Clinical Significance and Prognostic Value of Pentraxin-3 as Serologic Biomarker for Lung Cancer

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Abstract

**Purposes:** Lung cancer is prevalent worldwide and improvements in timely and effective diagnosis are need. Pentraxin-3 as a novel serum marker for lung cancer (LC) has not been validated in large cohort studies. The aim of the study was to assess its clinical value in diagnosis and prognosis. **Methods:** We analyzed serum PTX-3 levels in a total of 1,605 patients with LC, benign lung diseases and healthy controls, as well as 493 non-lung cancer patients including 12 different types of cancers. Preoperative and postoperative data were further assessed in patients undergoing LC resection. The diagnostic performance of PTX-3 for LC and early-stage LC was assessed using receiver operating characteristics (ROC) by comparing with serum carcinoembryonic antigen (CEA), cytokeratin 19 fragments (CYFRA 21-1). **Results:** Levels of PTX-3 in serum were significantly higher in patients with LC than all controls. ROC curves showed the optimum diagnostic cutoff was 8.03ng/mL (AUC 0.823, [95% CI 0.789-0.856], sensitivity 72.8%, and specificity 77.3% in the test cohort; 0.802, [95% CI 0.762-0.843], sensitivity 69.7%, and specificity 76.4% in the validate cohort). Similar diagnostic performance of PTX-3 was observed for early-stage LC. PTX-3 decreased following surgical resection of LC and increased with tumor recurrence. Significantly elevated PTX-3 levels were also seen in patients with non-lung cancers. **Conclusions:** The present data revealed that PTX-3 was significantly increased in both tissue and serum samples in LC patients. PTX-3 is a valuable biomarker for LC and improved identification of patients with LC and early-stage LC from those with non-malignant lung diseases.

**Keywords:** Lung neoplasm - serum marker - pentraxin-3 - diagnosis

Introduction

Lung cancer (LC) is the leading cause of cancer-related death worldwide (Jemal et al., 2011). More patients die from LC than breast cancer, colorectal cancer, and prostate cancer combined, overall 5-year survival of LC patients is 14% (Ferlay et al., 2010). The dismal outcome is due partly to the lack of an effective method for timely diagnosis in early stage, which leads to only 10-20% of patients with LC being suiTable for potentially curative treatments at the time of diagnosis (Groome et al., 2007). When LC is diagnosed at a localized stage, the 5-year survival is ~50%, whereas this rate drops to ~5% when diagnosis is made at the time of lymph node involvement or metastasis (Martini et al., 1995; Reed et al., 2004). Therefore, novel reliable tumour markers are urgently needed to improve clinical outcomes. Thus far, a number of such biomarkers have been reported for LC, including SCC antigen, carcinoembryonic antigen (CEA), neuron-specific enolase, cytokeratin 19 fragment (CYFRA 21-1), cancer antigen 125 (CA-125), and tissue polypeptide antigen (Shinkai et al., 1986). However, the expression of these antigens seems to be absent in sufficient sensitivity and specificity for the diagnosis of the majority of lung malignancies (Pujol et al., 1993).

Recently, new approaches in clinical proteomics have been developed to identify novel biomarkers of lung pathology (COPD, asthma, pleural effusion, and cancer) and to gain insights into disease mechanisms in which proteins play a major role. Some proteomics analyses of various biological fluids associated with the human airway have been reported (Alessandro et al., 2005; Banks et al., 2003). Using bottom-up proteomics analysis by a two dimensional LC-MS/MS strategy, PTX-3 are potentially useful as serological markers for lung cancer (Planque et al., 2009). Pentraxins are pivotal components of the innate immune system, and PTX3 expression has been recently reported in different tumours (Deban et al., 2010). Some studies demonstrated the signaling molecules of the innate immune system have co-opted with tumour cells for invasion, migration and metastasis (Kuper et al., 2000; Balkwill et al., 2001). Inflammatory cells is largely orchestrated the tumour microenvironment, is an indispensable participant in the neoplastic process,
fostering proliferation, survival and migration (Lisa et al., 2002). Recently, pentraxin-3 was identified as a novel serum marker, by commercial ELISA and with a blooded protocol (Diamandis et al., 2011). However, the report had limitations, such as small size, single-centre study design, absence of sufficient non-lung malignancies and no independent validation. Therefore, we designed a large-scale, multicenter validation study to assess the diagnostic accuracy of PTX-3 as a serum marker for lung cancer, as part of the National Cancer Institute’s Early Detection Research Network (EDRN)-defined phase 2 biomarker study (Pepe et al., 2001).

Materials and Methods

Study population

We analyzed a total of 1605 data for patients with lung cancer, benign lung diseases and healthy controls, were enrolled from January, 2011 to March, 2012. A validation cohort matched for age and sex were recruited from another centre in China between April, 2012 and January, 2013. We recruited consecutive patients with 390 diagnosed LC, 351 with benign lung diseases (chronic obstructive lung disease, acute infectious diseases, tuberculosis, asthma, and diffuse noninfectious interstitial diseases), and 417 healthy controls to a test cohort, from Henan province tumour hospital, Zhengzhou, China, from January, 2011 to March, 2012. The age(mean±SD) and gender (male: female) of each group are LC 51±16, 210:180; benign lung diseases 47±14, 196:155; health controls 48±11, 229:188. A validation cohort including 209 with lung cancer, 145 with benign lung diseases, and 93 healthy controls from another centre Second affiliated hospital of southeast university, Nanjing, China between April, 2012 and January, 2013. The age and gender of each group are LC 54±19, 117:92; benign lung diseases 49±17, 86:59; health controls 52±14, 54:39. Furthermore, we investigated the serum PTX-3 levels in 493 non-lung cancers patients including 12 different cancers, which age and gender are 51±13, 310:183. Preoperative and postoperative (postoperation day (POD) 3, 7, 14, and follow-up ranging from 3 months to12 months) PTX-3 levels were assessed in 61 patients undergoing lung cancer resection.

The diagnoses in all patients were confirmed each time by microscopic examination of the material obtained during bronchoscopy, biopsy, and/or surgery. For the purpose of the study, we classified stage O+I as Early-stage lung cancer, according to the American College of Chest Physicians. Healthy controls were eligible blood donors with normal biochemistry and examination. Serum samples were collected prior to initiation of treatment for lung cancer, and stored in -80°C until analysis. The study was approved by the institutional ethical reviews committee at each study centre. Informed consent was obtained from each patients included in the study, according to committees' regulation.

The relative quantitative real time RT-PCR of PTX-3 in tissue samples

To obverse expression status of PTX-3, parallel expression profiles of the protein were analyzed at messenger RNA (mRNA), protein, and secreted protein levels in LC-tissue and non-cancerous lung-tissue samples and in corresponding serum samples. We collected samples from 24 patients with LC (twelve with SCLC and twelve with NSCLC) and five healthy controls recruited at Henan Tumour Hospital, and eight patients with benign lung diseases recruited at the First Affiliated Hospital of Henan University of Traditional Chinese Medicine. The tissue samples were obtained immediately after surgical resection and were snap-frozen in liquid nitrogen and stored at -70°C. The serum samples were also stored at -70°C until assay.

Total RNA was extracted with TRizol reagent (Invitrogen, CA, USA). Reverse transcribed complementary DNA was synthesized by a PrimerScript RT reagent kit (Takara Bio, Shiga, Japan). Semi-quantitative reverse-transcription PCR experiments were undertaken with a HotStarTaq DNA polymerase (Qiagen, Shanghai, China). We used β-actin as an internal control. The cycling conditions were 5 min at 94°C, 28 (β-actin) or 32 cycles of 30 s at 94°C, 30 s at 57°C, 1 min at 72°C, with a final extension of 10 min at 72°C, in a 96-well Veriti Thermal Cycler system (Applied Biosystems, Carlsbad, CA, USA). We analyzed amplified products by 2% agarose gel electrophoresis. Quantitative real-time PCR was done with SYBR Premix Ex Taq (Takara Bio) in an ABI-Prism 7500 sequence detection system (Applied Biosystems). Relative concentrations of mRNA were calculated on the basis of threshold cycle (Ct) values, corrected by β-actin expression. The following primers were used in the semiquantitative reverse-transcription PCR and quantitative real-time PCR analyses: PTX-3 (GenBank GQ412351.1) forward primer: 5’-ccaatgcgttccagaagat-3’; reverse primer: 5’-tgagttggcttcctgataat-3’; β-actin (ACTB,GenBank NM_001101.3) forward primer: 5’-TTCCTCCATACAGAGCC-3’, reverse primer: 5’-GTCTGAGGACACTTCTC-3’. All the experiments were done in triplicate.

Testing of blood samples

PTX-3 was detected by ELISA according to the manufacture’s recommendations, and the ELISA kit was purchased from R&D systems. Briefly, 96-well Nunc-ImmuNo microtiter plates with Maxisorp surface were coated with streptavidin and incubated with biotinylated monoclonal antibody specific for PTX-3 for 45 minutes on the shaker at room temperature. Plated were washed, and pretreated standards and samples were added to the wells, incubated 2 hours on the shaker at room temperature. Any PTX-3 present was bound by the immobilized biotinylated antibody. After washed away any unbound substances, an enzyme-linked conjugate specific for PTX-3 is added to the wells for 2 hours on the shaker at room temperature. Following a wash to remove any unbound conjugate, a substrate solution was added to the wells for 30 minutes on the benchtop, and added stop solution to each well. The optical density was read at 450 nm and referenced to 540nm on a synergy 2 multimode plate reader. The concentrations of PTX-3 were obtained with a log/log curve, created a standard curve using computer software.


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Table 1. Results of Measurement of Serum PTX-3 in the Diagnosis of LC

|                  | Test Cohort | Validation |
|------------------|-------------|------------|
|                  | AUC(95%CI)  | Sensitivity (%)  | Specificity (%)  | PPV (%)  | NPV (%)  | AUC(95%CI)  | Sensitivity (%)  | Specificity (%)  | PPV (%)  | NPV (%)  |
| PTX-3            | 0.823(0.789-0.856) | 72.80%  | 77.30%  | 79.40%  | 70.80%  | 0.802(0.762-0.843) | 69.70%  | 76.40%  | 74.20%  | 70.20%  |
| CEA              | 0.729(0.688-0.770)  | 60.50%  | 78.60%  | 77.40%  | 62.70%  | 0.722(0.674-0.771)  | 54.80%  | 71.80%  | 69.40%  | 55.70%  |
| CYFRA21-1        | 0.744(0.704-0.784)  | 57.60%  | 80.20%  | 81.60%  | 54.10%  | 0.735(0.690-0.785)  | 62.00%  | 79.10%  | 78.80%  | 61.20%  |

Early-LC vs BLD, HC

|                  | Test Cohort | Validation |
|------------------|-------------|------------|
|                  | AUC(95%CI)  | Sensitivity (%)  | Specificity (%)  | PPV (%)  | NPV (%)  | AUC(95%CI)  | Sensitivity (%)  | Specificity (%)  | PPV (%)  | NPV (%)  |
| PTX-3            | 0.764(0.702-0.784) | 59.70%  | 72.20%  | 78.60%  | 59.70%  | 0.776(0.713-0.838) | 66.40%  | 75.90%  | 76.10%  | 65.70%  |
| CEA              | 0.748(0.683-0.814)  | 53.80%  | 87.80%  | 77.40%  | 70.40%  | 0.706(0.636-0.775)  | 53.40%  | 80.10%  | 81.20%  | 51.70%  |
| CYFRA21-1        | 0.720(0.636-0.781)  | 60.50%  | 72.00%  | 75.70%  | 60.50%  | 0.712(0.640-0.787)  | 63.10%  | 73.10%  | 70.40%  | 61.80%  |

LC, lung cancer; BLD, benign lung diseases; HC, healthy controls; AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; *The diagnostic cutoff value of serum PTX-3 was 8.02 ng/mL.
of PTX-3, a greater proportion of patients with LC were positive for PTX-3 than CEA or CYFRA21-1 (225[72.8%] vs 187[60.5%]; 225[72.8%] vs 178[57.6%], Figure 2).

### PTX-3 levels and LC tumour characteristics

The relationships between PTX-3 levels and tumour size, morphological classification or pathological stage are compared. There are no correlations between PTX-3 levels and tumour size or pathological stage, which maybe suggest PTX-3 preferentially overexpressed at the early stage of LC. In patients with three type’s tumour (small cell lung cancer, adenocarcinoma and squamous), PTX-3 levels had no obvious differences (Table 2).

### The levels PTX-3 in patient groups’ with 12 different types of cancers unrelated to the lung

We investigated serum PTX-3 concentrations in patients from 12 different types of cancers unrelated to the lung. Significantly elevated PTX-3 levels were seen in patients with colon cancer, stomach cancer, rectum cancer, oesophageal cancer, cervix cancer, liver cancer, breast cancer, prostate cancer, ovarian cancer bladder cancer, renal cancer, thyroid cancer (Figure 3). Serum PTX-3 levels in these patients were higher than in health controls (all $P<0.05$) and no difference were found between patients with lung cancer and 12 different types of cancers (all $P>0.05$).The results suggest PTX-3 is not a lung cancer-specific tumour marker.

### Table 2. PTX-3 of LC with Different Tumour Sizes, Morphological Classification and Pathological Types

| Tumour size(cm) | ≤3(n=38) | >3and ≤5(n=72) | ≥5(n=97) | Diffuse(n=43) |
|-----------------|----------|----------------|----------|--------------|
| PTX-3(ng/mL)    | 11.39(4.81-15.62) | 10.88(4.72-16.81) | 12.37(5.93-18.21) | 11.92(5.31-17.32) |
| Tumour stage    | Istage(n=53) | Istage(n=77) | IIstage(n=72) | IV stage(n=107) |
| PTX-3(ng/mL)    | 11.91(5.13-16.55) | 11.88(4.63-17.93) | 13.08(4.19-19.37) | 12.92(5.01-18.41) |
| Tumour type     | SCLC(n=83) | Adenocarcinoma(n=71) | Squamous(n=104) |
| PTX-3(ng/mL)    | 12.11(5.92-17.73) | 11.70(5.29-16.99) | 10.53(5.30-16.17) |

LC, lung cancer; SCLC, small cell lung cancer

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**Figure 3. Comparison of the Serum PTX-3 in Non-liver Maglignant Tumours.** Serum PTX-3 levels were increased in the non-liver malignant tumours. Black horizontal lines are means, and error bars are SEs.
than 100 μL serum, have low dependence on operator because generally such tests are non-invasive, require less and large-scale population studies (Locker et al., 2006), are the most applicable for clinical routine assessments.

cancer. However, protein markers measurable in serum and significantly improved diagnostic accuracy for lung as potential tool for non-invasive lung cancer diagnosis (et al., 2011; Sehramm et al., 2011), which were regarded methylated DNAs, RNAs (Keller et al., 2011; Rabman et al., 2012).

important goal in the diagnosis of cancer, especially for view, identification of novel serum biomarkers is an would adapt readily to clinical settings. From these points high sensitive, and specific new diagnostic methods that remains unknown. In the study, we demonstrated that of lung cancer. However, the biomarker had not been assessed in large cohort and validation in multicentre as well as the prognostic value of PTX-3 after LC surgery remains unknown. In the study, we demonstrated that PTX-3 was a valuable biomarker for LC, with comparable sensitivity and specificity to other currently used lung cancer biomarkers in different study centers.

Discussion

Despite many advances in diagnostic imaging of tumors, combination chemotherapy, and radiation therapy, little improvement has been achieved within the last decade in terms of prognosis and quality of life for patients with lung cancer (McWilliams et al., 2009). Equally desirable in prospect are minimally invasive, highly sensitive, and specific new diagnostic methods that would adapt readily to clinical settings. From these points of view, identification of novel serum biomarkers is an important goal in the diagnosis of cancer, especially for detection and screening in early-stage cancer (Hassanein et al., 2012).

Recently, many discoveries of non-protein serum markers have been documented—eg, mutated DNAs, methylated DNAs, RNAs (Keller et al., 2011; Rabman et al., 2011; Sehramm et al., 2011), which were regarded as potential tool for non-invasive lung cancer diagnosis and significantly improved diagnostic accuracy for lung cancer. However, protein markers measurable in serum are the most applicable for clinical routine assessments and large-scale population studies (Locker et al., 2006), because generally such tests are non-invasive, require less than 100 μL serum, have low dependence on operator expertise and special equipments, are low cost, have high reproducibility, and samples need no pretreatment (eg, extraction, purification or reverse transcription). Although many serum protein markers for cancer diagnosis have been proposed, few have been introduced into the clinic over the past 15 years (Wagner et al., 2004; Kulasingam et al., 2008), mainly because they have not met the following criteria: specific overexpression in cancer cells but not in corresponding normal cells; secreted proteins that can be easily detected in serum; and rare expression in human adult normal tissues except in embryonic tissues. PTX-3 meets these criteria: it is a secretory protein, is specifically overexpressed in cancer cells, and is hardly detectable in human adult normal tissues except in placenta and embryonic tissues (Planque et al., 2009; Diamandis et al., 2011). Therefore, this protein might have potential as a cancer-specific serum biomarker for various human cancers including LC (Willeke et al., 2005; Ravenna et al., 2009), and the integration of measurement of PTX-3 in serum into the diagnostic work-up. LC along with information on high risk stage, image examinations, and other clinicopathological features should be considered.

Human pentraxin-3 is a multimeric glycoprotein, whose composing subunits are made of 381 amino acids, and localized on chromosome 3 band q25. Pentraxins are pivotal components of the innate immune system (Deban et al., 2010). Based on the primary structure of the composing proteomes, pentraxins are divided into two groups: short and long pentraxins. C-reactive protein (CRP) are prototypic short pentraxins, whereas PTX3 subsequently identified proteins represent the long pentraxin arm of the family (Garlanda et al., 2005). Recently study identified PTX-3 as serum biomarker of lung cancer. However, the biomarker had not been assessed in large cohort and validation in multicentre as well as the prognostic value of PTX-3 after LC surgery remains unknown. In the study, we demonstrated that PTX-3 was a valuable biomarker for LC, with comparable sensitivity and specificity to other currently used lung cancer biomarkers in different study centers.

We assessed the diagnostic performance of PTX-3 for discriminating LC from normal controls and patients with benign lung diseases using ROC curve in test group. Comparing with the common tumour markers of LC, the AUC of PTX-3 (0.823, 95%CI: 0.789-0.856) was higher than CEA (0.729, 95%CI: 0.688-0.770) and CYFRA21-1 (AUC 0.729, 95%CI: 0.688-0.770). Improvement of survival for lung cancer is entirely dependent upon how early in its development the tumour is diagnosed. Lung cancer tends not to cause symptoms in its early stages, while in patients with more advanced disease symptoms are non-specific (Sapiro et al., 2007). It is therefore classically picked up late in its development. In view of assessing the diagnostic performance of PTX-3 for early stage LC, we used AJCC stage 0+I to define early-stage LC. Almost a quarter of patients belonged to AJCC stage 0+I (97 [24.9%] of 390 in the test cohort and 49 [23.4%] of 209 in the validation cohort). As a result, serum PTX-3 level did not correlate with tumour size as well as it had no correlation with TNM stage, and it had no significant difference in four type lung cancer. Consequently, the
diagnostic accuracy of serum PTX-3 was similar in the early-stage LC and all LC patients, as well as in the two cohorts, irrespective of the different proportions of patients. Another possible reason for the similarity is that LC is preferentially overexpressed at the early stage of prostate cancer (Ravenna et al., 2009), therefore, it might also be overexpressed in early-stage LC. However, this hypothesis needs to be explored further.

The elevations of PTX3 in serum of patients with LC are not well understood. Some studies showed that chronic inflammation increased the risk of carcinogenesis (Kuper et al., 2000; Balkwill et al., 2001). Conversely habitual use of nonsteroidal anti-inflammatory drugs such as aspirin will obviously reduce the risk of some type of cancer (IARC Working Group, 1997). The inflammatory response promotes carcinogenesis by damaging DNA, stimulating angiogenesis and cell proliferation and inhibiting apoptosis (Jackson et al., 1997; Jaiswal et al., 2000). A prospective study of serum C-reactive protein clarified that elevated levels of the protein in cancer-free individuals are associated with increased risk of cancer of any type cancer, including lung cancer (Allin et al., 2009). PTX-3 as one of pentraxins superfamily member has similar function with CRP, under conditions of tissue damage (e.g., myocardial infarction) or infection. PTX3 levels increase more rapidly than C-reactive protein (Okutani et al., 2006). PTX-3 positively correlated with tumor grade and severity and represents a candidate marker of inflammation (Loctelli et al., 2013). Therefore, we inferred the elevation of PTX-3 in serum of patients with lung cancer may be owing to clearance of cells undergoing apoptosis. In our study, serum PTX-3 was obviously elevated in common 12 types of cancers, which suggested the protein was non-specific tumour marker for LC.

The striking decrease in PTX-3 concentrations in serum after surgery suggests that this protein will be a useful surveillance biomarker to assess the therapeutic response of LC patients. We observed PTX-3 returned to high levels after LC relapse in 11 of 15 patients who had tumour recurrence. To further explore this potential role of the protein, we have been undertaken long-term follow-up of all the LC patients who underwent surgery in this study. The prognostic value of PTX-3 for lung cancer should be demonstrated by follow-up the more LC patients operating tumour resection. The elevation of serum PTX-3 after surgery in LC patients’ suggests the tumour recurrence or distant metastasis. Because our study is cross-sectional and retrospective in nature and, therefore, we plan to do a prospective study to assess whether use of PTX-3 can be validated in LC patients.

In summary, PTX-3 is a valuable serum marker that can aid in the diagnosis of LC, and be used in the surveillance of LC recurrence in postoperative management. We believe that serum PTX-3 has great potential to be a diagnostic protein biomarker for LC, because its accuracy in the test cohort, and was proven in an independent validation cohort, even with a different constitution. Our results indicate that serum PTX-3 could potentially be used to diagnose HCC, especially early-stage disease, and can be used to make differential diagnoses.

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