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Clinical significance of CA 19.9 and LINC01197 in pancreatic cancer

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Abstract. – OBJECTIVE: This study aimed to explore the expression and clinical significance of LINC01197 in serum of patients with pancreatic cancer (PC).

PATIENTS AND METHODS: Fifty PC patients (patient group) treated in our hospital from March 2012 to April 2014 were collected, and another 50 normal people (normal group) were collected for physical examination. The LINC01197 expression in serum of the two groups was detected by qRT-PCR method, and the CA 19.9 expression in serum was detected by Roche automatic biochemistry. The expression and diagnostic value of CA 19.9 and LINC01197 in PC were analyzed, and the relationship between LINC01197 and prognosis of PC patients was observed.

RESULTS: The CA 19.9 expression in the patient group was significantly higher than that in the normal group (p<0.001). Their area under the curve was 0.791 and 0.944 respectively. The incidence of phases III+IV, lymphatic invasion, and distant metastasis in patients with low expression of LINC01197 is significantly higher than that in those with high expression, and has higher diagnostic value. With the progress of clinical staging, the TNM expression decreased gradually and there were differences between groups (p<0.001). Spearman's test analysis found that the decreased TNM staging of LINC01197 increased gradually (r=-0.816, p<0.001), and the area under the curve of LINC01197 distinguishing phase I and phase II+phase+III+phase IV was 0.930. The 1-year survival rate and 5-year survival rate of patients in low expression group were lower than those in high expression group (p1 year =0.037, p5 year =0.014). Distant metastasis is an independent prognostic factor for PC patients to survive for 1 to 5 years. Differentiation, TNM staging, and LINC01197 are independent prognostic factors for PC patients to survive for 5 years.

CONCLUSIONS: The low expression of LINC01197 in PC patients indicates poor prognosis of patients and is expected to be a potential diagnostic and prognostic indicator of PC.

Key Words:
LINC01197, Pancreatic cancer, Prognosis, Diagnosis.

Introduction

With the continuous development of modern society, people's living standard and diet structure have changed, and the morbidity of digestive tract diseases has increased year by year[1]. Pancreatic cancer (PC) is a malignant tumor with the lowest 5-year survival rate clinically. Allemani et al[2] found that the 5-year net survival rate of PC decreased from 14.4% in 2000 to 9.9% in 2014 by monitoring the global cancer survival trend from 2000 to 2014, and the 5-year net survival rate of PC was the lowest among all cancers. How to improve the mortality of PC patients is one of the urgent problems for clinicians to solve at present[3]. Surgical treatment is the main treatment scheme for PC, but very few PC patients can undergo surgical treatment. Basically, more than 80% of those patients admitted to hospital are developed to advanced stage of disease[4,5]. Therefore, their early diagnosis is very critical.

At present, the gold standard of PC is clinical pathological biopsy, while magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) is the most accurate except pathological biopsy[6]. However, it is more expensive than pathological biopsy imaging analysis. Serological testing is a common and clinically inexpensive testing method. CA 19.9 is an important serological marker for PC diagnosis, but some studies[7-9] have found that the specificity of CA 19.9 is relatively low, and its expression in acute and chronic pancreatitis, bile duct obstruction, and hepatitis will change, and the expression is relatively low in poorly differentiated tumors.

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Therefore, the diagnosis of PC is affected to some extent.

LncRNA (Long non-coding RNAs) is a kind of long-chain non-coding RNA with a length of more than 200 nts[10]. Most beginners think lncRNA has no ability to encode proteins. However, with the discovery of various functions of lncRNA in recent years, it has epigenetic changes, transcriptional regulation and post-transcriptional modification, and it participates in the occurrence and development of various diseases through targeted regulation of microRNA and target proteins[11,12]. LINC01197 is a newly discovered lncRNA. Before this, it was mentioned in the expression profile[13]. Its expression in PC is still unclear. Ling et al[14] found that LINC01197 was lowly expressed in PC, but whether it could be used as a potential prognosis and diagnostic indicator of PC is still unclear. Therefore, this study explores the clinical significance of LINC01197 in PC, providing potential diagnostic and prognostic indicators for clinical use.

Patients and Methods

Patient Collection

Fifty PC patients (patient group) who were treated in our hospital from March 2012 to April 2014 were collected, so were the case on 50 normal people (normal group) who underwent physical examination in our hospital during the same period. The patient group consisted of 30 males and 20 females with an average age of 54.2±5.3 years, the normal group consisted of 25 males and 25 females with an average age of 55.2±4.1 years. There was no difference in gender and age between both groups (p>0.05). This investigation was approved by the Medical Ethics Committee of our hospital. Laboratory examination and imaging examination were normal in the normal group. The inclusion criteria of the patient group were as follows: the lesions of the patients could be detected and diagnosed as ductal pancreatic cancer by pathological biopsy and imaging. Those met the 8th edition of TNM staging standard[15]. Those had complete clinical data. The research was designed to inform the patients and their family to sign an informed consent. The exclusion criteria for patients were as follows: the patients received corresponding anti-tumor treatment (radiotherapy, chemotherapy, and surgical treatment) before this study. Those were pregnant women who expected to have a survival period of less than 1 month, but they did not cooperate with follow-up.

Main Reagents and Instruments

TRIzol reagent (Invitrogen, Carlsbad, CA, USA, 15596018), TransScript Green Two-Step qRT-PCR SuperMix (Beijing, China, TransGen Biotech, AQ201-01). CA 19.9 kit and automatic biochemical analyzer (Roche, Basel, Switzerland) and PCR instrument (Applied Biosystems, Foster City, CA, USA, 7500).

Collection and Detection of Samples

Altogether 5 mL of fasting peripheral venous blood was collected from the two groups, left standing for 30 min, and centrifuged at 3000 rpm for 10 min, and the supernatant was collected and subpackaged for CA 19.9 and LINC01197 expression detection respectively.

RNA Extraction and Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR)

The detection scheme of LINC01197 was as follows: total RNA was extracted from the collected serum by TRIzol reagent, and its purity, concentration, and integrity were detected by ultraviolet spectrophotometer and agarose gel electrophoresis. TransScript® miRNA RT Enzyme Mix in TransScript Green Two-Step qRT-PCR SupeMix kit and 2×TS miRNA Reaction Mix were used for reverse transcription. The experimental steps were tested according to the original kit. The amplification system was as follows: cDNA 1 μL, upstream and downstream primers 0.4 μL each, 2X TransScript® Tip Green qPCR SuperMix 10 μL, Passive Reference Dye (50X), Nuclease-free water supplemented to 20 μL. The amplification conditions were as follows: pre-denaturation at 94°C for 30 s, denaturation at 94°C for 5 s, annealing extension at 60°C for 30 s, a total of 40 cycles. Each sample was provided with 3 repeated holes, and the experiment was conducted for 3 times. GAPDH was employed as internal reference, and $2^{-\Delta ct}$ was employed to analyze the data[16], primer sequences were shown in Table I. Experiments were carried out by ABI 7500 PCR instrument.

Biochemical Analysis Test

CA 19.9 was analyzed by Roche automatic biochemical analyzer E170 module (Basel, Switzerland). The range of normal reference value is less than or equal to 37 U/mL.

Follow-Up of Patients

Patients were followed up for a period of 5 years. The follow-up methods were counted by telephones and clinic reexamination. In the first year of follow-up, follow-up was carried out at

the 3rd, 6th, 9th, and 12th months respectively, and in the following 4 years, it was carried out every 4 months.

Statistical Analysis

The collected data were statistically analyzed by SPSS 20.0 software package (IBM, Armonk, NY, USA), the required pictures were drawn by GraphPad 7 software package, and the distribution of measurement data was analyzed by Kolmogorov-Smirnov (K-S) test. The normal distribution data were expressed by mean±standard deviation (Meas±SD), and those did not conform to the normal distribution were expressed by median. The quartile interval was used to describe P_{50} (P_{25}-P_{75}), and the nonparametric test was applied, which expressed by Z. Inter-group comparison was under Independent-samples *t*-test and expressed by T. The counting data were analyzed by Chi-square test and expressed by x^2. Multi-group comparison was conducted through one-way analysis of variance (ANOVA) and expressed by *F*. Post-hoc pairwise comparison was under LSD-*t*-test, and the diagnostic value of LINC01197 and CA 19.9 in PC was plotted by ROC. The relationship between LINC01197 and TNM staging of patients was analyzed by Spearman's test. The 5-year survival situation of patients was drawn by Kaplan-Meier (K-M) survival curve, analyzed by Log-rank test, and independent risk factors affecting their prognosis were analyzed by multivariate Cox regression. $p<0.05$ was seen as statistical difference.

Results

Expression and Diagnostic Value of LINC01197 and CA 19.9 in PC

The LINC01197 and CA 19.9 expression levels in PC between the patient group and the normal group were detected. It was found that the CA 19.9 expression in the patient group was significantly higher than that in the normal group ($p<0.001$), while the LINC01197 expression in the patient group was significantly lower than that in the normal group ($p<0.001$). The ROC curve analysis revealed that both LINC01197 and CA 19.9 had higher value in diagnosing PC, and their area under the curve was 0.791 and 0.944, respectively (Tables II, III, and Figure 1).

Relationship Between LINC01197 and Pathological Data of PC Patients

According to the median value of LINC01197 expression, it was divided into the high and low expression groups. Analysis of the pathological data of patients in the two groups revealed that there was no correlation between gender, age, lesion site, differentiation, vascular invasion, and high and low expression of LINC01197. However, patients with low expression of LINC01197 had significantly higher probability of phases III+IV, lymphatic invasion, and distant metastasis than those with high expression. Therefore, we analyzed the LINC01197 expression in TNM staging, lymphatic invasion, and distant metas-

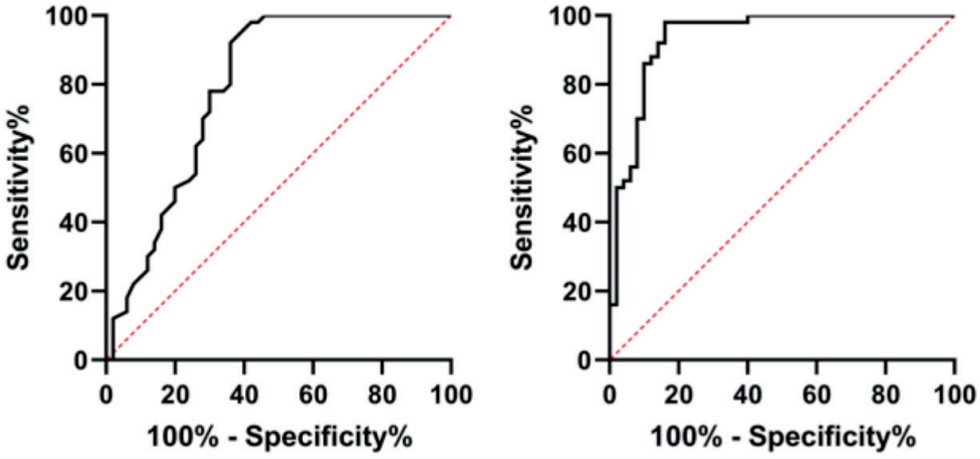

Figure 1. Area under the curve of LINC01197 and CA 19.9. **A,** The area under the curve of CA 19.9 was 0.833. **B,** The area under the curve of LINC01197 was 0.938.

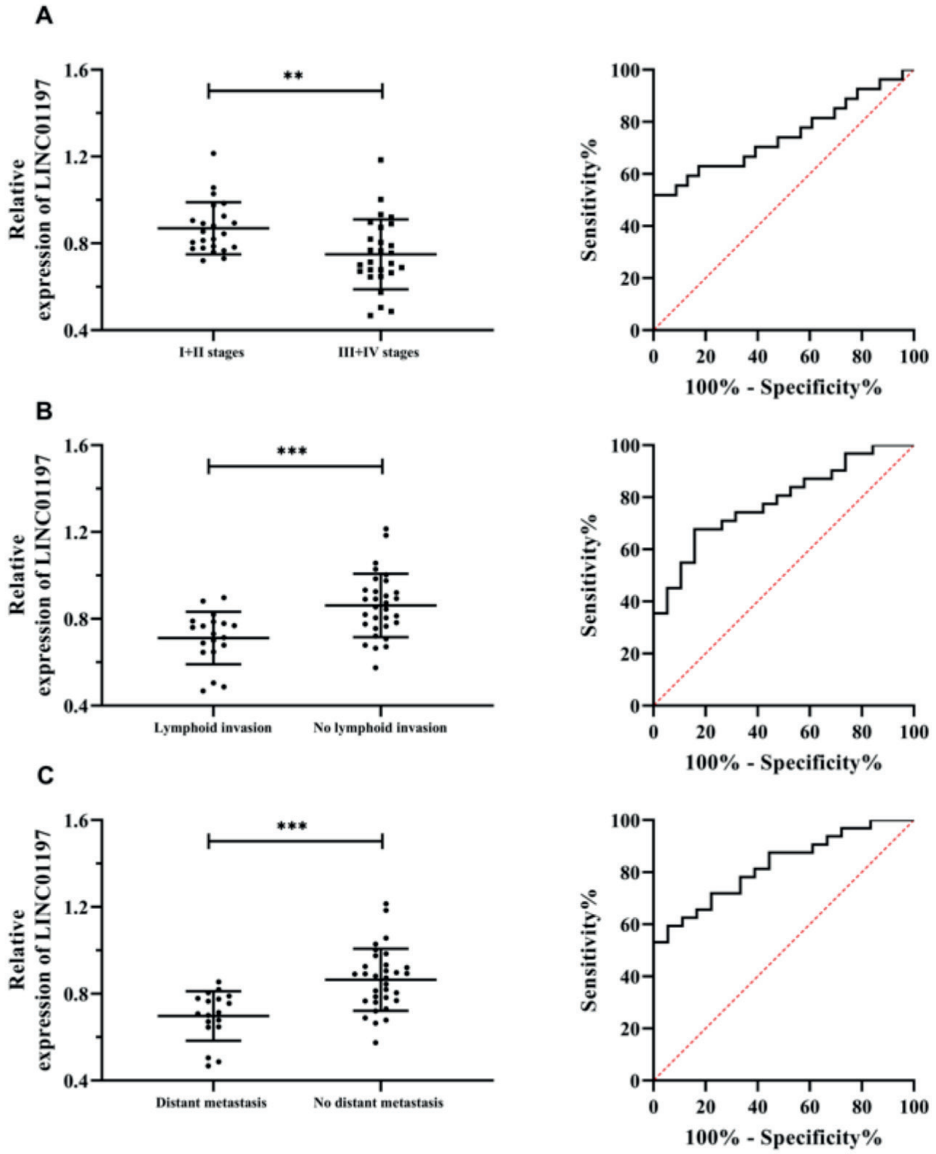

Figure 2. Expression of LINC01197 in patients with TNM staging, lymphatic invasion, and distant metastasis. **A,** The LINC01197 expression in patients with phases I+II is higher than that in patients with phases III+IV, and the area under the curve is 0.747. **B,** The LINC01197 expression in patients with lymphatic invasion is lower than that in patients without lymphatic invasion, and the area under the curve is 0.784. **C,** The LINC01197 expression in patients with distant metastasis is lower than that in patients without metastasis, and the area under the curve is 0.825. ** indicates $p<0.01$ and *** indicates $p<0.001$.

Table I. Gene Upstream primers Downstream primers.

Gene	Upstream primers	Downstream primers
LINC01197	TCCCAGGGAGAGGAGCTTTG	ACAAAGCGGAGAGGAGGTCA
GAPDH	GAAGAGAGAGACCCTCACGCTG	ACTGTGAGGAGGGGAGATTCAGT

tasis. In phases III+IV, the LINC01197 expression in patients with lymphatic invasion and distant metastasis was markedly lower than that in their corresponding groups, and ROC curve was drawn to find that LINC01197 had higher diagnostic value in TNM staging, lymphatic invasion, and distant metastasis (Table IV, V, and Figure 2).

Table II. LINC01197 and CA 19.9 expression levels in PC patients.

Index	Normal group (n=50)	Patient group (n=50)	*t/Z*-values	*p*-value
LINC01197 expression	1.084±0.083	0.805±0.155	11.308	<0.001
CA 19.9 (U/ml)	13.62 (8.49-18.90)	175.08 (20.11-405.98)	-5.016	<0.001

Table III. ROC parameters.

Factor	AUC	Std	95% CI	*p*-value	Specificity	Sensitivity	Youden index	Cut-off
LINC01197	0.944	0.027	0.886-0.997	<0.001	86.00%	100.00%	86.00%	> 0.9335
CA 19.9	0.791	0.047	0.699-0.883	<0.001	64.00%	92.00%	-	-

Table IV. Relationship between LINC01197 expression and pathological data.

Parameter		LINC01197 expression		x^2-value	*p*-value
		Low expression	High expression		
Gender					
	Male (n=30)	17 (68.00)	13 (52.00)	1.333	0.248
	Female (n=20)	8 (32.00)	12 (48.00)		
Age					
	≥55 years old (n=22)	13 (52.00)	9 (36.00)	1.299	0.255
	<55 years old (n=28)	12 (48.00)	16 (64.00)		
Lesion site					
	Head of pancreas (n=25)	14 (56.00)	11 (44.00)	0.720	0.396
	Rests (n=25)	11 (44.00)	14 (56.00)		
Differentiation					
	Low differentiation (n=25)	10 (40.00)	15 (60.00)	2.000	0.157
	Moderate+high differentiation (n=25)	15 (60.00)	10 (40.00)		
TNM staging					
	Phase I+II (n=23)	7 (28.00)	16 (64.00)	6.522	0.011
	Phase III+IV (n=27)	18 (72.00)	9 (36.00)		
Lymphatic invasion				6.876	0.009
	Yes (n=19)	14 (56.00)	5 (20.00)		
	No (n=31)	11 (44.00)	20 (80.00)		
Vascular invasion					
	Yes (n=20)	12 (48.00)	8 (32.00)	1.333	0.248
	No (n=30)	13 (52.00)	17 (68.00)		
Distant metastasis					
	Yes (n=18)	13 (52.00)	5 (20.00)	5.556	0.018
	No (n=32)	12 (48.00)	20 (80.00)		

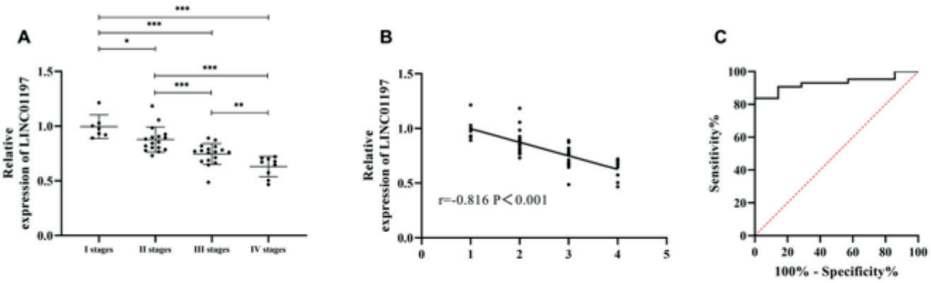

Figure 3. Diagnostic value of LINC01197 in clinical staging of PC patients. **A,** LINC01197 expression in PC of different staging. **B,** Correlation between LINC01197 and clinical staging. The diagnostic value of LINC01197 in distinguishing patients in phase I is 100.00% of the best specificity and 83.72% of the sensitivity when the cut-off value is 0.891. *indicates $p<0.05$, ** indicates $p<0.01$, and *** indicates $p<0.001$. 1 = Phase I, 2 = Phase II, 3 = Phase III, 4= Phase IV.

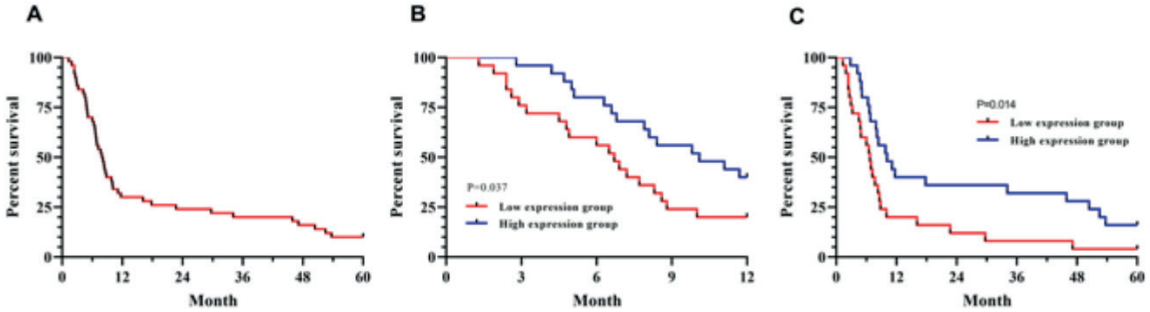

Figure 4. Survival analysis of LINC01197 and PC patients. **A,** Overall survival rate of PC patients. **B,** One-year survival of patients in the high and low expression group of LINC01197. **C,** Five-year survival of patients with high and low expression of LINC01197.

Relationship Between LINC01197 and Clinical Staging of Patients and its Early Diagnostic Value

Previously, we analyzed the expression and diagnostic value in patients in phases I+II and III+IV. Here, we further analyzed the relationship between LINC01197 and clinical staging of patients. First, we conducted Spearman's test analysis and found that TNM staging gradually increased with the decrease of LINC01197 (r=-0.816, $p<0.001$). Through variance analysis, we found that the expression gradually decreased with the progress of clinical staging and there were statistical differences between the groups ($p<0.001$). Finally, we drew ROC curve of LINC01197 in distinguishing early PC patients, and the result manifested that the area under the curve of LINC01197 was 0.930 (Figure 3).

Relationship Between LINC01197 and Patient Survival

The patients were followed up for 5 years and all 50 patients were followed up, with a 5-year survival rate of 10%. Furthermore, we analyzed their 1-year survival rate and 5-year survival rate in groups according to the median expression of LINC01197. It was found that their 1-year survival rate and 5-year survival rate in low expression group were lower than those in high expression group ($p_{1\ year}=0.037$, $p_{5\ year}=0.014$; Figure 4).

Cox Regression Analysis of Prognosis

The pathological data of patients were collected to analyze independent factors affecting their prognosis for 1 year and 5 years. Univariate Cox regression analysis revealed that TNM staging, lymphatic invasion, distant metastasis, and LINC01197 were independent factors affecting their prognosis for 1 year. Multivariate analysis found that distant metastasis (HR: 0.374 (95 CI%: 0.178-0.785)) was independent factor affecting their prognosis for 1 year. Further analysis of the 5-year prognosis of patients revealed that differentiation, TNM staging, lymphatic invasion, distant metastasis, and LINC01197 were the factors affecting their 5-year prognosis. Multivariate

Table V. ROC parameters.

Factor	AUC	Std	95% CI	*p*-value	Specificity	Sensitivity	Youden index	Cut-off
TNM staging	0.747	0.070	0.610-0.885	0.003	100.00%	51.85%	51.85%	<0.717
Lymphatic invasion	0.784	0.064	0.659-0.909	<0.001	84.21%	67.74%	51.95%	>0.797
Distant metastasis	0.825	0.057	0.713-0.936	<0.001	94.44%	59.38%	53.82%	>0.819

Table VI. Assignment table.

Factor	Assignment
Gender	Male = 1, female = 2
Age	≥ 55 = 1, < 55 = 2
Lesion site	Head of pancreas =1, rests =2
Differentiation	Low differentiation = 1, moderate+high differentiation = 2
TNM staging	I+II = 1, III+IV = 2
Lymphatic invasion	Yes = 1, no = 2
Vascular invasion	Yes = 1, no = 2
Distant metastasis	Yes = 1, no = 2
LINC01197	<0.788 = 1, ≥0.788 = 2

Table VII. Analysis of multivariate Cox prognostic factors in 1 and 5 years.

Factor	1-year single factor Cox		1-year multiple factor Cox		5-year single factor Cox		5-year multiple factor Cox	
	p-value	HR (95 CI%)	*p*-value	HR (95 CI%)	*p*-value	HR (95 CI%)	*p*-value	HR (95 CI%)
Gender	0.849	1.067 (0.548-2.079)			0.728	0.899 (0.493-1.638)		
Age	0.149	0.613 (0.315-1.191)			0.087	0.597 (0.331-1.078)		
Lesion site	0.631	0.850 (0.436-1.653)			0.271	0.718 (0.399-1.294)		
Differentiation	0.139	0.604 (0.310-1.177)			0.026	0.508 (0.280-0.921)	0.002	0.340 (0.169-0.681)
TNM staging	0.006	2.701 (1.335-5.462)	0.058	2.104 (0.974-4.545)	0.000	3.442 (1.751-6.765)	0.019	2.392 (1.156-4.947)
Lymphatic invasion	0.010	0.412 (0.211-0.806)	0.263	0.651 (0.308-1.379)	0.003	0.389 (0.207-0.732)	0.139	0.592 (0.295-1.185)
Vascular invasion	0.492	0.791 (0.405-1.546)			0.723	0.898 (0.494-1.631)		
Distant metastasis	0.001	0.318 (0.161-0.630)	0.009	0.374 (0.178-0.785)	0.001	0.352 (0.19-0.652)	0.006	0.406 (0.214-0.772)
LINC01197	0.041	0.496 (0.253-0.973)	0.683	0.849 (0.389-1.857)	0.016	0.477 (0.262-0.870)	0.028	0.432 (0.205-0.913)

analysis found that differentiation (HR: 0.340 (95 CI%: 0.169-0.681)), TNM staging (HR: 2.392 (95 CI%: 1.156-4.947)), distant metastasis (HR: 0.406 (95 CI%: 0.214-0.772)), and LINC01197 (HR: 0.432 (95 CI%: 0.205-0.913)) were independent factors affecting their 5-year prognosis (Tables VI and VII).

Discussion

LncRNA is a hot research field in recent years. It is a kind of long-chain non-coding RNA that can participate in various biological functions of human body by regulating miR and related proteins[17,18]. Several studies have found that ln-

cRNA is relevant the occurrence and development of various tumors. Nie et al[19] found that LncRNA-UCA1 could play a carcinogenic role by regulating miR-193a-3p in non-small cell lung cancer. Wei et al[20] reported that LncRNA XIST could promote PC cell proliferation by regulating miR-133a/EGFR. LINC01197 is a newly discovered lncRNA located on human 15q26.2 recently. Previously, Ling et al[14] found that LINC01197 could inhibit PC cell proliferation by mediating Wnt/β-catenin signaling pathway. However, there has not been any relevant research on whether LINC01197 can become a clinical observation indicator of PC. Therefore, this investigation explores the LINC01197 expression in PC patients to observe its potential clinical value and provide potential observation indicators for the treatment and diagnosis of clinicians.

In this research, we first compared the differences between LINC01197 and CA 19.9 in PC. CA 19.9 is a common tumor marker used in clinical screening of PC. Previous reports have shown that CA 19.9 has high sensitivity and specificity in PC, especially in predicting the prognosis and recurrence of those patients undergoing surgery. However, Liu et al[21] observed that CA 19.9 expression had a low specificity, and its expression would also increase when some digestive system diseases occur, which was bound to reduce the specificity of CA 19.9. In addition, Zhang et al[22] discovered that CA 19.9 expression in serum of more than 30% PC patients would not increase. We detected the CA 19.9 expression in serum of PC patients and found that it in the patient group was significantly higher than that in the normal group, while we found that the area under the curve was 0.791 by drawing ROC curve, which was basically consistent with other authors[23,24]. We further analyzed the LINC01197 expression in PC and found that it was also differentially expressed in PC. The expression in PC patients was remarkably lower than that in the normal group, and the area under the curve was 0.944, and the sensitivity was markedly higher than that of CA 19.9. This suggested that LINC01197 had higher clinical value in diagnosing PC than CA 19.9 and might be a potential indicator for PC diagnosis. We also analyzed the relationship between LINC01197 and PC pathological data. According to the LINC01197 expression, the patients in the low expression group of LINC01197 were divided into high and low expression groups. Through analysis, it was found that the patients in the low expression group of LINC01197 had significantly higher probability of phases III+IV, lymphatic invasion, and distant metastasis than those in the high expression group. Therefore, we further compared phases I+II and III+IV, lymphatic invasion, and non-invasion, the LINC01197 expression in serum of patients with distant metastasis and of those without metastasis was found to be different in each index, and it was also found that LINC01197 had a higher area under the curve of diagnostic value than 0.7 in distinguishing phases I+II and III+IV, lymphatic invasion, and distal metastasis. The above studies indicate that LINC01197 occurs as a low expression in PC and can be used as a potential indicator to distinguish PC from normal people, phases I+II, phases III+IV, lymphatic invasion, and distant metastasis. However, whether it can be used as a diagnostic indicator to distinguish patients with phase I is still unclear.

At the moment, there are few patients with PC phase I clinically. First, the main reason may be that the clinical characteristics of the early stage of PC onset are few and cannot be judged by clinical appearances. Most patients enter the advanced stage when they are admitted to hospital after the onset of the disease. Second, there is a lack of highly specific diagnostic indicators[25]. In this study, we further compared the relationship between LINC01197 and PC TNM staging. Through research, it is found that the LINC01197 expression is different in different staging and there is a negative correlation between the expression of LINC01197 and PC TNM staging, namely, TNM staging is higher and more serious as the LINC01197 expression gradually decreases. Analysis of ROC curve shows that LINC01197 has extremely high diagnostic value because its area under the curve of diagnosis I in PC is more than 0.9.

At the end of the study, we followed up the patients for 5 years, and their overall 5-year survival rate was 10%, which was basically consistent with the domestic and foreign reports[26,27]. Observing the 1-year and 5-year survival of patients in the LINC01197 high and low expression groups, we found that their 1-year and 5-year survival in the LINC01197 low expression group was lower than that of those in the high expression group, which showed that LINC01197 could be used as a potential indicator of patient prognosis. Therefore, we collected patient pathological data to analyze the independent factors affecting their 1-year and 5-year survival. Through analysis, we found that distant metastasis was an independent prognostic factor affecting the 1-year and 5-year survival of PC patients, while LINC01197 was not an independent prognostic factor in the short-term

prognosis, but an independent prognostic factor for 5-year survival of patients. Epstein et al[28] confirmed that distant metastasis was an independent factor affecting the prognosis of PC patients, and our study found that LINC01197 could be used as an independent factor for their 5-year prognosis. We firstly showed that LINC01197 was expected to become a potential observation indicator for their prognosis.

Nevertheless, we still have some limitations in this study. In the first place, we have not collected serum samples from patients with benign pancreatic lesions. Whether LINC01197 can distinguish patients with benign pancreatic lesions from those with PC still needs further research. In the second place, due to the small sample size, whether LINC01197 can be used as a prognostic indicator of PC still needs further study. Finally, the mechanism of LINC01197 affecting PC is still indistinct. Besides influencing Wnt/β-catenin signaling pathway, whether it also affects other pathways leading to PC occurrence needs further investigation. Hence, we hope to increase the type and number of samples in future research, further analyze the relevant mechanism of LINC01197 through bioinformatics, and carry out basic research to supplement and verify our results.

Conclusions

To sum up, low expression of LINC01197 in PC patients indicates poor prognosis of patients and is expected to be a potential indicator for early diagnosis and prognosis observation of PC.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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