Received: 11 February 2022 | Revised: 7 March 2022 | Accepted: 23 March 2022

DOI: 10.1002/jcla.24412

RESEARCH ARTICLE

WILEY

Application of collagen triple helix repeat containing-1 and mitotic spindle apparatus antibody in small cell lung cancer diagnosis

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Funding information
This work was kindly supported by the National Nature Science Foundation of China under Grant [grant number 81760382], the Innovative Special Fund Project for Graduate Students of Jiangxi Province [grant number YC2020-S045], and the Key Research and Development Program of Jiangxi Province-General projects [grant number 20192BBG70033].

Abstract

Background: The clinical significance of serum collagen triple helix repeat protein-1 (CTHRC1) and mitotic spindle apparatus antibody (MSA) in the diagnosis of small cell lung cancer (SCLC).

Methods: Of the 229 lung tumor patients selected, 62 patients were divided into SCLC, 94 patients with non-small cell lung cancer (NSCLC), and 73 patients with benign lung disease (BLD). The health controls (HC) had a span of 66 cases with normal physical condition. The serum extracted from each participator and enzyme-linked immunosorbent assay was adopted for measuring the serum CTHRC1 and MSA; in the meantime, automatic electrochemiluminescence immunoassay was used for the quantitative determination of serum NSA and CEA. And then, the differences in serum CTHRC1, MSA, NSE, and CEA were compared among involved groups.

Results: ① Compared with other groups, the concentrations of CTHRC1, MSA, and NSE showed a marked increase in the group of SCLC (all $p < 0.01$). Especially for SCLC patients with lymph node metastasis, CTHRC1 provided a notably higher level than those without metastasis. ② CTHRC1 and MSA established a diagnostic criterion with the specificity of 90.99% and 86.27% for SCLC, respectively. ③ In series, the specificity of CTHRC1 and NSE was the highest (99.30%), while MSA and NSE had the highest sensitivity (96.72%) in parallel. ④ Both CTHRC1 and MSA were hazardous factors interconnected with SCLC.

Conclusion: Serum CTHRC1 and MSA had a more exciting prospect of application. When used in conjunction with NSE and CEA, they could optimize the clinical diagnosis value of SCLC.

KEYWORDS
collagen triple helix repeat containing-1, mitotic spindle apparatus antibody, neuron-specific enolase, non-small cell lung cancer, small cell lung cancer

Yuhan Liu and Tingting Hu contributed equally to this work and should be considered co-first authors.

1 | INTRODUCTION

Small cell lung cancer (SCLC), accounting for 10%–15% of lung cancer, is a malignant neuroendocrine tumor dating from bronchial mucosa or glands.[1] But it is worth reminding that a large number of early SCLC patients do not have any keynote manifestations, and SCLC is frequently diagnosed during its final stage with widespread metastasis and invasion, which is rather prone to recur and make the treatment fail. In fact, the 5-year survival rate is only about 10%.[2] As a consequence, more promising serological markers with excellent specificity or sensitivity are urgently demanded for increasing the clinical diagnostic value of SCLC and monitoring early treatment response. Neuron-specific enolase (NSE), a kind of tumor marker bounded up with SCLC, is routinely used in clinical practice. When detected with carcinoembryonic antigen (CEA), it is helpful for differential diagnosis, prognosis, and follow-up of SCLC patients. The drawback of NSE and CEA, of course, is lacking sensitivity. In some circumstances, such as in a few SCLC patients with limited stage, the NSE level without increasing and CEA is also abnormally elevated in other tumor types. Up to now, ideal serum markers have not been found yet. In order to gain a preferable specificity or sensitivity, it is usually combined with two or more serum markers in the diagnosis of SCLC. The prophase work showed[3] that abnormal production of mitotic spindle apparatus antibody (MSA) in serum was conducive to the early diagnosis of SCLC. Collagen triple helix repeat indent-1 (CTHRC1), aberrant expression in many kinds of tumor tissues especially in NSCLC, has been turned out to be a tumor-related oncogene.[4] However, the expression of CTHRC1 in serum of lung cancer patients has not been reported. For this reason, the study detected and investigated CTHRC1, MSA, NSE, and CEA levels in serum of SCLC, NSCLC, benign lung diseases (BLD), and healthy control (HC) patients diagnosed in the Second Affiliated Hospital of Nanchang University. Concrete reports are shown below.

2 | MATERIALS AND METHODS

2.1 | Research objects

The capacity of this study contained 62 patients with SCLC, 94 patients with NSCLC, and 73 patients with BLD who were diagnosed in the Second Affiliated Hospital of Nanchang University from October 2019 to June 2021. There were 37 male and 25 female patients with SCLC, which were further classified into 43 cases with lymph node metastasis and 19 cases without, aged from 43 to 78 years old, with an average of 61.95 ± 8.442 years. The age of NSCLC patients, consisting of 58 males and 36 females, was between 34 and 84 years old, with an average of 59.95 ± 9.964 years, while BLD patients, including 40 males and 33 females, were in the 27~76 age range with an average of 60.26 ± 9.864 years. The clinical diagnostic criteria for diseases in this study were consistent with relevant diagnostic and treatment guidelines established by the International Union Against Cancer (UICC).[5] Sixty-six healthy controls who passed routine examinations at the same period were 37 males and 29 females, aged from 46 to 78 years, with an average of 59.58 ± 7.405 years. The differences were not statistically significant in age and gender among the four groups ($p > 0.05$). According to the Declaration of Helsinki, all the participants had reached an oral agreement or contracted informed consent. And this research has got past the censors by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (Ethical code: No. Review-2019–049).

2.2 | Inclusion and exclusion criteria

2.2.1 | Inclusion criteria

1) Lung cancer patients were identified by histopathological or cytological examination. 2) Clinical and laboratory information completed. 3) Healthy controls without abnormalities in routine examination, especially autoimmune disease. 4) Informed and voluntary participation.

2.2.2 | Exclusion criteria

1) Non-primary pulmonary tumors or combination of other tumors. 2) Associated with neurological and endocrine metabolic system diseases, for instance, hyperthyroidism. 3) Has received an extended period of standardized therapeutic intervention or empirical treatment. 4) Poor adherence.

2.3 | Methods

2.3.1 | Collection and storage of specimens

About 3 ml elbow venous blood was collected from all subjects with empty stomach in the early morning and placed in blood collection tubes containing procoagulants and separator gel. The blood was allowed to stand for 10 min at room temperature before centrifugation at 3500 rpm/min for 15 min at 4°C. The upper serum was then sucked out carefully and transferred into a new 2.0 ml microcentrifuge tube. Only serum samples without visible hemolysis and lipemia were placed in the −20°C freezer prior to measurement.

2.3.2 | Experimental methods

Serum levels of CTHRC1 (Huzhen Industrial Co. Ltd.) and MSA (R&D Systems Inc.) were estimated by enzyme-linked immunosorbent assays (ELISAs). Tumor biomarkers, including NSE and CEA, were assessed on an automatic electrochemistry luminescence

immunity analyzer (Roche), and the reagents were supplied by Roche Diagnostics Co., Ltd.. All relevant determination operations strictly followed the manufacturer's protocol and the quality management process of the Second Affiliated Hospital of Nanchang University. The intra- and inter-laboratory coefficients of variation were consistently satisfactory throughout the measurements.

2.4 | Statistical analysis

SPSS25.0 and MedCalc statistical software were used to basically describe and perform statistical analyses of the detection results, and plotting was carried out using GraphPad Prism software. The normal distribution and homogeneity of variances of continuous variables were assessed by the Kolmogorov–Smirnov (K-S) test and Levene statistic. Data with normal distribution were presented in the form of ($\bar{x} \pm s$), and skewed distribution data were presented as median with interquartile range. One-way ANOVA was conducted for comparison among groups of normally distributed data, while Kruskal–Wallis (K-W) test for the data of non-parametric distribution. Chi-square test was used to identify the differences between classification data groups. The receiver operating characteristic (ROC) curves were plotted to evaluate the diagnostic value. Logistic regression models were used to work out odds ratios (ORs) and 95% confidence intervals (CIs) interrelating serum marker concentration and SCLC risk. The difference was accepted as statistically significant when $p < 0.05$.

3 | RESULTS

3.1 | Differences in serological index expression levels among subjects

The levels of serum CTHRC1, MSA, NSE, and CEA in patients with SCLC, NSCLC, BLD, and HC are shown in Table 1. As we can see, compared with the other three groups, the results of CTHRC1, MSA, and NSE were generally elevated in SCLC patients according to the performances of one-way ANOVA test and Kruskal–Wallis (K-W) test ($p < 0.01$). Meanwhile, the CEA level in the SCLC group was higher than that of the BLD group and HC group, but no significant difference was found with that of the NSCLC group ($p > 0.05$). The detailed results can be found in Table 1.

3.2 | The association between CTHRC1 and lymph node metastasis in SCLC

Small cell lung cancer patients were divided into two groups, with metastasis positive in 43 cases (69.35% positive expression rate) and metastasis negative in 19 cases, on the basis of the condition of lymph node metastasis. We noticed that patients with lymph node metastasis showed higher CTHRC1 levels with 380.41 (309.64–516.49) (ng/ml) compared with those without lymph node metastasis with 217.93 (172.46–267.05) (ng/ml) ($p < 0.01$; Figure 1).

3.3 | Diagnostic performance of serological indexes in SCLC patients

To compare different sensitivities and specificities, we used receiver operating characteristic (ROC) curve analysis for each index. The outcomes demonstrated that the sensitivities of CTHRC1, MSA, NSE, and CEA in diagnosing SCLC were 58.06%, 77.42%, 85.48%, and 69.35%, respectively. For the corresponding specificities, there were 90.99%, 86.27%, 92.27%, and 64.38%, respectively. The areas under the curve (AUC) for CTHRC1 and MSA were around 0.808 and 0.906 with suggested cut-off values of 319.06 ng/ml and 56.07 pg/ml, respectively, which were the most discriminative to predict SCLC. More detailed results are reported in Table 2 and Figure 2.

3.4 | Diagnostic value of pairwise combination of indicators

The performance of each two indicators ligated in parallel or tandem showed that CTHRC1 obtained the highest specificity of 99.30% when connected with NSE in tandem. The sensitivity of diagnostic value was highest (96.72%) when MAS linked with NSE in parallel. See Table 3 for details.

TABLE 1 Comparison of the levels of biochemical indicators in each group

Indicator	SCLC	NSCLC	BLD	HC	*p* value
CTHRC1 (ng/ml)	$365.80 \pm 185.06^{\#,*}$	$245.75 \pm 74.12^{\#}$	146.01 ± 61.89	167.22 ± 83.80	<0.01
MSA (pg/ml)	$92.68 \pm 41.86^{\#,*}$	$50.71 \pm 19.76^{\#}$	21.99 ± 11.98	20.69 ± 10.89	<0.01
NSE (ng/ml)	$32.18 \pm 16.35^{\#,*}$	$9.99 \pm 4.76^{\#}$	4.53 ± 1.83	3.81 ± 1.61	<0.01
CEA (ng/ml)	$3.52(1.93–11.99)^{\#}$	2.74(1.42–6.86)	1.54(0.89–2.80)	1.32(0.77–1.93)	<0.01

Note: $p < 0.01$: $^{\#}$ compared with BLD and HC; * compared with NSCLC; Results are given as mean ± standard deviation or median (25th–75th percentiles). The difference was analyzed by one-way ANOVA test or Kruskal–Wallis (K-W) test.

Abbreviations: BLD, benign lung diseases; CEA, carcino-embryonic antigen; CTHRC1, collagen triple helix repeat containing-1; HC, healthy control; MSA, mitotic spindle apparatus antibody; NSCLC, non-small cell lung cancer; NSE, neuron-specific enolase; SCLC, small-cell lung cancer.

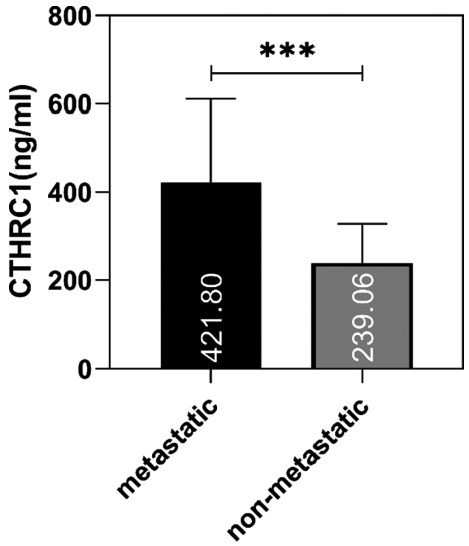

FIGURE 1 Association between CTHRC1 and lymph node metastasis in SCLC. Note: ***$p < 0.01$. Abbreviations: CTHRC1, collagen triple helix repeat containing-1

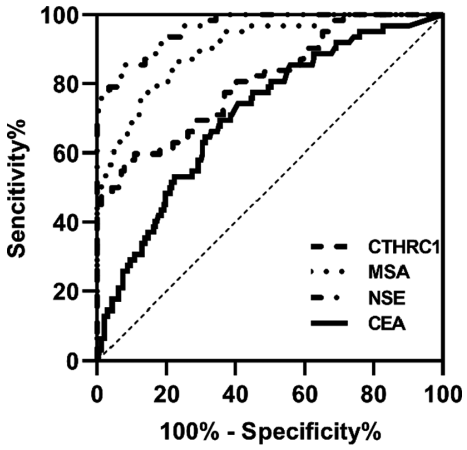

FIGURE 2 Comparison of the diagnostic ability between four indicators by ROC analysis

TABLE 2 The clinical values of four serum biomarkers in diagnosing SCLC

Indicator	AUC	Youden Index	Cut-off	Sensitivity (%)	Specificity (%)
CTHRC1 (ng/ml)	0.808	0.491	319.06	58.06	90.99
MSA (pg/ml)	0.906	0.637	56.07	77.42	86.27
NSE (ng/ml)	0.962	0.778	14.25	85.48	92.27
CEA (ng/ml)	0.709	0.337	2.43	69.35	64.38

Abbreviations: AUC, The area under the ROC curve; CEA, carcinoembryonic antigen; CTHRC1, collagen triple helix repeat containing-1; MSA, mitotic spindle apparatus antibody; NSE, neuron-specific enolase.

3.5 | Investigated the potential risk factors for diagnosing SCLC by binary logistic regression analysis

Binary logistic regression analysis was constructed to determine the risk factors associated with SCLC, and the results showed that CTHRC1, MSA, and NSE were the independent risk factors for diagnosing SCLC. As the levels of various indicators increased, the odds of developing SCLC also increased. As shown in Table 4.

4 | DISCUSSION

The incidence and death rate of lung cancer shows an upward trend year over year among all malignant tumors. The incidence of lung cancer, which poses a severe threat to human health, ranks highest among all malignant tumors in males and second only to breast cancer in females.[6,7] SCLC, a malignant and invasive tumor, progresses fastest in lung cancer and is most prone to relapse after treatment. Its tumor size, location, surrounding invasion, or complications are closely associated with clinical manifestations. At present, imaging is the fundamental method used for the detection of lung cancer in clinical settings. However, lung biopsy is still the gold standard procedure for diagnosing several lung disorders. But the proposed method displays certain limitations due to more trauma and contraindications during operation. Abnormal expression of serum proteins is well known to occur in the blood during the process of tumor cell proliferation and development. So, the most efficient and straightforward auxiliary method is to detect serological protein in clinical practice. When serological proteins are used in conjunction with multiple tumor markers, the sensitivity or specificity of early diagnosis for SCLC can be markedly improved. It may also yield valuable information for the progression of symptoms and the evaluation of the effectiveness of treatment.

Collagen triple helix repeat indent-1, a secreted glycoprotein, is strongly connected with vascular remodeling, wound healing, and the occurrence of osteoblasts. Several prior studies have confirmed that, as a potentially crucial associated gene of malignancy, CTHRC1 was highly expressed in a broad type of solid tumors, including those of the breast,[8] liver,[9] colorectal tissue,[10] and prostate[11] cancer. Upregulated CTHRC1 has the potential ability to enhance tumor proliferation, invasion, cell adhesion, and metastasis by activating multiple signaling pathways such as Wnt/β-catenin signaling. Furthermore, knockdown of CTHRC1 is beneficial for distinctly inhibiting tumor cells proliferation, migration, and adhesion capacity.[12,13] Xue-li Zhang et al.[10] have discovered through the animal model of colorectal cancer that CTHRC1 released from colorectal cancer cells could promote liver metastasis of tumor and was strongly correlated with macrophage infiltration of the immune system. Combination therapy of CTHRC1 monoclonal antibody and anti-PD-1 mAb is powerfully potent in suppressing metastasis, suggesting that CTHRC1 may be an intrinsic marker of tumor invasiveness and can be used as a potential biomarker to predict early prediction of a tumor. Nuzhat Sial et al.[14] reported that the CTHRC1 mRNA was upregulated in the blood of non-small cell patients and the expression level was closely related to the overall survival of patients. Notably, the association of serum CTHRC1 concentration with lung

TABLE 3 Diagnostic value of pairwise combination of indicators

	In series			In parallel		
Variables	**Sensitivity (%)**	**Specificity (%)**	**Youden index**	**Sensitivity (%)**	**Specificity (%)**	**Youden index**
CTHRC1/MSA	44.95	98.76	0.44	90.53	78.50	0.69
CTHRC1/NSE	49.63	99.30	0.49	93.91	83.96	0.78
CTHRC1/CEA	40.26	96.79	0.37	87.15	58.58	0.46
MSA/NSE	66.18	98.94	0.65	96.72	79.60	0.76
MSA/CEA	53.69	95.11	0.49	93.08	55.54	0.49
NSE/CEA	59.28	97.25	0.57	95.55	59.40	0.55

Note: Series sensitivity = A sensitivity × B sensitivity; Series specificity = A specificity+ [(1-A specificity) × B specificity]; Parallel sensitivity = A sensitivity+ [(1-A sensitivity) × B sensitivity]; Parallel specificity = A specificity × B specificity, where A = first variable, B = second variable.

Abbreviations: CEA, carcino-embryonic antigen; CTHRC1, collagen triple helix repeat containing-1; MSA, mitotic spindle apparatus antibody; NSE, neuron-specific enolase.

TABLE 4 Analysis of risk factors for SCLC

			95% CI for OR	
Indicator	***p* value**	**OR**	**Lower**	**Upper**
CTHRC1	0.000	1.017	1.008	1.027
MSA	0.023	1.037	1.005	1.071
NSE	0.000	1.400	1.204	1.629
CEA	0.003	0.861	0.778	0.951

Abbreviations: CEA, carcinoembryonic antigen; CTHRC1, collagen triple helix repeat containing-1; MSA, mitotic spindle apparatus antibody; NSE, neuron-specific enolase; OR, odds ratio.

cancer has not been well studied. The present research found that serum CTHRC1 levels markedly elevated in lung cancer patients, especially in SCLC patients, compared to BLD patients and HC. What is more, serum CTHRC1 concentration of SCLC patients with lymph node metastasis was 380.41 (309.64–516.49) (ng/ml), which was also significantly higher than those without lymph node metastasis. The result indicated that CTHRC1 not only played a crucial role in the occurrence and development of lung cancer but also had a certain correlation with tumor metastasis. High levels of CTHRC1 may be promoting tumor growth, invasion, and metastasis.

Asymmetric division of tumor cells is the root cause of abnormal tumor proliferation. The stabilization of spindle-associated proteins plays a fundamental role during mitosis. The aberrant expression of those proteins can interfere with the localization of dynein on the spindle and induce spindle multi-polarization leading to cell cycle instability and accelerating tumor progression. MSA is an autoantibody mostly against nuclear mitotic apparatus protein, which is a vital product synthesized by the immune system in the anti-tumor process.[15] Previous studies by our research group have shown that the MSA level was elevated in SCLC, making it an effective potential auxiliary tool for separating SCLC patients from NSCLC.[16] At the same time, this search yielded plasma MSA concentration in SCLC patients as 92.68 ± 41.86 pg/ ml. Application of cut-off value of 56.07 pg/ml supplied 86.27% specificity for SCLC diagnosing and the area under the ROC curve was 0.906, second only to NSE. In addition, we also evaluated the risk factors by performing binary logistic regression analysis, and it was found that CTHRC1 and MSA were risk factors associated with SCLC. Thereby, the risk of developing SCLC increased with their levels, suggesting that CTHRC1 and MSA have excellent predictive value.

Small cell lung cancer is a neuroendocrine tumor with the typical clinical feature of neuroendocrine phenomena.[17] Therefore, detecting neuroendocrine markers in serum can assist in diagnosing SCLC. NSE, also known as enolase-γ, is an acid protease unique to neurons and neuroendocrine cells and NSE can promote tumor angiogenesis by activating the JAK-STAT signaling pathway.[18] It is important to note that NSE is highly expressed in lung cancer tissues, especially in SCLC tissues. The level of NSE is 3 to 35 times than that at normal tissue and elevated in 75% of SCLC patients at the clinical diagnosis.[19] CEA is also most commonly used as a classical serum tumor marker in clinical practice. It is at a high level in the serum of patients with various malignant tumors with poor specificity, but it can be used in combination with other oncology indicators to provide adequate information for tumor diagnosis. In this study, both NSE and CEA levels were elevated in the serum of lung cancer patients. Among the four indicators, NSE had the highest sensitivity and specificity in the diagnosis of SCLC with 85.48% and 92.27%, respectively, indicating that NSE was still an effective reference indicator for the diagnosis of SCLC. The area under the ROC curve showed that the sensitivity and specificity of combined diagnosis were higher than that of single detection. The specificity of NSE and CTHRC1 in series was up to 99.30%. The parallel detection of NSE and MSA had a high sensitivity, up to 96.72%. As a result, the combined detection with NSE and other indicators could significantly improve the ability to diagnose SCLC.

5 | CONCLUSION

In conclusion, CTHRC1 and MSA are highly expressed in serum of SCLC patients, and their combined detection with classical tumor serum markers such as NSE and CEA can ameliorate the sensitivity and specificity for the diagnosis of SCLC, and the level of CTHRC1

can predict whether there is lymph node metastasis in SCLC. CTHRC1 and MSA are excellent complements of serum markers in SCLC diagnosis.

CONFLICT OF INTEREST

The authors declare with no conflicting financial interests relevant to this article.

AUTHOR CONTRIBUTION

Yuhan Liu and Tingting Hu: data curation, data analysis, visualization, and manuscript writing/editing. Xu Li and Xiaohang Li: data analysis and interpretation of the results. Jianlin Yu, Yang Wu, and Simei Chen: designed the work and manuscript review. Liming Tan: manuscript writing/editing.

DATA AVAILABILITY STATEMENT

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Liu Y, Hu T, Li X, et al. Application of collagen triple helix repeat containing-1 and mitotic spindle apparatus antibody in small cell lung cancer diagnosis. *J Clin Lab Anal*. 2022;36:e24412. doi:10.1002/jcla.24412