Clin. Lab. 2020;66:XXX-XXX

ORIGINAL ARTICLE

The Clinical Significance of Serum MASP-2 and IDH1 in the Early Diagnosis of Non-Small Cell Lung Cancer

Yan Chen [1, *], En-Dong Wu [2, *], Shang Ma [1], Wan-Qiu Bai [1], Yan-Jun Yin [1], Guang-Li Shi [1]

[*] *Co-first author*
[1] *Department of Clinical Laboratory, Beijing Tuberculosis Thoracic Tumor Institute/Beijing Chest Hospital Affiliated to Capital Medical University, Beijing, China*
[2] *Department of Medical Oncology, Beijing Tuberculosis Thoracic Tumor Institute/Beijing Chest Hospital Affiliated to Capital Medical University, Beijing, China*

SUMMARY

Background: **The lack of effective means for the early diagnosis of non-small cell lung cancer (NSCLC) is the leading cause of the high mortality of NSCLC. This study aims to evaluate the clinical significance of serum mannan-binding lectin associated serine protease (MASP)-2 and isocitrate dehydrogenase 1 (IDH1) in the early diagnosis of NSCLC.**

Methods: **The serum levels of MASP-2 and IDH1 were detected in 139 NSCLC patients, 46 patients with benign lung diseases and 61 healthy controls, using an enzyme linked immunosorbent method. The diagnostic significance in NSCLC of the two tumor markers were analyzed by receiver operating characteristic (ROC) curves. In addition, we compared the two markers with the current commonly used tumor marker cytokeratin 19 fragment (Cyfra21-1).**

Results: **The serum levels of MASP-2 and IDH1 in the NSCLC patients were significantly higher than those of healthy controls and patients with benign lung diseases. The differences were statistically significant ($p < 0.01$). The combined sensitivity of MASP-2, IDH1, and Cyfra21-1 in the NSCLC was 68.3%, which was significantly higher than that of the single tumor marker ($p < 0.01$). The sensitivities of MASP-2 and IDH1 in detecting early NSCLC (stage I and stage II) were 39.0% and 41.5%, which were significantly higher than that of Cyfra21-1 ($p < 0.05$). The area under the ROC curves (AUCs) of MASP-2 and IDH1 in the diagnosis of NSCLC were 0.621, and 0.840, which were higher than that of Cyfra21-1 (AUC = 0.606).**

Conclusions: **Serum MASP-2 and IDH1 may be used as potential tumor markers for the auxiliary diagnosis and early diagnosis of NSCLC.**

(Clin. Lab. 2020;66:xx-xx. DOI: 10.7754/Clin.Lab.2020.200249)

Correspondence:
Guang-Li Shi
Department of Clinical Laboratory
Beijing Tuberculosis Thoracic Tumor Institute/Beijing Chest Hospital Affiliated to Capital Medical University
Beiguan Street 9
Tongzhou District
101149 Beijing
China
Phone: +86 10 89509361
Fax: +86 10 89509393
Email: shiguangli878@sina.com

Manuscript accepted April 12, 2020

KEY WORDS

non-small cell lung cancer, mannan-binding lectin associated serine protease-2, isocitrate dehydrogenase 1, diagnosis

INTRODUCTION

Lung cancer is one of the major cancer diseases in the world. An estimated 1.3 million people die from lung cancer each year, and approximately 80% of lung cancer patients are non-small-cell lung cancer (NSCLC) [1]. In China, lung cancer is the leading cause of malig-

nant tumors, and about 20% of cancer patients die from lung cancer [2]. About 70% of lung cancer patients are found to be in advanced stage and have lost the opportunity for surgical treatment. The 5-year survival rate is only 15 - 20%, while early diagnosis can greatly improve the survival rate of lung cancer patients [3]. The National Academy of Clinical Biochemistry (NACB) and European Group on Tumor Markers (EGTM) suggested carcinoembryonic antigen (CEA), neuron-specific-enolase (NSE), serum cytokeratin 19 fragment (Cyfra21-1) as biomarkers for differential diagnosis, prognosis, and monitoring therapy of lung cancer [4]. However, these tumor markers for early diagnosis of lung cancer have some limitations because of the low sensitivity in the early stage (stage Ⅰ and stage Ⅱ) [5]. Therefore, it is urgent to search for new tumor markers with good sensitivity and specificity for diagnosing early NSCLC.

MASP-2 is a key enzyme of the lectin pathway of complement activation, which is synthesized and secreted in the liver. It plays an important role in immune regulation and monitoring [6]. Studies have shown that MASP-2 was closely related to the occurrence and development of tumors, and MASP-2 might cause the invasion and metastasis of tumor cells by promoting proliferation [7,8].

Isocitrate dehydrogenase (IDH) is ubiquitous in human cytoplasm and plays an important role in cell metabolism. Its main function is to participate in the body's defense against stress injury [9]. Current studies have shown that IDH1 was abnormally expressed in plasma of patients and was involved in the development of lung cancer [10,11].

In this study, the serum levels of MASP-2 and IDH1 in patients with NSCLC were detected, and compared with the tumor marker Cyfra21-1, which is commonly used in clinical practice, with the aim to explore the clinical value of serum MASP-2 and IDH1 in the auxiliary diagnosis and early diagnosis of NSCLC.

MATERIALS AND METHODS

Study subjects

Case group: One hundred and thirty-nine patients with NSCLC referred to the Beijing Chest Hospital, Capital Medical University between August 2017 and August 2018, were enrolled in the study. The study subjects included 82 males and 57 females. The median age was 50.3 years (range, 41 - 75 years). The cancer subtypes included 43 patients with squamous-cell lung carcinoma and 96 with adenocarcinoma. TNM classification was performed according to the Union for International Cancer Control (UICC) in 2009. There were 41 early stage (stage I + II) and 98 advanced stage (stage III + IV) patients. All cases were pathologically diagnosed with NSCLC and had not received previous treatment. Cases with a family history of malignant tumor or with severe complications were excluded.

Benign lung disease control group: Forty-six patients with pneumonia, tuberculosis or benign pulmonary nodules referred to the Beijing Chest Hospital, Capital Medical University were enrolled, including 24 males and 22 females. The median age was 41.2 years (range, 25 - 65 years). Cases with hypertension, hyperlipidemia, diabetes and other basic diseases were excluded.

Healthy control group: Sixty-one healthy staff who had a physical examination at Beijing Chest Hospital were enrolled, including 29 males and 32 females, aged 24 - 54 years, with normal blood pressure, blood lipids, blood glucose, liver and kidney function, blood routine, and other indicators. The baseline information of NSCLC patients, benign lung disease patients, and healthy individuals is shown in Table 1.

Sample collection

Venous blood samples (4 mL) were collected from NSCLC patients, benign lung disease patients and healthy individuals. The serum was separated after centrifugation at 3,000 rpm within 2 hours and then stored in an ultra-low temperature refrigerator at -80°C, until the levels of serum MASP-2, IDH1, and Cyfra21-1 were determined. This study was approved by the ethics committee of Beijing Tuberculosis Thoracic Tumor Institute.

Detection of serum MASP-2, IDH1, and Cyfra21-1

Levels of serum MASP-2 and IDH1 were measured by enzyme-linked immunoassay (ELISA) analysis kits (MASP-2: Hycult Biorech Inc., Denmark; IDH1: Modern Gaoda Inc., China) according to the manufacturer's protocols. Levels of serum Cyfra21-1 were detected by an automatic flow fluorescence immunoanalyzer (Model: TESMI; Toujing Inc., China). The cutoff values of serum MASP-2, IDH1, and Cyfra21-1 were defined as 60 ng/mL, 5 ng/mL and 4 ng/mL, respectively.

Statistical analysis

SPSS17.0 software was used for statistical analysis. The measurement data were expressed as median (M) and interquartile range (Q). Comparison of the levels of serum MASP-2, IDH1, and Cyfra21-1 among multiple groups were conducted by the Kruskal Wallis H test. Mann-Whitney U test was used for data comparison between the two groups. The diagnostic values of serum MASP-2, IDH1, and Cyfra21-1 for NSCLC were analyzed by receiver operating characteristic (ROC) curves, and 95% confidence interval (CI) was also calculated. Comparison of rates among multiple groups was conducted by the chi-square test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Levels of serum MASP-2, IDH1, and Cyfra21-1

As shown in Table 2 and Figure 1-3, the levels of serum MASP-2 in NSCLC patients were significantly higher

Table 1. Baseline information of the subjects.

Indexes	NSCLC (n = 139)	Benign lung disease (n = 46)	Healthy individuals (n = 61)
Average age	50.5 ± 12.6	40.8 ± 10.7	39.2 ± 10.1
Male	82	24	29
Female	57	22	32
Adenocarcinoma	96		
Squamous cell carcinomas TNM stage	43		
I	18		
II	23		
III	40		
IV	58		
Smoking	71	16	14
No smoking	68	29	31

Note: NSCLC (non-small cell lung cancer).

Table 2. Levels of MASP-2, IDH1, and Cyfra21-1 in NSCLC (M, Q).

Groups	n	MASP-2 (ng/mL)	IDH1 (ng/mL)	Cyfra21-1 (ng/mL)
NSCLC	139	56.2 (71.4)	7.18 (6.02)	8.61 (7.12)
Benign disease controls	46	39.9 (18.3)	1.88 (2.41)	2.02 (2.43)
Healthy controls	61	39.3 (17.8)	1.65 (2.43)	1.93 (2.51)
Z value		2.942	6.305	6.798
p-value		0.003 [a]	0.000 [b]	0.000 [c]

Note: NSCLC (non-small cell lung cancer), MASP-2 (mannan-binding lectin associated serine protease), IDH1 (isocitrate dehydrogenase 1), Cyfra21-1 (cytokeratin 19 fragment). Comparison among multiple groups, MASP-2: [a] - p < 0.01, IDH1: [b] - p < 0.001, Cyfra21-1: [c] - p < 0.001.

Table 3. Levels of MASP-2, IDH1 and Cyfra21-1 in different pathological classifications (M, Q).

Groups	n	MASP-2 (ng/mL)	IDH1 (ng/mL)	Cyfra21-1 (ng/mL)
Adenocarcinoma	96	57.8 (63.3)	7.31 (7.34)	7.59 (6.45)
Squamous cell carcinoma	43	50.1 (48.1)	6.99 (6.16)	10.6 (13.9)
Z value		0.407	0.349	2.689
p-value		0.684 [a]	0.728 [b]	0.014 [c]

Note: NSCLC (non-small cell lung cancer), MASP-2 (mannan-binding lectin associated serine protease), IDH1 (isocitrate dehydrogenase 1), Cyfra21-1 (cytokeratin 19 fragment). Comparison between adenocarcinoma and squamous cell carcinoma, MASP-2: [a] - p > 0.05, IDH1: [b] - p > 0.05, Cyfra21-1: [c] - p < 0.05.

than those of the benign lung disease group and the healthy controls, and the differences were statistically significant (Z = 2.942, p < 0.01). There were no significant differences in serum MASP-2 levels between the lung benign disease group and the healthy controls (Z = 0.573, p > 0.05). The serum IDH1 levels in NSCLC

Table 4. Levels of MASP-2, IDH1 and Cyfra21-1 in different TNM stages (M, Q).

Groups	n	MASP-2 (ng/mL)	IDH1 (ng/mL)	Cyfra21-1 (ng/mL)
Stage I + II	41	48.3 (43.1)	6.54 (5.66)	7.06 (6.61)
Stage III + IV	98	59.3 (64.2)	7.23 (7.18)	10.8 (14.6)
Z value		0.857	0.656	2.986
p-value		0.392 [a]	0.508 [b]	0.008 [c]

Note: NSCLC (non-small cell lung cancer), MASP-2 (mannan-binding lectin associated serine protease), IDH1 (isocitrate dehydrogenase 1), Cyfra21-1 (cytokeratin 19 fragment). Comparison between stage III + IV and stage I + II, MASP-2: [a] - $p > 0.05$, IDH1: [b] - $p > 0.05$, Cyfra21-1: [c] - $p < 0.01$.

Table 5. Sensitivity and specificity of serum MASP-2, IDH1 and Cyfra21-1 in NSCLC.

Markers	Sensitivity (%)	Specificity (%)
MASP-2	47.5	88.8
IDH1	46.0	88.8
Cyfra21-1	48.2	89.8
MASP-2 + IDH1 + Cyfra21-1	68.3	85.0
χ^2	11.60	1.026
p-value	0.001 [a]	0.418 [b]

Note: NSCLC (non-small cell lung cancer), MASP-2 (mannan-binding lectin associated serine protease), IDH1 (isocitrate dehydrogenase 1), Cyfra21-1 (cytokeratin 19 fragment). Comparison among multiple groups, sensitivity: [a] - $p < 0.01$, specificity: [b] - $p > 0.05$.

Table 6. Sensitivity of serum MASP-2, IDH1, and Cyfra21-1 in different pathological classification of NSCLC (%).

Groups	n	MASP-2 (ng/mL)	IDH1 (ng/mL)	Cyfra21-1 (ng/mL)
Adenocarcinoma	96	47.9	45.8	41.7
Squamous cell carcinoma	43	46.5	46.5	62.8
χ^2		0.166	0.005	5.308
p-value		0.716 [a]	1.000 [b]	0.021 [c]

Note: NSCLC (non-small cell lung cancer), MASP-2 (mannan-binding lectin associated serine protease), IDH1 (isocitrate dehydrogenase 1), Cyfra21-1 (cytokeratin 19 fragment). Comparison between adenocarcinoma and squamous cell carcinoma, MASP-2: [a] $p > 0.05$; IDH1: [b] $p > 0.05$; Cyfra21-1: [c] $p < 0.05$.

Table 7. Sensitivity of serum MASP-2, IDH1 and Cyfra21-1 in different TNM stage of NSCLC (%).

Groups	n	MASP-2	IDH1	Cyfra21-1
Stage I + II	41	39.0	41.5	14.6
Stage III + IV	98	51.0	47.9	62.2
χ^2		1.668	0.491	26.24
p-value		0.197 [a]	0.576 [b]	0.000 [c]

Note: NSCLC (non-small cell lung cancer), MASP-2 (mannan-binding lectin associated serine protease), IDH1 (isocitrate dehydrogenase 1), Cyfra21-1 (cytokeratin 19 fragment). Comparison between stage III + IV and stage I + II, MASP-2: [a] - $p > 0.05$, IDH1: [b] - $p > 0.05$, Cyfra21-1: [c] - $p < 0.001$.

Table 8. Sensitivity of serum MASP-2, IDH1 and Cyfra21-1 in early NSCLC.

Markers	Sensitivity (%)	χ^2	p-value
MASP-2	39.0	6.212	0.024 [a]
IDH1	41.5	7.312	0.013 [b]
Cyfra21-1	14.6		
MASP-2 + IDH1 + Cyfra21-1	56.1		

Note: NSCLC (non-small cell lung cancer), MASP-2 (mannan-binding lectin associated serine protease), IDH1 (isocitrate dehydrogenase 1), Cyfra21-1 (cytokeratin 19 fragment). Compared with Cyfra21-1, MASP-2: [a] - $p < 0.05$, IDH1: [b] - $p < 0.05$.

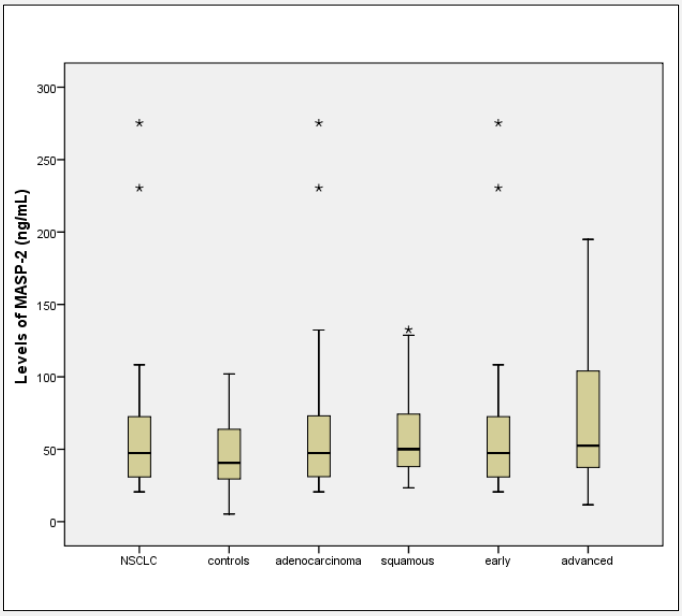

Figure 1. Serum levels of MASP-2 in all subjects.

patients were significantly higher than those of the benign lung disease group and the healthy controls. The differences were statistically significant ($Z = 6.305$, $p < 0.001$). There were no significant differences of serum IDH1 levels between the lung benign disease group and the healthy controls ($Z = 0.685$, $p > 0.05$). Moreover, the serum levels of Cyfra21-1 in NSCLC patients were significantly higher than those of benign lung disease group and healthy controls ($Z = 6.798$, $p < 0.001$).

Serum levels of MASP-2, IDH1, and Cyfra21-1 in different pathological classifications of NSCLC

As shown in Table 3 and Figure 1-3, there was no significant difference of serum MASP-2 levels between squamous cell carcinoma and adenocarcinoma ($Z = 0.407$, $p > 0.05$). Similarly, there was no significant difference of IDH1 levels in different pathological classifications of NSCLC ($Z = 0.349$, $p > 0.05$). However, levels of serum Cyfra21-1 in squamous cell carcinoma were significantly higher than those of adenocarcinoma. The difference was statistically significant ($Z = 2.689$, $p < 0.05$).

Serum levels of MASP-2, IDH1 and Cyfra21-1 in different TNM stages of NSCLC

As shown in Table 4 and Figure 1-3, there was no significant difference of serum MASP-2 levels between early NSCLC (stage I + II) and advanced NSCLC (stage III + IV). Similarly, there was no significant difference of IDH1 levels in different TNM stages of NSCLC

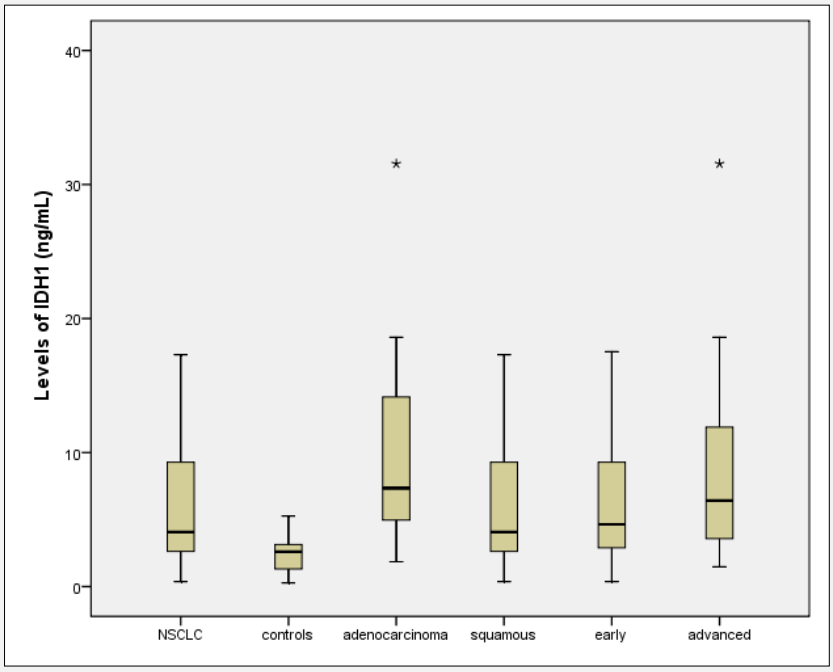

Figure 2. Serum levels of IDH1 in all subjects.

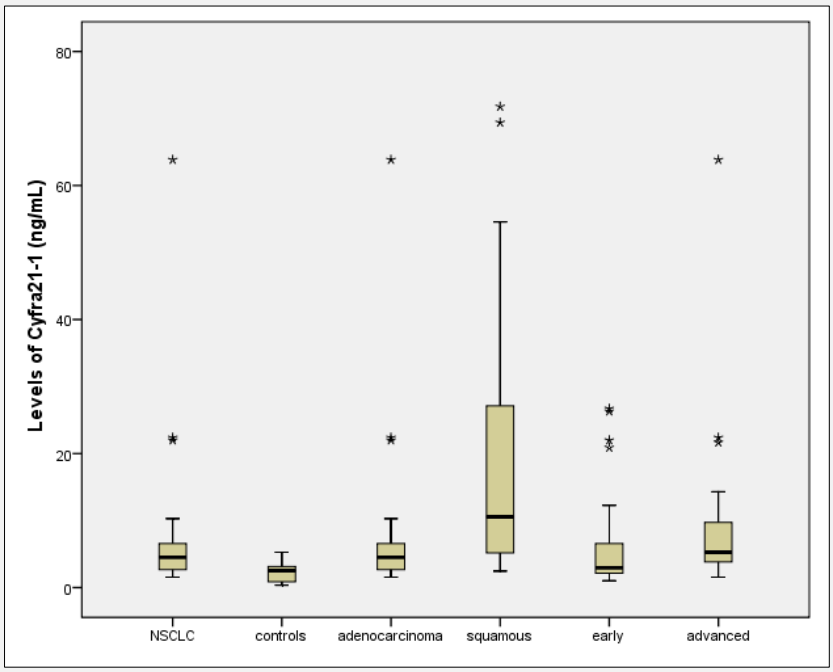

Figure 3. Serum levels of Cyfra21-1 in all subjects.

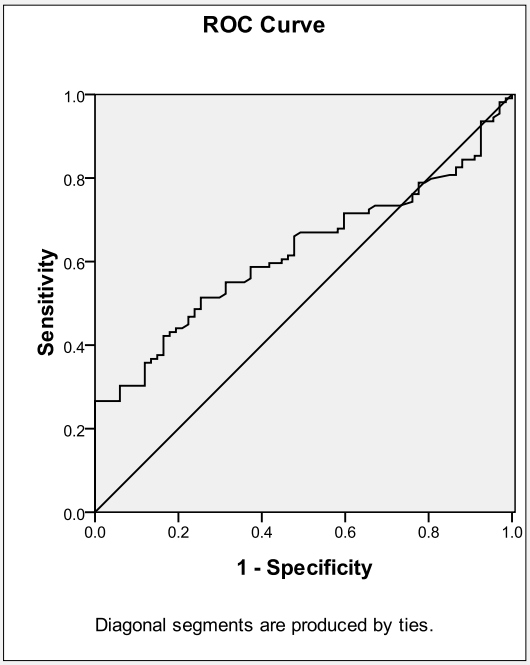

Figure 4. Receiver operating characteristic curve of serum MASP-2 in diagnosing NSCLC.

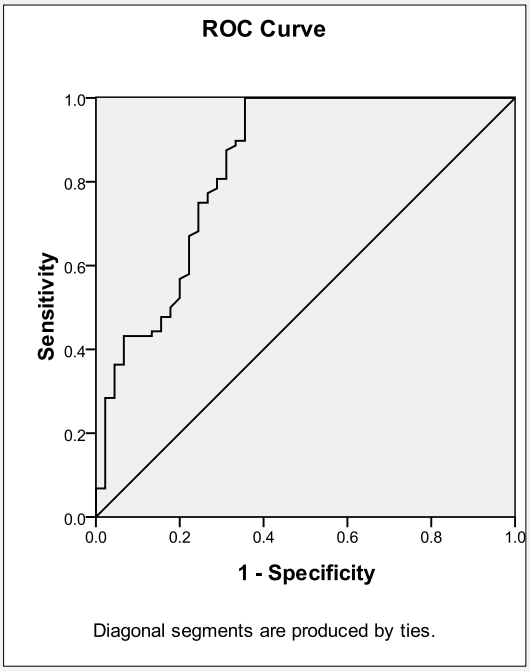

Figure 5. Receiver operating characteristic curve of serum IDH1 in diagnosing NSCLC.

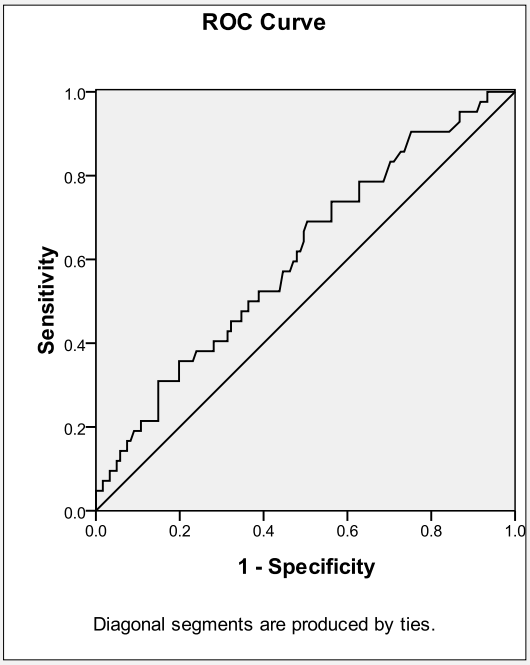

Figure 6. Receiver operating characteristic curve of serum Cyfra21-1 in diagnosing NSCLC.

(Z = 0.656, p > 0.05). However, levels of serum Cyfra21-1 in stage III + IV were significantly higher than those of stage I + II. The difference was statistically significant (Z = 2.986, p < 0.01).

Sensitivity and specificity of serum MASP-2, IDH1 and Cyfra21-1 in NSCLC

As shown in Table 5, the sensitivity of serum MASP-2, IDH1, and Cyfra21-1 in NSCLC was 47.5%, 46.0%, and 48.2% and the specificity was 88.8%, 88.8%, and 89.8%, respectively. The sensitivity of combining MASP-2, IDH1, and Cyfra21-1 was 68.3%, which was significantly higher than that of the single tumor marker. The differences were statistically significant (χ^2 = 11.60, p < 0.01). Moreover, the specificity of combining MASP-2, IDH1, and Cyfra21-1 was slightly decreased (85.0%). The differences were not statistically significant (χ^2 = 1.026, p > 0.05).

Sensitivity of serum MASP-2, IDH1, and Cyfra21-1 in different pathological classifications of NSCLC

As shown in Table 6, there was no significant difference of the sensitivity of serum MASP-2 between squamous cell carcinoma and adenocarcinoma (χ^2 = 0.166, p > 0.05). Similarly, there was no significant difference of the IDH1 sensitivity in different pathological classifications of NSCLC (χ^2 = 0.005, p > 0.05). However, the sensitivity of serum Cyfra21-1 in squamous cell carcinoma was significantly higher than that of adenocarcinoma. The difference was statistically significant (χ^2 = 5.308, p < 0.05).

Sensitivity of serum MASP-2, IDH1, and Cyfra21-1 in different TNM stages of NSCLC

As shown in Table 7, the sensitivity of serum MASP-2 in stage III + IV is higher than that in stage I + II, but the difference was not statistically significant (χ^2 = 1.668, p > 0.05). Similarly, there was no significant difference of IDH1 sensitivity in different TNM stages of NSCLC (χ^2 = 0.491, p > 0.05). However, the sensitivity of serum Cyfra21-1 in stage III + IV was significantly higher than that of stage I + II. The difference was statistically significant (χ^2 = 26.24, p < 0.001).

Sensitivity comparisons of serum MASP-2, IDH1, and Cyfra21-1 in early NSCLC

As shown in Table 8, the sensitivity of serum MASP-2 in the early NSCLC (stage I + II) was significantly higher than that of Cyfra21-1. The difference was statistically significant (χ^2 = 6.212, p < 0.05). Similarly, the sensitivity of IDH1 in stage I + II was higher than that of Cyfra21-1 (χ^2 = 7.312, p < 0.05). Moreover, the sensitivity of combining MASP-2, IDH1, and Cyfra21-1 in stage I + II was significantly increased, reaching up to 56.1%.

Diagnostic values of serum MASP-2, IDH1 and Cyfra21-1 in NSCLC

ROC curve (Figure 4 - 6) analysis showed that the area under ROC curve (AUC) of serum MASP-2 was 0.621 (95% CI = 0.540 - 0.702), and the AUC of serum IDH1 was 0.840 (95% CI = 0.761 - 0.919). The diagnostic values of serum MASP-2 and IDH1 in NSCLC were higher than that of Cyfra21-1 (AUC = 0.606, 95% CI = 0.508 - 0.704).

DISCUSSION

At present, chest X-ray, computed tomography (CT), bronchoscopy, and sputum deciduous cell examination are the most common diagnostic methods for NSCLC. However, the sensitivities of chest X-ray and sputum deciduous cell examination are low in the diagnosis of NSCLC. Bronchoscopy method is invasive and can cause traumatic injury. CT shows the high sensitivity in NSCLC, but it has limitations in the differential diagnosis of some benign lung nodules [12]. Although some experts suggested that low-dose spiral CT could be used for early screening of NSCLC, this method is still controversial and no expert consensus has been reached [13].

Most of the tumor markers are secreted by tumor cells, then enter blood or body fluids. These markers include proteins, enzymes and hormones. Tumor markers can reflect the development process of tumors. Tumor markers have important application value in the auxiliary diagnosis, early diagnosis, prognosis, and efficacy monitoring NSCLC. However, the sensitivities of the currently used tumor markers are low in NSCLC, especially in early NSCLC (stage I + II) [14]. Therefore, in order to find the patients with early NSCLC and improve the survival rate, it is urgent to search for new tumor markers with better sensitivity and specificity in NSCLC.

MASP-2 is a protein composed of 686 amino acids. MASP-2 coding gene is located on chromosome 1p36.3-36.2 and contains 12 exons [15]. MASP-2 is a key factor in the lectin activation pathway of the complement system and can directly activate the complement cascade reaction. The complement system is an important innate immune system, which is the first defense system against pathogens in the body. In the process of immune defense, MASP-2 activates complement and starts the function of antigen scavenging through phagocytes, promoting cell apoptosis and immune monitoring [16]. MASP-2 can stably exist in the serum of healthy individuals and is not affected by the factors of gender, exercise, menstrual period. However, levels of serum MASP-2 in different ethnic groups are not the same. The average levels of serum MASP-2 in African, American Indian, and Caucasian individuals were 196 ng/mL, 290 ng/mL, and 416 ng/mL, respectively [17]. Other studies found that levels of serum MASP-2 in children might be higher than those of adults [18]. Therefore, the cutoff value of serum MASP-2 should be established in each research laboratory. Ytting H et al. reported that serum MASP-2 was abnormally expressed in patients with colorectal cancer, and MASP-2 might play an important role in the occurrence and development of colorectal cancer [8]. Maestri CA et al. also reported that the level of serum MASP-2 was significantly increased in patients with cervical cancer, and closely related to the prognosis [19]. Swierzko et al. found that the levels of MASP-2 in cancer tissue and serum of patients with ovarian cancer were significantly higher than that of the control group and could be used for the judgment of prognosis [7]. However, to the best of our best knowledge, there has been no study on the levels of serum MASP-2 in patients with NSCLC.

The IDH1 gene is located on human chromosome 2q33 and exists in the cytoplasm. IDH1 is an important rate-limiting enzyme in the tricarboxylic acid cycle and can promote the production of NADPH. IDH1 also participates in the metabolic function of cells and diverse biological pathways, exerting various biological functions [20,21]. Chen et al. found that the level of serum IDH1 in patients with esophageal cancer was significantly higher than that of healthy controls. IDH1 might be used as a new tumor marker indicator for the auxiliary diagnosis and prognosis of esophageal cancer [22]. Sun N et al. reported that the level of IDH1 in the plasma of NSCLC patients was significantly higher than that of the healthy controls ($p < 0.001$). The sensitivity and specificity of IDH1 in NSCLC were 75.8% and 89.6%, respectively [10].

This study showed that the levels of serum MASP-2 and IDH1 in patients with NSCLC were significantly higher than those of the benign lung disease group and healthy controls, indicating that the two markers might be related to the occurrence and development of NSCLC. The results of the current study also show that the sensitivity of combining MASP-2, IDH1, and Cyfra21-1 was 68.3%, which was significantly higher than that of the single tumor marker ($p < 0.01$). Moreover, the sensitivities of serum MASP-2 and IDH1 in early NSCLC (stage I + II) were significantly higher than that of Cyfra21-1 ($p < 0.05$). The AUC of serum MASP-2 and IDH1 were higher than that of Cyfra21-1. These results indicate that serum MASP-2 and IDH1, as tumor markers, had potential clinical application values for screening NSCLC and could be used as reference indicators for the early diagnosis of NSCLC. The diagnostic values of serum MASP-2 and IDH1 towards early NSCLC were better than Cyfra21-1. Combining detection of serum MASP-2, IDH1, and Cyfra21-1 could greatly improve the sensitivity of NSCLC.

CONCLUSION

In summary, our study shows that the levels of serum MASP-2 and IDH1 in NSCLC patients were significantly increased, indicating that the two markers have

potential clinical application value for screening NSCLC. The results of this study also show that the diagnostic values of serum MASP-2 and IDH1 towards early NSCLC were better than Cyfra21-1, indicating that the two markers could be used as reference indicators for the early diagnosis of NSCLC. However, because the sample size of the subject group was smaller and did not include the patients with small cell lung cancer (SCLC), the diagnostic values of serum MASP-2 and IDH1 towards early lung cancer detection require further investigation.

Acknowledgment:
This research was supported by Beijing Municipal Health Bureau.

Declaration of Interest:
The authors declare no conflict of interest.

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30 (PMID: 30285281).
2. Edwards BK, Noone AM, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 2014;120: 1290-314 (PMID: 24343171).
3. Ettinger DS. Ten years of progress in non-small cell lung cancer. J Natl Compr Canc Netw 2012;10:292-5 (PMID: 22393190).
4. Diamandis EP, Hoffman BR, Sturgeon CM. National academy of clinical biochemistry laboratory medicine practice guidelines for the use of tumor markers. Clin Chem 2008;54:1935-39 (PMID: 18801938).
5. Zhou C, Chen Z, Dong J, et al. Combination of serum miRNAs with Cyfra21-1 for the diagnosis of non-small cell lung cancer. Cancer Lett 2015;367:138-46 (PMID: 26213369).
6. Hertle E, Arts IC, van der Kallen CJ, et al. Distinct longitudinal associations of MBL, MASP-1, MASP-2, MASP-3, and MAp44 with endothelial dysfunction and intima-media thickness: the cohort on diabetes and atherosclerosis maastricht (CODAM) study. Arterioscler Thromb Vasc Biol 2016;36:1278-85 (PMID: 27055 907).
7. Swierzko AS, Szala A, Sawicki S, et al. Mannose-binding lectin (MBL) and MBL-associated serine protease-2 (MASP-2) in women with malignant and benign ovarian tumours. Cancer Immunol Immunother 2014;63:1129-40 (PMID: 25038892).
8. Ytting H, Christensen IJ, Steffensen R, et al. Mannan-binding lectin (MBL) and MBL-associated serine protease 2 (MASP-2) genotypes in colorectal cancer. Scand J Immunol 2011;73:122-7 (PMID: 21198752).
9. Chotirat S, Thongnoppakhun W, Wanachiwanawin W, Auewarakul CU. Acquired somatic mutations of isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) in preleukemic disorders. Blood Cells Mol Dis 2015;54:286-91 (PMID: 25486927).
10. Sun N, Chen Z, Tan F, et al. Isocitrate dehydrogenase 1 is a novel plasma biomarker for the diagnosis of non-small cell lung cancer. Clin Cancer Res 2013;19:5136-45 (PMID: 24046070).
11. Toth LN, de Abreu FB, Tafe LJ. Non-small cell lung cancers with isocitrate dehydrogenase 1 or 2 (IDH1/2) mutations. Hum Pathol 2018;78:138-43 (PMID: 29723602).
12. Bellomi M, Rampinelli C, Funicelli L, Veronesi G. Screening for lung cancer. Cancer Imaging 2006;6:S9-12 (PMID: 17114084).
13. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 2012;307: 2418-29 (PMID: 22610500).
14. Shin YM, Yun J, Lee OJ, et al. Diagnostic value of circulating extracellular miR-134, miR-185, and miR-22 levels in lung adenocarcinoma associated malignant pleural effusion. Cancer Res Treat 2014;46:178-85 (PMID: 24851110).
15. Frauenknecht V, Thiel S, Storm L, et al. Plasma levels of mannan-binding lectin (MBL)-associated serine proteases (MASPs) and MBL-associated protein in cardio and cerebrovascular diseases. Clin Exp Immunol 2013;173:112-20 (PMID: 23607747).
16. Silva AA, Catarino SJ, Boldt ABW, Pedroso MLA, Beltrame MH, Messias-Reason IJ. Effects of MASP2 haplotypes and MASP-2 levels in hepatitis C-infected patients. Int J Immunogenet 2018;45:118-27 (PMID: 29675993).
17. Ytting H, Christensen IJ, Thiel S, et al. Biological variation in circulating levels of mannan-binding lectin (MBL) and MBL-associated serine protease-2 and the influence of age, gender and physical exercise. Scand J Immunol 2007;66:458-64 (PMID: 178 50591).
18. Sallenbach S, Thiel S, Aebi C, et al. Serum concentrations of lectin-pathway components in healthy neonates, children and adults: mannan-binding lectin (MBL), M-, L-, and H-ficolin, and MBL-associated serine protease-2 (MASP-2). Pediatr Allergy Immunol 2011;22:424-30 (PMID: 21226765).
19. Maestri CA, Nisihara R, Mendes HW, et al. MASP-1 and MASP-2 serum levels are associated with worse prognostic in cervical cancer progression. Front Immunol 2018;9:2742 (PMID: 30532 757).
20. Cimino PJ, Kung Y, Warrick JI, Chang SH, Keene CD. Mutational status of IDH1 in uveal melanoma. Exp Mol Pathol 2016;100: 476-81 (PMID: 27155448).
21. Reitman ZJ, Sinenko SA, Spana EP, Yan H. Genetic dissection of leukemia associated IDH1 and IDH2 mutants and D-2-hydroxyglutarate in Drosophila. Blood 2015;125:336-45 (PMID: 25398 939).
22. Chen X, Li Q, Wang C, et al. Prognostic and diagnostic potential of isocitrate dehydrogenase 1 in esophageal squamous cell carcinoma. Oncotarget 2016;7:86148-60 (PMID: 27863386).