Clinical Trial/Experimental Study

Medicine

OPEN

Combination of serum ACSL4 levels and low-dose 256-slice spiral CT exhibits the potential in the early screening of lung cancer

Wenlong Yu, BM[a], Li Wang, MM[b], Shi Liu, MD[c], Ying Liu, MM[d], Shuying Wang, BM[b], Xuejia Sun, BM[b,*]

Abstract

Background: The prognosis of lung cancer is related to the stage of the disease at the time of detection, and early diagnosis can prolong survival time. In this prospective observational cohort research, we aimed to analyze the diagnostic performance of the combined application of ACSL4 and low-dose 256-slice spiral computed tomography (CT) to lung cancer.

Methods: This prospective observational cohort research enrolled a total of 512 patients with pulmonary nodules (PN) who were found with PN by CT. All patients were divided into 2 groups through biopsy operation, including 449 patients with benign PN and 63 patients with malignant PN. Both groups were scanned with a Philips Brilliance 256iCT machine. Imaging features of PN were recorded. All images of the nodules were used for data measurement and image analysis by the Lung Nodule Assessment analysis software. The serum ACSL4, carcinoembryonic antigen (CEA), cytokeratin 19 fragment 21-1 (CYFRA21-1), neuron-specific enolase, carbohydrate antigen 199 (CA199) and carbohydrate antigen 125 (CA125) levels were measured by enzyme-linked immunosorbent assay method. The demographic data and clinical data, including age, sex, body mass index, smoke condition, TNM stage, lymph node metastasis and distant metastasis were collected. All the patients were followed for 5 years. Statistical analysis was conducted using SPSS software with $P < .05$ as statistically different.

Results: The diameter of nodules, the proportion of burr signs and smoking status, and the serum levels of CEA, CYFRA21-1, CA199, CA125 were significantly higher in malignant nodules group compared with the benign nodules group. Serum ACSL4 levels of malignant nodules group (19.33 ± 6.92 ng/mL) were remarkably lower than the benign nodules group (25.34 ± 3.78 ng/mL). ACSL4 was negatively correlated with CEA, CYFRA21-1, CA199, and CA125. ACSL4 was associated with the clinical outcomes in malignant PN patients and lower ACSL4 predicted poor clinic outcomes and prognosis. In addition, ACSL4 combined with low-dose 256-slice spiral CT had satisfactory diagnostic value for lung cancer.

Conclusion: In summary, our results showed that combination application of ACSL4 and low-dose 256-slice spiral CT might be a potential method for the early screening of lung cancer.

Abbreviations: ACSL4 = long-chain acyl-CoA synthetase 4, CA125 = carbohydrate antigen 125, CA199 = carbohydrate antigen 199, CEA = carcinoembryonic antigen, CT = computed tomography, CYFRA21-1 = cytokeratin 19 fragment 21-1, ELISA = enzyme-linked immunosorbent assay, NSE = neuron-specific enolase, PN = pulmonary nodules, SIRT1 = sirtuin1.

Keywords: ACSL4, combination application, low-dose 256-slice spiral computed tomography (CT), lung cancer, pulmonary nodules (PN)

1. Introduction

Lung cancer is one of the most common malignant tumors, with a high incidence and mortality rate worldwide.[1] Lung cancer accounted for 11.4% of all new cancer cases and 18.0% of new cancer-related deaths according to GLOBOCAN 2020, with more than 500,000 Chinese diagnosed with lung cancer each year.[2,3] The prognosis of lung cancer is related to the stage of

The present study was supported by Qiqihar Science and Technology Plan Joint Guidance Project (LHYD-202106).

All authors agreed the submission and the policy of the journal and copyright.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This research has obtained approval from the ethic committee of the Third Affiliated Hospital of Qiqihar Medical University and keep compliance with the Declaration of Helsinki.

[a] Department of Ultrasound, The Third Affiliated Hospital of Qiqihar Medical University, Qiqihar, China, [b] Diagnostic Radiology Center, The Third Affiliated Hospital of Qiqihar Medical University, Qiqihar, China, [c] Department of General Surgery and Central Laboratory, The Third Affiliated Hospital of Qiqihar Medical University, Qiqihar, China, [d] Department of Oncology, The Third Affiliated Hospital of Qiqihar Medical University, Qiqihar, China.

** Correspondence: Xuejia Sun, Department of Radiology center, The Third Affiliated Hospital of Qiqihar Medical University, No. 27, Taishun Street, Tiefeng District, Qiqihar, Heilongjiang 161000, China (e-mail: xuejias@webmailcn.com).*

How to cite this article: Yu W, Wang L, Liu S, Liu Y, Wang S, Sun X. Combination of serum ACSL4 levels and low-dose 256-slice spiral CT exhibits the potential in the early screening of lung cancer. Medicine 2023;102:5(e32733).

Received: 12 September 2022 / Received in final form: 4 January 2023 / Accepted: 4 January 2023

http://dx.doi.org/10.1097/MD.0000000000032733

the disease at the time of detection, and early diagnosis can prolong survival time.[4,5] Therefore, early diagnosis of lung cancer is particularly important.

Low-dose spiral computed tomography (CT), with the advantages of low cost, convenient operation and no obvious trauma, has been widely used in the early diagnosis of lung cancer.[6] The early manifestation of lung cancer is pulmonary nodules (PN). Radiologists use low-dose spiral CT to diagnose PN, and then preliminarily distinguish benign and malignant PN according to their density, size and shape, etc.[7,8] One study has shown that 96.4% of high-risk lung cancer patients with PN were benign nodules.[9] Using surgery or bronchoscopy to further diagnose suspicious PN has high risk and costs that are unacceptable to some patients. Thus, it's urgent to find new diagnostic methods and potentially novel biomarkers to combine low-dose spiral CT for early diagnosis of lung cancer. As a member of the long-chain acyl-coenzyme synthetase (ACSL) family, long-chain acyl-CoA synthetase-4 (ACSL4) is involved in the catabolism and biosynthesis of fatty acids.[10] Some studies have indicated that ACSL4 was associated with the development of multiple cancers, including colon cancer,[11] liver cancer,[12] breast cancer[13] and so on. TCGA database shows that the expression of ACSL4 decreases in patients with lung cancer.[14] However, so far, no clinical studies focus on the role of ACSL4 in lung cancer development and diagnosis.

In this prospective observational cohort research, we aimed to explore the serum ACSL4 levels in patients with lung cancer and its correlation with clinical results and analyze the diagnostic performance of the combined application of ACSL4 and low-dose 256-slice spiral CT to lung cancer. This study might reveal the clinical significance of ACSL4 in patients with lung cancer, as well as provide a valuable diagnostic method for lung cancer.

2. Methods and materials

2.1. Patients

This prospective observational cohort research enrolled a total of 512 patients with PN who were found with PN by CT. All patients went to our hospital from March 2013 to December 2016. The criteria for inclusion were as follows: age ≥ 18 years; nodule diameter between 6 and 30 mm; the lung tissue around the nodule was normal and without atelectasis and hilar abnormalities; the patient received biopsy operation and had pathological findings. The exclusion criteria included: patients who received chemotherapy or radiotherapy before the study; patients with other cancers; patients with serious infection, severe liver, renal, and cardiovascular dysfunctions. All patients were divided into 2 groups through biopsy operation, including 449 patients with benign PN and 63 patients with malignant PN. All patients signed written informed consent. The present study was approved by the Ethical Committee of the Third Affiliated Hospital of Qiqihar Medical University.

2.2. Chest CT image analysis

Both groups were scanned with a Philips Brilliance 256iCT machine: foreign bodies were removed before the scan, the scan area was from the thoracic inlet to the adrenal level, and the parameters were set before the scan: iDose 4th generation iterative algorithm was selected: iDose4 3, tube current was 80 mAs, tube voltage was 100 kV, reconstruction matrix was 512 × 512, pitch was 0.8, rotation time was 0.5 second, and layer thick neuron-specific enolase (NSE) and spacing were 1 mm. The patient was placed in a supine posture with arms up, and an experienced physician instructed the patient to inhale forcefully, hold his breath during the scan, and then breathe normally afterward. After scanning, the images were transferred to the Philips 256iCT EBW processing workstation. All images of the nodules were used for data measurement and image analysis by the Lung Nodule Assessment analysis software. Two clinical radiologists with more than 5 years of experience processed and evaluated the data and images separately and reached a unanimous opinion. Imaging features of PN were recorded including: position, density (solid, or mixed), diameter, the internal structure (vacuolar sign, calcification, tracheal signs), edge features (smooth, lobulated, burr signs), etc. The imaging pictures of conscientious PN and malignant PN are shown in Figure 1.

2.3. Blood sampling measured by ELISA

The serum ACSL4, carcinoembryonic antigen (CEA), cytokeratin 19 fragment 21-1 (CYFRA21-1), NSE, carbohydrate antigen 199 (CA199) and carbohydrate antigen 125 (CA125) levels were measured by enzyme-linked immunosorbent assay (ELISA) method. Briefly, fasting cubital venous blood (5 mL) of all patients were collected within 24 hours after admission. The blood samples were collected and were centrifuged at 2000 g for 15 minutes. After centrifugation, the levels of ACSL4, CEA, CYFRA21-1, NSE, CA199, and CA125 were tested using commercially available ELISA kits (ACSL4 MBS9331516 MyBioSource, CEA MBS2568098 MyBioSource, CYFRA21-1 MBS162081 MyBioSource, NSE MBS761831 MyBioSource, CA199 MBS3802688 MyBioSource, CA125 MBS162768 MyBioSource) strictly according to the manufacturer's instructions.

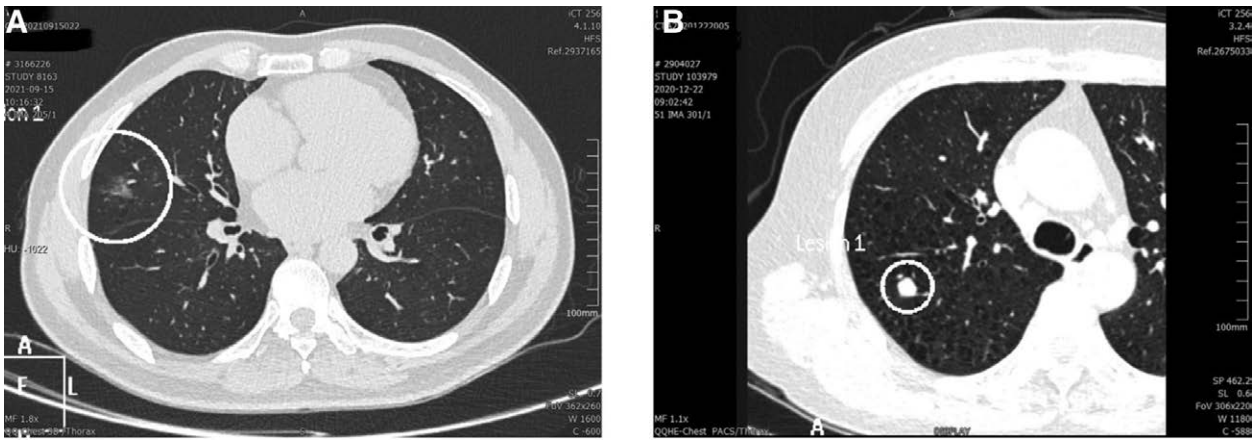

Figure 1. A. Malignant nodule image from a 56-year-old male patient by low-dose 256-slice spiral CT. B. Benign nodule image from a 57-year-old female patient by low-dose 256-slice spiral CT. CT = computed tomography.

2.4. Data collection and follow-up

Demographic data of all patients including age, sex, body mass index, smoke condition, TNM stage, lymph node metastasis, and distant metastasis were collected. All patients were followed up for 5 years and survival time and recurrence time were recorded.

2.5. Statistical analysis

Continuous data were presented by mean ± SD or median (range) according to distribution, which was confirmed by Kolmogorov–Smirnov analysis. Comparison between the two groups was conducted by Student's *t* test for normally distributed data. Chi squared analysis was used to analyze the rates. The correlation among ACSL4 and tumor factors was analyzed by Pearson's rank correlation analysis. Kaplan–Meier (K-M) curve was used for analyzing the survival time. Receiver operating characteristic curve was used for analysis of ACSL4 and imaging diagnosis in PN patients. $P < .05$ regarded significant difference. All data used SPSS 18.0 to statistical analyses.

3. Results

3.1. Basic clinical characteristics and imaging characteristics of all patients

This study enrolled a total of 512 patients with PN, including 449 patients with benign PN and 63 patients with malignant PN. The smoking proportion and the serum levels of CEA, CYFRA21-1, CA199, CA125 were significantly higher in the malignant nodules group compared with the benign nodules group (Table 1). Compared with the benign nodules group, the diameter of nodules and the proportion of burr signs were markedly higher in malignant nodules group from the imaging characteristics. No other significant difference was found.

3.2. Serum ACSL4 levels in all patients and correlation with the cancer-related biomarkers

Then, the serum ACSL4 levels was determined. It was found that serum ACSL4 levels of the malignant nodules group (19.33 ± 6.92 ng/mL) were remarkably lower than the benign nodules group (25.34 ± 3.78 ng/mL) the suggesting ACSL4 was associated with deterioration of PN (Fig. 2). Pearson's analysis showed that ACSL4 was negatively correlated with CEA, CYFRA21-1, CA199, and CA125 (Table 2).

3.3. Correlation between serum ACSL4 level and the clinical outcome of patients with malignant PN

To further investigate the role of ACSL4 in malignant PN, all patients with malignant PN were divided into ACSL4 high levels group and low levels group according to its mean value (19.33 ng/mL) and the clinical characteristics were compared. As summarized in Table 3, the diameter of tumors and the serum levels of CYFRA21-1, CA199 in the ACSL4 low levels group were significantly increased compared with the patients with high ACSL4 levels ($P < .05$). Besides, compared with the ACSL4 high levels group, the diameter of nodules and the proportion of tumor stage III-IV, lymph node metastasis and distant metastasis were also significantly increased in the ACSL4 low levels group. These results suggested that ACSL4 was associated with clinical outcomes and severity in patients with malignant PN.

3.4. Correlation between serum ACSL4 and lung cancer patients

The 5-year survival and relapse rates were analyzed in two groups of patients with high/low serum ACSL4 levels by K-M curve. The results showed that the low levels group had shorter 5-year survival time and higher recurrence rate (Fig. 3, $P < .001$).

3.5. Diagnostic value of ACSL4 for lung cancer

We draw receiver operating characteristic curves to evaluate the diagnostic value of ACSL4 for lung cancer. The result showed that ACSL4 could be a potential diagnostic biomarker of lung cancer (Fig. 4), the AUC of ACSL4 was 0.762, cutoff value was 20.70 ng/mL, with a sensitivity of 65.1%, specificity of 90.2%.

3.6. Combination of serum ACSL4 and low-dose 256-slice spiral CT in the diagnosis of lung cancer

Finally, we analyzed the combined application of serum ACSL4 and low-dose 256-slice spiral CT in the diagnosis of lung cancer, using the following formula: sensitivity = true positive/(true positive + false negative) × 100%; specificity = true negative/(true negative + false positive) × 100%; accuracy = (true positive + true negative)/(true positive + false negative + false positive + true negative) × 100%. As shown in Table 4, the

Table 1

Basic demographic data and clinical characteristics of all patients.

Variables	Benign nodules, n = 449	Malignant nodules, n = 63	*P*
Age, yr	47 (18–74)	42 (18–74)	.622
Sex, Female (%)	216 (48.11)	37 (58.73)	.156
BMI	25.70 (20.89–29.32)	25.89 (20.96–29.22)	.715
Current smoker, n (%)	268 (59.69)	51 (80.95)	.02
CEA (ng/mL)	18.10 ± 3.91	24.44 ± 6.58	<.001
NSE (ng/mL)	39.52 ± 8.56	38.20 ± 6.51	.242
CYFRA21-1 (ng/mL)	9.48 ± 1.10	11.74 ± 2.13	<.001
CA125 (kU/L)	14.85 ± 2.83	20.44 ± 3.69	<.001
CA199 (U/mL)	17.86 ± 4.89	24.62 ± 4.77	<.001
Nodules diameter, mm	13 (6–21)	20 (11–29)	<.001
Burr signs, n (%)	149 (33.18)	36 (57.14)	.01
Vacuolar signs, n (%)	54 (12.03)	10 (15.87)	.542
Tracheal signs, n (%)	76 (16.93)	12 (19.05)	.854
Lobulated, n (%)	91 (20.27)	16 (25.54)	.498

P comparison between benign nodules patients and all malignant nodules patients.

BMI = body mass index, CA125 = carbohydrate antigen 125, CA199 = carbohydrate antigen 199, CEA = carcinoembryonic antigen, CYFRA21-1 = cytokeratin 19 fragment 21-1, NSE = neuron-specific enolase.

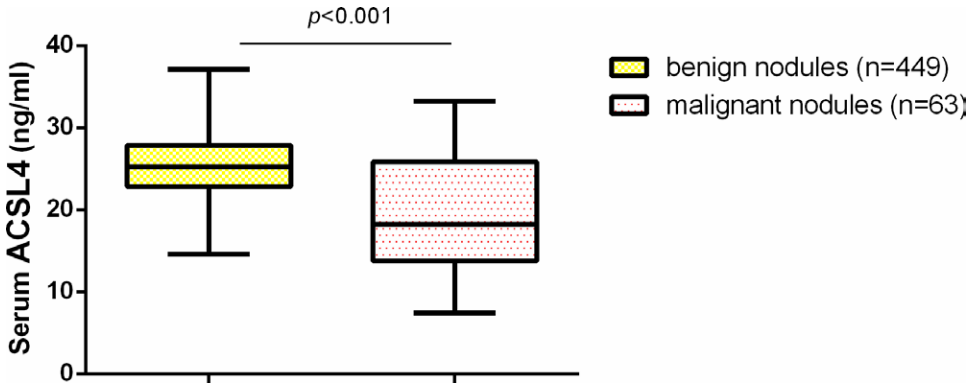

Figure 2. Serum ACSL4 levels were significantly enhanced in patients with benign PN. ACSL4 = long-chain acyl-CoA synthetase 4, PN = pulmonary nodules.

Table 2

Correlation analysis among ACSL4 and the cancer-related biomarkers.

	ACSL4	CEA	NSE	CYFRA21-1	CA199	CA125
ACSL4						
Pearson's correlation	1	−0.268	0.020	−0.328	−0.272	−0.224
P		<.001	.658	<.001	<.001	<.001
CEA						
Pearson's correlation	−0.268	1	−0.008	0.293	0.200	0.233
P	<.001		.858	<.001	<.001	<.001
NSE						
Pearson's correlation	0.002	−0.008	1	−0.041	0.010	−0.033
P	.658	.858		.357	.818	.454
CYFRA21-1						
Pearson's correlation	−0.328	−0.293	−0.041	1	−0.358	−0.282
P	<.001	<.001	.357		<.001	<.001
CA199						
Pearson's correlation	−0.224	0.233	−0.033	0.282	0.210	1
P	<.001	<.001	.454	<.001		<.001
CA125						
Pearson's correlation	−0.272	0.200	0.010	0.358	1	0.210
P	<.001	<.001	.818	<.001	<.001	

ACSL4 = long-chain acyl-CoA synthetase 4, BMI = body mass index, CA125 = carbohydrate antigen 125, CA199 = carbohydrate antigen 199, CEA = carcinoembryonic antigen, CYFRA21-1 = cytokeratin 19 fragment 21-1, NSE = neuron-specific enolase.

application of ACSL4 combined low-dose 256-slice spiral CT had highest sensitivity in the diagnosis of lung cancer with the sensitivity of 95.24%, specificity of 75.29% and accuracy of 88.64% in the diagnosis of lung cancer. The above results showed that ACSL4 combined with low-dose 256-slice spiral CT had satisfactory diagnostic value for lung cancer.

4. Discussion

Though the diagnostic methods for Lung cancer have developed in the last decades, early diagnosis for Lung cancer lesions is still improving.[15] A study showed that the 5-year survival rate for lung cancer was only 15%, but early diagnosis could increase it to 70% to 80%.[16] Thus, it is urgent to develop new comprehensive approaches to reduce the mortality of lung cancer by prompt diagnosis. In the present study, we showed that serum ACSL4 levels were decreased in lung cancer patients. Lower ACSL4 levels predicted poor prognosis and lower ratio of 5-year survival. Moreover, combination application of ACSL4 and low-dose 256-slice spiral CT might be a potential method for the early screening of lung cancer.

Due to the difficulty of early diagnosis of lung cancer, various biomarkers have been used as potential prognostic biomarkers and diagnostic biomarkers of lung cancer. A retrospective study by Gharabaghi[17] found that sirtuin1 and baculoviral inhibitors of apoptosis repeat-containing 6 were significantly correlated with the progression of lung cancer, sirtuin1 and baculoviral inhibitors of apoptosis repeat-containing 6 might be new therapeutic targets for lung cancer. Zhu et al[18] found that circular RNAs could be used as a diagnostic biomarker for the early screening of lung adenocarcinoma. A clinical study by Au-Duhier et al[19] confirmed plasma miRNA-21 was significantly higher in patients with lung cancer compared with healthy individuals, which could be used as an efficient biomarker for early detection of patients with lung cancer. Some common tumor markers (CEA,[20] CA125, CA199,[21] CYFRA 21-1[22]) can be also used to screen for lung cancer. ACSL4 had been shown to play a role in several cancers. Ye et al[23] study supported ACSL4 knockdown promoted subcutaneous xenografts' growth in a mice model, and ACSL4 had an inhibitory effect on gastric cancer. Another study revealed that ACSL4 expression were negatively correlated with the severity of cervical cancer, and ACSL4 knockdown increased the proliferation of Hela cells.[24] A clinical observational study by Sha et al[25] found ACSL4 was correlated with the clinical staging of tumors, in which higher ACSL4 levels were related to a better survival rate. However, there is no more relevant report about the role of ACSL4 in lung cancer. In the present research, we found that the serum levels of ACSL4 were decreased in patients with lung cancer and correlated with the severity of lung cancer, imaging characteristics of PN and tumor markers. In addition, we indicated that ACSL4 can be a potential clinical biomarker for diagnosed lung cancer.

Table 3

Comparison between serum ACSL4 high levels group and ACSL4 low levels group in patients malignant PN.

Variables	ACSL4 low, n = 34	ACSL4 high, n = 29	*P*
Age, yr	43.79 ± 15.41	45.45 ± 17.40	.690
Sex, Female (%)	20 (58.82)	17 (58.62)	1.000
BMI	25.76 (20.96–29.22)	26.62 (21.08–28.88)	.967
Current smoker, n (%)	27 (79.41)	24 (82.76)	.589
CEA (ng/mL)	25.63 (13.70–38.67)	24.48 (12.81–33.03)	.069
NSE (ng/mL)	37.31 (26.60–49.24)	38.65 (27.31–49.19)	.684
CYFRA21-1 (ng/mL)	12.59 ± 2.12	10.75 ± 1.70	<.001
CA125 (kU/L)	21.23 ± 4.09	19.52 ± 2.97	.060
CA199 (U/mL)	26.14 ± 4.96	22.85 ± 3.91	.005
Tumor diameter, mm	21.41 ± 4.84	17.38 ± 3.88	.001
TNM stage			
I–II	15 (44.12)	27 (93.10)	<.001
III–IV	19 (55.88)	2 (6.90)	<.001
Lymph node metastasis, n (%)	21 (61.76)	4 (13.97)	<.001
Distant metastasis, n (%)	8 (23.53)	0 (0)	<.001
Burr signs, n (%)	21 (61.76)	15 (51.72)	.199
Vacuolar signs, n (%)	4 (11.76)	6 (20.69)	.127
Tracheal signs, n (%)	6 (17.65)	6 (20.69)	.721
Lobulated, n (%)	9 (26.47)	7 (24.14)	.870

ACSL4 = long-chain acyl-CoA synthetase 4, BMI = body mass index, CA125 = carbohydrate antigen 125, CA199 = carbohydrate antigen 199, CEA = carcinoembryonic antigen, CYFRA21-1 = cytokeratin 19 fragment 21-1, NSE = neuron-specific enolase, PN = pulmonary nodules.

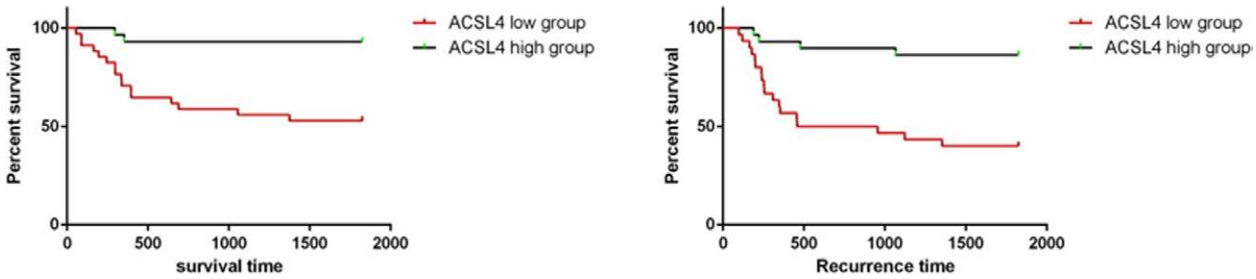

Figure 3 . K-M curves for 5-year survival and recurrence time for malignant PN patients with high/low serum levels of ACSL4. ACSL4 = long-chain acyl-CoA synthetase 4, PN = pulmonary nodules.

Low-dose spiral CT has become the primary means of early diagnosis of lung cancer with the development of imaging technology.[26] However, the accuracy of low-dose spiral CT is related to the experience of doctors and the false positive rate is high.[27] Some studies have shown that the specificity and accuracy of combined diagnosis are higher. Li et al[28] confirmed that combining serum CEA, CYFRA21-1, miRNA-21-5p, miRNA-574-5p and clinical features and imaging features could improve the malignant nodule prediction accuracy. Another study of a large number of lung cancer patients showed that combining miR-1268b and miR-6075 to diagnose early-stage lung cancer had high sensitivity and specificity (sensitivity 99%, specificity 99%).[29] Yu et al[30] found combining the fusion of 3D CT and clinical biomarkers for the diagnosis of pathological types on PN had higher average accuracy (0.906) in a fusion model. However, there were no more studies on combining biomarkers with low-dose spiral CT in the diagnosis of lung cancer. Our present study illustrated that the combination of serum ACSL4 and low-dose 256-slice spiral CT exhibited the potential in the early screening of lung cancer. Okamura et al[31] found that the common tumor marker CEA for the diagnosis of lung cancer with a sensitivity of 69% and specificity of 68%, while the sensitivity and specificity of CYFRA 21-1 were 43% and 89%. In addition, Chen et al[32] found the highest specificity (99.4%) of CA199 for the diagnosis of lung cancer. Compared with these studies, ACSL4 combined with low-dose 256-layer spiral CT was found to have a higher sensitivity (95.24%) in the diagnosis of lung cancer in our study. Overall, most of the studies suggested that the combined diagnosis has more valuable in the clinical diagnosis of lung cancer.[31,33] Thus, it seems that low-dose 256-layer spiral CT combined with ACSL4 and common tumor markers (e.g., CEA and CA199) may have better diagnostic value for lung cancer, which needs to be verified by more prospective studies in the future.

5. Limitation

This research also has some limitations. First, we only included a small size of study population. Secondly, the molecular mechanism of ACSL4 affecting lung cancer development is unclear. Finally, the diagnostic value of low-dose spiral CT was not fully addressed. Further studies are needed to solve the above problems.

6. Conclusion

This study showed that serum ACSL4 levels were decreased in patients with lung cancer and were associated with patients' clinical outcomes, imaging characteristics and severity. Lower ACSL4 levels predicted poor prognosis and lower ratio of 5-year survival. Moreover, ACSL4 as well as combination application of ACSL4 and low-dose 256-slice spiral CT might be a potential method for the early screening of lung cancer. This observational study might provide novel research targets for PN and new diagnostic methods for the early stage of lung cancer.

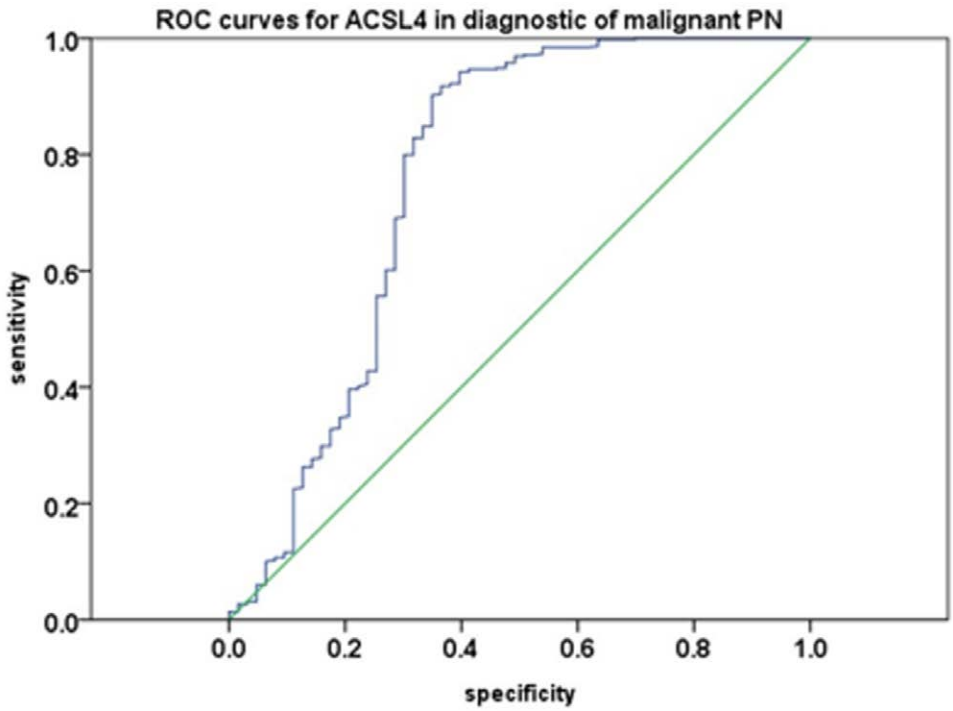

Figure 4. ROC curves for diagnostic value of ACSL4 of malignant PN. ACSL4 = long-chain acyl-CoA synthetase 4, PN = pulmonary nodules, ROC = receiver operating characteristic.

Table 4

Combination of serum ACSL4 levels and low-dose 256-slice spiral CT in the diagnosis of lung cancer.

Methods	True positive	False positive	True negative	False negative	Sensitivity (%)	Specificity (%)	Accuracy
Low-dose 256-slice spiral CT	49	14	373	76	77.78	83.07	93.99
ACSL4	41	22	405	44	65.08	90.20	99.33
ACSL4 + low-dose 256-slice spiral CT	60	3	338	111	95.24	75.29	88.64

Sensitivity = true positive/(true positive + false negative) × 100%; specificity = true negative/(true negative + false positive) × 100%; accuracy = (true positive + true negative)/(true positive + false negative + false positive + true negative) × 100%.
ACSL4 = long-chain acyl-CoA synthetase 4, CT = computed tomography.

Author contributions

Conceptualization: Xuejia Sun.
Data curation: Wenlong Yu, Li Wang, Shi Liu.
Formal analysis: Shi Liu, Shuying Wang.
Methodology: Ying Liu.
Writing – original draft: Wenlong Yu.
Writing – review & editing: Xuejia Sun.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
[2] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
[3] Barta JA, Powell CA, Wisnivesky JP. Global epidemiology of lung cancer. Ann Global Health. 2019;85:8.
[4] Ahmad A, Gadgeel SM. Lung Cancer and Personalized Medicine: Novel Therapies and Clinical Management. Preface. Adv Exp Med Biol. 2016;890:v–vi.
[5] Moyer VA; Force* USPST. Screening for lung cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:330–8.
[6] Ettinger DS, Wood DE, Akerley W, et al. Non–small cell lung cancer, version 6.2015. J Natl Compr Canc Netw. 2015;13:515–24.
[7] Kramer BS, Berg CD, Aberle DR, et al. Lung cancer screening with low-dose helical CT: results from the National Lung Screening Trial (NLST). J Med Screen. 2011;18:109–11.
[8] Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol. 2014;15:1332–41.
[9] National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395–409.
[10] Rossi Sebastiano M, Konstantinidou G. Targeting long chain acyl-coa synthetases for cancer therapy. Int J Mol Sci. 2019;20:3624.
[11] Cao Y, Dave KB, Doan TP, et al. Fatty acid CoA ligase 4 is up-regulated in colon adenocarcinoma. Cancer Res. 2001;61:8429–34.
[12] Nwosu ZC, Megger DA, Hammad S, et al. Identification of the consistently altered metabolic targets in human hepatocellular carcinoma. Cell Mol Gastroenterol Hepatol. 2017;4:303–323.e1.
[13] Wu X, Li Y, Wang J, et al. Long chain fatty Acyl-CoA synthetase 4 is a biomarker for and mediator of hormone resistance in human breast cancer. PLoS One. 2013;8:e77060e77060.
[14] Zhang Y, Li S, Li F, et al. High-fat diet impairs ferroptosis and promotes cancer invasiveness via downregulating tumor suppressor ACSL4 in lung adenocarcinoma. Biol Direct. 2021;16:1–13.
[15] McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013;369:910–9.
[16] Bade BC, Cruz CSD. Lung cancer 2020: epidemiology, etiology, and prevention. Clin Chest Med. 2020;41:1–24.
[17] Gharabaghi MA. Diagnostic investigation of BIRC 6 and SIRT 1 protein expression level as potential prognostic biomarkers in patients with non-small cell lung cancer. Clin Resp J. 2018;12:633–8.

[18] Zhu X, Wang X, Wei S, et al. hsa_circ_0013958: a circular RNA and potential novel biomarker for lung adenocarcinoma. FEBS J. 2017;284:2170–82.
[19] Abu-Duhier FM, Javid J, Sughayer MA, et al. Clinical significance of circulatory miRNA-21 as an efficient non-invasive biomarker for the screening of lung cancer patients. Asian Pac J Cancer Prev. 2018;19:2607.
[20] Grunnet M, Sorensen JB. Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer. 2012;76:138–43.
[21] Molina R, Auge JM, Escudero JM, et al. Mucins CA 125, CA 19.9, CA 15.3 and TAG-72.3 as tumor markers in patients with lung cancer: comparison with CYFRA 21-1, CEA, SCC and NSE. Tumor Biol. 2008;29:371–80.
[22] Okamura K, Takayama K, Izumi M, et al. Diagnostic value of CEA and CYFRA 21-1 tumor markers in primary lung cancer. Lung Cancer. 2013;80:45–9.
[23] Ye X, Zhang Y, Wang X, et al. Tumor-suppressive functions of long-chain acyl-CoA synthetase 4 in gastric cancer. IUBMB Life. 2016;68:320–7.
[24] Xiaofei J, Mingqing S, Miao S, et al. Oleanolic acid inhibits cervical cancer Hela cell proliferation through modulation of the ACSL4 ferroptosis signaling pathway. Biochem Biophys Res Commun. 2021;545:81–8.
[25] Sha R, Xu Y, Yuan C, et al. Predictive and prognostic impact of ferroptosis-related genes ACSL4 and GPX4 on breast cancer treated with neoadjuvant chemotherapy. EBioMedicine. 2021;71:103560.
[26] Wood DE. National Comprehensive Cancer Network (NCCN) clinical practice guidelines for lung cancer screening. Thorac Surg Clin. 2015;25:185–97.
[27] Gierada DS, Pinsky P, Nath H, et al. Projected outcomes using different nodule sizes to define a positive CT lung cancer screening examination. J Natl Cancer Inst. 2014;106:dju284.
[28] Li X, Zhang Q, Jin X, et al. Combining serum miRNAs, CEA, and CYFRA21-1 with imaging and clinical features to distinguish benign and malignant pulmonary nodules: a pilot study. World J Surg Oncol. 2017;15:1–8.
[29] Asakura K, Kadota T, Matsuzaki J, et al. A miRNA-based diagnostic model predicts resectable lung cancer in humans with high accuracy. Commun Biol. 2020;3:1–9.
[30] Fu Y, Xue P, Li N, et al. Fusion of 3D lung CT and serum biomarkers for diagnosis of multiple pathological types on pulmonary nodules. Comput Methods Programs Biomed. 2021;210:106381.
[31] Ghosh I, Bhattacharjee D, Das AK, et al. Diagnostic role of tumour markers CEA, CA15-3, CA19-9 and CA125 in lung cancer. Indian J Clin Biochem. 2013;28:24–9.
[32] Chen F, Li WM, Wang DM, et al. [Clinical value of combined detection of serum tumor markers in lung cancer diagnosis]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2008;39:832–5.
[33] Wang CF, Peng SJ, Liu RQ, et al. The combination of CA125 and NSE is useful for predicting liver metastasis of lung cancer. Dis Markers. 2020;2020:18850873–10.