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Original Article

Prognostic value of hypoxia-responsive long non-coding RNAs in gastric cancer: a meta-analysis

Jun Zhang*, Shuai Guo*, Zhe Dong, Zhi-Chao Zheng, Yue Wang, Yan Zhao

*Department of Gastric Cancer, Liaoning Cancer Hospital and Institute (Cancer Hospital of China Medical University), Shenyang 110042, Liaoning Province, China. *Equal contributors.*

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Abstract: Background: Considerable evidence has shown that the hypoxic tumor microenvironment is closely associated with gastric cancer (GC) progression and prognosis. However, many of these studies included very few patients. Therefore, to improve the statistical relevance, this systematic review and meta-analysis was conducted to determine a scientific conclusion. This study examined the impact of hypoxia-responsive long non-coding RNAs (HRLs) on overall survival (OS) in gastric cancer. Methods: This study searched relevant published studies from Pubmed and Embase databases (up to December 2017). Standard meta-analysis methods were used to estimate the prognostic role of HRLs in patients with GC. Pooled hazard ratios (HRs), odds radio (OR) and their corresponding 95% confidence intervals (CIs) were calculated. Results: A total of 15 studies with 1,505 patients were identified and 5 long non-coding RNAs (lncRNAs (HOTAIR, H19, UCA1, GAPLINC, and MALAT1) were assessed in this meta-analysis. Elevated HOTAIR was predictive of poorer OS in GC (HR: 1.55; 95% CI: 1.21-1.88), as was high H19 and UCA1. Expression of GAPLINC and MALAT1 was not related to patient outcomes. Regarding clinicopathology, increased H19 was associated with positive lymph node metastasis (OR = 1.68, 95% CI: 1.02-2.76), deeper tumor invasion (OR = 3.53, 95% CI: 1.37-9.10), and advanced TNM stages (OR = 2.17, 95% CI: 1.33-3.56). Conclusion: Specific hypoxia-responsive lncRNAs may serve as novel prognostic markers in GC.

Keywords: LncRNA, gastric cancer, hypoxia, prognosis, meta-analysis, biomarker

Introduction

Despite the decline in global incidence of gastric cancer (GC) in recent years [1], this form of cancer is still the second most common and the second leading cause of cancer-related deaths in China [2]. Although treatment strategies have improved, the median overall survival (OS) of advanced GC is less than one year [3], with more than half of the patients experiencing recurrence within 5 years of surgery and adjuvant chemotherapy [1, 2]. As a result, it is vital to identify effective biomarkers that aid GC prognosis and therapy.

Considerable evidence has shown that the hypoxic tumor microenvironment is closely associated with cancer progression and metastasis [4, 5]. Hypoxia-induced factors (HIFs) HIF-1 and HIF-2 play a synergistic role in mediating the cellular response to low oxygen tensions [6]. Under hypoxic conditions, accumulated HIFs bind to the hypoxia response elements (HREs) of genes at their promoters and regulate their expression transcriptionally [7]. Overexpression oncogenes promote cellular proliferation, angiogenesis, invasion, and metastasis [8, 9]. Zhai W et al. [10] and Yang F et al. [11] showed that besides regulating the expression of protein-coding genes, HIFs were able to induce expression of long non-coding RNAs (lncRNA), which in turn regulated expression of downstream genes. The average length of lncRNAs is greater than 200 nucleotides and most lncRNAs lack evident protein coding potential [12, 13]. During the last two decades, the understanding of lncRNAs has evolved from transcriptional "noise" to close association with diverse biological processes. LncRNAs regulate gene expression at multiple levels, including epigenetic, transcriptional, post-transcriptional, and translational [14]. Two types of lncRNA-HIFs interactions have been observed: direct regulation of lncRNA expression by the local hypoxia or positive/negative regulation of HIF

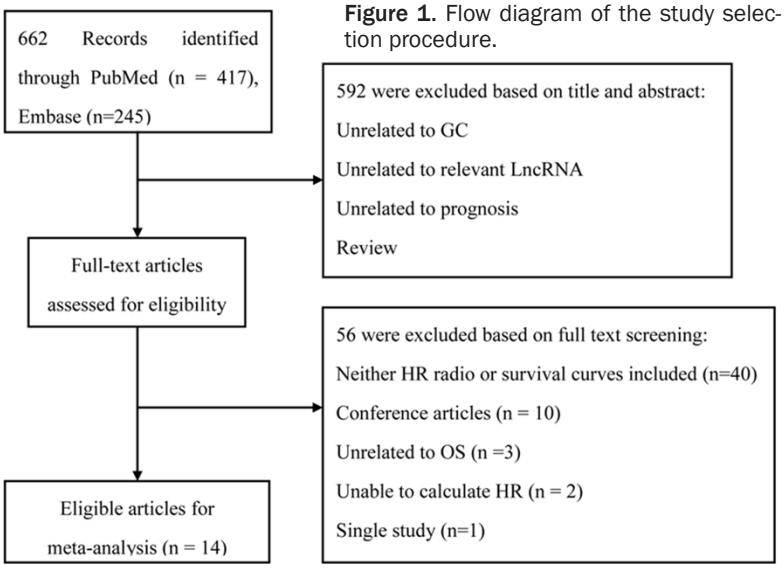

Figure 1. Flow diagram of the study selection procedure.

signaling by lncRNA. These two kinds of lncRNAs are known as hypoxia-responsive lncRNAs (HRLs) [15]. There are strong indications that HRLs may play an important role in regulating malignant phenotypes.

HRLs are involved in several biological functions, including epithelial-mesenchymal transition (EMT), reprogramming of stem cells, and regulation of exosomes in different cancers [16-18]. In addition, some studies have focused on the prognostic significance of HRLs in GC [19-21]. Several meta-analyses have mentioned sporadic HRLs in tumors [22-24]. However, no specific meta-analyses have been conducted assessing the prognostic value of HRLs in GC. Therefore, this systematic review was conducted to identify the correlation between HRLs expression and GC prognosis.

Materials and methods

Search strategy

A computerized search of Pubmed and Embase databases was conducted to identify relevant articles published up to December 2017. The search strategy included the following keywords: names of hypoxia-responsive lncRNAs (HOTAIR, H19, UCA1, NUTF2P3-001, EFNA3, HINCUT-1, GAPLINC, lincRNA-p21, aHIF, MALAT1, NEAT1, lncRNA-SARCC, and WT1-AS), "stomach neoplasm", "gastric cancer", "prognostic", and "prognosis". Additional studies were obtained by manually screening reference lists.

Eligibility criteria

Studies were considered eligible if they met following inclusion criteria: a) Focused on patients treated for GC; b) Measured lncRNA expression in human cancer tissues; and c) Analyzed the correlation between survival outcomes and lncRNA expression. Studies were excluded if they were: a) Review articles, case reports, or letters; b) Lacked sufficient data for calculation of HRs and 95% Cis; and c) Not in English.

Quality assessment

The quality of included studies was assessed according to the Newcastle-Ottawa Scale (NOS). NOS ranged from 0 to 9. Studies with NOS scores of more than 5 were considered as high quality. NOS scores of all studies included in this meta-analysis ranged from 5 to 9, with a mean value of 7.9.

Data extraction

Data were extracted independently by two investigators. Primary extracted data included first author's name, year of publication, country, number of cases, follow-up duration, lncRNAs, assessment methods of lncRNAs expression, cut-off values, clinicopathological parameters, and HRs for OS, 95% CIs, and *P* values. If HRs and 95% CIs could not be extracted from the original study directly, these values were calculated using available numerical or graphical data with the methods described by Parmar et al. [25] and Tierney et al. [26].

Statistical analysis

This study pooled HRs (95% CI) using Stata 12.1 software (StatCorp, College Station, TX, USA). Heterogeneity was assessed using the Cochran Q test and Higgins I^2 test. *P*-values less than 0.1 and I^2 values > 50% indicated significant heterogeneity among studies. A fixed effects model was applied in the absence of inter-study heterogeneity ($P > 0.1$), while a random effects model was used when heterogeneity was observed ($P < 0.1$). HR > 1 implies a worse survival for the group with elevated

Table 1. Main characteristics of enrolled studies

Study	lncRNA	N	Population	Assay	Cut-off value	Survival analysis	Analysis type	Quality score	Follow-up (months)
Xu 2013	HOTAIR	83	Chinese	qRT-PCR	N/A	OS	Kaplan-Meier curve	7	over 60
Hu 2014	GAPLINC	90	Chinese	ISH	median	OS	Kaplan-Meier curve	8	over 60
Li 2014	H19	74	Chinese	qRT-PCR	6-fold	OS	Kaplan-Meier curve	7	over 50
Liu 2014	HOTAIR	78	Chinese	qRT-PCR	median	OS	Kaplan-Meier curve	7	over 40
Okugawa 2014	HOTAIR	150	Japanese	qRT-PCR	0.239	OS	Multivariate	9	over 60
Okugawa 2014	MALAT1	150	Japanese	qRT-PCR	0.985	OS	Kaplan-Meier curve	9	over 60
Zhang 2014	H19	80	Chinese	qRT-PCR	mean	OS	Multivariate	8	over 60
Chen 2016	H19	128	Chinese	qRT-PCR	median	OS	Multivariate	8	median 36
Gao 2015	UCA1	20	Chinese	qRT-PCR	N/A	OS	Multivariate	5	N/A
Zhang 2015	HOTAIR	50	Chinese	qRT-PCR	median	OS	Kaplan-Meier curve	8	over 45
Zhao 2015	HOTAIR	168	Chinese	qRT-PCR	median	OS	Multivariate	9	over 60
Zheng 2015	UCA1	112	Chinese	qRT-PCR	median	OS	Kaplan-Meier curve	9	over 60
Li 2016	H19	361	Chinese	qRT-PCR	N/A	OS	Kaplan-Meier curve	6	over 50
Liu 2016	GAPLINC	33	Chinese	qRT-PCR	2.03	OS	Kaplan-Meier curve	6	over 60
Li 2017	MALAT1	78	Chinese	qRT-PCR	N/A	OS	Kaplan-Meier curve	5	over 60

N, number of patients; qRT-PCR, quantitative real time polymerase chain reaction; ISH, in situ hybridization; N/A, not available; OS, overall survival.

lncRNA expression, while HR < 1 implies a worse survival for the group with decreased lncRNA expression. Funnel plots with Egger's bias test were used to assess publication bias.

Results

Characteristics of included studies

As shown in **Figure 1**, the initial search returned 662 publications. After assessing the titles and abstracts, 592 articles were excluded. An additional 56 articles were excluded after reviewing the full text. Finally, 14 articles [19, 21, 27-38] with 1,505 GC patients and 5 different lncRNAs were evaluated. Detailed information and data are summarized (**Table 1**).

HOTAIR and GC prognosis

Five studies (n = 529) associated high tumoral expression of HOTAIR (HOX transcript antisense intergenic RNA) with poor OS in GC. Zhao et al. [27] only reported advanced gastric adenocarcinoma (III-IV stage). Okugawa et al. [30] and Zhao et al. [27] used multivariate analyses. The pooled HR of the five studies was 1.55 (95% CI: 1.21-1.88) (**Figure 2**). No significant inter-study heterogeneity was observed (P = 0.576, I^2 = 0%). There was no evidence of publication bias (Egger's test, P = 0.302) (**Figure 5A**).

H19 and GC prognosis

Four studies (n = 643) reported that upregulation of H19 (the imprinted oncofetal long non-coding RNA) was associated with OS in GC. All patients included in these studies had resectable tumors. Zhang et al. [19] and Li et al. [33] enrolled patients without perioperative therapy. A fixed-effects model revealed that elevated H19 expression was predictive of poorer OS (combined HR: 1.15; 95% CI: 1.01-1.29) (**Figure 3**). There was no significant publication bias (Egger's test, P = 0.256) (**Figure 5B**).

UCA1 and GC prognosis

Two studies (n = 132) evaluated the impact of UCA1 (urothelial carcinoma associated 1) on prognosis of GC patients. None of the patients received preoperative chemotherapy prior to surgical resection. Gao et al. [35] performed multivariate analyses. Elevated UCA1 expression was associated with shorter OS in GC, with the combined HR of 2.13 (95% CI 1.17-3.09). No significant heterogeneity was observed (I^2 = 0, P = 0.749) (**Figure 4**).

GAPLINC and GC prognosis

Two studies (n = 123) evaluated the effects of GAPLINC (gastric adenocarcinoma predictive

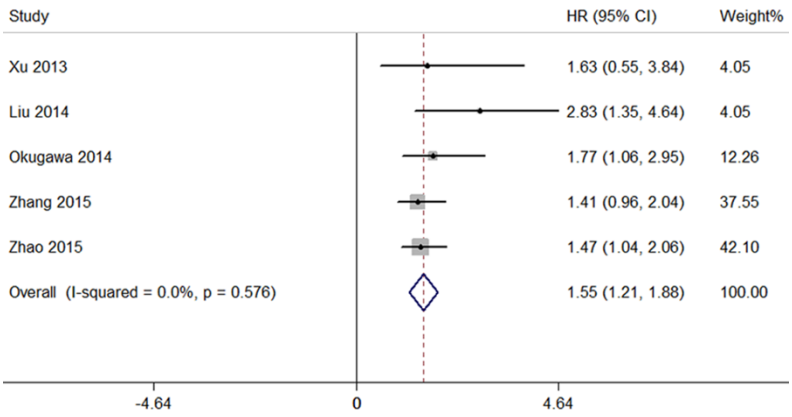

Figure 2. Forest plot of HRs for the association between high tissue HOTAIR level and overall-survival.

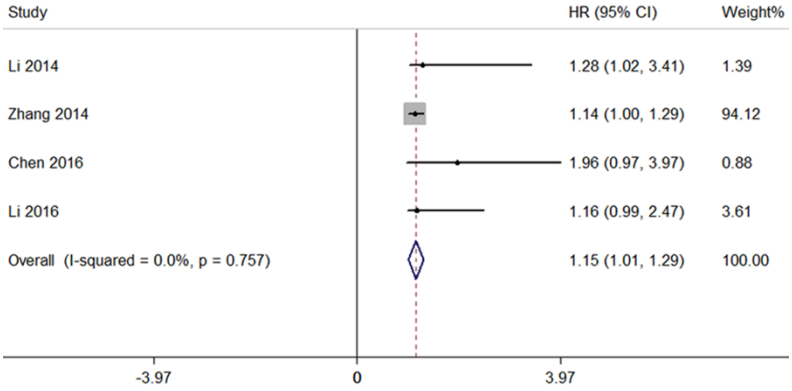

Figure 3. Forest plot of HRs for the association between high tissue H19 level and overall-survival.

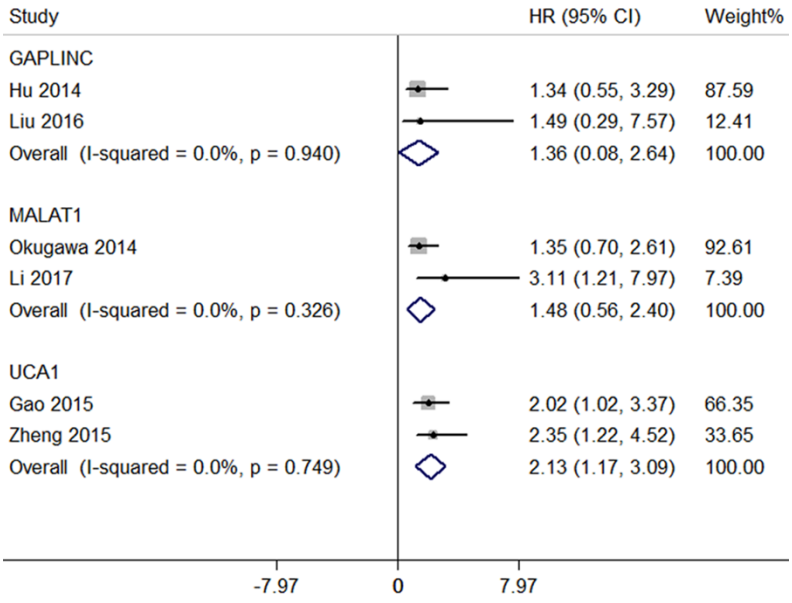

Figure 4. Forest plot of HRs for the association of high tissue GAPLINC, MALAT1, and UCA1 levels with overall-survival.

long intergenic non-coding RNA) on prognosis of GC patients. Hu et al. [37] enrolled patients without preoperative chemotherapy or radiotherapy and evaluated expression levels of GAPLINC by *in situ* hybridization. A fixed effects model indicated that expression levels of GAPLINC were not predictive of OS, with the combined HR of 1.36 (95% CI: 0.08-2.64, I^2 = 0, P = 0.940) (**Figure 4**).

MALAT1 and GC prognosis

Two articles (n = 228) assessed the association between MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) expression and prognosis in GC, with results differing significantly. Okugawa et al. [30] calculated a univariate HR. A fixed-effects model showed that high MALAT1 was not predictive of poor OS (HR: 1.48; 95% CI: 0.56-2.40) (**Figure 4**).

Correlation between H19 expression and clinical characteristics

As shown in **Table 2**, meta-analyses results indicated that overexpressed H19 was correlated with positive lymph node metastasis (OR = 1.68, 95% CI: 1.02-2.76, *P* = 0.04), deeper tumor invasion (OR = 3.53, 95% CI: 1.37-9.10, *P* = 0.009), and advanced TNM stages (OR = 2.17, 95% CI: 1.33-3.56, *P* = 0.002). No significant correlation was observed between H19 expression and gender or histologic grade (*P* > 0.05).

In conclusion, specific hypoxia-responsive lncRNAs may

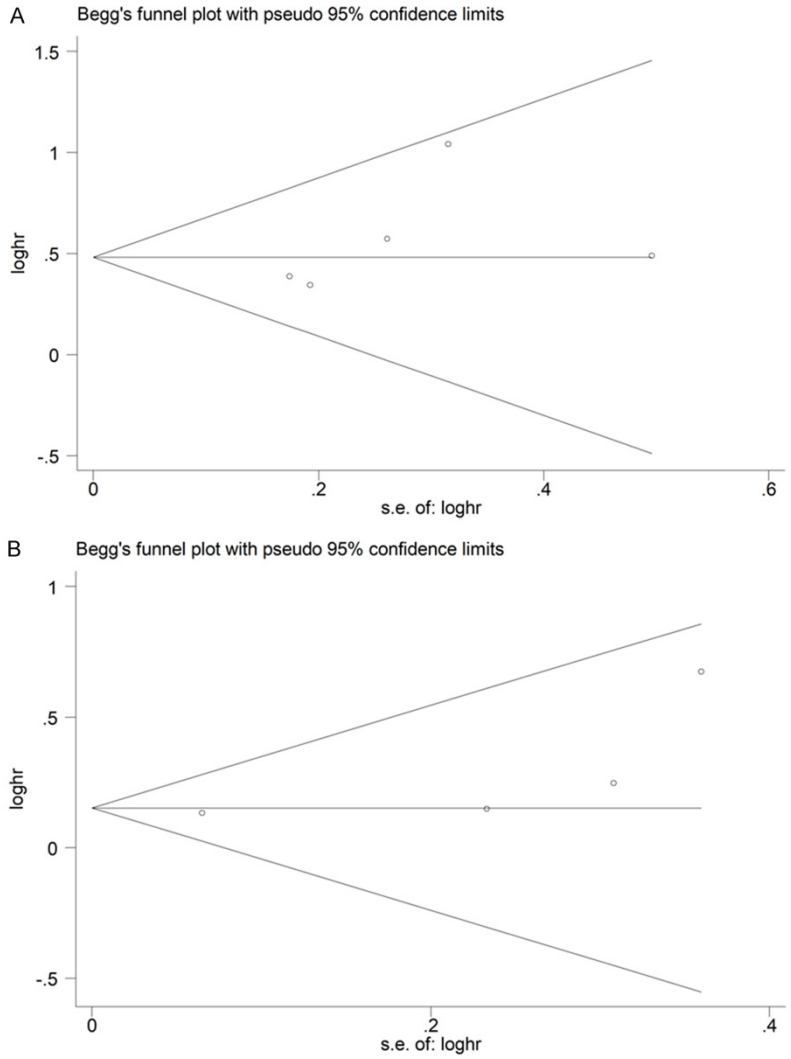

Figure 5. Funnel plots of publication bias on the correlation between HOTAIR expression and OS in GC (A). Funnel plots of publication bias on the correlation between H19 expression and OS in GC (B).

serve as novel molecular prognostic markers in GC and predict clinicopathological characteristics. Further studies are necessary to confirm these results.

Discussion

Over past decades, next generation sequencing has made the diagnosis and prognosis of GC more accurate, based on the genome and transcriptome of individual tumors. Evidence from studies integrating lncRNA and gene expression profiles shows that transcriptional regulation is widely mediated by lncRNAs. In view of the indispensable role of the hypoxic tumor microenvironment in GC, analysis of functional HRLs in tumorigenesis may reveal novel therapeutic and prognostic markers. With this objective, addressing inconsistencies in current studies, this study conducted a systematic review and meta-analysis of studies on the association of HRLs and GC. To the best of our knowledge, this is the first comprehensive report focusing on this association, in which 14 studies involving 1,505 subjects were analyzed. A total of 5 HRLs (HOTAIR, H19, UCA1, GAPLINC, and MALAT1), potentially involved in GC survival, were compared.

Two previous meta-analyses studied the diagnostic potential of lncRNAs in GC [39, 40]. Another two studied the association of SPRY4-IT1 [41] and HOTAIR [42] with overall survival, but none have focused on the HRLs with prognostic relevance. The current meta-analysis discovered that overexpression of HOTAIR [21, 27-30], H19 [19, 31-33] and UCA1 [34, 35] was associated with poor survival in GC patients, while GAPLINC [36, 37] and MALAT1 [30, 38] did not affect prognosis. Although more than 10 lncRNAs have been reported to be associated with hypoxia or HIFs, information regarding association with GC survival has been either lacking or only identified by a single study (NEAT1). Only the five abovementioned HRLs were confirmed by more than one study.

HOTAIR is located on chromosome 12 on the opposite strand of the Homeobox C Cluster (HOXC) gene locus. It was the first lncRNA associated with tumorigenesis and metastasis [43], later confirmed by Zhang et al. [29] and Okugawa et al. [30]. Other studies have also reported HOTAIR as a negative prognostic fac-

Table 2. Meta-analyses of H19 expression stratified by clinicopathologic characteristics

Clinicopathological characteristics	Number of studies	Number of patients	Model	Pooled OR (95% CI)	*P* value	Heterogeneity	
						I^2 (%)	*P* value
Lymph node metastasis (positive vs. negative)	2	208	Fixed	1.68 (1.02-2.76)	0.04	0%	0.34
Depth of tumor Invasion (T2/3/4 vs. T1)	2	203	Fixed	3.53 (1.37-9.10)	0.009	0%	0.43
TNM stages (III/IV vs. I II)	2	208	Fixed	2.17 (1.33-3.56)	0.002	0%	0.46
Histologic grade (G3 vs. G1, 2)	2	208	Fixed	1.44 (0.87-2.39)	0.77	0%	0.15
Gender (male vs. female)	2	208	Fixed	1.09 (0.67-1.76)	0.74	0%	0.92

OR: odds radio; CI: confidence interval.

tor for various cancer types [22, 44, 45], which is consistent with present conclusions. Zhou et al. demonstrated an HIF-1α binding site in the promoter region that upregulated expression of HOTAIR in non-small cell lung cancer (NSCLC) [46]. It was the first report on the expression of HOTAIR in the tumor hypoxic microenvironment. One classical HIF-HOTAIR interaction mechanism is that HIF-1α can bind to hypoxia response elements (HREs) present in the HOTAIR promoter under hypoxia. Bhan A et al. verified this hypothesis by showing an enrichment of histone methylase-transferase MLL1 and histone acetylase p300, along with a concomitant increase in methylation in, the HOTAIR promoter, under hypoxia. In other words, they correlated HIF1α with HOTAIR upregulation [47]. HOTAIR can also function as a competing endogenous RNA to regulate HER2, which has been closely associated with overall survival (OS) of GC [48] and may also be a potential target of HIF-1α [49, 50] expression in GC.

H19 was the first reported HRL [51]. It is the transcription product of imprinted oncofetal gene H19 [52] that is highly expressed in the embryonic stage and reappears in adult tissues only during tumorigenesis [53]. H19 overexpression has been correlated with various aspects of the malignant phenotype, such as angiogenesis, cell survival, and proliferation [52, 54]. H19 can also induce epithelial-to-mesenchymal transition (EMT) to promote metastasis in ovarian cancer [54] and GC [55]. In addition, recent evidence supports H19 as an oncogenic factor that is tightly correlated with aberrantp53 expression in bladder cancer [56] and GC [57]. Hypoxia induces H19 expression in p53 deficient cell lines via HIF-1α [58]. H19 has also been implicated in maintaining stem-like properties of tumor cells [51] and inducing P-glycoprotein expression under hypoxia [59]. In a recent study, H19 upregulated PDK1 expression and maintained glycolysis under hypoxia in a mouse xenograft tumor [17]. H19 acted as a competitive endogenous RNA (ceRNA) which, along with miRNA let-7, released HIF-1α leading to PDK1 overexpression. Finally, a role of H19 in apoptosis, precisely in the FADD/Caspase8/Caspase3 pathway, has been reported in GC [55].

UCA1 overexpression has been reported in bladder cancer cells. HIF-1α binding UCA1 promoter HREs were confirmed by electrophoretic mobility shift assay and chromatin immunoprecipitation. Upregulated UCA1 inhibited apoptosis and increased cell proliferation, migration, and invasion [60]. Bladder cancer cells secrete exosomes to remodel the hypoxic microenvironment. UCA1-enriched exosomes have been identified by transmission electron microscopy and nanoparticle tracking analysis. These hypoxia-induced exosomal UCA1 could promote tumor growth and metastasis through EMT. UCA1-enriched exosomes are also abundantly expressed in the serum of bladder cancer patients [18]. UCA1 is a potential diagnostic biomarker of triple-negative breast cancer (TNBC) since its expression is increased in patient plasma [61]. Overexpression of UCA1 contributes to tumor metastasis by degrading GRK2 [62] and promoting GC progression via AKT pathways [63, 64].

GAPLINC, a gastric cancer oncogenic factor, has been associated with copy number variations (CNV) and oncogenic transcription factors. It acts as a molecular decoy to target bind miR211-3p and then regulates expression of CD44 [36, 37]. Furthermore, Lei Liu et al. demonstrated via luciferase reporter and chromatin immunoprecipitation assays that HIF-1α also binds to the promoter region of GAPLINC and activates its transcription [36]. Although studies have focused on the carcinogenic mecha-

nisms of GAPLINC in GC [37, 65-67], its prognostic value remains ambiguous.

Michalik KM et al. [68] reported high MALAT1 expression under hypoxia, associating it with migratory endothelial cell phenotypes. Silencing or pharmacological inhibition of MALAT1 has reduced vascular growth in xenograft models. Subsequent studies have indicated a positive correlation between MALAT1 overexpression and HIF-2α in hepatocellular carcinoma (HCC) tissues and cells [69, 70]. MALAT1 disassociated VHL and HIF binding and inhibited HIFs ubiquitination. The MALAT1/HIFs positive feedback loop promoted tumor growth *in vivo* and increased the Warburg effect [70, 71]. Furthermore, Tee AE et al. demonstrated that MALAT1 was also upregulated in human neuroblastoma cell lines under hypoxia, while silencing it inhibited endothelial cell migration and vasculature formation [72]. However, the precise molecular mechanisms of MALAT1, whether HIF-1α or HIF-2α is the key regulated factor, under hypoxia remain unclear. Yuan P et al. [71] and Lelli A et al. [73] preferred the latter while Zhang ZC et al. [74] envisaged a MALAT1/mTOR/HIF-1α loop that induces angiogenesis in osteosarcoma (OS). Taken together, these contradictory data should be clarified in further studies.

Some limitations must be considered when interpreting results of the current study. First, the median value was used as a cut-off in six of the studies included. Only one study used means as a cut-off value while another used ROC curves. This diversity may have generated methodological heterogeneity. Second, the sample sizes of some articles were relatively small and 3 of the 5 meta-analyses contained only two records, which might have caused errors in the results. Therefore, large prospective studies are necessary to increase analysis power. Third, the method of tissue preservation differed across studies (paraffin fixed or freshly frozen tumors), which may have led to differences in the concentrations of lncRNAs measured. Moreover, the normalization in qRT-PCR was also inconsistent. Though most studies used GAPDH as the internal control, some studies chose β-Actin or TBP. Fourth, due to absence of data in some relevant articles, subgroup analysis based on related therapy and clinical characteristics could not be performed, which may have resulted in partial heterogeneity. Fifth, ten of the studies included in the meta-analyses lacked HR ratios or other available numerical data. Therefore, this study extracted relevant data using Kaplan-Meier analysis, which might be less accurate compared to primary data directly obtained from articles. Sixth, all studies included were derived from Asian studies. Since articles with positive results are more likely to be published, potential publication bias might exist. It should be noted that some studies developed combined expression signatures of multiple lncRNAs, which provides a robust validation strategy. Hence, developing a new molecular signature by using diverse lncRNAs, investigating their efficacy, may be useful.

In conclusion, despite the limitations mentioned above, the present meta-analysis reveals that HRLs, especially HOTAIR, H19, and UCA1, could be promising and convenient prognostic biomarkers in GC. However, due to limited information available on HRLs, more high quality studies are required to coordinate possible discrepancies, elucidating the value of these novel biomarkers.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yan Zhao, Department of Gastric Cancer, Liaoning Cancer Hospital and Institute (Cancer Hospital of China Medical University), No. 44 Xiaoheyan Road, Dadong District, Shenyang 110042, Liaoning Province, China. E-mail: zhaoyan@CancerHosp-LN-CMU.com

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