

## Research Article

# Downregulated Expression of linc-ROR in Gastric Cancer and Its Potential Diagnostic and Prognosis Value

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**Background.** Gastric cancer (GC) is one of the global mortality diseases and has a poor prognosis due to the lack of ideal tumor biomarkers. Numerous studies have shown that long noncoding RNAs (lncRNAs) can affect the occurrence and development of cancer through a variety of signaling pathways. The abnormal expression and specificity of lncRNAs in tumors make them potential biomarkers of cancers. Nevertheless, the diagnostic roles of lncRNAs in GC have been poorly understood. So this study focuses on the clinical diagnostic value of lncRNAs in GC. **Materials and Methods.** Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was used to investigate the expression of the linc-ROR (long intergenic noncoding RNA, regulator of reprogramming) in 105 paired GC tissues and adjacent normal tissues. Receiver operating characteristic (ROC) curve and area under the curve (AUC) were established to assess the diagnostic value of linc-ROR. The relationship between expression of linc-ROR and clinicopathological factors of patients with GC was further explored. Kaplan-Meier analysis was performed to evaluate the prognostic value of linc-ROR expression. **Results.** The linc-ROR expression level was significantly decreased in GC tissues compared with its adjacent nontumor tissues ( $n = 105$ ,  $P < 0.001$ ). We also discovered that linc-ROR was evidently downregulated in 68.6% (72/105) of GC tissues. The AUC's value of linc-ROR was up to 0.6495, with sensitivity and specificity of 0.7524 and 0.5143, respectively. Intriguingly, the linc-ROR expression levels were obviously associated with tumor differentiation ( $P = 0.004$ ). Notably, the overall survival rate of GC patients with high expression of linc-ROR was significantly higher than those with low expression. **Conclusion.** Our data revealed that linc-ROR has clinical potential as a biomarker for the diagnosis of GC and assessment of its prognosis.

## 1. Introduction

GC is a very common malignant tumor with a high mortality rate, especially in Southeast Asian countries<sup>1–3</sup>. With the development of modern medicine, the overall survival rate of patients with GC has improved, but most patients with early-stage gastric cancer (EGC) have no obvious characteristic performance<sup>4, 5</sup>. Unfortunately, most patients are diagnosed at an advanced stage and missed the best treatment time. In the diagnosis of GC, upper gastrointestinal (GI) endoscopy is the gold standard for the diagnosis of GC<sup>6</sup>, but endoscopy is an invasive technique that can cause pain to the patient and this is not a routine examination<sup>7</sup>. Importantly,

the 5-year survival rate of patients with EGC can reach more than 90% and the survival rate of patients with metastatic gastric cancer is just only 18%<sup>8, 9</sup>. Clinically, the sensitivity and specificity of traditional tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and CA72-4 are relatively low<sup>10–12</sup>. Therefore, it is particularly important and urgent to find minimally invasive or even noninvasive biomarkers that can diagnose GC early.

More than 70% of the human genome can be transcribed, and most of them are transcribed into noncoding RNAs, including circular RNAs (circRNAs), long noncoding RNAs (lncRNAs), microRNAs (miRNAs), and so on<sup>13–15</sup>. Among them, lncRNAs are a type of noncoding RNA of more than

200 nt in length. Because they do not have the ability to encode proteins, they were once considered to be the noise of gene transcription<sup>16</sup>. However, studies have shown that lncRNAs, as a regulatory molecule in gene expression, are directly involved in the development of various human diseases, especially various cancers<sup>17–19</sup>. lncRNAs can be used as oncogenes or tumor suppressor genes to participate in the growth, proliferation, metastasis, and drug resistance of GC<sup>20</sup>. In addition, long intergenic (or intermediate) ncRNAs (lincRNAs) are located between the coding and noncoding genes and do not overlap with the exons of other genes. Besides, the characteristic SNP (single nucleotide polymorphism, SNP) content of lincRNAs is high, indicating that they can play a role in the characteristic correlation regions between genes<sup>21, 22</sup>. Because of their unique secondary structure and their high stability and specificity, lincRNAs can be stably present in body fluids (such as blood, saliva, and urine). Therefore, free lincRNAs in body fluids can be determined by quantitative detection methods. In addition, more and more researches show that the abnormal expression of lincRNA has clinical significance for the diagnosis of GC<sup>23–25</sup>. Zhang et al. identified five lincRNAs from the plasma of GC patients, which can be distinguished between GC patients and healthy people via using five lincRNAs as joint indicators<sup>26</sup>. Another study also found that lincRNA ZNF1-AS1 and HULC are differentially expressed in the plasma of GC patients and healthy people, indicating that ZNF1-AS1 and HULC are promising in the clinical diagnosis of GC<sup>27</sup>. lincRNA reprogramming regulator (linc-ROR) can regulate iPSC reprogramming<sup>28</sup>. The study found that linc-ROR can respond to DNA damage by interacting with heterogeneous ribonucleoprotein I (hnRNP I) to inhibit p53 translation<sup>29</sup>. Besides, linc-ROR promotes the growth of breast cancer cells independent of estrogen<sup>30</sup>. Importantly, linc-ROR has a potential role in the diagnosis of cancer. Upregulated linc-ROR may be a potential biomarker for the diagnosis and dynamic monitoring of breast cancer<sup>31</sup>. The existing researches about linc-ROR indicate that it not only plays an important role in the occurrence and development of tumors but also has considerable potential in tumor diagnosis.

In this study, our purpose was to find early tumor biomarkers that can distinguish GC patients from healthy people. qRT-PCR was used to investigate the expression of linc-ROR in 105 pairs of GC tissues and its corresponding adjacent tissues. Additionally, we have constructed a receiver operating characteristic (ROC) curve and survival curves to assess its potential for diagnosis and prognosis of GC markers. The results revealed that the expression of linc-ROR in GC tissues was significantly lower than that of adjacent normal tissues. The area under curve (AUC) also disclosed that linc-ROR has potential as a diagnostic marker, and the Kaplan-Meier plotter showed that the survival rate of GC patients with high expression of linc-ROR was significantly higher than that of patients with low expression of linc-ROR.

## 2. Materials and Methods

**2.1. Specimens and Clinical Data.** The 105 GC tissues and paired adjacent nontumorous tissues were collected from

the Yinzhou People's Hospital in Ningbo between January 2010 and December 2015. All tissue specimens were obtained from GC patients who had not undergone any treatment before surgery, and the GC tissues were taken from the mucosa of the tumor center, more than 5 cm from the adjacent tissues. Specimens were removed from the patient with GC, then placed in a solution (Biotek, China) at once to avoid RNA degradation. Finally, they were stored at  $-80^{\circ}\text{C}$  until use. All specimens were eventually confirmed as GC according to histopathology, and the tumor staging was determined by the International Union Against Cancer's Tumor-Node-Metastasis (TNM) staging system version 832, 33. Assessment of histological grades was according to the National Comprehensive Cancer Network (NCCN) Cancer Clinical Practice Guidelines (V.1.2011)<sup>34</sup>. Written informed consent was obtained from all patients, and the study protocol was approved by the Human Research Ethics Committee of Ningbo First Hospital (IRB No. 2019-R012). All experiments follow the appropriate guidelines and regulations.

**2.2. Total RNA Extraction.** Total RNA of GC tissue sample extraction was performed using a TRIzol reagent (Invitrogen, Karlsruhe, Germany) following the manufacturer's protocol. Subsequently, the quality and concentration of RNA were measured by a NanoDrop spectrophotometer (DeNovix, Wilmington, USA). The absorbance ratio of RNA A260/A280 should be between 1.8 and 2.0 for subsequent experiments. The RNA with the desired purity was reverse transcribed into complementary DNA (cDNA), and the remaining was stored in  $-80^{\circ}\text{C}$  for backup.

**2.3. Reverse Transcription.** 2  $\mu\text{g}$  of total RNA was performed to synthesize cDNA using the GoScript RT System (Promega, Madison, WI, USA) with random primers according to the manufacturer's instructions.

**2.4. Real-Time Polymerase Chain Reaction.** We used the GoTaq qPCR Master (Promega, USA) for qRT-PCR. The reaction volume was 25  $\mu\text{l}$ , including 12.5  $\mu\text{l}$  of GoTaq<sup>®</sup> qPCR Master Mix (2x), 1  $\mu\text{l}$  of forward primer (10  $\mu\text{M}$ ), 1  $\mu\text{l}$  of reverse primer (10  $\mu\text{M}$ ), 5  $\mu\text{l}$  of cDNA, and 5.5  $\mu\text{l}$  of RNase-free ddH<sub>2</sub>O on the Mx3005P real-time PCR system (Stratagene, USA). The sequences of qRT-PCR for linc-ROR were 5'-CTTGATGGCATTGTCGC-3' and 5'-TCCTGTGGTTTCATTGTCC-3'. And  $\beta$ -actin was performed as the internal negative control and normalized the levels of linc-ROR. The sequences of  $\beta$ -actin were 5'-AAGCCACCCCACTTCTCTCTAA-3' and 5'-AATGCTATCACCTCCCCTGTGT-3'. The reaction mixtures were incubated at  $95^{\circ}\text{C}$  for 5 min, followed by 40 cycles at  $95^{\circ}\text{C}$  for 15 s,  $58^{\circ}\text{C}$  for 30 s, and  $72^{\circ}\text{C}$  for 30 s. The melt curve was used to verify the specificity of the qRT-PCR products. All experiments were carried out in triplicate. Each sample amplified specific linc-ROR and  $\beta$ -actin RNA. The  $\Delta C_q$  method was used for analysis. First, we detect the  $C_q$  value of each sample through the Mx3005P QPCR System. Then, we calculated  $\Delta C_q$  values according to the formula  $\Delta C_q = C_{q\text{linc-ROR}} - C_{q\beta\text{-actin}}$ ;  $\Delta\Delta C_q$  value is determined by the

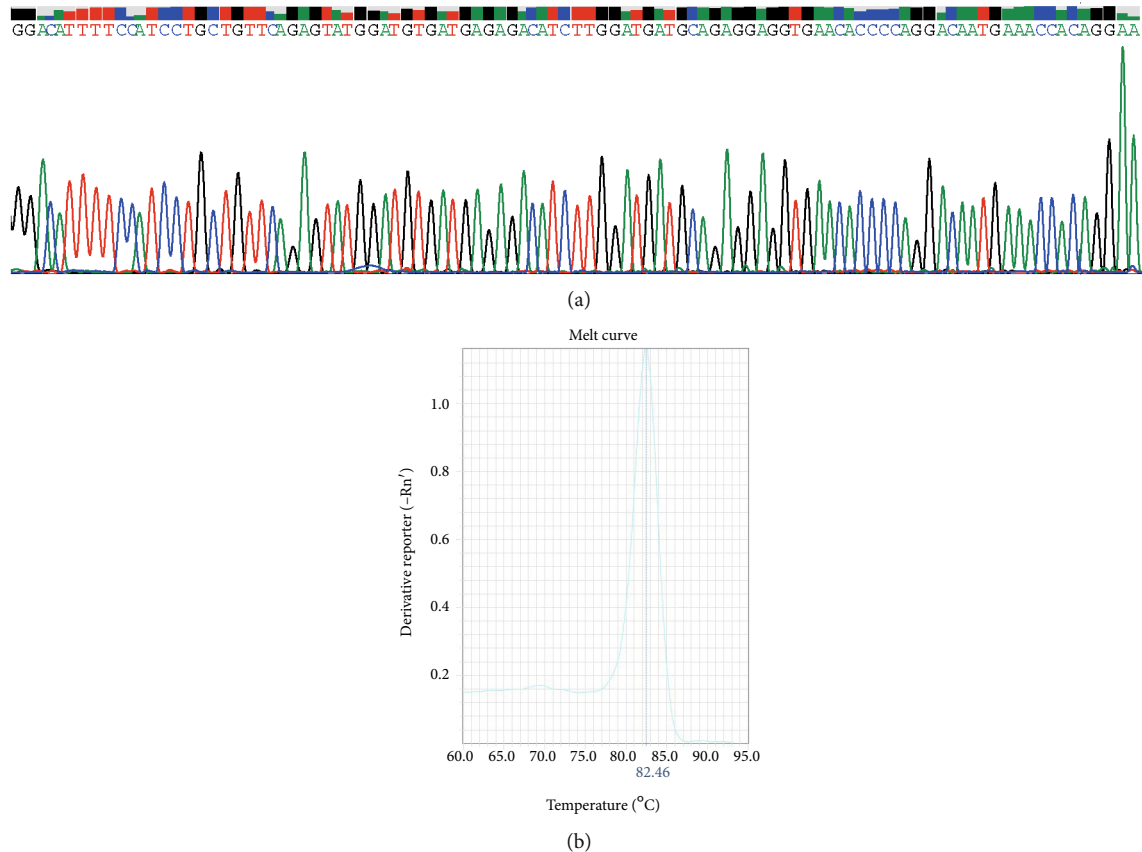


FIGURE 1: Amplification of linc-ROR. (a) Sanger sequence results of qRT-PCR products of linc-ROR in GC tissues. (b) The single peak of the melting curve of linc-ROR. qRT-PCR: quantitative reverse transcription-polymerase chain reaction.

formula  $\Delta\Delta Cq = \Delta Cq_{\text{gastric cancer group}} - \Delta Cq_{\text{adjacent normal group}}$ . The relative expression level of linc-ROR in adjacent normal tissues and gastric cancer tissues was determined using the  $\Delta Cq$  method<sup>34</sup>. If the  $\Delta Cq$  value is relatively high, the expression of linc-ROR is relatively low<sup>35</sup>. The  $\log_2^{-\Delta\Delta Cq} < 0$  was used to analyze the relative lower linc-ROR expression samples in gastric cancer tissues.

**2.5. Statistical Analysis.** Statistical calculations were analyzed by the Statistical Product and Service Solutions 19.0 software (SPSS, Chicago, IL, USA). For comparing the expression of linc-ROR between GC tissues and paired adjacent nontumor tissues, two-tailed Student's *t*-test was used. ROC and AUC were used to evaluate the diagnostic value of linc-ROR. A chi-square test was used to compare the relationship between the expression of linc-ROR and pathological factors in patients with GC. Results were considered statistically significant when the *P* value was less than 0.05.

### 3. Results

**3.1. linc-ROR Was Downregulated in GC Tissues.** To determine the expression of linc-ROR in GC tissues, we analyzed their expression in 105 pairs of GC tissues and corresponding adjacent tissues by qRT-PCR. The Sanger sequence results of the qRT-PCR product (165 bp) were consistent with the orig-

inal sequence (Figure 1(a)), and the single peak of the melting curve of linc-ROR verified the specificity of the primer (Figure 1(b)). As a result, the expression level of linc-ROR in GC tissues was much lower than that in the corresponding adjacent cancer tissues (Figures 2(a) and 2(b)). Among all samples, the lower expression samples accounted for more than 68.6% (72/105, Figure 2(c)). Correlation analysis showed that the expression of linc-ROR in the GC group was related to the degree of differentiation ( $P = 0.004$ ). However, linc-ROR expression level was not correlated with age ( $P = 0.324$ ), gender ( $P = 0.748$ ), tumor size ( $P = 0.767$ ), lymph node metastasis ( $P = 0.807$ ), invasion ( $P = 0.675$ ), distant metastasis ( $P = 0.811$ ), TNM stage ( $P = 0.291$ ), CEA ( $P = 0.392$ ), and CA19-9 ( $P = 0.509$ ) (Table 1).

**3.2. linc-ROR Has Potential as a Diagnostic and Prognostic Biomarker in GC.** To investigate the prognosis of linc-ROR in GC, we analyzed the survival curve to show that patients with higher linc-ROR expression had a longer overall survival and vice versa ( $P = 0.0437$ ; Figure 2(d)). We further evaluated the diagnostic value of linc-ROR in GC tissues and corresponding adjacent tissues by constructing ROC curves. Analysis of the ROC curve results showed that the AUC value of linc-ROR was 0.6495 (Figure 3(a)), the cutoff value was greater than 16.79, with sensitivity and specificity 0.7524 and 0.5143, respectively (Figure 3(b)).

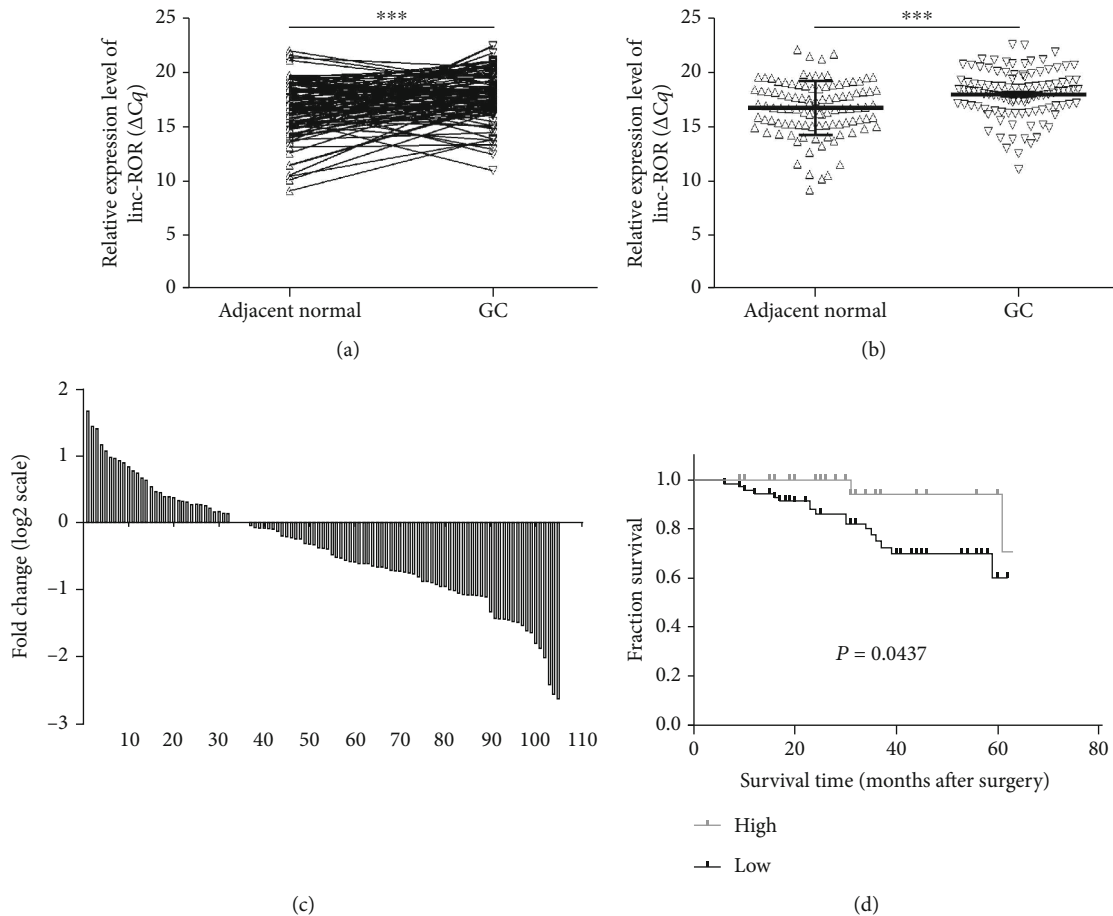


FIGURE 2: The relative expression level of linc-ROR in gastric cancer tissues. Statistical significance was defined as two-sided. \*\*\* $P < 0.001$ . (a) Expression levels of linc-ROR in each patient, with comparison between tumor tissues and the normal adjacent tissues ( $n = 105$ ). Higher  $\Delta Cq$  value indicates lower expression. \*\*\* $P < 0.001$ . (b) The expression levels of linc-ROR were significantly lower than those in adjacent normal tissues ( $n = 105$ ,  $P < 0.001$ ). (c) The percentage of low expression of linc-ROR in GC tissues accounts for 68.6% (72/105). (d) Kaplan-Meier analysis of OS based on linc-ROR expression in all GC patients.

**3.3. linc-ROR Has the Potential to Bind RBP to Exert Biological Functions.** A large number of studies have shown that lincRNAs can act as a molecular sponge or bait of RNA binding protein (RBP) through its RBP binding site, thereby regulating the expression of all target genes of the corresponding target RBP36, 37. We have found two RBPs (ADAR and FUS) that can be combined with linc-ROR (Table 2) through the bioinformatic database starBase v3.0 (<http://starbase.sysu.edu.cn/>) laying the foundation for future research on whether or not to play a biological role in GC.

#### 4. Discussion

Although the current diagnosis and treatment of GC has made a breakthrough, GC is still the third leading cause of cancer death; the patient's 5-year survival rate is also very low38. Since reducing mortality is closely related to early diagnosis of gastric cancer, there is an urgent need to identify new tumor biomarkers for early diagnosis so that patients can be treated within the optimal treatment time and improve survival. In the clinical diagnosis of GC, gastroscopy

is the gold standard, but it is invasive and the patient feels uncomfortable. Additionally, the effect of traditional tumor biomarkers is not ideal. So, minimally invasive liquid biopsy has become the mainstream of finding tumor markers, and lincRNAs have a potential role in the diagnosis of cancer39. We found that the expression levels of linc-ROR were lower in GC tissues compared with its adjacent normal tissues (Figures 2(a) and 2(b)). And the expression of linc-ROR in GC tissues was related to the degree of differentiation in clinicopathological factors (Table 1). As a GC tissue-based biomarker, the AUC of linc-ROR reached 0.6495 (Figure 3(a)). The sensitivity and specificity were 0.7524 and 0.5143, respectively (Figure 3(b)). Its false positive rate was 0.4857, and false negative rate was 0.2476. The positive predictive value (PPV) was 0.6077, and negative predictive value (NPV) was 0.675. It was worth noting that the expression of linc-ROR in GC tissues was related to the prognosis of patients with GC (Figure 2(d)). Compared with the low expression linc-ROR group, the high expression linc-ROR group had a better prognosis.

linc-ROR is a lincRNA capable of reprogramming differentiated cells into induced pluripotent stem cells. Studies

TABLE 1: The relationship between linc-ROR expression levels ( $\Delta Cq$ ) in GC tissues and clinicopathological factors of GC patients.

Characteristics	No. of cases (%)	Mean $\pm$ SD	P value
<i>Age (years)</i>			0.324
<60	26 (24.8)	17.6 $\pm$ 2.51	
$\geq$ 60	79 (75.2)	18.09 $\pm$ 2.08	
<i>Gender</i>			0.748
Male	79 (75.2)	18.01 $\pm$ 2.17	
Female	26 (24.8)	17.85 $\pm$ 2.29	
<i>Diameter (cm)</i>			0.767
<5	45 (42.9)	17.89 $\pm$ 1.92	
$\geq$ 5	60 (57.1)	18.02 $\pm$ 2.38	
<i>Differentiation</i>			0.004
Well	16 (15.2)	19.51 $\pm$ 2.39	
Moderate	53 (50.5)	17.92 $\pm$ 2.22	
Poor	36 (34.3)	17.35 $\pm$ 1.73	
<i>Lymphatic metastasis</i>			0.807
N0	36 (34.28)	18.22 $\pm$ 2.03	
N1	19 (18.10)	18.04 $\pm$ 1.97	
N2	14 (13.33)	17.82 $\pm$ 2.3	
N3	36 (34.29)	17.73 $\pm$ 2.15	
<i>Invasion</i>			0.675
T1 & TIS	19 (18.10)	17.77 $\pm$ 2.18	
T2	11 (10.47)	18.72 $\pm$ 1.33	
T3	8 (7.62)	18.06 $\pm$ 3.41	
T4	67 (63.81)	17.89 $\pm$ 2.15	
<i>Distal metastasis</i>			0.811
M0	96 (91.4)	17.98 $\pm$ 2.2	
M1	9 (8.6)	17.8 $\pm$ 2.2	
<i>TNM stage</i>			0.291
I & II	43 (40.9)	18.24 $\pm$ 1.97	
III & IV	62 (59.1)	17.78 $\pm$ 2.32	
<i>CEA</i>			0.392
Positive	92 (87.6)	17.9 $\pm$ 2.18	
Negative	13 (12.4)	18.46 $\pm$ 2.25	
<i>CA19-9</i>			0.509
Positive	61 (58.1)	17.85 $\pm$ 2.35	
Negative	44 (41.9)	18.13 $\pm$ 1.95	

SD: standard deviation.

have shown that linc-ROR can act as a miRNA sponge<sup>40, 41</sup>, promote tumor cell proliferation and metastasis, and increase chemotherapy resistance<sup>30, 42, 43</sup>. For example, Gao et al. found that linc-ROR was significantly upregulated in pancreatic cancer tissues and acted as a ceRNA (competing endogenous RNA) to adsorb miR-145, thereby activating the inhibition of the core transcription factor Nanog<sup>44</sup>. In particular, linc-ROR also can be used as one of the indicators for judging the prognosis of pancreatic cancer<sup>41</sup>. The expres-

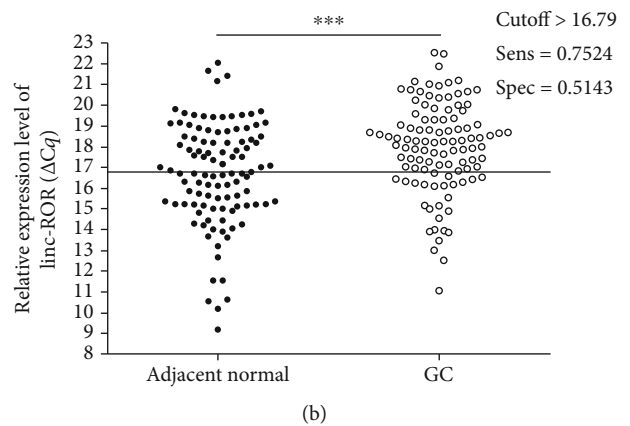
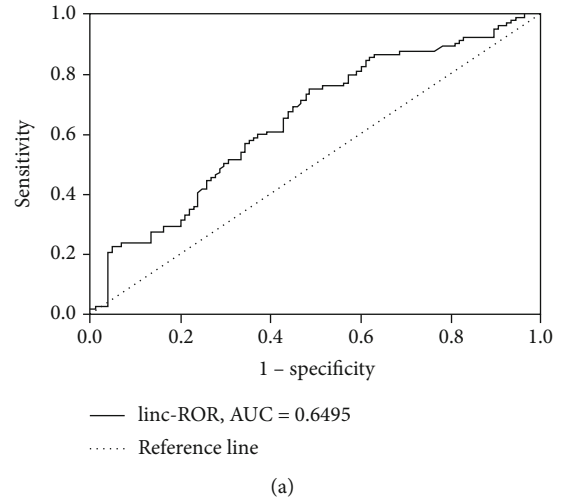


FIGURE 3: The diagnostic values of linc-ROR in gastric cancer. (a) The ROC curve of linc-ROR in differentiating GC tissues from controls. The area under the curve was up to 0.6495. (b) The cutoff value, sensitivity, and specificity were established by ROC curve. ROC: receiver operating characteristic.

TABLE 2: Bioinformatics predicts RBP ( ADAR and FUS ) that can potentially bind to linc-ROR via starBase V3.0.

RBP	Gene ID	Gene name	Gene type
ADAR	ENSG00000258609	linc-ROR	lincRNA
FUS	ENSG00000258609	linc-ROR	lincRNA

RBP: RNA binding protein.

sion level of linc-ROR was elevated in hepatocellular carcinoma, and the sponge action of linc-ROR on miR-876-5p released FOXM1, thus forming a positive feedback loop. Interestingly, linc-ROR showed the sensitivity to sorafenib in HCC (hepatocellular carcinoma) cell lines<sup>45</sup>. Besides, He et al. examined the expression levels of linc-ROR in liver cancer cell lines and their exosomes, and it was found that linc-ROR was enriched in exosomes of the HepG2 cell line and promoted the growth of other liver cancer cell lines<sup>46</sup>. However, there is no report about the early diagnosis of GC by linc-ROR, so we mainly focus on the diagnostic value of

linc-ROR. Our results revealed that linc-ROR has potential as a biomarker for the diagnosis of GC.

In general, linc-ROR is expected to be a tumor diagnostic biomarker for GC, but there are still many shortcomings in this research. Firstly, the quantity of tissue sample is limited, and it is necessary to increase the number of samples in the future research. Secondly, the expression of linc-ROR needs to be detected in blood samples to be more suitable for a tumor biomarker. At present, the combination of biomarkers for early diagnosis of cancer is superior than the single biomarker. Therefore, in the future, we will continue to seek multiple specific markers for GC and build more appreciate models for diagnosis and prognostic evaluation. In addition, the mechanism of linc-ROR in gastric cancer is unclear. Exploring possible molecular mechanisms will help to establish more valuable diagnostic and prognostic biomarkers and provide new molecular targets for the treatment of GC.

## 5. Conclusions

To sum up, our data revealed that linc-ROR expression was significantly decreased in GC tissues. The downregulated linc-ROR expression levels were obviously associated with tumor differentiation, and the high expression linc-ROR group had a better prognosis. Our result suggests that linc-ROR has clinical potential as a biomarker for the diagnosis of GC and assessment of its prognosis.

## Data Availability

(1) The quantitative reverse transcription-polymerase chain reaction (qRT-PCR) of linc-ROR data used to support the findings of this study are included within the article. (2) Data and materials availability: all data associated with this study are present in the paper.

## Conflicts of Interest

The authors declare no conflict of interest with respect to the research, authorship, and publication of this article.

## Acknowledgments

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## References

- [1] L. A. Torre, F. Bray, R. L. Siegel, J. Ferlay, J. Lortet-Tieulent, and A. Jemal, "Global cancer statistics, 2012," *CA: a Cancer Journal for Clinicians*, vol. 65, no. 2, pp. 87–108, 2015.
- [2] Y. Hayakawa, N. Sethi, A. R. Sepulveda, A. J. Bass, and T. C. Wang, "Oesophageal adenocarcinoma and gastric cancer: should we mind the gap?," *Nature Reviews. Cancer*, vol. 16, no. 5, pp. 305–318, 2016.
- [3] L. Zhu, T. Li, Y. Shen, X. Yu, B. Xiao, and J. Guo, "Using tRNA halves as novel biomarkers for the diagnosis of gastric cancer," *Cancer Biomarkers*, vol. 25, no. 2, pp. 169–176, 2019.
- [4] X. Mo, Y. Wu, L. Chen et al., "Global expression profiling of metabolic pathway-related lncRNAs in human gastric cancer and the identification of RP11-555H23.1 as a new diagnostic biomarker," *Journal of Clinical Laboratory Analysis*, vol. 33, article e22692, 2019.
- [5] N. Bernards, G. J. Creemers, G. A. P. Nieuwenhuijzen, K. Bosscha, J. F. M. Pruijt, and V. E. P. P. Lemmens, "No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy," *Annals of Oncology*, vol. 24, no. 12, pp. 3056–3060, 2013.
- [6] P. W. Y. Chiu, N. Uedo, R. Singh et al., "An Asian consensus on standards of diagnostic upper endoscopy for neoplasia," *Gut*, vol. 68, no. 2, pp. 186–197, 2019.
- [7] I. J. Choi, J. H. Lee, Y.-I. Kim et al., "Long-term outcome comparison of endoscopic resection and surgery in early gastric cancer meeting the absolute indication for endoscopic resection," *Gastrointestinal Endoscopy*, vol. 81, no. 2, pp. 333–341.e1, 2015.
- [8] D. Mizrak Kaya, G. M. Noguera-González, K. Harada et al., "Potentially curable gastric adenocarcinoma treated without surgery," *European Journal of Cancer*, vol. 98, pp. 23–29, 2018.
- [9] Z. Tan, "Recent advances in the surgical treatment of advanced gastric cancer: a review," *Medical Science Monitor*, vol. 25, pp. 3537–3541, 2019.
- [10] A. I. Kotzev and P. V. Draganov, "Carbohydrate antigen 19-9, carcinoembryonic antigen, and carbohydrate antigen 72-4 in gastric cancer: is the old band still playing?," *Gastrointestinal Tumors*, vol. 5, no. 1-2, pp. 1–13, 2018.
- [11] J. Lu, P.-y. Zhang, J.-w. Xie et al., "Hsa\_circ\_0000467 promotes cancer progression and serves as a diagnostic and prognostic biomarker for gastric cancer," *Journal of Clinical Laboratory Analysis*, vol. 33, no. 3, article e22726, 2018.
- [12] M. Abbas, A. Ahmed, G. J. Khan et al., "Clinical evaluation of carcinoembryonic and carbohydrate antigens as cancer biomarkers to monitor palliative chemotherapy in advanced stage gastric cancer," *Current Problems in Cancer*, vol. 43, no. 1, pp. 5–17, 2019.
- [13] S. Djebali, C. A. Davis, A. Merkel et al., "Landscape of transcription in human cells," *Nature*, vol. 489, no. 7414, pp. 101–108, 2012.
- [14] K. V. Morris and J. S. Mattick, "The rise of regulatory RNA," *Nature Reviews. Genetics*, vol. 15, no. 6, pp. 423–437, 2014.
- [15] J. L. Rinn and H. Y. Chang, "Genome regulation by long non-coding RNAs," *Annual Review of Biochemistry*, vol. 81, no. 1, pp. 145–166, 2012.
- [16] M. N. Cabili, C. Trapnell, L. Goff et al., "Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses," *Genes & Development*, vol. 25, no. 18, pp. 1915–1927, 2011.
- [17] X. Bai, W. Wang, P. Zhao et al., "LncRNA CRNDE acts as an oncogene in cervical cancer through sponging miR-183 to regulate CCNB1 expression," *Carcinogenesis*, vol. 41, no. 1, pp. 111–121, 2020.
- [18] J. Shi, J. Li, S. Yang et al., "LncRNA SNHG3 is activated by E2F1 and promotes proliferation and migration of non-small-cell lung cancer cells through activating TGF- $\beta$  pathway

- and IL-6/JAK2/STAT3 pathway,” *Journal of Cellular Physiology*, vol. 235, no. 3, pp. 2891–2900, 2020.
- [19] K. Zhou, J. Yang, X. Li, and W. Chen, “Long non-coding RNA XIST promotes cell proliferation and migration through targeting miR-133a in bladder cancer,” *Experimental and Therapeutic Medicine*, vol. 18, pp. 3475–3483, 2019.
- [20] Y. Wang and J. Zhang, “Identification of differential expression lncRNAs in gastric cancer using transcriptome sequencing and bioinformatics analyses,” *Molecular Medicine Reports*, vol. 17, pp. 8189–8195, 2018.
- [21] X. Li and Z. Wu, “lncRNAs: insights into their function and mechanics in underlying disorders,” *Mutation Research, Reviews in Mutation Research*, vol. 762, pp. 1–21, 2014.
- [22] M. J. Hangauer, I. W. Vaughn, and M. T. McManus, “Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding RNAs,” *PLoS Genetics*, vol. 9, no. 6, article e1003569, 2013.
- [23] D. Hashad, A. Elbanna, A. Ibrahim, and G. Khedr, “Evaluation of the role of circulating long non-coding RNA H19 as a promising novel biomarker in plasma of patients with gastric Cancer,” *Journal of Clinical Laboratory Analysis*, vol. 30, no. 6, pp. 1100–1105, 2016.
- [24] S. Fattahi, M. Kosari-Monfared, M. Golpour et al., “LncRNAs as potential diagnostic and prognostic biomarkers in gastric cancer: a novel approach to personalized medicine,” *Journal of Cellular Physiology*, vol. 235, no. 4, pp. 3189–3206, 2019.
- [25] Y. Dong, Z. G. Wang, and T. S. Chi, “Long noncoding RNA Lnc01614 promotes the occurrence and development of gastric cancer by activating EMT pathway,” *European Review for Medical and Pharmacological Sciences*, vol. 22, pp. 1307–1314, 2018.
- [26] K. Zhang, H. Shi, H. Xi et al., “Genome-wide lncRNA microarray profiling identifies novel circulating lncRNAs for detection of gastric cancer,” *Theranostics*, vol. 7, no. 1, pp. 213–227, 2017.
- [27] H. P. Xian, Z. L. Zhuo, Y. J. Sun, B. Liang, and X. T. Zhao, “Circulating long non-coding RNAs HULC and ZNF1-AS1 are potential biomarkers in patients with gastric cancer,” *Oncology Letters*, vol. 16, pp. 4689–4698, 2018.
- [28] S. Loewer, M. N. Cabili, M. Guttman et al., “Large intergenic non-coding RNA-RoR modulates reprogramming of human induced pluripotent stem cells,” *Nature Genetics*, vol. 42, no. 12, pp. 1113–1117, 2010.
- [29] A. Zhang, N. Zhou, J. Huang et al., “The human long non-coding RNA-RoR is a p53 repressor in response to DNA damage,” *Cell Research*, vol. 23, no. 3, pp. 340–350, 2013.
- [30] W. X. Peng, J. G. Huang, L. Yang, A. H. Gong, and Y. Y. Mo, “Linc-RoR promotes MAPK/ERK signaling and confers estrogen-independent growth of breast cancer,” *Molecular Cancer*, vol. 16, no. 1, p. 161, 2017.
- [31] T. Zhao, L. Wu, X. Li, H. Dai, and Z. Zhang, “Large intergenic non-coding RNA-ROR as a potential biomarker for the diagnosis and dynamic monitoring of breast cancer,” *Cancer Biomarkers*, vol. 20, no. 2, pp. 165–173, 2017.
- [32] J. Zhang, S. Zou, R. Luo, Z. Zhu, H. Xu, and B. Huang, “Proposal of a novel stage grouping of the Eighth Edition of American Joint Committee on Cancer TNM Staging System for Gastric Cancer: results from a retrospective study of 30 years clinical data from a single institute in China,” *Expert Review of Gastroenterology & Hepatology*, vol. 14, no. 1, pp. 55–64, 2020.
- [33] S. Tanaka, S. Komatsu, A. Ohta et al., “Validation of the 8th edition of the UICC TNM classification for stage gastric cancer,” *Gan to Kagaku Ryoho*, vol. 46, no. 3, pp. 502–504, 2019.
- [34] T. Li, Y. Shao, L. Fu et al., “Plasma circular RNA profiling of patients with gastric cancer and their droplet digital RT-PCR detection,” *Journal of Molecular Medicine (Berlin, Germany)*, vol. 96, no. 1, pp. 85–96, 2018.
- [35] T. Yao, Q. Chen, Z. Shao, Z. Song, L. Fu, and B. Xiao, “Circular RNA 0068669 as a new biomarker for hepatocellular carcinoma metastasis,” *Journal of Clinical Laboratory Analysis*, vol. 32, no. 8, article e22572, 2018.
- [36] K. Li, S. Zhong, Y. Luo et al., “A long noncoding RNA binding to QKI-5 regulates germ cell apoptosis via p38 MAPK signaling pathway,” *Cell Death & Disease*, vol. 10, no. 10, p. 699, 2019.
- [37] X. Yang, S. Qu, L. Wang et al., “PTBP3 splicing factor promotes hepatocellular carcinoma by destroying the splicing balance of NEAT1 and pre-miR-612,” *Oncogene*, vol. 37, no. 50, pp. 6399–6413, 2018.
- [38] G. Mankaney, C. Macaron, and C. A. Burke, “Refining risk factors for gastric cancer in patients with Lynch syndrome to optimize surveillance esophagogastroduodenoscopy,” *Clinical Gastroenterology and Hepatology*, vol. 18, no. 4, pp. 780–782, 2020.
- [39] A. Di Meo, J. Bartlett, Y. Cheng, M. D. Pasic, and G. M. Yousef, “Liquid biopsy: a step forward towards precision medicine in urologic malignancies,” *Molecular Cancer*, vol. 16, no. 1, p. 80, 2017.
- [40] L. Feng, L. Shi, Y. F. Lu et al., “Linc-ROR promotes osteogenic differentiation of mesenchymal stem cells by functioning as a competing endogenous RNA for miR-138 and miR-145,” *Molecular Therapy - Nucleic Acids*, vol. 11, pp. 345–353, 2018.
- [41] L. Wang, X. Yu, Z. Zhang et al., “Linc-ROR promotes esophageal squamous cell carcinoma progression through the derepression of SOX9,” *Journal of Experimental & Clinical Cancer Research*, vol. 36, no. 1, p. 182, 2017.
- [42] H. X. Zhan, Y. Wang, C. Li et al., “LincRNA-ROR promotes invasion, metastasis and tumor growth in pancreatic cancer through activating ZEB1 pathway,” *Cancer Letters*, vol. 374, no. 2, pp. 261–271, 2016.
- [43] G. Eades, B. Wolfson, Y. Zhang, Q. Li, Y. Yao, and Q. Zhou, “lincRNA-RoR and miR-145 regulate invasion in triple-negative breast cancer via targeting ARF6,” *Molecular Cancer Research*, vol. 13, no. 2, pp. 330–338, 2015.
- [44] S. Gao, P. Wang, Y. Hua et al., “ROR functions as a ceRNA to regulate Nanog expression by sponging miR-145 and predicts poor prognosis in pancreatic cancer,” *Oncotarget*, vol. 7, pp. 1608–1618, 2016.
- [45] Y. Zhi, M. Abudoureyimu, H. Zhou et al., “FOXO1-mediated LINC-ROR regulates the proliferation and sensitivity to sorafenib in hepatocellular carcinoma,” *Molecular Therapy - Nucleic Acids*, vol. 16, pp. 576–588, 2019.
- [46] X. He, J. J. Yu, L. Xiong et al., “Exosomes derived from liver cancer cells reprogram biological behaviors of LO2 cells by transferring Linc-ROR,” *Gene*, vol. 719, p. 144044, 2019.