

# LncRNA CADM1-AS1 serves as a new prognostic biomarker for gastric cancer

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**Abstract. – OBJECTIVE:** To investigate the expression of the long non-coding RNA CADM1-AS1 (lncRNA CADM1-AS1) in gastric cancer and its clinical significance.

**PATIENTS AND METHODS:** The real time fluorescence quantitative polymerase chain reaction (qRT-PCR) was performed to detect the expression difference of lncRNA CADM1-AS1 between gastric cancer and its adjacent normal tissues. Then, the correlation between the expression of CADM1-AS1 in gastric cancer and the clinicopathological characteristics was analyzed by the Chi-square test. Moreover, the potential of lncRNA CADM1-AS1 in predicting the prognosis of patients with GC after the operation was assessed by the Log-rank test and the Cox's proportional hazards regression model.

**RESULTS:** The expression of lncRNA CADM1-AS1 was significantly decreased in tumor tissues. According to the mean expression of lncRNA CADM1-AS1, the patients were divided into a high expression group and a low expression group, and the expression of lncRNA CADM1-AS1 in gastric cancer was significantly correlated with tumor differentiation, N stage, M stage, and TNM stage. Moreover, the gastric cancer patients with higher expression of lncRNA CADM1-AS1 had a statistically better overall survival (OS) time and progression-free survival (PFS) time. In univariate analyses and multivariate analyses, the expression of lncRNA CADM1-AS1 was an independent prognosis index of patients with gastric cancer.

**CONCLUSIONS:** LncRNA CADM1-AS1 might be a new prognostic biomarker for gastric cancer.

*Key Words:*

Gastric cancer, Long non-coding RNA CADM1-AS1 (lncRNA CADM1-AS1), Prognosis.

idity rate and the second in the mortality rate, globally<sup>1</sup>. The symptoms of gastric cancer are not typical in the early stages, so the patients were usually in an advanced stage when diagnosed. Besides, about half of the patients suffer from postoperative relapse<sup>2</sup>. Although multidisciplinary comprehensive treatments and researches on new drugs including targeted drugs had made much progress, the early detection rate, the diagnostic rate, and the radical resection rate of gastric cancer were still at a low level, leading to a low rate of 5-year survival<sup>3,4</sup>. Therefore, it was urgent to further comprehend the molecular mechanism of the occurrence and development of gastric cancer and to explore new biomarkers and effective therapeutic targets.

Long non-coding ribonucleic acids (lncRNAs) are a class of non-coding RNA molecules with a transcript length of more than 200 nucleotides that do not encode proteins, which can regulate the expression of genes in epigenetic regulation, transcriptional regulation, and post-transcriptional regulation<sup>5,6</sup>. lncRNAs were initially considered as by-products of RNA polymerase II transcription, that was, a kind of transcriptional noise without any biological function<sup>7</sup>. However, studies<sup>8,9</sup> reported that lncRNAs showed many features including X-chromosome silencing, chromosome modification, genome modification, transcriptional activation, transcriptional interference, intranuclear transport, and some other processes. As the research further developed, it was found that the conservative property and spatial structure stability of lncRNAs were poor, so they were more sensitive to some regulations of organisms and were extensively involved in various biological and diseasing processes that include cancer<sup>10-13</sup>. The abnormally expressed lncRNAs might influence the behavior of tumor cells by regulating the relat-

## Introduction

Gastric cancer is one of the most common malignant tumors, ranking the fourth in the mor-

ed proteins or microenvironment. Also, lncRNAs were found to be considered as molecular markers for the diagnosis and treatment of the related tumors due to their differential expression<sup>14-16</sup>. Although some investigations<sup>17-19</sup> reported that the abnormal expression of lncRNAs was related to gastric cancer, there were still a lot of lncRNAs worth studying.

Cell adhesion molecule-1 (CADM1)-AS1, as a newly discovered lncRNA, is located in the anti-sense direction of the tumor suppressor gene CADM1 coding exons. It could be speculated that it may regulate tumors by influencing the expression of CADM1. Yao et al<sup>20</sup> discovered for the first time that CADM1-AS1 was lowly expressed in clear-cell renal-cell carcinoma and these patients had a poorer prognosis, indicating that CADM1-AS1 might play a role as a tumor suppressor gene. However, the expression and functions of CADM1-AS1 in gastric cancer remain unclear for the time being.

## Patients and Methods

### Tissue Specimens Collected

The gastric cancer tissues and para-carcinoma tissues (more than 5 cm away from cancer tissues) were harvested from 120 patients undergoing radical or palliative resection in The Children and Women's Healthcare of Laiwu City from December 2016 to October 2018, and the personal information and detailed clinical data of patients were collected intact. Moreover, all patients were followed up for general conditions and clinical symptoms, through imaging by telephone and reviewing after discharge from December 2016 to October 2018. This study was approved by the Ethics Committee of The Children and Women's Healthcare of Laiwu City.

### Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) Analysis

The tissue samples stored in the liquid nitrogen were collected and ground to be spread in the liquid nitrogen. The total RNAs were obtained according to the instructions of the TRIzol reagent (Invitrogen, Carlsbad, CA, USA). To remove the DNA that may be polluted, the extracted RNAs were treated with DNase I and extracted using the phenol-chloroform. The purified RNAs were dissolved with diethylpyrocarbonate. The concentration and integrity of RNAs were tested *via* Agilent (Santa Clara, CA, USA) 2100 bioanalyzer. SYBR<sup>®</sup> Premix Ex Tag<sup>™</sup> II (TaKaRa, Otsu, Shiga, China) was adopted to detect the expression level of CADM1-AS1 in the tissues. With U6 as an internal reference, the level of CADM1-AS1 was calculated with the 2<sup>-ΔΔCt</sup> method. The sequences are shown in Figure 1.

### Statistical Analysis

The data were analyzed using the Statistical Product and Service Solutions (SPSS) 17.0 software (SPSS Inc., Chicago, IL, USA) and the results were used for statistical analysis. The measurement data were presented as ( $\bar{x} \pm s$ ), and the *t*-test was used for the intergroup comparison of data. Pearson  $\chi^2$ -test was employed for the enumeration data. Overall survival (OS) and progression-free survival (PFS) of the patients were evaluated *via* the Kaplan-Meier survival analysis, and the intergroup differences were analyzed by the log-rank test. The factors with significant influence on overall survival were incorporated into the multivariate COX regression analysis model for the analyses.  $p < 0.05$  suggested that the difference was statistically significant.

Gene	Primers	Primer sequence
lncRNA CADM1-AS1	Forward primers	5'-TGACAAAGGCAGGAGGTA-3'
	Reverse primers	5'-GCACTATGGCTGAGGAAA-3'
GAPDH	Forward primers	5'- CAGGGCTGCTTTTAACTCTGGTAA -3'
	Reverse primers	5'- GGGTGAATCATATTGGAACATGT -3'

**Figure 1.** The sequences of the primers related to lncRNA CADM1-AS1 detection.

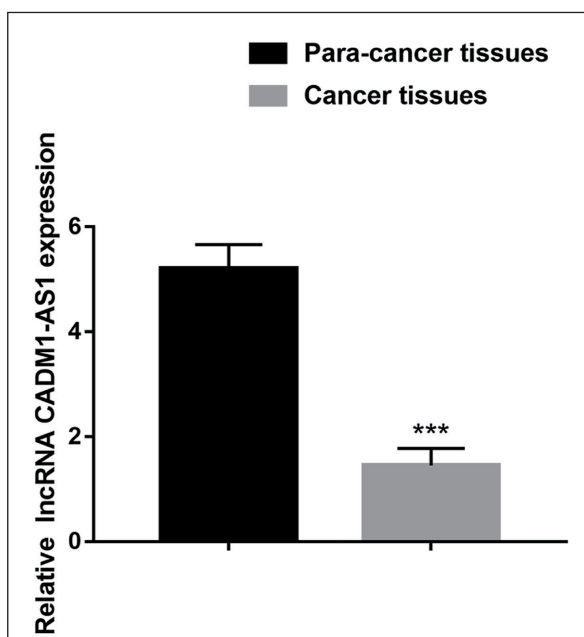
## Results

### ***LncRNA CADM1-AS1 Expression Was Decreased in Gastric Cancer***

The expression of lncRNA CADM1-AS1 in 120 gastric cancer tissues and para-normal tissues was detected. The results showed that the expression of lncRNA CADM1-AS1 in cancer tissues was much lower than that of para-normal tissues, and the difference was statistically significant ( $p < 0.001$ ) (Figure 2).

### ***Association Between Clinicopathological Characteristics and LncRNA CADM1-AS1 Expression***

The patients were divided into the lncRNA CADM1-AS1 high-expression group ( $n=63$ ) and low-expression group ( $n=57$ ) according to the mean expression level of lncRNA CADM1-AS1 (2.889). Then, the association between lncRNA CADM1-AS1 expression and clinicopathological features of patients was analyzed, and it was found that the lncRNA CADM1-AS1 expression was not associated with the patient's gender, age, tumor size, tumor position, and T stage, displaying no statistically significant differences ( $p > 0.05$ ). However, its expression was associated with the tumor differentiation, N stage, M stage, and TNM stage, displaying statistically significant differences ( $p < 0.05$ ) (Table I).



**Figure 2.** The expression of lncRNA CADM1-AS1 were measured in the tissues by qRT-PCR.

### ***Effect of LncRNA CADM1-AS1 on the Prognosis of Patients with Gastric Cancer***

The Kaplan-Meier survival analysis and the Log-rank test were performed to analyze the correlations of the pathological parameters of gastric cancer and lncRNA CADM1-AS1 with PFS and OS of patients. The results showed that gastric cancer patients with low expression of lncRNA CADM1-AS1 were more likely to relapse compared with patients with a high expression of lncRNA CADM1-AS1 ( $p < 0.05$ ). Also, the high expression of lncRNA CADM1-AS1 in cancer patients means a better survival rate ( $p < 0.05$ ) (Figure 3).

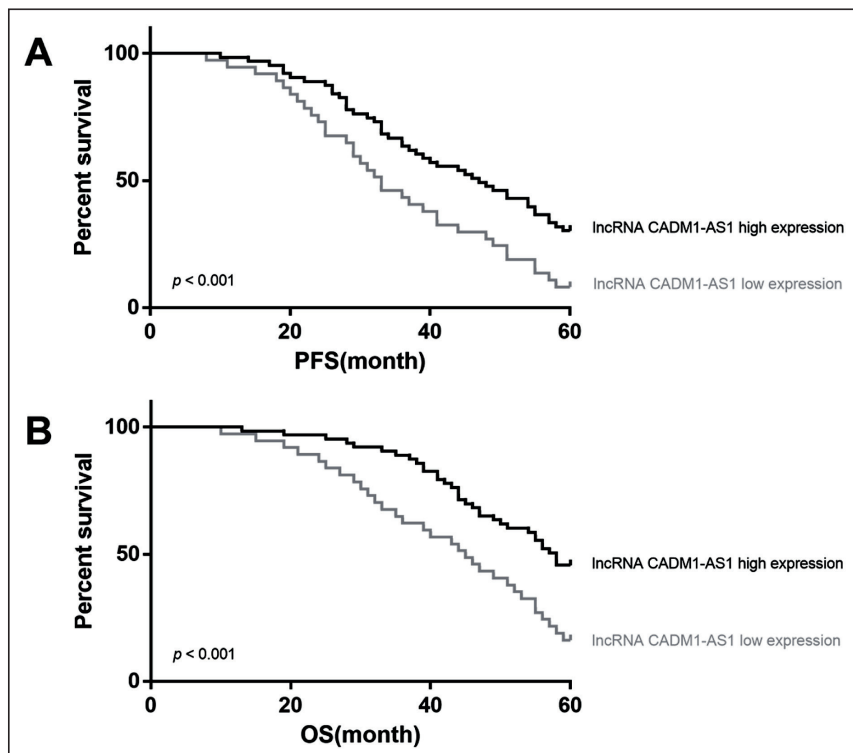
The COX regression analysis model was used to analyze the pathological parameter of gastric cancer and CADM1-AS1 as survival predictors for patients with gastric cancer. The factors with significant influence on survival were incorporated into the multivariate COX regression analysis model for further analyses. The results are shown in Table II, and we found that, similar to the influence factor-like tumor differentiation, N stage, M stage, and TNM stage, the expression of lncRNA CADM1-AS1 was an independent prognosis index of patients with gastric cancer ( $p < 0.05$ ).

## Discussion

To maintain homeostasis, the cells were required to have a constant response to a series of minor changes at any time in order to adapt the changes and keep dynamic equilibrium. Many factors like nutrition state and signals might trigger different cellular responses, such as metabolic status, proliferation, differentiation, or apoptosis<sup>21</sup>. The regulation of the gene expression was the basic way in which the cells respond to micro-environmental changes. RNA acted as the bridge between deoxyribonucleic acid (DNA) and proteins, and its importance lied in its coding effect besides tRNA and rRNA<sup>22</sup>. With the development of high-throughput sequencing technique, many lncRNAs have been detected. Even though its specific functions were not entirely clear, some lncRNAs were involved in the process of maintaining the cells and tissues. However, their imbalanced expression also played important roles in the pathogenesis and progress of many diseases. Sauvageau et al<sup>23</sup> indicated that some mice

**Table I.** LncRNA CADM1-AS1 expression and clinical features of patients with gastric cancer.

Features	No.	LncRNA CADM1-AS1		p
		High	Low	
No.	120	63	57	
Gender				0.668
Male	49	26	23	
Female	71	37	34	
Age (year)				0.735
< 60	53	29	24	
≥ 60	67	34	33	
Tumor size (cm)				0.990
< 5	82	42	40	
≥ 5	38	19	17	
Tumor position				0.401
Fundus of stomach	21	9	12	
Body of stomach	50	28	22	
Antrum of stomach	49	26	23	
Tumor differentiation				0.008
Well + moderate	66	45	21	
Poor + undifferentiated	54	18	36	
T stage				0.822
T <sub>1</sub> + T <sub>2</sub>	55	29	26	
T <sub>3</sub> + T <sub>4</sub>	65	34	31	
N stage				0.001
N <sub>0</sub> + N <sub>1</sub>	77	51	26	
N <sub>2</sub> + N <sub>3</sub>	43	12	31	
M stage				0.002
M0	103	61	42	
M1	17	2	15	
TNM stage				0.000
I + II	62	50	12	
III + IV	58	13	45	



**Figure 3.** The relationship of LncRNA CADM1-AS1 expression with progression free survival and overall survival of gastric cancer patients.

**Table II.** Univariate and multivariate analyses of postoperative prognosis in patients with gastric cancer.

Features	Univariate analysis		Multivariate analysis	
	Hazard ratio/CI (95%)	<i>p</i>	Hazard ratio/CI (95%)	<i>p</i>
Gender	0.983/0.754-1.248	0.868		
Ages	1.103/0.813-1.199	0.913		
Tumor size	1.627/0.917-2.425	0.071		
Tumor position	0.955/0.600-1.136	0.492		
Tumor differentiation	2.120/1.138-3.869	0.033	2.006/1.091-3.106	0.049
T stage	1.455/0.920-2.861	0.195		
N stage	3.374/1.821-5.429	0.007	3.173/1.720-4.851	0.030
M stage	3.987/2.349-4.780	0.012	3.294/2.322-4.234	0.027
TNM stage	4.102/3.076-5.371	0.003	3.722/2.926-5.110	0.008
LncRNACADM1-AS1 expression level	2.994/1.670-4.051	0.009	2.584/1.621-3.880	0.015

with lncRNAs partially knocked out, would suffer from different degrees of developmental defects. With the results of such researches, the sequence, once considered as “transcriptional noise”, was deemed to be an important factor in life adjustment and adaption.

The malignant tumors were a result of somatic variation and escaped from the control of the gene expression programs that maintain intracellular homeostasis with gene regulatory networks and usually prevent their uncontrolled growth. Subtle changes in these programs or regulatory networks might have given rise to cell transformation, increasing the risk of canceration. Given that lncRNAs play an important role in tumor progression and can also be easily detected, they would be very promising tumor markers<sup>24-27</sup>.

In the present study, the expression of lncRNA CADM1-AS1 in gastric cancer tissues was detected *via* qRT-PCR, and its clinical significance was analyzed combined with the clinical data. The results showed that the expression of lncRNA CADM1-AS1 was significantly downregulated in gastric cancer tissues than that in para-carcinoma normal tissues, and the expression of lncRNA CADM1-AS1 was significantly associated with the tumor differentiation, N stage, M stage, and TNM stage. According to the survival analysis, both PFS and OS in lncRNA CADM1-AS1 high-expression group were better than those in the low-expression group. In addition, it was found that the lncRNA CADM1-AS1 expression could be used as an independent marker for poor prognosis. In conclusion, lncRNA CADM1-AS1 was repressed in gastric cancer tissues and associated with the prognosis of patients, which might be a potential prognostic marker in patients with gastric cancer.

In the past 20 years, the mysterious veil of the transcriptome has been uncovered, and a lot of lncRNAs have been found<sup>28-30</sup>. Although protein was still the effector of cellular processes, the roles of RNAs have been gradually surfaced. lncRNAs were crucial in the regulation of gene expression and cell functions. The balanced expression of such transcription was the key point of maintaining the stability of the intracellular environment. The roles of lncRNAs in the regulation of the gene expression were significant, and they could be used as a new generation of therapeutic targets.

## Conclusions

We demonstrated that lncRNA CADM1-AS1 might be a new prognostic biomarker for gastric cancer.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

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