The utility of six serum tumor markers in early detection of lung cancer

Qingwen Jiang
Ningbo First Hospital
Xu Zheng
Ningbo Medical Center Lihuili Eastern Hospital
Yiting Li
Ningbo First Hospital
Weina Huang
Ningbo First Hospital
Xinjian Li
Ningbo First Hospital
Chao Cao (caocdoctor@163.com)
Ningbo First Hospital https://orcid.org/0000-0003-0429-7617

Research article

Keywords: tumor markers, lung cancer, diagnosis, serum tumor associated material

Posted Date: December 6th, 2019

DOI: https://doi.org/10.21203/rs.2.18342/v1

Abstract

Background: Lung cancer has become the leading cause of cancer-related death in China. However, most of patients were diagnosed at advanced stage. Thus, novel lung cancer diagnostic tests, which can be used to screen individuals in early stage, are required.

Methods: A total of 208 patients involving 161 cases of lung cancer and 47 cases of benign diseases were enrolled. Serum concentration of GTM, CETM, PTM, CTM, ETM and HTM were analyzed by kits according to the manufacturer's guidelines.

Results: The results showed significant difference in serum concentrations of GTM, CETM, PTM, CTM, ETM, and HTM between patients with lung cancer and benign diseases. In addition, when compared with benign diseases, higher levels of those six markers were also observed in patient with SCC and SCLC, but not for ADC. Receiver operating characteristic (ROC) curves were further suggested a high sensitivity and specificity of six markers to identify lung cancer.

Conclusion: The serum levels of GTM, CETM, PTM, CTM, ETM and HTM in lung cancer were significantly higher than those of benign diseases. Moreover, these six biomarkers showed a high sensitivity and specificity to identify a patient with malignant. These findings suggested that detection of those six biomarkers in serum might be helpful for differential diagnosis of lung cancer.

Background

Lung cancer has become the leading cause of cancer-related death in China, occupying approximately 25 percent of morality rate.(1),(2) Quantities of smokers, mostly are youth and middle-aged population, leads to steadily growth of pulmonary tumor incidence and mortality rate each year.(1),(3) Because of lacking typical clinic symptoms, over 80% cases diagnosed at advanced stage and missed proper therapy.(3) Studies have demonstrated that five-year survival rate was just 4% in cancer metastases patients, much less than non-invasive ones whose living percentage went up to 55% after surgery.(4) Low-dose computed tomography (LDCT) was recommended to high risk individuals for its reduction of 20% mortality when compared with traditional chest X-ray.(3),(5) However, its low specificity of 60% and accumulate radiation risk eliminated potential priority in widely single use for lung cancer screening.(5)

Recently, advanced detection technology in analyzing the progress of tumor initiation and development had found series of tumor proteins, genomics and proteomics. Some molecular biomarkers, including autoantibodies against tumor-associated antigens (TAAs)(6),(7), microRNAs(8),(9), and circulating tumor cells(10), presented considerable potential to the discovery of early-stage cancer. However, majority of tumor markers could not be widely used due to the low sensitivity and specificity. We therefore performed this study to evaluate the levels of six indicators (GTM, CETM, PTM, CTM, ETM, HTM) in serum for differential diagnosis of lung cancer.

Methods

Subjects

In our study, patients were enrolled from Ningbo First Hospital from June 2017 to February 2018. They were 18 age or older, no acute disease before hospitalization, and were found lung lesion or pulmonary nodules by CT scan. Those who had other malignant tumors, accepted anti-tumor therapy before surgery, merged with autoimmune system disease, pregnant or renal failure, were excluded for minimizing the effect to investigation results. The enrolled patients were finally confirmed by surgery and pathological analysis. The study protocol was approved by the Institutional Review Board of Human Studies of Ningbo First Hospital. Smoking pack-years was defined at 1 year prior for tumor patients and benign controls.

Measurement of serum GTM, CETM, PTM, CTM, ETM, HTM

The blood samples were collected in fasting state within two weeks before surgery, and serum were separated and stored at 4 °C within two weeks. The content measurement of these six indicators was accomplished on Serum Tumor Associated Material Testing Kit (Qingdao Bo-Xin Biotechnology Co.Ltd), and the concentrations of six tumor markers were detected by colorimeter. Brief steps were introduced as following: (1) For each cases, making three calibration tubes included o.1 ml calibration solution and 2.0 ml chromogenic reagent, and one measuring tube with 0.1 ml sera and 2.0 ml chromogenic reagent. (2) Mixing these tubes thoroughly, then launch and maintain chemical reactions in boiling water for 15 minutes. (3) Taken tubes out quickly and put into cool water below 25 °C for 5 minutes to terminate the reaction. (4) The measuring tube is centrifuged at 3000 rpm for 10 minutes, to precipitate macromolecular protein. (5) Extract the supernatant and set the values of wavelength to 450, 442, 406, 420, 470,486 nm respectively. By adjusting to zero value with distilled water, the absorbance of each tube is detected. Each marker is calculated by multiplying the absorbance ratio (measuring / calibration-mean) by 100 to get the final results.

Statistical analysis

Basic characteristics of patients' data were presented as the means ± standard error of the mean (SEM), and chisquare test was performed to compare the distribution of categorical variables. The levels of every tumor marker conformed to normal distribution, and the student's t-test was taken to verify the existence of differences in statistics, while comparison among three pathology types of tumor was conducted by Kruskal-Wallis one-way ANOVA test and illustrated as inter quartile ranges (IQR) and median. A P value was calculated in two-tailed and expressed statistical differences when it was less than 0.05. Receiver operating characteristic (ROC) curves were constructed to evaluate the diagnostic value of each tumor marker, the corresponding sensitivity, specificity, the area under the curves (AUC) and 95% confidence intervals (CI) were calculated. The optimum cut-off point was chosen by assessing two items: likelihood ratio and the maximum value of the sum of specificity and sensitivity. The process of data analysis was operated on GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA).

Results

Patients

A total of 208 patients were enrolled in this study and basic characteristics were summarized in Table 1. Based on postoperative histopathology, eligible patients were divided into two groups: malignant tumor (161 cases) and benign diseases (47 cases). Lung cancer included 128 cases of adenocarcinoma, 28 cases of squamous cell carcinoma, 4 cases of small cell carcinoma, and 1 case of adenosquamous carcinoma, according to histological typing. Benign diseases had 11 cases of benign neoplasms, 8 cases of inflammatory pseudotumor, 5 cases of granuloma, 4 cases of hamartoma, 1 case of inflammatory hyperplasia, 1 case of inflammatory granuloma, 1 case of neuroendocrine tumor, 1 case of benign mass, 1 case of benign pulmonary occupying, 1 case of tuberculous granuloma, 1 case of lung abscess, 1 case of epithelial tumor and 1 case of atypical adenoid hyperplasia. There was no significant difference in age (59.3 ± 0.9 years vs 56.6 ± 1.6 years, P = 0.171), gender, body mass index (BMI, 22.2 ± 0.2 kg/m^2 vs 23.0 ± 0.4 kg/m^2, P = 0.097), or smoking status (39.5 ± 4.1 years vs 31.3 ± 3.7 years, P = 0.428).

The levels of six serum tumor markers between lung cancer and benign diseases

The serum levels of GTM, CETM, PTM, CTM, ETM, HTM in lung cancer were separately compared with benign diseases. The concentration of GTM was significantly higher in malignant patients than in benign ones (92.8 ± 1.1 U/ml vs 84.1 ± 1.3 U/ml, P = 0.0002; Fig. 1A). Similar circumstances were presented in CETM (90.6 ± 0.9 U/ml vs 85.1 ± 1.4 U/ml, P = 0.0066, Fig. 1B) and PTM (88.3 ± 0.9 U/ml vs 82.1 ± 1.3 U/ml, P = 0.0019, Fig. 1C). The serum levels of CETM and PTM increased statistically in the comparison of these two groups. By comparing and analyzing, CTM were in considerable reference value to identify the nature of malignance (94.3 ± 1.2 U/ml vs 85.1 ± 1.3 U/ml, P = 0.0001, Fig. 1D). ETM also presented intense and statistical significance in the discrimination of lung cancer from benign groups (106.9 ± 1.4 U/ml vs 96.5 ± 1.5 U/ml, P = 0.0002,

Fig. 1E). HTM showed higher concentration in lung cancer than that in benign diseases (65.0 ± 0.9 U/ml vs 58.9 ± 1.6 U/ml, P = 0.0009, Fig. 1F).

The levels of six serum tumor markers among different tumor histology

We further investigated the levels of those six biomarkers in squamous cell carcinoma (SCC), adenocarcinoma (ADC), and small cell carcinoma (SCLC). Statistically significant differences were found in six serum tumor markers between patients with SCC and SCLC when compared with benign diseases (Fig. 2). The levels of GTM in SCC, ADC and SCLC were 106.1 ± 2.9 U/ml, 89.6 ± 1.1 U/ml and 100.9 ± 7.3 U/ml respectively, while in benign group was 84.1 ± 1.3 U/ml (P < 0.01,Figure 2A). CETM were statistically higher in patients with SCC and SCLC (98.2 ± 2.2 U/ml, 97.7 ± 5.8 U/ml) than in benign ones (85.1 ± 1.4 U/ml), however, there was no significant difference between ADC and benign controls (88.7 ± 1.0 U/ml vs 85.1 ± 1.4 U/ml, P = 0.0758; Fig. 2B). The elevated levels of PTM were observe in different tumor cell types of lung cancer (97.2 ± 2.3 U/ml of SCC, 86.1 ± 1.0 U/ml of ADC, 100.9 ± 7.3 U/ml of SCLC vs 82.1 ± 1.3 U/ml of benign diseases, respectively, Fig. 2C). Similar tendency were presented at CTM, ETM and HTM. In CTM, patients with SCC was 107.7 ± 3.0 U/ml, ADC was 91.5 ± 1.1 U/ml, and SCLC was 101.4 ± 7.2 U/ml, while benign group was 84.2 ± 1.8 U/ml (Fig. 2D). The comparison of ETM concentrations among tumor subtypes were 122.7 ± 3.3 U/ml for SCC (P < 0.0001), 103.2 ± 1.4 U/ml for ADC (P = 0.0093) and 115.8 ± 9.2 U/ml for SCLC (P = 0.0016) vs 96.5 ± 1.5 U/ml for benign diseases (Fig. 2E). Patients with different cell types of lung cancer also had increased levels of serum HTM (SCC 73.3 ± 2.1 U/ml, ADC 62.8 ± 0.9 U/ml, SCLC 72.7 ± 7.0 U/ml vs Benign 58.9 ± 1.1 U/ml, Fig. 2F).

The diagnostic value of six serum tumor markers in lung cancer

The results of previous analysis have illustrated that GTM, CETM, PTM, CTM, ETM and HTM have the potential to become novel tumor markers for screening lung cancer. Then, we constructed ROC curves to assess the diagnostic value of these six serological indicators (Table 2). GTM was the best marker with sensitivity of 63.35% (95% CI, 55.41% − 70.80%) and specificity of 72.34% (95% CI, 57.36% − 84.38%) in the level of 86.80 U/ml (AUC = 0.6840; 95% CI, 0.6076–0.7603; Fig. 3A), to identify the malignant of pulmonary. CTM occupied the maximum area under the curves (AUC = 0.6868; 95% CI, 0.6108–0.7628; Fig. 3D), with the cut-off value of 87.75 U/ml, corresponding to the sensitivity of 62.11% (95% CI, 54.14% − 69.63%) and specificity of 70.21% (95% CI, 55.11% − 82.66%). The utility of ETM is close to other tumor markers for having reached AUC of 0.6750 (95% CI, 0.5991–0.7510) to recognize malignant patients and benign patients (Fig. 3E). Comparing lung cancer patients with benign ones, the AUC of PTM for lung cancer were 0.6445 (95% CI, 0.5637–0.7253) in the threshold value of 83.55 U/ml (Fig. 3C), and the utility of HTM is relatively low with the area of 0.6493 (95% CI, 0.5690–0.7297) for distinguishing lung cancer from benign diseases (Fig. 3F). CETM was at the lowest area of the under curves (AUC = 0.6314; 95% CI, 0.5482–0.7147; Fig. 3B), with the sensitivity of 59.01% (95% CI, 50.99%-66.68%) and specificity of 68.09% (95% CI, 52.88–80.91%) in the cut-off value of 86.70 U/ml. We further analyzed the clinical value of six indicators in differential diagnosis and sought suitable cut-off for different cell types of lung cancer, the corresponding data were presented in Table 2.

Discussion

Currently, the diagnosis and management of lung cancer are still in intractable challenges worldwide. In order to achieve the early detection of screening lung cancer, it is necessary to take actions in the pre-cancerous and diagnoses in early stages.(11) For high risk population whose smoking pack-years over thirty in the past or at present, blood testing was recommended as the assistance for chest imaging examination with minor trauma instead of continual CT scan(11),(12),(13). CT scan showed a low specificity for lung cancer screening.(6),(14) We therefore performed this study to estimate the clinical value of six tumor markers in discriminating lung cancer from benign diseases.

The results showed higher concentration of GTM, CETM, PTM, CTM, ETM and HTM in patients with lung cancer than those with benign diseases, which may be useful for recognizing pulmonary malignant. Moreover, when lung cancer was classified

into the pathological subtype groups, statistically significant differences in the serum levels of six biomarkers were observed in the comparison with benign diseases. Each marker showed considerable sensitivity and specificity for recognizing patients with SCC and SCLC. For adenocarcinoma, GTM, PTM, CTM, ETM and HTM were significant increased in cancer patients, which was not found in CETM.

GTM showed the highest sensitivity of 63.35% and specificity of 72.34%, with the under area of 0.6840 by ROC curves, to differentiating lung cancer from benign diseases. Similar results were also observed for CETM, PTM, CTM, ETM and HTM in differential diagnosis of lung cancer. It has been reliably proved that GTM was closely related to tumor initiation and invasion(15),(16),(17). In this study, its utility for screening malignant cancer was close to the results of Li et al, which enrolled 155 colorectal cancer and found notable differences with the comparison in the serum concentrations of 66 non-cancer diseases, representing the diagnostic value of 0.881 for discrimination.(18) Several researches also had reported the usefulness of materials therein CETM(19),(20), PTM(21), CTM, ETM(22) and HTM(23),(24) in lung cancer differential diagnosis, therapy monitoring and prognostics(25),(26). Age, gender, and smoking history had been found seldom effect for research population.(18)

In subgroup analysis by tumor histology, the concentrations of six tumor markers were significant higher in patients with SCC and SCLC than benign ones. With the optimum threshold of 89.65 U/ml, GTM showed the highest sensitivity of 89.29% and specificity of 82.98% with 0.9054 of AUC, to identify a patient with SCC, CETM, PTM, CTM, ETM and HTM were in equivalent and intensive ability to predict the malignant nature. For patients of SCLC, six tumor markers' sensitivity were collectively up to 75.00%, and GTM, CTM, ETM presented 89.36% of specificity to recognize malignant patients and benign ones. Several studies set out by local hospitals in different distribution region revealed remarkable alternative function for early malignant tumors instead of using conventional markers like carcinoembryonic antigen, carbohydrate antigen 125, carbohydrate antigen 19 – 9.(27),(28),(29) Carcinoembryonic antigen, squamous cell associated antigen, neuron specific enolase as traditional tumor markers, have been reported passable specificity about 70%-80% in single detection for lung cancer,(20),(22) however, in this study, there were no statistical differences between patients groups and control ones (figures were not shown). Bad diagnostic relevance was found in these six tumor markers for ADC, and there was no significantly increased in serum concentration of CETM among patients with ADC.

Conclusions

To the best of our knowledge, this is the first study for these six tumor markers to identify lung cancer from benign diseases. Our study showed the serum levels of GTM, CETM, PTM, CTM, ETM and HTM in lung cancer were significantly higher than those of benign diseases. Moreover, these six biomarkers showed a high sensitivity and specificity to identify a patient with malignant. These findings suggested that detection of those six biomarkers in serum might be helpful for differential diagnosis of lung cancer.

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Institutional Review Board of Human Studies of Ningbo First Hospital. The written informed consent to participate in the study was be obtained from all participants.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All the data supporting our findings can be found in the results section of the paper.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

This study was supported by Beijing Xisike-Zhenhe Clinical Oncology Research Foundation (Y-2019Genecast-048).

AUTHORS' CONTRIBUTIONS

Qw Jiang, X Zheng and C Cao designed the experiments, performed most experiments, analyzed the data, and wrote the manuscript. Yt Li contributed to clinical patient information management and provided all clinical patient serum samples. Weina Huang, Xinjian Li and C Cao provided overall project supervision and revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors thank the support of Beijing Xisike-Zhenhe Clinical Oncology Research Foundation for this study.

Abbreviations

GTM, general tumor marker; CETM, carcinoma embryo tumor marker; PTM, protein tumor marker; CTM, carbohydrate tumor marker; ETM, enzyme tumor marker; HTM, hormone tumor marker; SCC, squamous cell carcinoma; ADC, adenocarcinoma; SCLC, small-cell lung cancer.

References

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA: A Cancer Journal for Clinicians. 2016;66(2):115-32.
2. Veeraraghavan S, Ramalingam SS, Khuri FR. Early detection of lung cancer in China: The immediate imperative. Cancer. 2015;121(S17):3055-7.
3. Hong Q-Y, Wu G-M, Qian G-S, Hu C-P, Zhou J-Y, Chen L-A, et al. Prevention and management of lung cancer in China. Cancer. 2015;121(S17):3080-8.
4. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA: A Cancer Journal for Clinicians. 2016;66(4):271-89.
5. Tanoue LT, Tanner NT, Gould MK, Silvestri GA. Lung Cancer Screening. American Journal of Respiratory and Critical Care Medicine. 2015;191(1):19-33.
6. Hasan N, Kumar R, Kavuru MS. Lung cancer screening beyond low-dose computed tomography: the role of novel biomarkers. Lung. 2014;192(5):639-48.
7. Ren S, Zhang S, Jiang T, He Y, Ma Z, Cai H, et al. Early detection of lung cancer by using an autoantibody panel in Chinese population. OncoImmunology. 2017;7(2).
8. Inamura K, Ishikawa Y. MicroRNA In Lung Cancer: Novel Biomarkers and Potential Tools for Treatment. J Clin Med. 2016;5(3).
9. Zhu W, Zhou K, Zha Y, Chen D, He J, Ma H, et al. Diagnostic Value of Serum miR-182, miR-183, miR-210, and miR-126 Levels in Patients with Early-Stage Non-Small Cell Lung Cancer. PLoS One. 2016;11(4):e0153046.
10. Park SM, Wong DJ, Ooi CC, Kurtz DM, Vermesh O, Aalipour A, et al. Molecular profiling of single circulating tumor cells from lung cancer patients. Proc Natl Acad Sci U S A. 2016;113(52):E8379-E86.
11. Mazzone P, Powell CA, Arenberg D, Bach P, Detterbeck F, Gould MK, et al. Components necessary for high-quality lung cancer screening: American College of Chest Physicians and American Thoracic Society Policy Statement. Chest.

2015;147(2):295-303.
12. Jun Y, Takashi KJCS. Molecular footprints of human lung cancer progression. 2010;95(3):197-204.
13. Rivera MP, Henderson LM. Lung cancer screening and shared decision making in cancer survivors: the long and winding road. Translational Lung Cancer Research. 2019;8(2):119-23.
14. Hamid UI, Al-Saudi R, Paul I, Graham A. Role of preoperative blood markers as prognostic factors for lung cancer surgery. Asian Cardiovascular and Thoracic Annals. 2019;27(4):288-93.
15. Bose KSC, Prerna Vyas G, Sunil D, Manika SJJoNSB, Medicine. Quantitative evaluation and correlation of serum glycoconjugates: Protein bound hexoses, sialic acid and fucose in leukoplakia, oral sub mucous fibrosis and oral cancer. 2013;4(1):122-5.
16. Jacob TV, Ramesh M, Murali S, Ramesh K, Sanjay PR, Abraham PJJoCR, et al. A non-invasive study to estimate and compare salivary sialic acid level as tumor marker in patients with pre-cancer and oral cancer. 2016;12(2):634.
17. Pelak MJ, Jarosz B, Straczynska-Niemiec A, Krawczyk P, Skoczylas P, Pecka KM, et al. The presence and clinical implications of α-2,6-galactose-linked sialic acids in non-small-cell lung cancer brain metastases–preliminary study. 2014;52(2):104.
18. Pei-Long LI, Zhang X, Zhang Y, Wang HC, Wang YL, Yang YM, et al. Significance of the detection of Bo Xin serum tumor-associated material(BXTM) in the diagnosis of colorectal cancer. Chinese Journal of Clinical Laboratory Science. 2014.
19. Grunnet M, Sorensen JB. Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer. 2012;76(2):138-43.
20. Strauss HG, Laban C, Lautenschlager C, Buchmann J, Schneider I, Koelbl H. SCC antigen in the serum as an independent prognostic factor in operable squamous cell carcinoma of the cervix. European journal of cancer (Oxford, England : 1990). 2002;38(15):1987-91.
21. Chen Z, Zhu B, Ou C, Li Y. Serum ferritin and primary lung cancer. Oncotarget. 2017;8(54):92643-51.
22. Nisman B, Heching N, Biran H, Barak V, Peretz T. The prognostic significance of circulating neuroendocrine markers chromogranin a, pro-gastrin-releasing peptide and neuron-specific enolase in patients with advanced non-small-cell lung cancer. Tumour Biol. 2006;27(1):8-16.
23. Khare P, Bose A, Singh P, Singh S, Javed S, Jain SK, et al. Gonadotropin and tumorigenesis: Direct and indirect effects on inflammatory and immunosuppressive mediators and invasion. Mol Carcinog. 2017;56(2):359-70.
24. Chu HL, Chen HW, Tseng SH, Hsu MH, Ho LP, Chou FH, et al. Development of a growth-hormone-conjugated nanodiamond complex for cancer therapy. ChemMedChem. 2014;9(5):1023-9.
25. Scheble VJ, Braun M, Wilbertz T, Stiedl AC, Petersen K, Schilling D, et al. ERG rearrangement in small cell prostatic and lung cancer. Histopathology. 2010;56(7):937-43.
26. Chen F, Luo X, Zhang J, Lu Y, Luo R. Elevated serum levels of TPS and CYFRA 21-1 predict poor prognosis in advanced non-small-cell lung cancer patients treated with gefitinib. Med Oncol. 2010;27(3):950-7.
27. Shu J, Li CG, Liu YC, Yan XC, Xu X, Huang XE, et al. Comparison of serum tumor associated material (TAM) with conventional biomarkers in cancer patients. Asian Pac J Cancer Prev. 2012;13(5):2399-403.
28. Li CG, Huang XE, Xu L, Li Y, Lu YY. Clinical application of serum tumor associated material (TAM) from non-small cell lung cancer patients. Asian Pac J Cancer Prev. 2012;13(1):301-4.
29. Zamay TN, Zamay GS, Kolovskaya OS, Zukov RA, Petrova MM, Gargaun A, et al. Current and Prospective Protein Biomarkers of Lung Cancer. Cancers (Basel). 2017;9(11).

Tables

Table 1. Clinical characteristics of patients in lung cancer and benign diseases			
	Lung cancer (n = 161*)	**Benign diseases (n = 47)**	***P* value**
Age, years			0.171
Mean ± SEM	59.3 ± 0.9	56.6 ± 1.6	
Gender, n(%)			0.868
Male	80(49.7%)	24(51.1%)	
Female	81(50.3%)	23(48.9%)	
Body mass index, kg/m^2			
Mean ± SEM	22.2 ± 0.2	23.0 ± 0.4	0.097
Smoking status, n(%)			0.081
Smokers	52(32.3%)	9(19.2%)	
Non-smokers	109(67.7%)	38(80.8%)	
Pack-years	39.5 ± 4.1	31.3 ± 3.7	0.428
Cell type, n(%)			
Squamous cell carcinoma	28(17.5%)		
Adeocarcinoma	128(80.0%)		
Small cell lung cancer	4(2.5%)		
*1 lung cancer patient is adenosquamous carcinoma.			
BMI, body mass index.			

Table 2. Diagnostic value of six serum tumor markers in lung cancer

	AUC	Cut-off(U/ml)	Sensitivity(%)	95%CI	Specificity(%)	95%CI	Likelihood ratio
GTM							
Total	0.6840	86.80	63.35	55.41% -70.80%	72.34	57.36%-84.38%	2.29
SCC	0.9054	89.65	89.29	71.77% - 97.73%	82.98	69.19%-92.35%	5.25
ADC	0.6294	86.55	56.25	47.21% - 65.00%	65.96	50.69% -79.14%	1.65
SCLC	0.8165	94.40	75.00	19.41% -99.37%	89.36	76.90% -96.45%	7.05
CETM							
Total	0.6314	86.70	59.01	50.99%-66.68%	68.09	52.88%-80.91%	1.85
SCC	0.8153	88.65	82.14	63.11%-93.94%	72.34	57.36%-84.38%	2.97
SCLC	0.8245	90.80	75.00	19.41%-99.37%	80.85	66.74%-90.85%	3.92
PTM							
Total	0.6445	83.55	60.25	52.25% - 67.86%	63.83	48.52% - 77.33%	1.67
SCC	0.8177	86.40	78.57	59.05% - 91.70%	75.44	62.24% - 85.87%	3.20
ADC	0.5661	84.50	50.78	41.80% - 59.72%	66.67	52.94% - 78.60%	1.52
SCLC	0.8246	84.80	75.00	19.41% - 99.37%	66.67	52.94% - 78.60%	2.25
CTM							
Total	0.6868	87.75	62.11	54.14%-69.63%	70.21	55.11% - 82.66%	2.09
SCC	0.8898	91.15	82.14	63.11% - 93.94%	85.11	71.69%-93.80%	5.52
ADC	0.6361	87.55	57.03	47.99%-65.74%	68.09	52.88% - 80.91%	1.79
SCLC	0.8298	94.80	75.00	19.41% -99.37%	89.36	76.90%-96.45%	7.05
ETM							
Total	0.6750	99.40	60.87	52.88% - 68.45%	70.21	55.11%-82.66%	2.04
SCC	0.8929	103.4	82.14	63.11% - 93.94%	85.11	71.69%-93.80%	5.52
ADC	0.6210	99.3	54.69	45.65% - 63.50%	68.09	52.88%-80.91%	1.71
SCLC	0.8245	108.2	75.00	19.41% - 99.37%	89.36	76.90%-96.45%	7.05
HTM							
Total	0.6493	69.70	60.87	52.88% - 68.45%	68.09	52.88%-80.91%	1.91
SCC	0.8511	60.95	89.29	71.77% - 97.73%	74.47	59.65%-86.06%	3.50
ADC	0.5960	59.70	53.13	44.10%-62.00%	68.09	52.88%-80.91%	1.66
SCLC	0.8670	63.25	75.00	19.41%-99.37%	76.60	61.97% - 87.70%	3.20

GTM, general tumor marker; CETM, carcinoma embryo tumor marker; PTM, protein tumor marker; CTM, carbohydrate tumor marker; ETM, enzyme tumor marker; HTM, hormone tumor marker; SCC, squamous cell carcinoma; ADC, adenocarcinoma; SCLC, small-cell lung cancer.

Figures

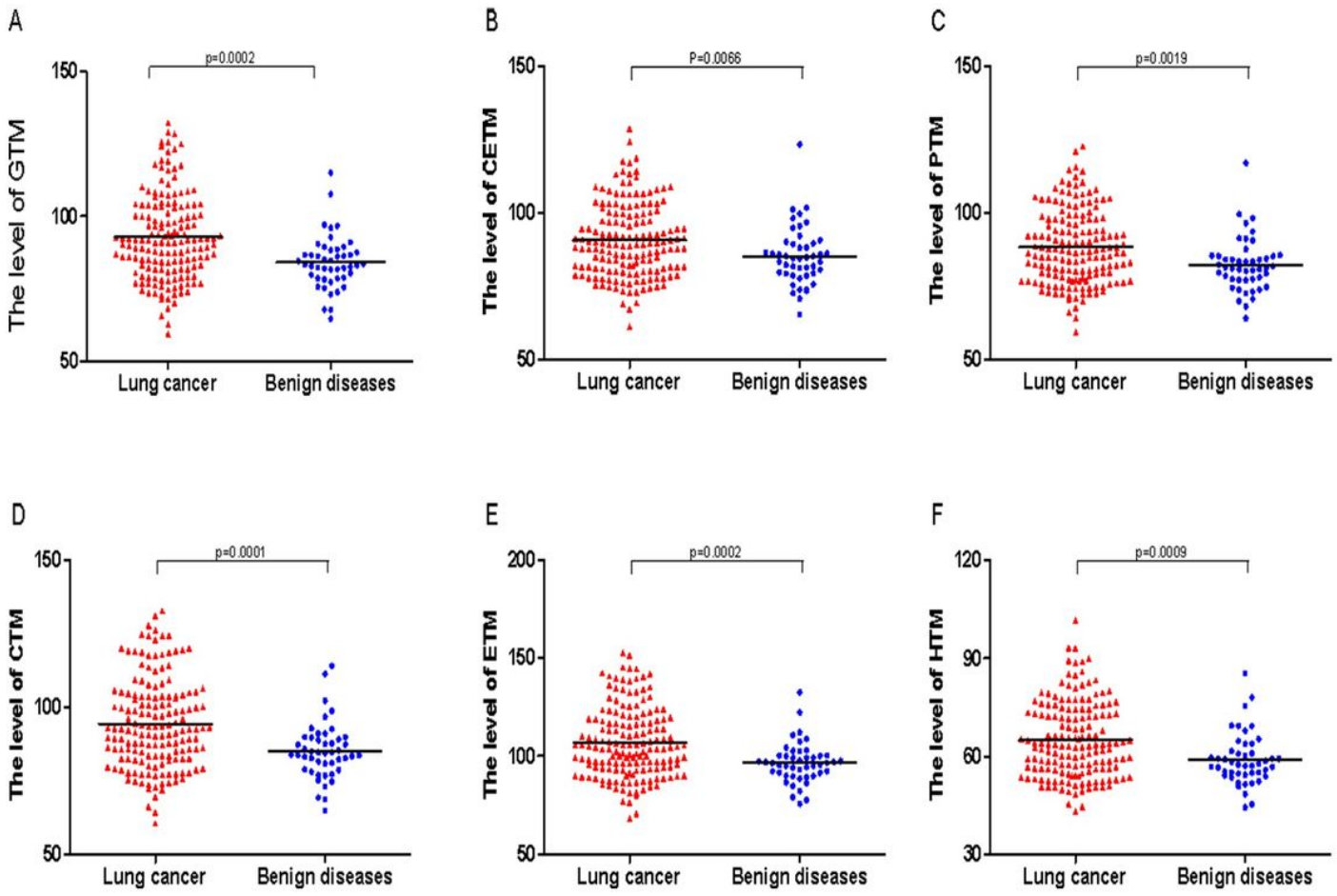

Figure 1

The levels of GTM, CETM, PTM, CTM, ETM and HTM between lung cancer and benign diseases. (A) The concentration of GTM was significantly higher in malignant patients than in benign ones (P = 0.0002). (B) CETM also reached notable differences between lung cancer and benign diseases (P = 0.0066). (C) The serum levels of PTM increased statistically in the comparison of the two groups (P = 0.0019). (D) By comparing and analyzing, CTM were in considerable reference value to identify the nature of malignance (P = 0.0001). (E) ETM presented intense and statistical significance in the discrimination of lung cancer from benign groups (P = 0.0002). (F) The serum level of HTM in lung cancer showed higher concentration in lung cancer than that in benign diseases (P = 0.0009).

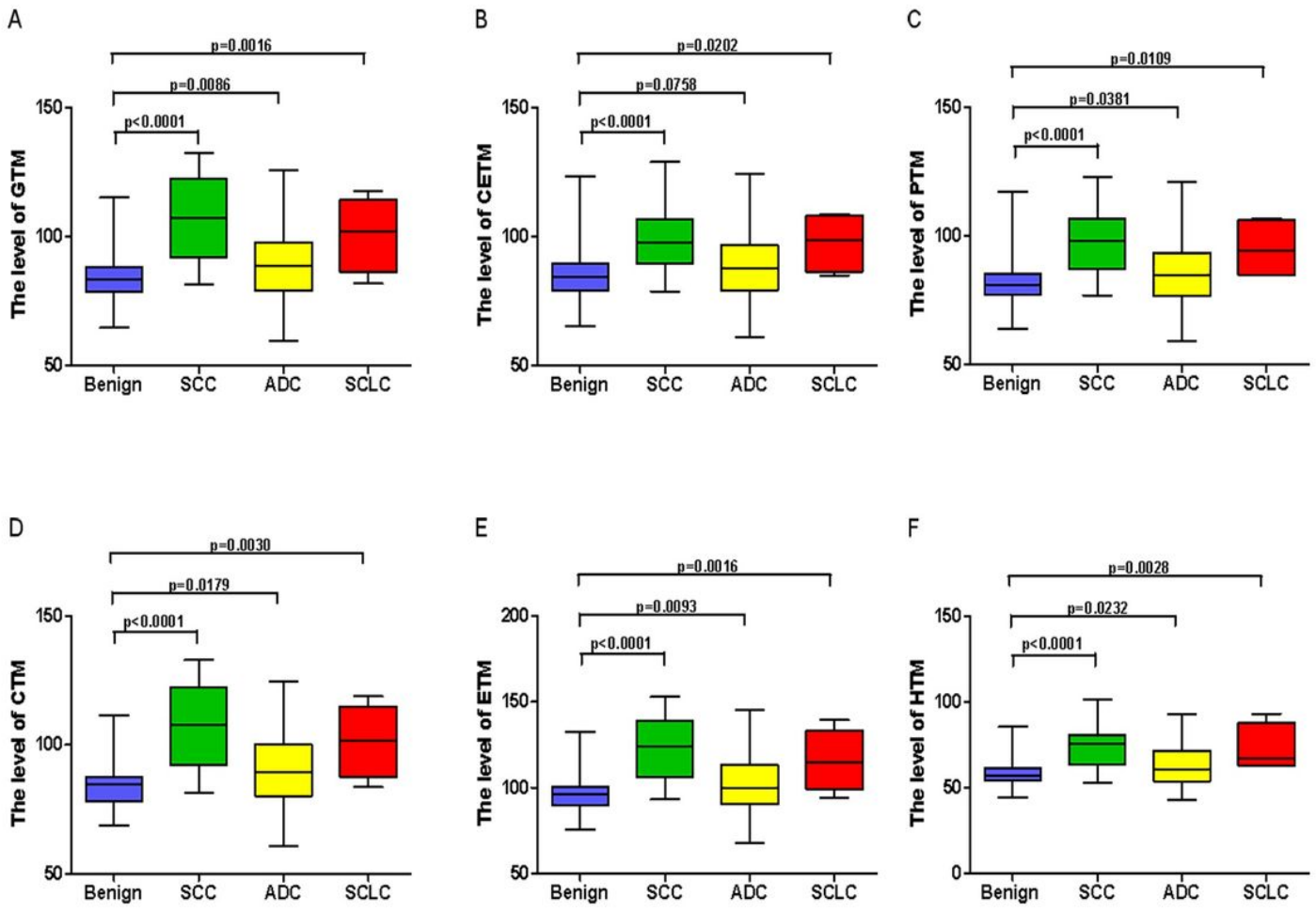

Figure 2

The levels of GTM, CETM, PTM, CTM, ETM and HTM in tumor subtypes. (A) Comparison of GTM levels among tumor subgroup. The levels of GTM were collectively raised in lung cancer than benign controls ($P < 0.01$). (B) Serum CETM in different cell types of lung cancer. The levels of CETM were statistically higher in SCC and SCLC ($P < 0.01$), while not found in ADC ($P = 0.0758$). (C) The concentrations of PTM in tumor subtypes were elevated in patients with lung cancer ($P < 0.05$). (D) In tumor subgroup, CTM presented higher concentration in the serum of lung cancer patients than benign ones ($P < 0.05$). (E) The comparison of ETM concentrations among tumor subtypes had significant differences between lung cancer and benign diseases ($P < 0.01$). (F) The levels of HTM were also increasing in tumor subtypes ($P < 0.05$). SCC, squamous cell carcinoma; ADC, adenocarcinoma; SCLC, small-cell lung cancer.

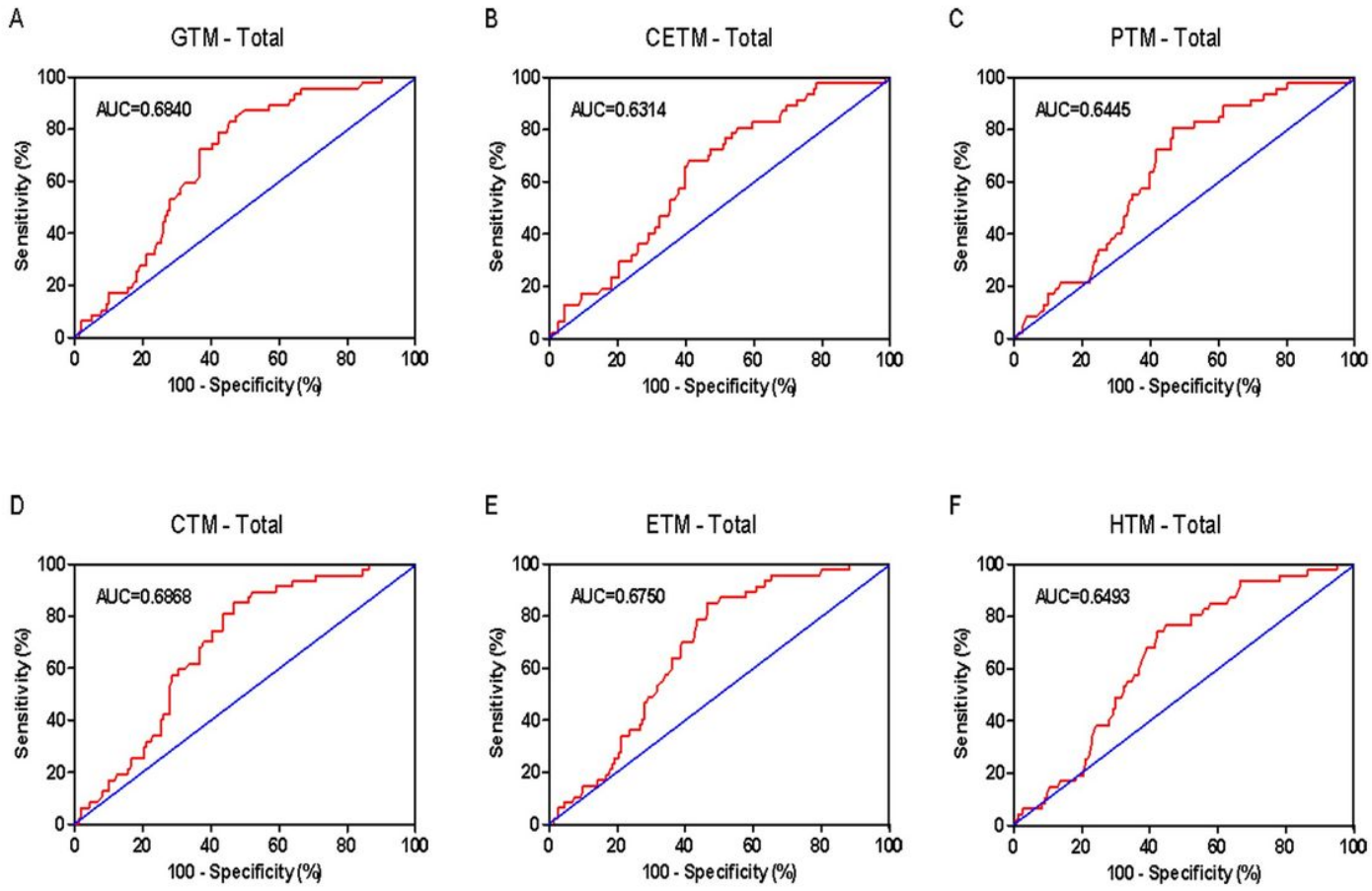

Figure 3

The diagnostic value of GTM, CETM, PTM, CTM, ETM and HTM in lung cancer. Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic value of these six serological indicators. (A) GTM was the best marker with sensitivity of 63.35% and specificity of 72.34% in the level of 86.80 U/ml (AUC = 0.6840; 95% CI, 0.6076 - 0.7603) for discriminating patients with lung cancer from benign ones. (B) CETM was at the lowest diagnostic value to identify malignant tumor (AUC = 0.6314; 95% CI, 0.5482 - 0.7147). (C) Comparing lung cancer patients with benign ones, the AUC of PTM for lung cancer were 0.6445 (95% CI, 0.5637 - 0.7253) in the threshold value of 83.55 U/ml. (D) CTM occupied the maximum area under the curves (AUC = 0.6868; 95% CI, 0.6108 - 0.7628), with the cut-off value of 87.75U/ml, corresponding to the sensitivity of 62.11% and specificity of 70.21%. (E) sThe utility of ETM is close to other tumor markers for having reached AUC of 0.6750 (95% CI, 0.5991 - 0.7510) to distinguish lung cancer from benign diseases. (F) HTM showed relatively low curves with the area of 0.6493 (95% CI, 0.5690 - 0.7297).