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Thymidine kinase 1 combined with CEA, CYFRA21-1 and NSE improved its diagnostic value for lung cancer

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ABSTRACT

Aims: Thymidine kinase 1 (TK1) is a tumor biomarker in human malignancies. The purpose of this study was to evaluate the diagnostic efficiency of this marker for lung cancer using the combined analysis of carcinoembryonic antigen (CEA), cytokeratin-19 fragment (CYFRA21-1), neuron specific enolase (NSE) and TK1.

Main methods: From 2013 to 2014, 147 patients with lung cancer and 228 patients with lung benign diseases who were admitted to our hospital were reviewed. Peripheral blood samples were collected for the detection of TK1, CEA, CYFRA21-1 and NSE. The diagnostic value of each marker was analyzed using receiver operating characteristic (ROC) curves and logistic regression equations.

Key findings: The serum levels of TK1, CEA, CYFRA21-1 and NSE were significantly higher than those in patients with lung benign diseases (all $P < 0.05$). The TK1 concentration was dependent on TNM stage ($P = 0.005$). The ROC curve analyses showed that the diagnostic value of TK1 combined with CEA, CYFRA21-1 and NSE in lung cancer was significantly higher than that of each biomarker alone (all $P < 0.0001$). In addition, TK1 combined with CEA, CYFRA21-1, or NSE could also improve the diagnosis of the squamous cell carcinoma, adenocarcinoma and small cell lung cancer subtypes, respectively.

Significance: The combined detection of TK1 and the other three markers significantly improved the diagnosis of lung cancer. Furthermore, the detection of TK1 combined with that of CYFRA21-1, CEA or NSE increased the diagnostic value of TK1 for lung squamous cell carcinoma, adenocarcinoma and SCLC, respectively.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. In China in 2010, 605,900 patients were diagnosed with and 486,600 patients died of lung cancer [1]. Despite advances in chemotherapy, radiotherapy and surgical treatment, the prognosis of this disease remains poor [2]. Therefore, early detection of lung cancer is of great importance, and the detection of a lung cancer biomarker is an effective and common approach by which individuals can be screened for lung cancer.

Carcinoembryonic antigen (CEA) was first described by Gold and Freedman in 1965 as an antigen present in gastrointestinal carcinoma cells [3]. Elevated expression of CEA was also found in patients with lung cancer, especially in those with adenocarcinoma [4]. The CYFRA21-1 protein, which is a fragment of cytokeratin subunit 19, was first reported in 1993 [5]. CYFRA21-1 over-expression has been observed in lung cancer, colorectal cancer and bladder cancer, and especially in squamous cell carcinoma [6–8]. Neuron specific enolase (NSE) is generally recognized as a marker that can be used in the diagnosis of small cell lung cancer (SCLC) [9]. Normal reference values of CEA, CYFRA21-1 and NSE are < 5.0 ng/mL, < 3.3 ng/mL and > 13.0 ng/mL, respectively.

Although serum levels of CEA, CYFRA21-1 and NSE have been extensively used as tumor markers for the diagnosis of lung adenocarcinoma, squamous cell carcinoma and SCLC, respectively, false -positive results often occur due to infections, benign tumors, and pregnancy, among other factors [10].

Thymidine kinase 1 (TK1) is a biomarker of proliferation that is associated with the salvage pathway of DNA precursor synthesis. The expression of TK1 is S-phase-dependent, and high levels of TK1 have

Abbreviations: TK1, Thymidine kinase 1; CEA, Carcinoembryonic antigen; NSE, Neuron specific enolase; SCLC, Small cell lung cancer; ROC, Receiver operating characteristic; AUC, Areas under the ROC curve; TNM, tumor-node-metastasis classification

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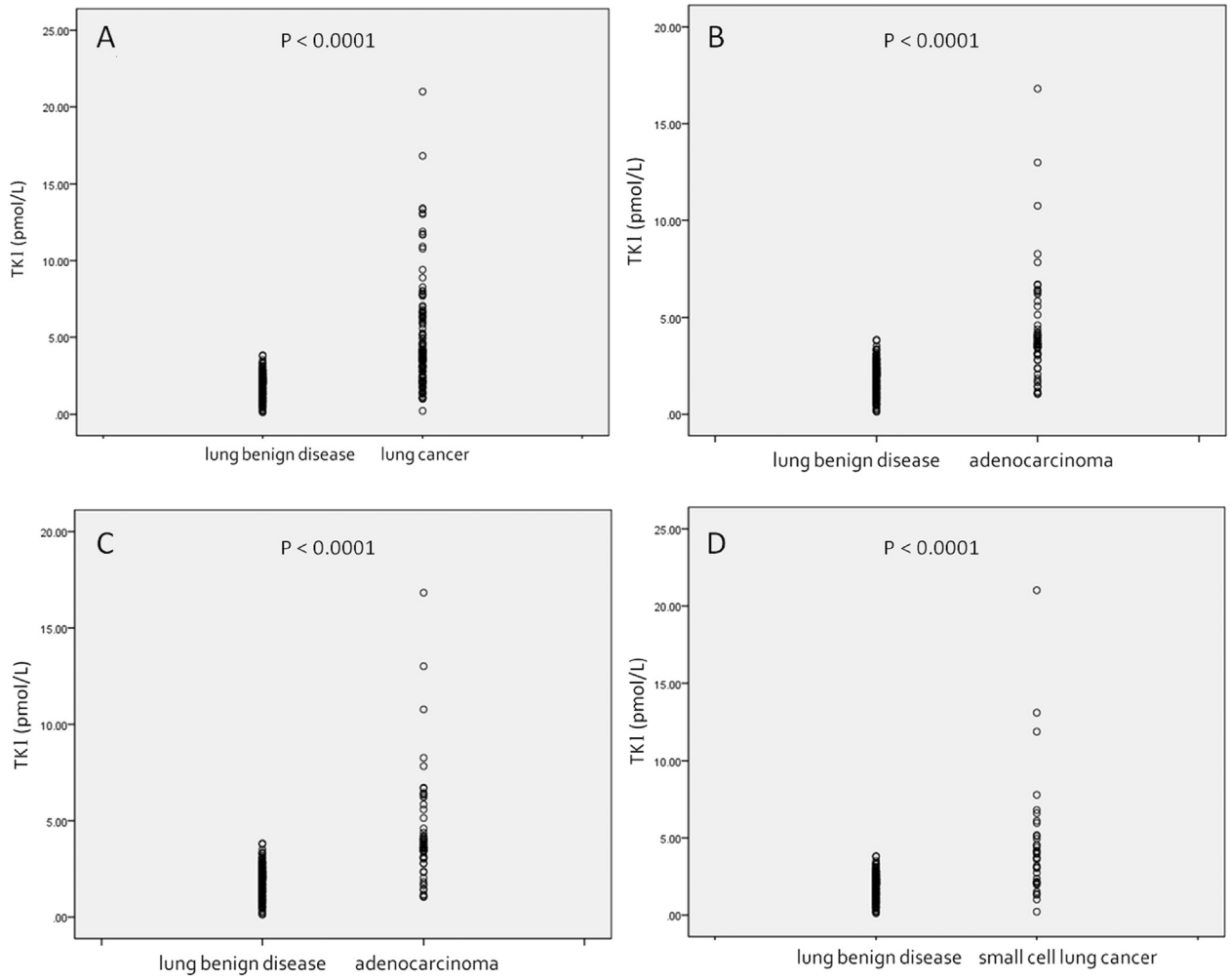

Fig. 1. The serum levels of TK1 in the peripheral blood from patients with lung cancer (A), squamous cell carcinoma (B), adenocarcinoma (C) and small cell lung cancer (D) compared with benign lung disease group.

Table 1
Relationships between the TK1 concentration and clinic-pathologic characteristics in 147 lung cancer patients. Data were presented as Median (P_{25}-P_{75}).

Items	Cases (n)	TK1 (pmol/L)	P-value
Gender			0.244
Male	111	3.87 (2.75–5.96)	
Female	36	3.66 (2.15–4.91)	
Age, year			0.805
< 60	54	3.82 (2.86–4.50)	
≥ 60	92	3.75 (2.38–6.35)	
Pathological type			0.477
Squamous	51	4.03 (2.56–6.97)	
Adenocarcinoma	59	3.63 (3.03–4.60)	
Small cell lung cancer	37	3.72 (2.15–5.15)	
TNM stage			0.005
I + II	32	2.85 (1.80–4.16)	
III + IV	115	3.94 (3.08–6.10)	

been observed in malignant cells [11]. Serological TK1 can be a useful marker to detect the early development of any type of malignancy [12]. Korkmaz et al. demonstrated a significant correlation between serum TK1 level and maximum uptake by primary tumors in positron emission tomography (PET) scans [13]. Furthermore, TK1 activity was also considered as a useful marker for assessment tumor cell proliferation in breast and colorectal cancer [14]. A previous analysis showed that a serum TK1 level of > 2.0 pmol/L might indicate a risk for the development of cancer [15].

Hence, the combined detection of various tumor markers is urgently needed to enhance the diagnosis of lung cancer. The present study was conducted to investigate the diagnostic value of the combined detection of CEA, CYFRA21-1, NSE and TK1 in the diagnosis of lung cancer.

2. Patients and methods

2.1. Patients

This retrospective study reviewed the clinical data of 147 patients with lung cancer and 228 patients with lung benign diseases at the Department of Geriatric Pulmonary in the First Affiliated Hospital of Anhui Medical University between 2013 and 2014. The study protocol was approved by the Medical Ethics and Human Clinical Trial Committee of Anhui Medical University.

The diagnosis of lung cancer was based on the pathologic data obtained by bronchofiberscope or CT-guided lung biopsy and was confirmed by two pathologists. Patients with lung cancer were evaluated according to the revised tumor-node-metastasis (TNM) classification [16]. Lung benign diseases included pneumonia, and chronic obstructive pulmonary disease, among others.

Peripheral blood samples were obtained from all the patients after diagnosis. Serum samples were separated by centrifugation at 3000 rpm for 10 min and were stored at − 20 °C until analysis. The TK1 assay was performed using a commercial kit, based on an enhanced chemiluminescence dot blot assay (SSTK Biotech Ltd., Shenzhen, China). Briefly,