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ORIGINAL RESEARCH

Diagnostic and Prognostic Values of HIF1A-AS2 and LINC00511 in Gastric Cancer with *Helicobacter pylori* Infection

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Purpose: Gastric cancer (GC) is the fifth most common type of cancer worldwide. Despite the growing interest in Helicobacter pylori (*H. pylori*) infection, targeted diagnostic and prognostic markers are yet to be fully developed. The purpose of this study is to explore potential biomarkers for the diagnosis and prognosis of GC associated with *H. pylori* infection.

Patients and Methods: The differentially expressed long non-coding RNAs (lncRNAs) in *H. pylori*-related GC were acquired from the Gene Expression Omnibus (GEO) and a literature review. Clinicopathological features, tumors, and adjacent non-tumor tissues were collected from 80 patients with GC. Expression of hypoxia-inducible factor 1alpha antisense RNA 2 (HIF1A-AS2) and long intergenic non-protein coding RNA 511 (LINC00511) was determined by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). The relationship between HIF1A-AS2 or LINC00511 expression and the clinicopathological features of GC patients was evaluated. Receiver operating characteristic (ROC) curves were created to assess the diagnostic values of HIF1A-AS2 or LINC00511. The Kaplan-Meier method was employed to evaluate the prognostic value of HIF1A-AS2 or LINC00511.

Results: HIF1A-AS2 and LINC00511 were identified as key lncRNAs in *H. pylori*-related GC. High expression of HIF1A-AS2 and LINC00511 was associated with large tumor size, advanced tumor node metastasis (TNM) stage, high levels of serum tumor biomarkers, and the incidence of *H. pylori* infection and lymph node metastasis. HIF1A-AS2 or LINC00511 indicated high diagnostic values for GC, and their combination showed higher sensitivity and specificity. Increased expression of HIF1A-AS2 and LINC00511 is related to poor 5-year overall survival rates, indicating that HIF1A-AS2 and LINC00511 are prognostic factors for GC.

Conclusion: HIF1A-AS2 and LINC00511 are related to *H. pylori*-related GC and serve as potential biomarkers for the diagnosis and prognosis of GC.

Keywords: hypoxia-inducible factor 1alpha antisense RNA 2, long intergenic non-protein coding RNA 511, gastric cancer, *Helicobacter pylori*, prognostic values

Introduction

Gastric cancer (GC) ranks as the fifth most common malignancy globally, with approximately 660,000 new cases reported in 2020.[1] Despite advances in treatment strategies—including surgery, radiotherapy, chemotherapy, immunotherapy, and complementary traditional Chinese medicine—GC remains the third leading cause of cancer-related mortality, accounting for nearly 800,000 deaths (7.7% of all cancer fatalities) in the same year.[2–6] This poor prognosis is largely due to the disease's insidious onset and late diagnosis.

A major risk factor for GC is infection with *Helicobacter pylori* (*H. pylori*), a Gram-negative bacterium classified as a Group 1 carcinogen by the WHO.[7] Chronic *H. pylori* infection can trigger gastritis and gastric atrophy, ultimately progressing to GC, and is implicated in 65–80% of non-cardia gastric cancer cases.[1,8] Although serum biomarkers such as CEA, CA19-9, and CA72-4 are routinely used to aid diagnosis and prognosis, they lack specificity for *H. pylori*-associated GC[9–11] Thus, there is a pressing need to identify more reliable diagnostic and prognostic tools tailored to this GC subtype.

Long non-coding RNAs (lncRNAs), defined as transcripts longer than 200 nucleotides with limited protein-coding potential, have emerged as key regulators of tumor invasion, metastasis, and patient outcomes in GC.[12–14] Notably,

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LINC00511 promotes GC progression via the miR-29c-3p/TRIP13 and AKT/mTOR pathways,[15,16] while HIF1A-AS2 enhances proliferation and metastasis through the miR-429/PD-L1 axis.[17] Although several lncRNAs—such as FOXD2-AS1, LINC00152, and H19—have shown promise as biomarkers, particularly in *H. pylori*-positive GC, their clinical utility remains incompletely explored.[18,19] A systematic understanding of lncRNA involvement in *H. pylori*-driven GC is still lacking.

To address this gap, we integrated transcriptomic data from *H. pylori*-infection-related datasets and GC gene expression profiles from the GEO repository (GSE224056).[20] Through this approach, we identified HIF1A-AS2 and LINC00511 as candidate lncRNAs and further validated their diagnostic and prognostic significance in *H. pylori*-associated GC. This study aims to establish a foundation for lncRNA-based stratification tools to guide individualized treatment strategies.

Materials and Methods

Data Resource and Processing

We acquired RNA-Seq expression data (from five GC patients) from GSE224056 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE224056) in the GEO database. Differentially expressed genes in GC were identified using GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/) with FDR ≤0.05, and fold change ≥2. To identify potential *H. pylori* infection-related differentially expressed lncRNAs, the intersection between differentially expressed genes from GSE224056 and *H. pylori* infection-related differentially expressed lncRNAs reported in a previous study was analyzed in Venny 2.1.0 (http://www.liuxiaoyuyuan.cn/).[20]

Patients and Tissue Samples

A total of 80 pairs of tumor and paracancerous tissues from patients with GC were retrospectively collected from Dongying People's Hospital from January 2022 to December 2024. Two pathologists verified the clinicopathological features and GC diagnoses of the patients. All subjects completed informed consent forms, and their medical records, including sex, age, tumor size, pathological type, *H. pylori* infection, tumor node metastasis (TNM) stage, lymph node metastasis, and serum concentrations of GC biomarkers, were recorded. Patients with GC who had received radiation therapy or chemotherapy were excluded. After radical resection, GC tissues and nearby normal tissues (at least 2 cm from the primary cancer site) were removed and promptly frozen at −80°C until total RNA extraction. Patients were followed up for 60 months after surgery from June 7th, 2019, unless death occurred. This study was approved by the Ethics Committee of Dongying People's Hospital (Approval No: 2024–082).

Quantitative Reverse Transcriptase Polymerase Chain Reaction (qRT-PCR)

Total RNA from the tumor and adjacent tissues was extracted with the TRIzol™ Plus RNA Purification Kit (12183555, ThermoFisher, Waltham, MA, USA), and RNA quality was identified by the A260/280 ratio using an ultraviolet spectrophotometer. The SuperScript™ VILO™ complementary DNA (cDNA) Synthesis Kit (11754050, ThermoFisher) was used to generate cDNA). Afterwards, the cDNA and primers were used for qRT-PCR with the help of Fast SYBR™ Green Master Mix (4385612, Thermo Fisher) in a QuantStudio™ 7 Pro real-time PCR instrument (A43165, Thermo Fisher), with the following conditions: 95°C for 20s, and 40 cycles at 95°C for 3s and 60°C for 30s. Finally, all obtained data were processed according to the $2^{-\Delta\Delta CT}$ method with GAPDH as the internal control. The primer sequences used are listed in Table 1.[21]

Detection of CEA, CA 19-9, and CA 72-4

Assay kits for CEA (V517440, Snibe, Shenzhen, China), CA 19–9 (V517453, Snibe), and CA 72–4 (V253864, Mindray, Shenzhen, China) were purchased. The concentrations of the GC biomarkers CEA, CA 19–9, and CA 72–4 in the serum of patients were detected using the electrochemiluminescence method on a Centro XS3 LB 960 Microplate Luminometer (Stuttgart, Germany).

Table 1 Sequences of Primers Used in This Study

Name	Sequence
HIF1A-AS2_F	GTGGCTACCACGTACTGCTG
HIF1A-AS2_R	ACTGCAGGGTGAAGAATTACTCA
LINC00511_F	AAGGAGACAGGTGATGTTAC
LINC00511_R	AGTGAGGTATATGTGGGTTC
GAPDH_F	CATGTGGGCCATGAGGTCCACCAC
GAPDH_R	GGGAAGCTCACTGGCATGGCCTTCC

Abbreviations: HIF1A-AS2, hypoxia-inducible factor 1 alpha antisense RNA 2; LINC00511, long intergenic non-protein coding RNA 511.

Statistical Analyses

Data analysis was performed using GraphPad Prism 8.4 (GraphPad, Inc., La Jolla, California, USA) and SPSS Statistics 27.0 software (IBM Corp., Armonk, NY, USA). Pearson's $\chi 2$ test or two-sided Fisher's exact test was used to evaluate associations between discrete variables. An independent *t*-test was used to examine expression variations between the two groups. Pearson's correlation coefficient was used to analyze the correlation between the two continuous variables. Utilizing a receiver operating characteristic (ROC) curve, the diagnostic value (specificity and sensitivity) was assessed using a receiver operating characteristic curve. The time between a patient's date of curative surgery and their death or their final contact date if they were still alive was referred to as overall survival (OS). The Kaplan-Meier method was used to study the probability of survival. Additionally, in multivariate studies, the prognostic value of different covariates was determined using the Cox proportional hazards model. Statistical significance was set at $P < 0.05$.

Results

Identification of Differentially Expressed lncRNAs in H. pylori Infection-Related GC Cancer

A total of 24,253 differentially expressed genes were identified in the GSE224056 dataset (Figure 1A). These genes were intersected with 73 differentially expressed lncRNAs in *H. pylori*-infected GC cell lines, resulting in 24 candidate lncRNAs (Figure 1B). Therein, we found that HIF1A-AS2 and LINC00511 who were in top 50 *H. pylori* infection-associated differentially expressed lncRNAs have been experimentally verified to be highly expressed in GC by literature screening. Subsequently, we extracted the expression profiles of HIF1A-AS2 and LINC00511 from the GSE224056 dataset. As shown in Figure 1C, HIF1A-AS2 was highly expressed in tumor tissues compared to that in paracancerous tissues (para-tissue). In addition, upregulation of LINC00511 was observed in tumor tissues relative to paracancerous tissues (Figure 1D). In short, HIF1A-AS2 and LINC00511 were abnormally highly expressed in GC tumor tissues.

Validation and Clinical Values of HIF1A-AS2 and LINC00511

To verify the high expression levels of HIF1A-AS2 and LINC00511, we examined their levels in 80 pairs of tumor and adjacent non-tumor tissues from patients with GC by qRT-PCR. As shown in Figure 2A and B, we observed markedly high expressions of HIF1A-AS2 and LINC00511 in tumor tissues ($P < 0.001$). Further, we divided patients into two groups (Low and High) with median values as cut-off values to analyze the correlation between clinicopathological factors and HIF1A-AS2 or LINC00511 expression. We found that high levels of HIF1A-AS2 or LINC00511 were related to tumor size, *H. pylori* infection, TNM stage, and lymph node metastasis (Table 2). The bar graphs affirmed that HIF1A-AS2 and LINC00511 are highly expressed in patients with tumor size >5 cm, H. pylori infection, stage III and IV, and lymph node metastasis (Figure 2C–J, $P < 0.01$). These findings indicate that high expression levels of HIF1A-AS2 and LINC00511 are involved in the clinicopathological factors of GC patients.

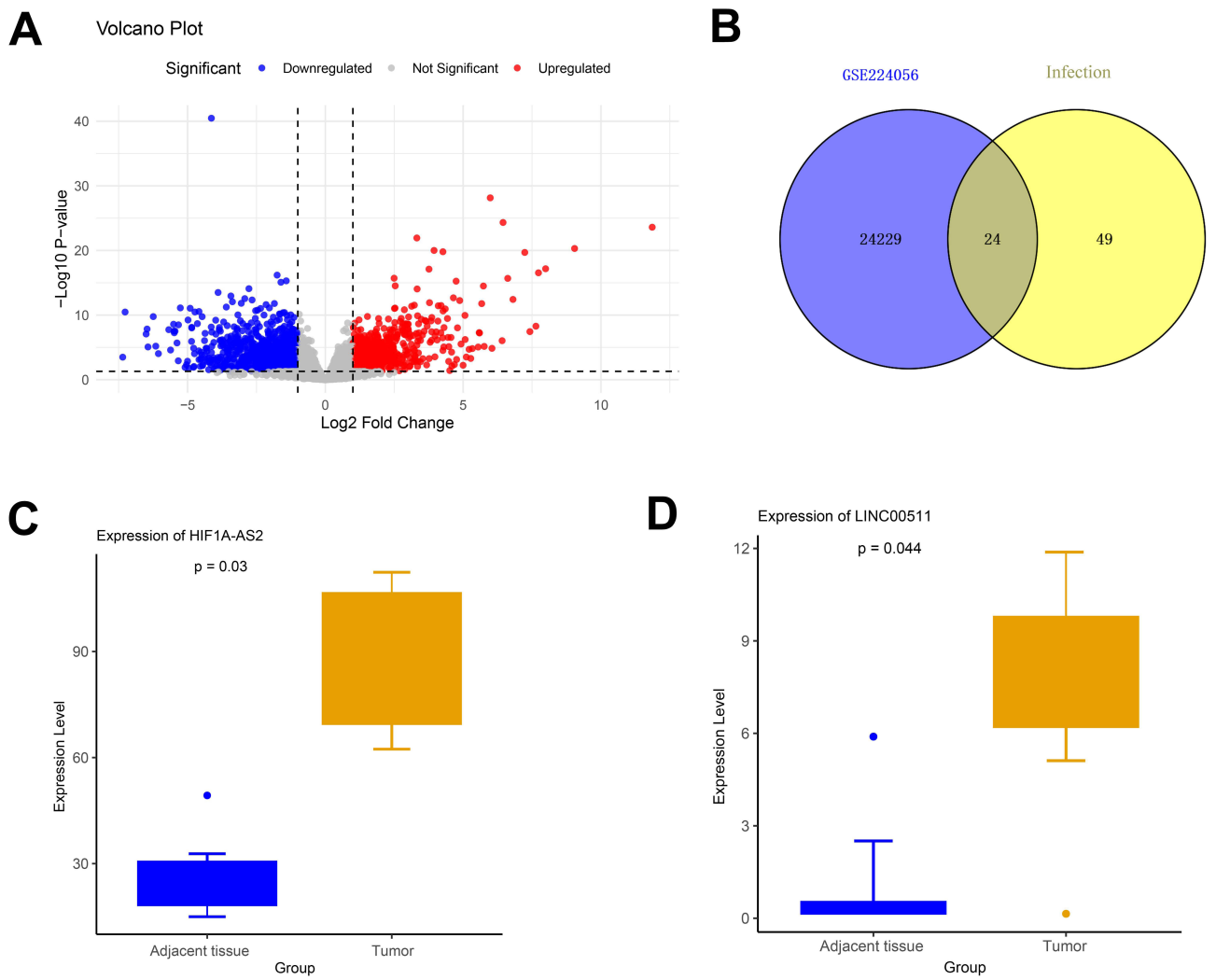

Figure 1 Identification of differentially expressed lncRNAs in *H. pylori* infection-related GC. (**A**) The volcano plot of GSE224056 (n=5). Blue = down; red = up; grey = no difference. (**B**) The Venn diagram of differentially expressed genes from GSE224056 and differentially expressed lncRNAs related to *H. pylori* infection in GC cell lines. (**C**) HIF1A-AS2 expression in GSE224056 dataset. (**D**) LINC00511 expression in GSE224056 dataset. HIF1A-AS2, hypoxia-inducible factor 1alpha antisense RNA 2; LINC00511, long intergenic non-protein coding RNA 511.

Correlations Between HIF1A-AS2 and LINC00511 with Concentrations of Serum CEA, CA 19-9, and CA 72-4

Moreover, the Pearson correlation coefficient showed that HIF1A-AS2 expression positive correlated with the levels of the GC biomarkers CEA (Figure 3A, $P < 0.001$, r = 0.705), CA 19–9 (Figure 3B, $P < 0.001$, r = 0.637), and CA 72–4 (Figure 3C, $P < 0.001$, r = 0.710). In addition, positive correlations between LINC00511 expression and CEA (Figure 3D, $P < 0.001$, r = 0.600), CA 19–9 (Figure 3E, $P < 0.001$, r = 0.705), and CA 72–4 (Figure 3F, $P < 0.001$, r = 0.632) levels were found in GC patients. These results demonstrated that HIF1A-AS2 and LINC00511 expression is positively correlated with the levels of GC serum biomarkers. Also, HIF1A-AS2 expression was positive correlated with LINC00511 expression (Figure 3G, $P < 0.001$, r = 0.590).

Diagnose Values of HIF1A-AS2 and LINC00511

The ROC curve was generated to assess the prognostic significance of HIF1A-AS2 and LINC00511 in GC patients. For HIF1A-AS2, the area under the curve (AUC) was 0.759. The specificity and sensitivity for GC were 75% and 70%, respectively (Figure 4A and Table 3, $P < 0.001$). For LINC00511, the AUC was 0.816, with a specificity of 72.5% and

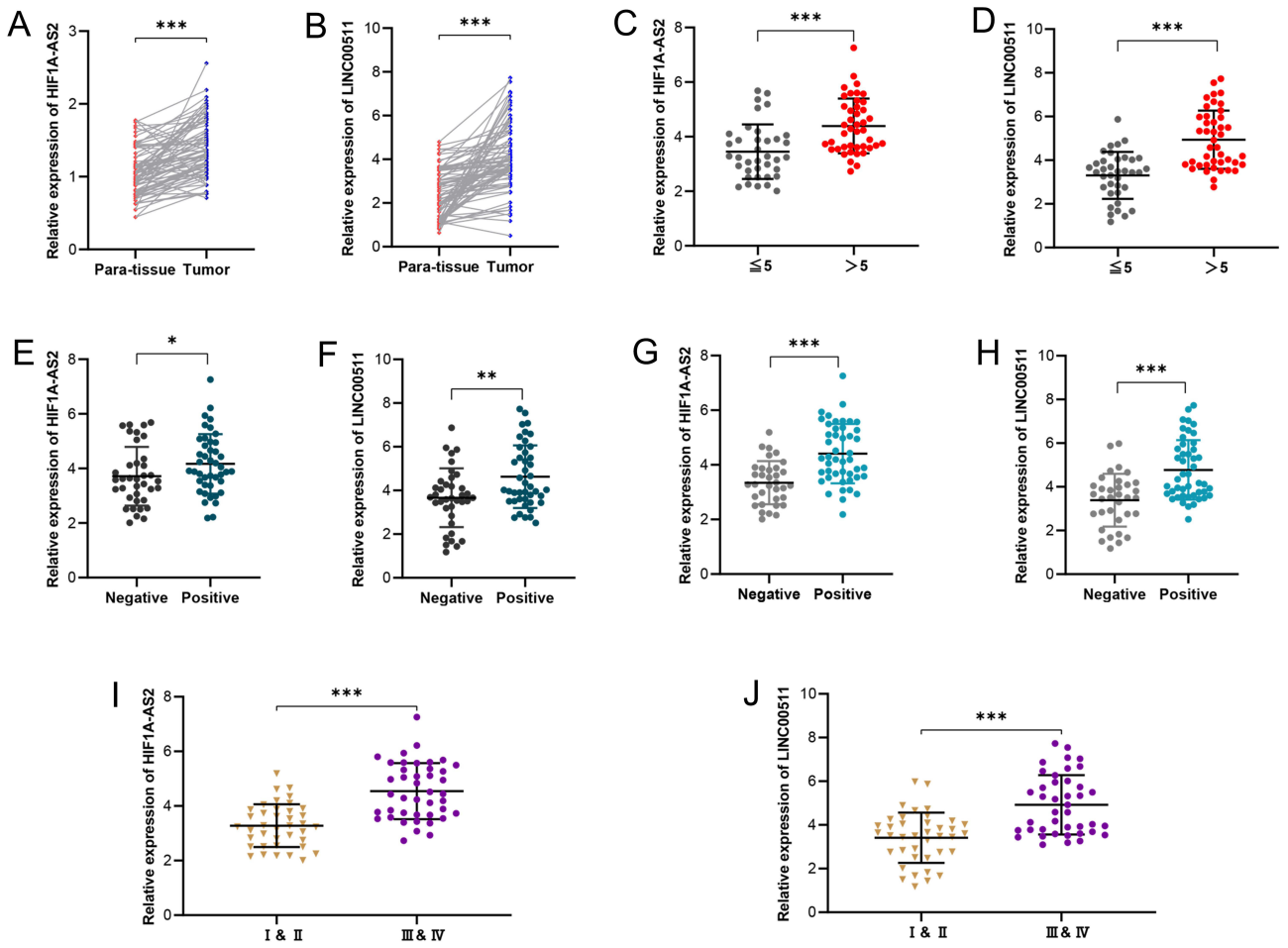

Figure 2 Validation and clinical values of HIF1A-AS2 and LINC00511. (**A** and **B**) Relative expression levels of HIF1A-AS2 (**A**) and LINC00511 (**B**) in tumor and adjacent non-tumor tissues from GC patients (n=80) were detected by qRT-PCR. (**C** and **D**) The differential expressions of HIF1A-AS2 (**C**) and LINC00511 (**D**) in two groups classified by tumor size (≤5 cm vs >5 cm). (**E** and **F**) The differential expressions of HIF1A-AS2 (**E**) and LINC00511 (**F**) in two groups classified by *H. pylori* infection (negative vs positive). (**G** and **H**) The differential expressions of HIF1A-AS2 (**G**) and LINC00511 (**H**) in two groups classified by lymph node metastasis (negative vs positive). (**I** and **J**) The differential expressions of HIF1A-AS2 (**I**) and LINC00511 (**J**) in different TNM stages.

Note: *P < 0.05, **P < 0.01, ***P < 0.001.

Abbreviations: qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; *H. pylori, Helicobacter pylori*; TNM, tumor node metastasis.

sensitivity of 80% (Figure 4B and Table 3, $P < 0.001$). We then predicted the combined diagnostic value of HIF1A-AS2 and LINC00511. As shown in Figure 4C and Table 3, the AUC was 0.839 ($P < 0.001$), and the specificity and sensitivity for GC were 71.25% and 81.25%, respectively. Altogether, the high expression of HIF1A-AS2 and LINC00511 showed good diagnostic value for GC, and the combined diagnosis of HIF1A-AS2 and LINC00511 had a superior effect.

Table 2 Association of HIF1A-AS2 and LINC00511 with Clinicopathologic Characteristics of GC Patients

Clinicopathological Features	HIF1A-AS2 Expression		*P*	LINC00511 Expression		*P*
	Low (n=40)	High (n=40)		Low (n=40)	High (n=40)	
Sex			0.485			0.485
Male	24	27		27	24	
Female	16	13		13	16	
Age (year)			0.469			0.228
≤60	14	11		15	10	
>60	26	29		25	30	

(*Continued*)

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Table 2 (Continued).

Clinicopathological Features	HIF1A-AS2 Expression		*P*	LINC00511 Expression		*P*
	Low (n=40)	High (n=40)		Low (n=40)	High (n=40)	
Tumor size (cm)			0.044*			<0.001*
≤5	23	14		26	11	
>5	17	26		14	29	
Pathological type			0.494			1.000
Adenocarcinoma	38	40		39	39	
Signet Ring Cell Carcinoma	2	0		1	1	
H. pylori infection			0.014*			0.044*
Positive	16	27		27	26	
Negative	24	13		23	14	
TNM stage			<0.001*			0.004*
I and II	27	12		26	13	
III and IV	13	28		14	27	
Lymph node metastasis			0.002*			0.007*
Positive	16	30		17	29	
Negative	24	10		23	11	

Note: *Represents significant.
Abbreviations: GC, gastric cancer; TNM, tumor node metastasis.

Prognostic Values of HIF1A-AS2 and LINC00511

Furthermore, according to the median expression of HIF1A-AS2/LINC00511, patients were divided into two groups, high expression and low expression, to evaluate the prognostic value of HIF1A-AS2 and LINC00511 alone or in combination. The survival curves in Figure 5A and B showed that increased expressions of HIF1A-AS2 and LINC00511 was associated with poor 5-year OS ($P < 0.05$). Similarly, patients with high HIF1A-AS2/low LINC00511 (Figure 5C) showed significantly reduced survival ($P < 0.05$). The high LINC00511/low HIF1A-AS2

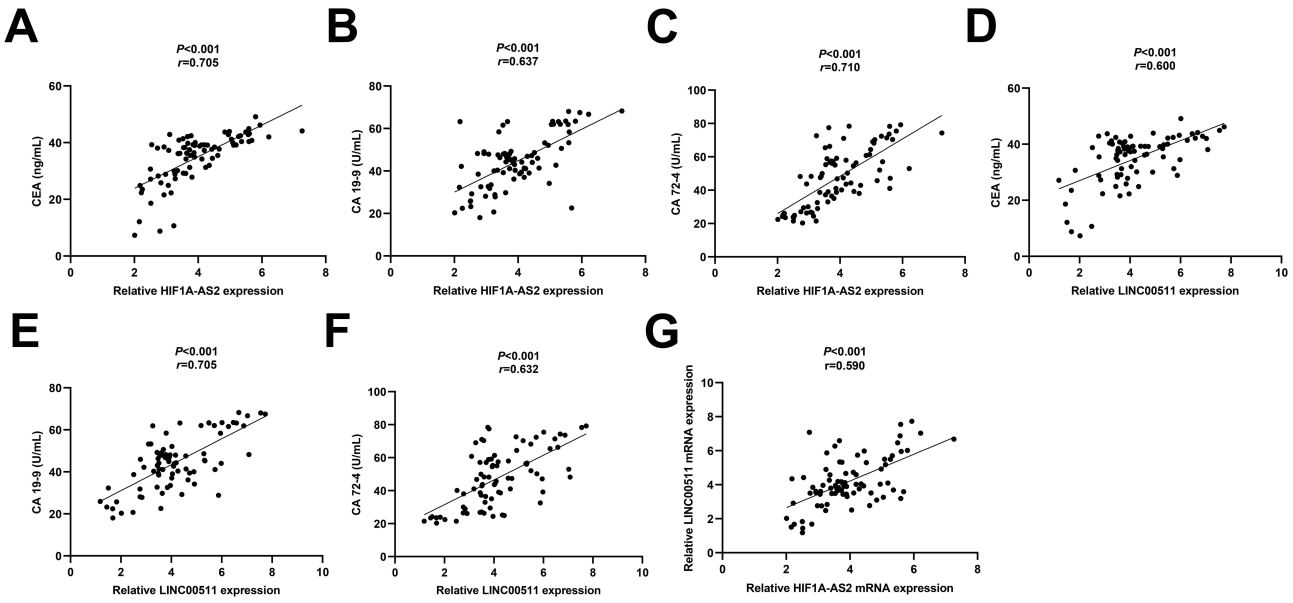

Figure 3 Correlation of HIF1A-AS2 and LINC00511 expressions with levels of serum tumor markers. (**A**–**C**) Correlations of HIF1A-AS2 expression with levels of CEA (**A**), CA 19–9 (**B**), and CA 72–4 (**C**). (**D**–**F**) Correlations of LINC00511 expression with levels of CEA (**D**), CA 19–9 (**E**), and CA 72–4 (**F**). (**G**) The correlation of HIF1A-AS2 expression with LINC00511 expression.
Abbreviations: CEA, carcinoembryonic antigen; CA 19–9/72-4, carbohydrate antigen 19–9/72-4.

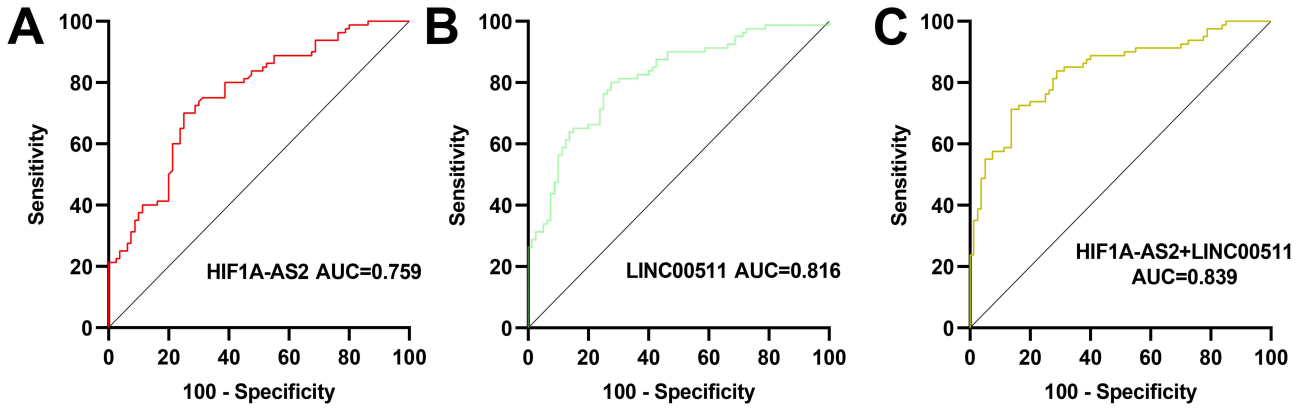

Figure 4 Diagnose values of HIF1A-AS2 and LINC00511. (**A**–**C**) ROC curves of HIF1A-AS2 (**A**), LINC00511 (**B**) and HIF1A-AS2 combined with LINC00511 (**C**).
Abbreviations: ROC, receiver operating characteristic.

subgroup (Figure 5D) exhibited a moderately elevated risk of mortality ($P < 0.05$). In contrast, the low HIF1A-AS2/low LINC00511 group (Figure 5E) and high HIF1A-AS2/high LINC00511 expression group (Figure 5F) were not associated with the worst survival. Univariate and multivariate Cox regression analyses were performed to explore the prognostic values of HIF1A-AS2 and LINC00511. As shown in Table 4, the expression of HIF1A-AS2 (P=0.014; HR=1.855; 95% CI=1.135–3.031) and LINC00511 (P=0.018; HR=1.808; 95% CI=1.107–2.955) were significantly associated with OS of GC patients, and other clinicopathological factors including tumor size, TNM stage, and lymph node metastasis were also presented relevant with OS.

Discussion

Comparatively, lncRNAs are more tissue-specific and are increasingly used as leading-edge diagnostic and prognostic indicators. The earliest study on lncRNA expression in GC was published in 1997, in which heterozygosity for H19 was observed in 28 patients.[22] To date, lncRNA H19 overexpression has been shown to promote the carcinogenesis and metastasis of GC and is regarded as a potential diagnostic marker in GC.[23,24] In addition, a large number of lncRNAs have been reported to be involved in GC progression through a variety of pathways, such as epigenetic, chemoresistance, and metabolic reprogramming.[25–27] However, only a few studies have focused on lncRNAs in *H. pylori*-related GC. Our study identified two key lncRNAs, HIF1A-AS2 and LINC00511, and explored their diagnostic and prognostic value in *H. pylori*-associated GC.

HIF1A-AS2 serves as a specific negative regulator of hypoxia-inducible factor-1 alpha (HIF-1α).[19] Yang et al found that HIF1A-AS2 was highly expressed in GC tumor tissues from 50 patients and cell lines and suggested that the upregulation of HIF1A-AS2 is involved in poor 5-year survival.[17] Furthermore, HIF1A-AS2 was reported to promote the proliferation and metastasis of GC cells through miR-429/PD-L1.[17] A previous study indicated that overexpression of HIF1A-AS2 was correlated with various clinical indicators, including TNM classification, tumor invasiveness, lymphatic spread, and adverse prognosis.[28] Chen et al reported that the AUC of the ROC curve for HIF1A-AS2 was as high as 0.673.[28] Similarly, we also suggest that HIF1A-AS2 expression is related to clinicopathological characteristics and has great potential as a diagnostic biomarker of GC.

Table 3 AUC Results of ROC Curve Analysis by HIF1A-AS2 and LINC00511 in GC Patients

Group	Index	AUC (95% CI)	*P*	Sensitivity (%)	Specificity (%)	Youden Index
Tumor vs adjacent	HIF1A-AS2	0.759 (0.685 to 0.832)	<0.001*	70.00	75.00	0.450
	LINC00511	0.816 (0.751 to 0.882)	<0.001*	80.00	72.50	0.525
	Combine	0.839 (0.777 to 0.900)	<0.001*	81.25	71.25	0.575

Note: *Represents significant.
Abbreviations: AUC, area under the curve; CI, confidence interval.

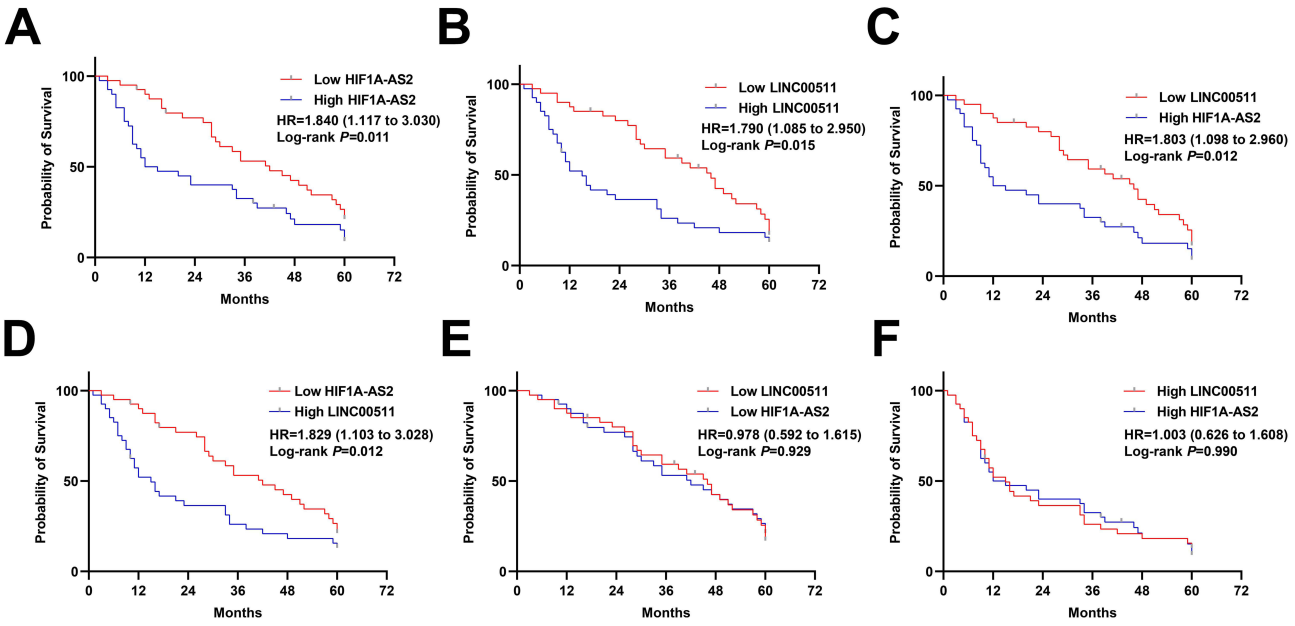

Figure 5 Prognostic values of HIF1A-AS2 and LINC00511. (**A**) Kaplan-Meier estimates of OS in 80 GC samples based on two groups classified using the median expression of HIF1A-AS2. (**B**) Kaplan-Meier estimates of OS in 80 GC samples based on two groups classified using the median expression of LINC00511. (**C**–**F**) Kaplan-Meier estimates of high HIF1A-AS2/low LINC00511 subgroup (**C**), high LINC00511/low HIF1A-AS2 subgroup (**D**), low HIF1A-AS2/low LINC00511 subgroup (**E**) and high HIF1A-AS2/high LINC00511 subgroup (**F**).
Abbreviations: OS, overall survival.

In addition, high LINC00511 expression has been observed in GC tumor tissues and cells, which leads to GC progression. For instance, Cui et al demonstrated that LINC00511 expression in tumor tissues was higher than that in adjacent tissues from 50 GC patients, and LINC00511 active signal transducer and activator of transcription 3 (STAT3) pathways expedites GC cell promotion and migration.[29] Wang et al revealed that LINC00511 mediates PTEN promoter methylation to enhance the proliferation, migration, and stemness of GC cells by activating the AKT/mTOR pathway.[30] Importantly, the correlation between LINC00511 expression and the clinical features of patients with GC has attracted attention. In a previous study enrolling 25 patients with GC, increased LINC00511 expression was reported to be related to larger tumor size (> 5 cm) and advanced TNM stage.[31] We observed that some larger tumors (>5 cm) showed low HIF1A-AS2 and LINC00511 expression. This may be due to tumor heterogeneity or alternative pathways making these

Table 4 Univariate and Multivariate Cox Proportional Hazard Analysis of Prognosis Factor in GC Patients

Variables	Univariate Analysis		*P*	Multivariate Analysis		*P*
	HR	95% CI		HR	95% CI	
Sex	0.844	0.501–1.422	0.525			
Age (year)	1.232	0.726–2.090	0.439			
Tumor size (cm)	1.658	1.012–2.716	0.045*	0.828	0.432–1.585	0.569
Pathological type	0.322	0.077–1.341	0.120			
H. pylori infection	1.391	0.850–2.276	0.189			
TNM stage	3.244	1.931–5.449	<0.001*	1.631	0.553–4.813	0.376
Lymph node metastasis	3.387	1.968–5.829	<0.001*	2.100	0.7772–5.713	0.146
HIF1A-AS2	1.855	1.135–3.031	0.014*	1.199	0.699–2.055	0.510
LINC00511	1.808	1.107–2.955	0.018*	1.385	0.803–2.389	0.241

Note: *Represents significant.
Abbreviation: HR, hazard ratio.

lncRNAs less critical in advanced stages. Here, we further confirmed that high LINC00511 expression has a strong correlation with clinicopathological characteristics including tumor size, TNM stage, H. pylori infection, lymph node metastasis, and serum GC biomarkers, and suggested that LINC00511 has a huge diagnostic value in GC. In addition, our study also suggested the diagnostic value of HIF1A-AS2 and LINC00511 in *H. pylori*-related GC. The PI3K/AKT and JAK/STAT pathways were activated in *H. pylori*-induced GC, which may explain the link between HIF1A-AS2 and LINC00511 with *H. pylori*-related GC.[32] Unexpectedly, elevated lncRNA levels also occurred in some H. pylori-negative or node-negative samples. This could stem from prior undetected H. pylori exposure or other non-H. pylori drivers such as EBV or metabolic factors.

There has been little clinical research on the role of LINC00511 in GC. Only Huang et al revealed that the increase in LINC00511 expression in tumor tissues is associated with poor OS in patients with GC using the Kaplan-Meier method.[33] Our study suggests a correlation between high LINC00511 expression and poor prognosis in GC patients in 5 years. The prognostic value of LINC00511 has also been identified in other cancers. A meta-analysis involving 1024 cancer patients revealed that patients with malignant tumors may have lower OS and disease-free survival (DFS) if their LINC00511 expression levels are elevated.[34] Specifically, high levels of LINC00511 are associated with worse OS in multi-system cancers, such as breast cancer, renal cell cancer, glioma, hepatocellular carcinoma, pancreatic ductal adenocarcinoma, non-small-cell lung cancer, ovarian cancer, and cervical cancer osteosarcoma.[34] In addition, HIF1A-AS2 has been regarded as a novel prognostic biomarker for triple-negative breast cancer.[35] Guan et al reported that HIF1A-AS2 is a potential prognostic factor in human papillomavirus-related cervical cancer.[36] In lung adenocarcinoma specimens, HIF1A-AS2 levels were elevated, which is indicative of worse OS and DFS.[37] These findings suggest that HIF1A-AS2 and LINC00511 are associated with poor prognosis in patients with cancer, suggesting that HIF1A-AS2 and LINC00511 are prognostic markers in multiple cancers.

This study innovatively identified HIF1A-AS2 and LINC00511 as key lncRNAs significantly associated with *H. pylori*-infected GC. Their elevated expression correlates strongly with aggressive clinicopathological features and serves as a powerful diagnostic and prognostic biomarker, highlighting their critical role in *H. pylori*-driven GC progression and offering new potential for precise patient stratification. However, despite the analytical exploration of the clinical correlation of HIF1A-AS2 and LINC00511, additional limitations must be acknowledged when interpreting the findings of the current study. First, we collected tumor tissues and adjacent tissues of GC patients for expression level detection but did not include normal individuals in this study. This is insufficient to fully clarify the clinical value of HIF1A-AS2 and LINC00511. Second, inadequate validation testing without animal models and GC cell lines may necessitate future refinement of the experimental design for more precise biological observations. Finally, elucidation of the molecular mechanisms regulating the effects of HIF1A-AS2 and LINC00511 on GC tumorigenesis and progression requires additional research.

Conclusion

In conclusion, this study revealed that high expression of HIF1A-AS2 and LINC00511 is associated with clinicopathological factors in gastric cancer patients. HIF1A-AS2 and LINC00511 showed high sensitivity and specificity in the diagnostic models for gastric cancer. Elevated expression of LINC00511 and HIF1A-AS2 has been linked to low 5-year overall survival rates. These findings provide compelling evidence that HIF1A-AS2 and LINC00511 are potential biomarkers for the diagnosis and prognosis of gastric cancer.

Abbreviations

GC, Gastric cancer; *H. pylori, Helicobacter pylori*; lncRNAs, long non-coding RNAs; GEO, Gene Expression Omnibus; HIF1A-AS2, hypoxia-inducible factor 1alpha antisense RNA 2; LINC00511, long intergenic non-protein coding RNA 511; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; ROC, Receiver operating characteristic; TNM, tumor node metastasis; WHO, World Health Organization; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; CA72-4, carbohydrate antibody 72-4; FOXD2-AS1, forkhead box D2 antisense RNA 1; cDNA, complementary DNA; OS, overall survival; AUC, area under the curve; HIF-1α, hypoxia-inducible factor-1 alpha; STAT3, signal transducer and activator of transcription 3; DFS, disease-free survival.

Data Sharing Statement

All the results are presented in the article. Further inquiries can be directed to the corresponding authors.

Ethics Statement

The research protocol was approved by the Ethics Committee of Dongying People's Hospital (No. 2024-082). All experiments and procedures were performed according to the Declaration of Helsinki (as revised in 2013).

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Disclosure

The authors report no conflicts of interest in this work.

References

1. 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(3):209–249. doi:10.3322/caac.21660
2. Kranenbarg EK, van de Velde CJ. Surgical treatment of gastric cancer. *Ann. Chir. Gynaecol*. 2000;89(3):199–206.
3. Nie SF, Wang CY, Li L, Yang C, Zhu ZM, Fei JD. Tumor recurrence and survival prognosis in patients with advanced gastric cancer after radical resection with radiotherapy and chemotherapy. *World J Gastrointest Surg*. 2024;16(6):1660–1669. doi:10.4240/wjgs.v16.i6.1660
4. Meade A, Santero M, Savall-Esteve O, et al. Immunotherapy or targeted therapy versus best supportive care for advanced gastric cancer: a systematic review and meta-analysis of randomized trials. *J Gastrointest Cancer*. 2025;56(1):75. doi:10.1007/s12029-024-01155-y
5. Gao S, Wang W, Li J, Wang Y, Shan Y, Tan H. Unveiling polysaccharides of Houttuynia cordata Thunb.: extraction, purification, structure, bioactivities, and structure-activity relationships. *Phytomedicine*. 2025;138:156436. doi:10.1016/j.phymed.2025.156436
6. Gao S, Li J, Wang W, Wang Y, Shan Y, Tan H. Rabdosia rubescens (Hemsl.) H. Hara: a potent anti-tumor herbal remedy - Botany, phytochemistry, and clinical applications and insights. *J Ethnopharmacol*. 2025;340:119200. doi:10.1016/j.jep.2024.119200
7. Schistosomes, liver flukes and Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum*. 1994;61:1–241.
8. Businello G, Angerilli V, Parente P, et al. Molecular Landscapes of Gastric Pre-Neoplastic and Pre-Invasive Lesions. *Int J Mol Sci*. 2021;22 (18):9950. doi:10.3390/ijms22189950
9. Hu Y, Wang JL, Tao HT, et al. Expression and significance of TSGF, CEA and AFP in patients before and after radical surgery for colon cancer. *Asian Pac J Cancer Prev*. 2013;14(6):3877–3880. doi:10.7314/APJCP.2013.14.6.3877
10. He B, Zhang HQ, Xiong SP, Lu S, Wan YY, Song RF. Changing patterns of serum CEA and CA199 for evaluating the response to first-line chemotherapy in patients with advanced gastric adenocarcinoma. *Asian Pac J Cancer Prev*. 2015;16(8):3111–3116. doi:10.7314/APJCP.2015.16.8.3111
11. Yu J, Zheng W. An alternative method for screening gastric cancer based on serum levels of CEA, CA19-9, and CA72-4. *J Gastrointest Cancer*. 2018;49(1):57–62. doi:10.1007/s12029-016-9912-7
12. Huarte M. The emerging role of lncRNAs in cancer. *Nat Med*. 2015;21(11):1253–1261. doi:10.1038/nm.3981
13. Mi Y, Li Y, He Z, Chen D, Hong Q, You J. Upregulation of Linc-ROR promotes the proliferation, migration, and invasion of gastric cancer cells through miR-212-3p/FGF7 Axis. *Cancer Manag Res*. 2021;13:899–912. doi:10.2147/CMAR.S287775
14. Alsadat Mahmoudian R, Lotfi Gharaie M, Abbaszadegan R, Forghanifard MM, Abbaszadegan MR. Interaction between LINC-ROR and stemness state in gastric cancer cells with helicobacter pylori infection. *Iran Biomed J*. 2021;25(3):157–168. doi:10.52547/ibj.25.3.157
15. Li Z, Chen Y, Zhao Y, Li Q. The methylation and expression of LINC00511, an important angiogenesis-related lncrna in stomach adenocarcinoma. *Int J Mol Sci*. 2025;26(5).
16. Wu Y, Guo X, Jin L, Huang G, Niu L, Zhao Y. Lnc-LINC00511 promotes gastric cancer progression by regulating MiR-29c-3p/TRIP13 axis through AKT/mTOR pathway. *Int J Biol Macromol*. 2024;281(Pt 3):136455. doi:10.1016/j.ijbiomac.2024.136455
17. Mu L, Wang Y, Su H, et al. HIF1A-AS2 promotes the proliferation and metastasis of gastric cancer cells through mir-429/pd-l1 axis. *Dig Dis Sci*. 2021;66(12):4314–4325. doi:10.1007/s10620-020-06819-w
18. Rajabi A, Bastani S, Maydanchi M, et al. Moderate Prognostic Value of lncRNA FOXD2-AS1 in gastric cancer with helicobacter pylori infection. *J Gastrointest Cancer*. 2022;53(3):687–691. doi:10.1007/s12029-021-00686-y
19. Yang T, Zeng H, Chen W, et al. Helicobacter pylori infection, H19 and LINC00152 expression in serum and risk of gastric cancer in a Chinese population. *Cancer Epidemiol*. 2016;44:147–153. doi:10.1016/j.canep.2016.08.015
20. Li N, Ouyang Y, Chen S, et al. Integrative analysis of differential lncrna/mrna expression profiling in helicobacter pylori infection-associated gastric carcinogenesis. *Front Microbiol*. 2020;11:880. doi:10.3389/fmicb.2020.00880
21. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. *Methods*. 2001;25(4):402–408. doi:10.1006/meth.2001.1262
22. Wu MS, Wang HP, Lin CC, et al. Loss of imprinting and overexpression of IGF2 gene in gastric adenocarcinoma. *Cancer Lett*. 1997;120(1):9–14. doi:10.1016/S0304-3835(97)00279-6
23. Li H, Yu B, Li J, et al. Overexpression of lncRNA H19 enhances carcinogenesis and metastasis of gastric cancer. *Oncotarget*. 2014;5 (8):2318–2329. doi:10.18632/oncotarget.1913
24. Yörüker EE, Keskin M, Kulle CB, Holdenrieder S, Gezer U. Diagnostic and prognostic value of circulating lncRNA H19 in gastric cancer. *Biomed Rep*. 2018;9(2):181–186. doi:10.3892/br.2018.1116

25. Luo Y, Zheng S, Wu Q, et al. Long noncoding RNA (lncRNA) EIF3J-DT induces chemoresistance of gastric cancer via autophagy activation. *Autophagy*. 2021;17(12):4083–4101. doi:10.1080/15548627.2021.1901204
26. Fang L, Huang H, Lv J, et al. m5C-methylated lncRNA NR_033928 promotes gastric cancer proliferation by stabilizing GLS mRNA to promote glutamine metabolism reprogramming. *Cell Death Dis*. 2023;14(8):520. doi:10.1038/s41419-023-06049-8
27. Fang D, Ou X, Sun K, et al. m6A modification-mediated lncRNA TP53TG1 inhibits gastric cancer progression by regulating CIP2A stability. *Cancer Sci*. 2022;113(12):4135–4150. doi:10.1111/cas.15581
28. W-m C, M-d H, Kong R, et al. Antisense Long Noncoding RNA HIF1A-AS2 is upregulated in gastric cancer and associated with poor prognosis. *Dig Dis Sci*. 2015;60(6):1655–1662. doi:10.1007/s10620-015-3524-0
29. Cui N, Sun Q, Liu H, et al. Long non-coding RNA LINC00511 regulates the expression of microRNA-625-5p and activates signal transducers and activators of transcription 3 (STAT3) to accelerate the progression of gastric cancer. *Bioengineered*. 2021;12(1):2915–2927.
30. Wang Q, Mao X, Luo F, Wang J. LINC00511 promotes gastric cancer progression by regulating SOX4 and epigenetically repressing PTEN to activate PI3K/AKT pathway. *J Cell Mol Med*. 2021;25(19):9112–9127.
31. Wang D, Liu K, Chen E. LINC00511 promotes proliferation and invasion by sponging miR-515-5p in gastric cancer. *Cell Mol Biol Lett*. 2020;25:4. doi:10.1186/s11658-020-0201-x
32. Alipour M. Molecular mechanism of helicobacter pylori-induced gastric cancer. *J Gastrointest Cancer*. 2021;52(1):23–30. doi:10.1007/s12029-020-00518-5
33. Huang HG, Tang XL, Huang XS, Zhou L, Hao YG, Zheng YF. Long noncoding RNA LINC00511 promoted cell proliferation and invasion via regulating miR-124-3p/EZH2 pathway in gastric cancer. *Eur Rev Med Pharmacol Sci*. 2020;24(8):4232–4245. doi:10.26355/eurrev_202004_21003
34. Ding J, Cao J, Chen Z, He Z. The role of long intergenic noncoding RNA 00511 in malignant tumors: a meta-analysis, database validation and review. *Bioengineered*. 2020;11(1):812–823. doi:10.1080/21655979.2020.1795384
35. Wang Y, Zhang G, Han J. HIF1A-AS2 predicts poor prognosis and regulates cell migration and invasion in triple-negative breast cancer. *J Cell Biochem*. 2019;120(6):10513–10518. doi:10.1002/jcb.28337
36. Guan H-M, Li WQ, Liu J, Zhou J-Y. LncRNA HIF1A-AS2 modulated by HPV16 E6 regulates apoptosis of cervical cancer cells via P53/caspase9/caspase3 axis. *Cell. Signalling*. 2022;97:110390. doi:10.1016/j.cellsig.2022.110390
37. Si J, Ma Y, Lv C, Hong Y, Tan H, Yang Y. HIF1A-AS2 induces osimertinib resistance in lung adenocarcinoma patients by regulating the miR-146b-5p/IL-6/STAT3 axis. *Mol Ther Nucleic Acids*. 2021;26:613–624. doi:10.1016/j.omtn.2021.09.003