive rate of lung squamous cell carcinoma is higher than that of lung adenocarcinoma. A number of studies have shown that *CYFRA 21-1* has a relatively high sensitivity and specificity for the diagnosis of lung cancer compared with other classical tumor markers, which is consistent with the statistical results of this study. Single tumor markers do not have sufficient diagnostic efficiency for the diagnosis of lung cancer, especially the sensitivity is not high enough.

HE4 was originally discovered by Kiechhoff et al.,

Table 1. Serum Levels of *HE4, CEA, NSE* and *CYFRA21-1* in Each Group (Median, Quartile)

Group	n	*HE4* (pmol/L)	*CEA* (ug/L)	*NSE* (ng/ml)	*CYFRA21-1* (ng/ml)
Lung cancer	90	88.130	4.135	13.885	3.845
		(32.48~1500.00)	(0.77~999.00)	(1.72~289.20)	(1.01~158.10)
Tuberculosis	30	45.335	2.000	8.985	2.075
		(31.04~283.10)	(0.50~7.27)	(6.57~15.44)	(1.10~5.09)
Pneumonia	30	78.345	2.765	11.465	2.410
		(35.96~980.50)	(0.89~140.70)	(7.72~110.40)	(1.01~123.30)
Health physical examination	30	45.600	2.605	7.635	2.080
		(29.70~81.51)	(0.89~4.32)	(5.53~18.19)	(1.02~4.87)

(1991), in the epithelium of the distal epididymis, and is a member of the inhibitory protease family, encoded by the *WFDC2* gene. The *HE4* gene is located on chromosome *20q12-13.* 1 and consists of 5 exons and 4 introns. *HE4* is highly expressed in the epithelium of the female reproductive system and the epididymis and vas deferens of the male reproductive system, and is a sensitive marker of ovarian cancer (Chen et al. 2014; Karlsen et al., 2015; Gislefoss et al., 2015; Ferraro et al., 2018; Lycke et al., 2018), also important for endometrial cancer (Minář et al., 2015; Hu et al., 2016; Angioli et al., 2016). As a new marker, *HE4* is also highly expressed in lung cancer. Serum *HE4* may be a potential marker for the diagnosis and prognosis of lung cancer and has important diagnostic value for lung cancer (Liu et al., 2013; Wang et al., 2014; Lamy et al., 2015). This study shows that the diagnostic efficiency of *HE4* for lung cancer is comparable to that of *CYFRA 21-1*, and superior to *CEA* and *NSE*.

The study found that the median of serum *HE4* level was significantly higher in the pneumonia group. There was no significant difference in the levels of *HE4*, *CEA* and *NSE* between the lung cancer group and the pneumonia group. The difference in the level of *CYFRA21-1* was statistically significant between the lung cancer group and the pneumonia group. With health physical examination group as normal controls and 76.885 pmol/L as the optimal cut-off value, the sensitivity of *HE4* in the diagnosis of lung cancer was 66.7%, and the specificity was 96.7%.This indicates that serum *HE4* levels are highly specific in distinguishing lung cancer patients from normal people, and the specificity is not high in distinguishing lung cancer patients from pneumonia patients.

AUC is used to evaluate the efficiency of the diagnostic experiment. The greater the value, the greater the diagnostic value of the experiment. From the current data, in this study, taking health physical examination group as normal controls, combined detection of *HE4*, *CEA*, *NSE* and *CYFRA21-1* had the largest *AUC*, followed by *HE4*, *CYFRA21-1*, *CEA* and *NSE*. This indicates that combined detection of *HE4*, *CEA*, *NSE* and *CYFRA21-1* for lung cancer is superior to single marker, especially in distinguishing between normal population and lung cancer patients, the combined detection for lung cancer has good sensitivity and specificity, which are 82.2% and 90.0% respectively.

In summary, this study shows that *HE4* is a new marker of lung cancer. The diagnostic efficiency of *HE4* for lung cancer is comparable to that of *CYFRA 21-1*, and better than *CEA* and *NSE*. In distinguishing between lung cancer patients and normal population, *HE4* has high specificity, but the sensitivity is slightly lower. The combined detection of *HE4*, *CEA*, *NSE* and *CYFRA21-1* has good sensitivity and specificity. In distinguishing between lung cancer patients and pneumonia patients, the specificity of *HE4* is not high, and it is not as good as *CYFRA21-1*.

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