


# Clinicopathological and prognostic value of lncRNAs expression in gastric cancer

## A field synopsis of observational studies and databases validation

Xiaona Xu, MD<sup>a</sup>, Fujiao Duan, PhD<sup>b,c</sup>, Shiutin Ng, PhD<sup>d</sup>, Haili Wang, BS<sup>a</sup>, Kaijuan Wang, PhD<sup>c,e</sup>, Yilin Li, MD<sup>b</sup>, Guanghui Niu, MD<sup>b</sup>, Erping Xu, PhD<sup>a,\*</sup> 

**Background:** The purpose of this study was to evaluate existing evidence in the field of long non-coding RNAs (lncRNAs) and prognosis of gastric cancer.

**Methods:** A comprehensive literature search was performed through the electronic database. The combined hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of overall survival (OS), disease-free survival (DFS), or progression free survival (PFS) were calculated to assess the strength of the association. Kaplan–Meier (KM) plotter was used to verify lncRNA HOX transcript antisense RNA (HOTAIR) expression and OS.

**Results:** Overall, a significant correlation between high lncRNAs expression and poor OS was explored in patients with gastric cancer (HR = 1.78,  $P < .001$ ). Subgroup analysis based on statistical methods indicated the high expression of lncRNAs in log-rank (HR = 1.87,  $P < .001$ ) and multivariate analysis (HR = 1.71,  $P < .001$ ) were all significantly correlated with the poor OS. Clinicopathological parameters analysis showed the lncRNA expression were significantly associated prognosis, including TNM stage, tumor size, pathological differentiation, lymph nodes metastasis, distance metastasis, invasion depth and Lauren's classification. It was consistent with the verification results of bioinformatics database for lncRNA HOTAIR ( $P < .001$ ).

**Conclusion:** Our study confirmed the expression of lncRNAs and clinicopathological features may serve as effective indicators of prognosis in patients with gastric cancer.

**Abbreviations:** CIs = confidence intervals, DFS = disease-free survival, DSS = disease specific survival, HOTAIR = HOX transcript antisense RNA, HRs = hazard ratios, KM = Kaplan Meier, lncRNAs = long non-coding RNAs, OS = overall survival, PFS = progression free survival, RFS = recurrence-free survival, TNM = tumor-node-metastasis.

**Keywords:** bioinformatics, clinicopathological factors, field synopsis, gastric cancer, lncRNAs, prognosis

### 1. Introduction

Gastric cancer is a highly lethal malignancy tumor in the world. It is the fourth most common cancer and the second leading cause of cancer death.<sup>[1,2]</sup> The incidence rate and mortality rate in East Asia is the highest in the worldwide.<sup>[3]</sup> Although surgical operation, chemotherapy and radiotherapy regimens can help reduce the incidence and mortality rates of gastric cancer, the overall 5 year survival rate is still only about 25%.<sup>[4,5]</sup>

In recent years, with the extensive research of gastric cancer coding proteins, the research of long noncoding RNA (lncRNAs) has attracted more and more attention.<sup>[6]</sup> The lncRNAs are transcribed RNA with a length of more than 200 nt and cannot encode proteins.<sup>[7]</sup> lncRNAs have attracted attention in different studies on transcriptional, post-transcriptional, and epigenetic levels to modify the expression of protein coding genes,<sup>[8]</sup> and they regulate diverse biological processes, such as signal transduction, cellular functions, proliferation, differentiation, and apoptosis.<sup>[9–11]</sup>

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*The datasets generated during and/or analyzed during the current study are publicly available.*

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<sup>a</sup> School of Traditional Chinese Medicine (Zhongjing College), Henan University of Traditional Chinese Medicine, Zhengzhou, China, <sup>b</sup> Department of Hematology and Medical Research Office, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, Henan, China, <sup>c</sup> Key Laboratory of Tumor Epidemiology of Henan Province, Zhengzhou, Henan Province, China, <sup>d</sup> The First Clinical Medical College

of Henan University of Traditional Chinese Medicine, Zhengzhou, China, <sup>e</sup> College of Public Health, Zhengzhou University, Zhengzhou, Henan Province, China.

\*Correspondence: Erping Xu, School of Traditional Chinese Medicine (Zhongjing College), Henan University of Traditional Chinese Medicine, Zhengzhou, 156 Jinshui East Road, Zhengzhou, Henan 450018, China (e-mail: xuerping@hactcm.edu.cn).

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Emerging evidence has demonstrated the significance of dys-regulated lncRNAs expression in malignancies<sup>[12]</sup> and lncRNAs as oncogenes or tumor suppressors in pathological processes of cancer.<sup>[13,14]</sup> Recent studies have evaluated the abnormal lncRNAs expression in gastric cancer and test in clinical correlated diagnosis, treatment and prognostic prediction.<sup>[6,14–17]</sup> It was believed that specific changes of lncRNAs could make them ideal biomarkers for prognosis of gastric cancer.<sup>[18]</sup> Therefore, the clinical value of lncRNAs need to identify and to predict the prognosis in gastric cancer patients.

The role of lncRNAs in the prevention of gastric cancer remains elusive. A comprehensive meta-analysis of clinical evidence will help resolve the critical issue on whether lncRNAs could predict the prognosis of gastric cancer. So far, there was one related systematic review<sup>[19]</sup> published in 2017, which reported a similar question. It only included 38 studies ranging from 2014 to 2016.

The Meta-analysis of gastric cancer-related lncRNA has mainly focused on the systematic evaluation of single lncRNA<sup>[20,21]</sup> and the risk of gastric cancer or the prognosis of lncRNA and different cancers.<sup>[21,22]</sup> In addition to including more recent studies, in our study, a 2-sample Z-test was used to see whether the HR differ by log rank or multivariate analysis. Meanwhile, we compared the results with log rank and multivariate analysis to verify the reliability and stability of the results. For the clinicopathological parameters, the main evaluating indicator is different. We pooled all the clinicopathological data from the multivariate analysis results of the included studies, the evaluating indicator was HR. But Zhu M, et al study used OR to explore the correlation between lncRNAs transcription level and clinicopathological parameters, it ignores the influence of survival time factors.

The aim of our work is to fill the gap in the world published medical literature by performing the systematic synopsis of the available evidence in the sphere of lncRNAs and prognosis of gastric cancer including the overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), Disease Specific Survival (DSS), recurrence-free survival (RFS) or clinicopathological factors. Furthermore, we used Kaplan–Meier (KM) plotter to verify the effect of lncRNA HOTAIR expression on survival using 631 gastric cancer patients with OS.

## 2. Materials and Methods

The present study was performed according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology.<sup>[23]</sup> In the process of constructing the clinical significance of gastric cancer related lncRNA, we completed the study design based on the principles of population, intervention, comparison, outcome, and research design.

### 2.1. Search strategy

A 2-step search strategy was adopted. The first step a systematic review of original articles was performed by searching PubMed, Excerpta Medica database, Web of Science, and Chinese database (Wanfang and China national knowledge infrastructure) to April 16, 2021. The search included the following 3 groups of terms: “tumor,” and “cancer” “carcinoma”; “stomach” and “gastric”; “lncRNA,” “long noncoding RNA”; “lincRNA,” “long intergenic non-coding RNA”; “prognosis” and “survival.” Searches were conducted using all combinations of at least one term from each group.

The second step, we manually retrieved bibliography of relevant articles to further determine the potential studies that has not been retrieved by databases exploration. Two investigators (FJD and XNX) performed this comprehensive online search.

### 2.2. Inclusion and exclusion criteria

The included studies met the following criteria: cohort studies that investigated associations between lncRNAs expression

and gastric cancer with OS, DFS, RFS, PFS, and/or clinicopathological features, gastric cancer were divided into 2 groups according to the high and low expression of lncRNAs, hazard ratios (HRs) and 95% CIs were reported or could be calculated from given data, published in English or Chinese. Exclusion criteria for the articles included: letters, reviews, expert opinions, meta-analysis and case reports, duplicate publications; studies with insufficient data to calculate the HRs and 95% CIs.

If the data overlaps with other published literature, we select a newly published and /or larger sample article.

### 2.3. Data extraction

The data included in the study were independently evaluated by 2 authors (FJD and XNX). If there were different opinions, it should be determined after consultation with the third author (KJW).

The data of the following items were extracted: The name of first author’s, year of publication, ages and genders, sample size, follow-up time, pathology subtypes, clinicopathological characteristics, OS and DFS/ PFS/DSS/RFS and 95% CIs. For the OS, the starting point is diagnostic time, and operation day or treatment time for others. When HR and/or 95%CI were not reported, the methods of Parmar<sup>[24]</sup> and Tierney<sup>[25]</sup> were used for extrapolation.

### 2.4. LncRNA HOTAIR expression profile and prognosis

The KM plotter is a summary analysis based on biomarker evaluation to measure the effect of lncRNA HOTAIR expression level on OS in 631 gastric patients.<sup>[26]</sup> Meanwhile, the statistical correlation and the visualization of cutoff value were presented.

### 2.5. Statistical analysis

The pooled HRs with 95% CIs were conducted by Revman 5.3.5 (Cochrane Collaboration, Oxford, UK) to evaluate the relationship between lncRNA expression, clinicopathological features and prognosis. Inter-study heterogeneity was quantified using  $Q$  tests and the I-squared ( $I^2$ ) statistic.<sup>[27]</sup> According to the results of heterogeneity analysis, a fix effects or random model was performed. In the absence of significant heterogeneity ( $P_{\text{heterogeneity}} \geq 0.10$  or  $I^2 \leq 50\%$ ), a fixed-effects model<sup>[28]</sup> was applied to assess the combined effect size, otherwise ( $P_{\text{heterogeneity}} < 0.1$  and  $I^2 > 50\%$ ) the random-effects model<sup>[29]</sup> was conducted. For studies that did not report the HRs with 95% CIs, Engauge Digitizer 10.0 (<https://sourceforge.net/projects/digitizer/>) was used to deduce the original data from a KM curve. Subgroup analyses were performed by different prognoses, regions, cutoff values and clinicopathological features. Begg’s<sup>[30]</sup> and Egger’s test<sup>[31]</sup> were used to assess the publication bias in STATA 13.1MP.

All  $P$  values were 2-sided and  $P < .05$  was considered statistically significant. The KM plotter split is median, and the lncRNA HOTAIR expression profile from gastric cancer samples and paired normal tissues.

## 3. Results

### 3.1. Characteristics of eligible studies

A total of 1870 records were retrieved according to the literature search strategy. According to the inclusion and exclusion criteria, 1 article<sup>[32]</sup> was eliminated due to significant overlap with a previously published article by Xu et al.<sup>[33]</sup> As a result, we identified 169 eligible articles (174 studies) (Table S1, Supplemental Digital Content, <http://links.lww.com/MD/H400>) comprising 16280

patients (range of sample size: 32–373, mean: 100) with gastric cancer. Three articles<sup>[34–36]</sup> performed 2 cohort studies in different populations, 1 article<sup>[37,38]</sup> included 2 pathological types of gastric cancer, and we considered them as 2 studies, respectively. The details on the flow diagram of the literature search strategy was presented in Figure 1. Three articles<sup>[35,39,40]</sup> contained 2 lncRNAs, and the other 2 articles<sup>[36,41]</sup> contain 12 and 5 lncRNAs, respectively (Table S1, Supplemental Digital Content, <http://links.lww.com/MD/H400>). Therefore, a total of 185 gastric cancer related lncRNAs were analyzed. All included studies were from 2013 to 2021. Based on the study of regional sources, 97.1% of the studies were Chinese (169/174). Four eligible studies were specified the histological subtypes (intestinal, diffuse and adenocarcinoma) of gastric cancer (n = 5, 2.9%). The methods of lncRNA detection in tissue (n = 169, 97.1%) or serum (n = 5, 2.9%) were quantitative real-time polymerase chain reaction (qRT-PCR). The cutoff values of lncRNA were most taken as the median (n = 102, 58.6%) (Table S1, Supplemental Digital Content, <http://links.lww.com/MD/H400>).

### 3.2. Analysis of deviation statistics

A 2-sample Z test was used to detected whether the HR differ by log rank (KM Curve) or multivariate analysis (Cox-analysis), there was no statistically significant difference between the 2 groups ( $Z = 0.2336$ ,  $P = .8155$ , Fig. 2A). T test was used to identified difference between clinicopathological features of OS and DFS, and the results showed no statistical significance ( $P = .3625$ , Fig. 2B).

### 3.3. Association between lncRNA expression level and OS

One hundred and seventy-four studies (185 lncRNAs dataset) were included for the analysis of correlation between expression of lncRNA and OS in patients with gastric cancer. Obvious heterogeneity existed ( $I^2 = 87\%$ ,  $P_{\text{heterogeneity}} < 0.001$ ) among 165 studies (185 lncRNAs dataset). Therefore, a random effect was applied, and a significant correlation between high lncRNAs expression and poor OS in patients with gastric cancer was explored (HR = 1.78, 95% CI: 1.64–1.93,  $P <$

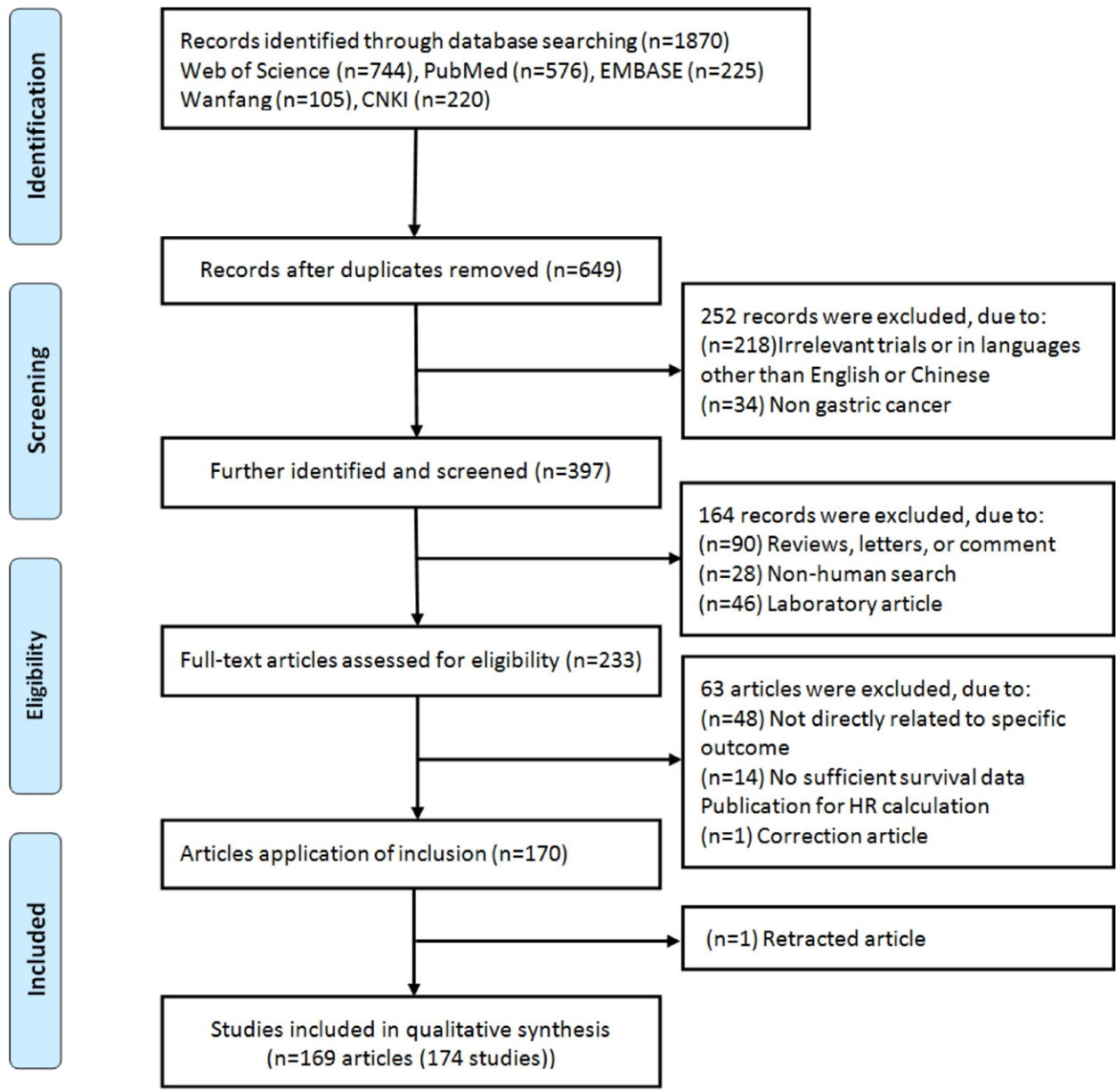
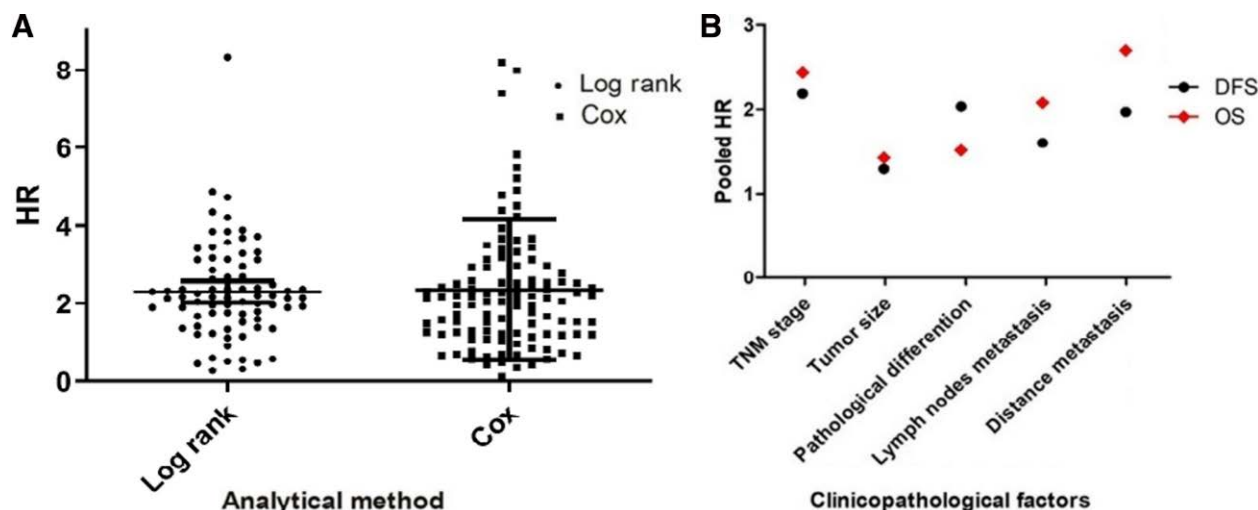


Figure 1. Flow chart of literature search and study selection.



**Figure 2.** (A) Z test between the Log rank and multivariate analysis. (B) T test for the OS and DFS of clinicopathological features. DFS = disease-free survival, OS = overall survival.

.001). Subgroup analysis was performed according to statistical methods, the results showed that the high lncRNAs expression were significantly correlated with poor OS in log rank (HR = 1.87, 95%CI: 1.66–2.10,  $P < .001$ ) and multivariate analysis (HR = 1.71, 95%CI: 1.55–1.89,  $P < .001$ ). For subgroups analyses, the results indicated that there was no heterogeneity between subgroups ( $I^2 = 23.6\%$ ,  $P = .25$ ) (Table 1).

Analyses of subgroups were conducted by cutoff, and the results revealed a significant correlation between high expression of lncRNAs and poor OS in median (HR = 1.87, 95%CI: 1.69–2.08,  $P < .001$ ), normal (HR = 1.64, 95%CI: 1.45–1.88,  $P = .006$ ) and mean subgroups (HR = 4.77, 95%CI: 2.98–7.65,

$P < .001$ ). Meanwhile, our analysis revealed a positive link between high lncRNAs expression and poor OS in China (HR = 1.78, 95% CI: 1.64–1.94,  $P < .001$ ) and other countries (HR = 1.72, 95% CI: 1.16–2.54,  $P = .007$ ) (Table 1).

### 3.4. Association between lncRNA expression level and DFS/ PFS/DSS/RFS

A total of 58 studies (61 lncRNAs) were included to analyze the correlation between lncRNA expression and DFS/ PFS/ DSS/RFS. There was obvious heterogeneity among studies ( $I^2 = 84\%$ ,  $P_{\text{heterogeneity}} < 0.001$ ), and a random-effects model was applied to calculate the pooled HR and 95%CI. The results

**Table 1**

Main results of pooled HRs in the meta-analysis.

Comparisons	Heterogeneity test			Summary HR (95% CI)	Hypothesis test		Studies	LncRNAs Number
	I <sup>2</sup> (%)	P	Model		Z	P		
OS (Low vs High)								
Total	87	<.001	Random	1.78(1.64, 1.93)	13.84	<.001	165	185
Log rank (KM)	80	<.001	Random	1.87(1.66,2.10)	10.29	<.001	75	78
Multivariate analysis (Cox)	85	<.001	Random	1.71(1.55,1.89)	10.53	<.001	90	107
Subgroup differences cutoff (High vs Low)	23.6	.25						
Median	86	<.001	Random	1.87(1.69,2.08)	11.66	<.001	98	104
Normal	84	<.001	Random	1.64(1.45,1.88)	6.47	<.001	62	80
Mean				4.77(2.98,7.65)	6.49	<.001	1	1
Country								
China	87	<.001	Random	1.78(1.64,1.94)	13.67	<.001	161	179
Others	53	.06	Random	1.72(1.16,2.54)	2.71	.007	4	6
LncRNAs								
LncRNA HOTAIR	46	<.001	Fixed	1.83(1.55,2.15)	7.27	<.001	10	11
LncRNA AFAP1-AS1	29	<.001	Fixed	2.73(1.76,4.22)	4.50	<.001	3	3
Others	87	<.001	Random	1.75(1.61,1.90)	12.91	<.001	152	171
Subgroup differences DFS/PFS/DSS/RFS	32	.23						
Total	84	<.001	Random	1.74(1.47,2.06)	4.32	<.001	58*	61
DFS	80	<.001	Random	1.65(1.38,1.97)	5.56	<.001	39	41
PFS	90	<.001	Random	2.08(1.28,3.38)	2.95	.003	14	15
DSS	79	.003	Random	1.30(0.70,2.43)	0.83	.40	4	4
RFS				2.76(1.42,5.36)	2.99	.03	1	1
Subgroup differences	14.4	.32						

Cox = survival data from a Cox-analysis, DFS = disease-free survival, DSS = disease specific survival, KM = survival data from a Kaplan–Meier curve, OS = overall survival, PFS = progressive free survival, RFS = recurrence-free survival.



showed that the pooled HR of disease progression lncRNAs expression and DFS/PFS/DSS/RFS in patients with gastric cancer was 1.74 (95% CI: 1.47–2.06). Meanwhile, stratified analysis showed that the HR of the high lncRNAs expression group versus the low lncRNAs expression group in DFS, PFS, DSS and RFS were 1.65 (95% CI: 1.38–1.97), 2.08 (95% CI: 1.28–2.38), 1.30 (95% CI: 0.70–2.43), and 2.76 (95% CI: 1.42–5.36), respectively. For subgroups analyses, the results showed that there was no heterogeneity among these groups ( $I^2 = 14.4\%$ ,  $P = .32$ ) (Table 1).

**3.5. Association between lncRNA expression and clinicopathological parameters**

We combined all the clinicopathological data from the multivariate analysis results to explore the association between lncRNA expression and clinicopathological features (Table 2).

For the OS, the results revealed that the expression of lncRNA were significantly correlated with the clinicopathological parameters, including TNM (HR = 2.07, 95% CI: 1.83–2.34,  $P < .001$ ), tumor size (HR = 1.32, 95% CI: 1.21–1.45,  $P < .001$ ), pathological differentiation (HR = 1.35, 95% CI: 1.16–1.57,  $P < .001$ ), lymph nodes metastasis (HR = 1.90, 95% CI: 1.58–2.28,  $P < .001$ ), distance metastasis (HR = 2.81, 95% CI: 2.29–3.45,  $P < .001$ ), invasion depth (HR = 1.53, 95% CI: 1.08–1.60,  $P < .001$ ), Lauren’s classification (HR = 1.31, 95% CI: 1.08–1.60,  $P = .006$ ).

For the DFS, the results indicated that there was significantly associated with TNM stage (HR = 2.32, 95% CI: 2.02–2.66,  $P < .001$ ), lymph nodes metastasis (HR = 1.81, 95% CI:

1.56–2.10,  $P < .001$ ), distance metastasis (HR = 2.20, 95% CI: 1.82–2.66,  $P < .001$ ), and invasion depth (HR = 1.45, 95% CI: 1.07–1.97,  $P = .02$ ). However, the association of lncRNA expression with tumor size (HR = 1.05, 95% CI: 1.00–1.10,  $P = .07$ ), pathological differentiation (HR = 1.55, 95% CI: 1.02–2.36,  $P = .04$ ) and invasion depth (HR = 1.40, 95% CI: 0.98–2.01,  $P = .07$ ) and the risk of gastric cancer was at a statistically significant threshold.

**3.6. Sensitivity analyses and assessment of publication bias**

Sensitivity analysis was implemented by omitting removing a study at one time, and recalculating the combined HR, the pooled HR was not substantially changed, which indicated the combined HR was stable (Data not shown).

Begg’s and Egger’s tests were used to estimate the bias of publication. The results didn’t explore any evidence of publication bias (Table 3), and the funnel plots shape was basically symmetrical (Fig. 3).

**3.7. Expression of lncRNA HOTAIR and prognosis in database test**

For the OS, there was a highly significant association between high expression and pool OS in gastric cancer patients (HR = 1.74, 95% CI: 1.39–2.19,  $P < .001$ ) (Fig. 4A). The results of direct sequencing and lncRNA HOTAIR expression were consistent with the combined results of our individual studies. The linear relationship between statistical correlation and cutoff value was shown in Figure 4B.

**Table 2**  
Multivariate analysis of independent prognostic factors of pooled HRs in the meta-analysis.

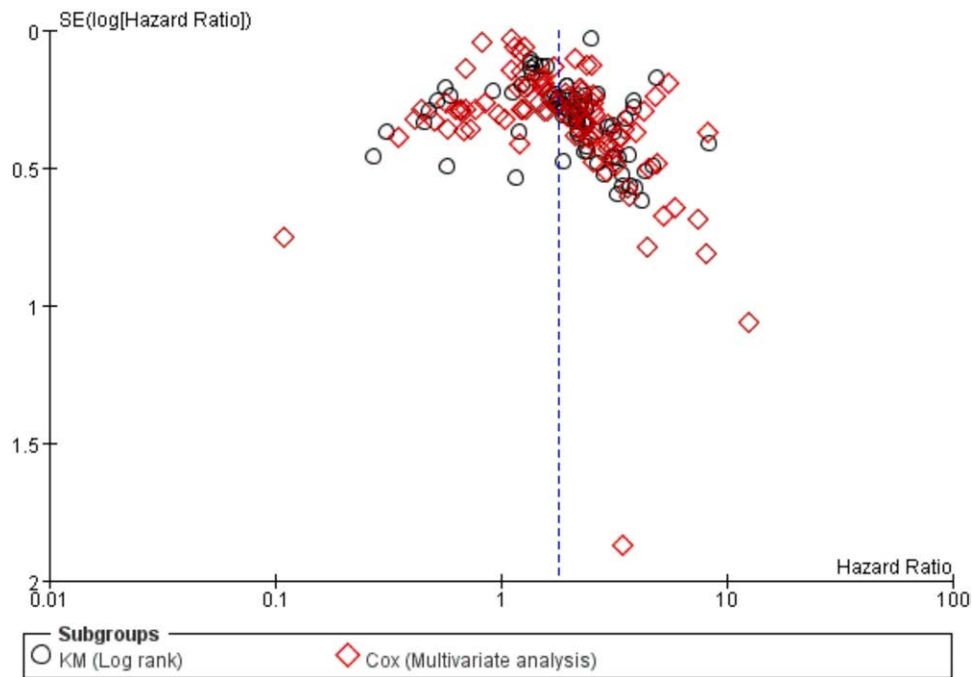
Characteristics	Comparisons	Case number	Heterogeneity test			Summary HR (95% CI)	Hypothesis test		Model	Studies
			Q	P	I <sup>2</sup> (%)		Z	P		
<b>OS</b>										
TNM stage	III + IV vs I + II	9014	233.24	<.001	71	2.07(1.83,2.34)	11.5	<.001	Random	68
Tumor size	≥5 vs < 5	3390	38.77	.05	33	1.32(1.21,1.45)	5.93	<.001	Fixed	27
Pathological differentiation	Poor vs Well-moderate	4429	65.68	<.001	53	1.35(1.16,1.57)	3.96	<.001	Random	32
Lymph nodes metastasis	Positive vs Negative	6802	242.68	<.001	79	1.90(1.58,2.28)	6.92	<.001	Random	52
Distance metastasis	Positive vs Negative	5386	95.85	<.001	61	2.81(2.29,3.45)	9.88	<.001	Random	38
Invasion depth	T3 + T4 vs T1 + T2	4153	97.44	<.001	65	1.53(1.33,1.77)	5.86	<.001	Random	35
Lauren’s classification	Diffuse vs Intestinal	1181	6.43	.49	0	1.31(1.08,1.60)	2.73	.006	Fixed	8
<b>DFS</b>										
TNM stage	III + IV vs I + II	3264	17.08	.81	0	2.32(2.02,2.66)	12.02	<.001	Fixed	24
Tumor size	≥5 vs < 5	932	3.68	.05	0	1.05(1.00,1.10)	1.81	.07	Fixed	6
Pathological differentiation	Poor vs Well-moderate	918	21.84	<.001	77	1.55(1.02,2.36)	2.06	.04	Random	6
Lymph nodes metastasis	Positive vs Negative	2066	19.07	.09	37	1.81(1.56,2.10)	7.75	<.001	Fixed	13
Distance metastasis	Positive vs Negative	1829	5.18	.92	0	2.20(1.82,2.66)	8.11	<.001	Fixed	12
Invasion depth	T3 + T4 vs T1 + T2	1389	29.88	<.001	67	1.40(0.98,2.01)	1.84	.07	Random	11

DFS = disease-free survival, OS = overall survival.

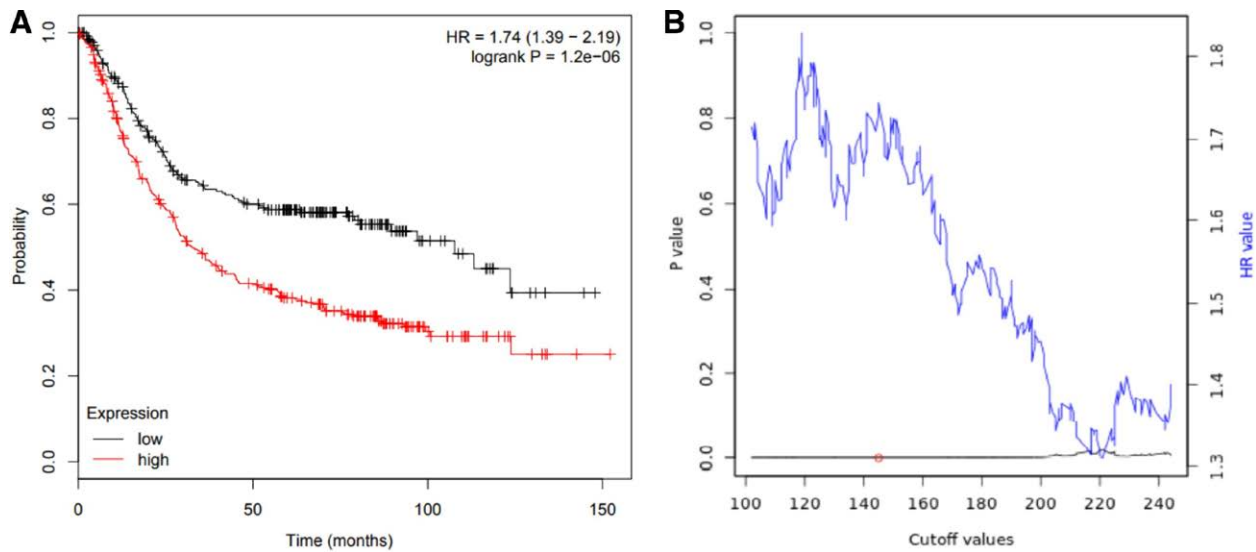
**Table 3**  
Publication bias of lncRNA for Begg’s test and Egger’s test.

Comparisons	Begg’s test			Egger’s test	
	Z	P	t	P	95% CI
OS-Combine	2.50	.013	2.55	.012	0.257-2.063
Log rank (KM)	1.67	.097	-0.81	.075	-1.411-0.681
Multivariate analysis (Cox)	1.73	.084	1.76	.083	-0.121-1.912
PFS	1.64	.101	1.55	.132	-0.588-0.958
DFS	0.62	.533	-1.29	.229	-6.080-4.125

Cox = survival data from a Cox-analysis, KM = survival data from a Kaplan–Meier curve.



**Figure 3.** Begg's funnel plot of publication bias on the relationship between lncRNA expression and OS. lncRNAs = long non-coding RNAs, OS = overall survival.



**Figure 4.** (A) Kaplan–Meier survival curves for OS according to lncRNA HOTAIR expression in gastric cancer patients. OS of patients with high versus low lncRNA HOTAIR expression was shown. (B) Significance versus cutoff values between lower and upper quartiles of expression. HOTAIR = HOX transcript anti-sense RNA, lncRNAs = long non-coding RNAs, OS = overall survival.

**4. Discussion**

Gastric cancer is one of the most aggressive malignant tumors,<sup>[42]</sup> and most patients with gastric cancer are diagnosed as advanced and have a poor prognosis.<sup>[43,44]</sup> In recent years, more and more evidence shows that the abnormal lncRNAs expression is related to the clinical prognosis of cancer patients. The lncRNAs have made great contributions to the mechanism, function and translation of cancer biology, and play an important role in the occurrence and progression of gastric cancer.<sup>[45]</sup> Thus, more sensitive gastric cancer biomarkers for improving screening, diagnosis and prognostic assessment are urgently needed. In order to clarify the expression significance of lncRNAs and the value of

clinical pathological parameters in gastric cancer, we conducted the present field synopsis of observational studies, and then databases validation.

In order to identify lncRNAs with potential biological functions, we used log-rank and multivariate cox regression analysis to analyze the correlation between lncRNAs expression, clinicopathological characteristics, and patient overall survival. We validated that no statistically significant difference between the log-rank and multivariate analysis ( $P = .25$ ). Meanwhile, the T-test was used to identified distributed difference between the OS and DFS of clinicopathological features, and the results showed no significant difference ( $P = .3625$ ).

The pooled analysis results showed that a significant correlation was revealed between high lncRNAs and poor OS in gastric cancer patients (HR = 1.78, 95% CI: 1.64–1.93,  $P < .001$ ). In subgroup analysis, we explored that the high lncRNAs expression in both log-rank (HR = 1.87, 95% CI: 1.66–2.10,  $P < .001$ ) and multivariate cox regression analysis (HR = 1.71, 95% CI: 1.55–1.89,  $P < .001$ ) was significantly related with poor OS. The stratified analysis was performed by cutoff, and a positive link between elevated lncRNAs and poor OS in median, normal and mean subgroups were revealed. Meanwhile, our analysis revealed a significant correlation between high lncRNAs expression and poor OS in China and other countries.

For the DFS/ PFS/DSS/RFS, combined HR of correlation between elevated expression of lncRNAs and poor DFS/PFS/ DSS/RFS in patients with gastric cancer was 1.74 (95% CI: 1.47–2.06), stratified analysis shows that association was statistically significant difference in DFS, PFS, DSS, and RFS, respectively.

In analysis of clinicopathological features and prognosis, we found significant changes in the correlation between dys-regulated lncRNAs and clinicopathological characteristics. The pooled results showed that lncRNAs were significantly related to TNM stage, tumor size, pathological differentiation, lymph nodes metastasis, distance metastasis, invasion depth in OS, and TNM stage, lymph nodes metastasis, distance metastasis, invasion depth in DFS, but no association was explored between lncRNA expression and other clinicopathological features (Lauren's classification in OS; tumor size and pathological differentiation in DFS). The aberrant lncRNAs expression supported the corresponding clinical value in identifying clinicopathological features, especially TNM stage.

To confirm the reliability of the results, we selected 11 studies on lncRNA HOTAIR to explore the prognostic value of lncRNA HOTAIR in GEO, EGA and TCGA, and then verify our results. We used 631 gastric cancer tissues and normal tissues in the public database. The results showed that the lncRNA HOTAIR expression was significantly higher than that in the normal control group. These findings further validate our conclusions and suggest that lncRNA HOTAIR can be used as an independent prognostic factor for OS in patients with gastric cancer.

In recent decades, accumulating evidences have shown that lncRNAs are crucial in tumorigenesis.<sup>[44]</sup> It is a functional end product, and the lncRNA expression level is directly related to the level of active molecules.<sup>[46]</sup> Using lncRNA to diagnose and assess the prognosis has intrinsic advantages compared with other protein-coding RNAs. According to the data set of the included studies in this study, 97.6% of lncRNA expression was measured in tissue. Compared to miRNAs and protein-coding mRNAs, lncRNAs show greater tissue specificity, which makes them suitable for the novel diagnostic and prognostic cancer biomarkers.<sup>[47]</sup>

Accumulating evidence indicates that lncRNAs have a biological role in regulating the occurrence and development of gastric cancer.<sup>[48–50]</sup> Furthermore, tumor specific lncRNAs may also be link to metastasis and invasion of gastric cancer. Lymph nodes metastasis, which is the most common metastasis pathway of gastric cancer, and it is of great significance for the diagnosis and prognosis, TNM staging and treatment of patients with gastric cancer. According to our results, we demonstrated that there was a significant correlation between lncRNAs expression and lymph nodes metastasis in OS and DFS, indicating that lncRNAs should be a potential bio-marker for judging lymph nodes metastasis in patients of gastric cancer.

Nevertheless, certain limitations of the present study should be presented. Firstly, most of included articles were from China, and studies from other countries might attain different outcomes. Secondly, the confounding factors induced by diverse RNA extraction methods and RNA detection platforms may

limit the validity of this study. Thirdly, the diverse sample sources resulted in significant heterogeneity between individual studies, although the random-effects model was performed to reduce the influence of heterogeneity on our results. Fourthly, although no evidence of publication bias was explored, the included studies were all published in public databases, there was no unpublished data in the database we used, which may generate publication bias. Finally, in the included studies, the cutoff value of lncRNAs expression was different, and the real value may be deviated due to different algorithms.

## 5. Conclusions

The high expression of lncRNA can predict the poor clinical prognosis of gastric cancer, and the abnormality of lncRNA is related to the clinicopathological features, suggesting lncRNA may serve as a novel valuable biomarker for the prognostic of gastric cancer, especially lncRNA HOTAIR. Future studies need to use multiply reliable and sensitive detection methods in large-scale multicenter studies to validate the true prognostic significance of lncRNAs in patients with gastric cancer.

## Author contributions

Conceptualization: Xiaona Xu.

Data curation: Fujiao Duan.

Formal analysis: Haili Wang.

Investigation: Shiutin Ng.

Project administration: Kaijuan Wang.

Software: Yilin Li.

Supervision: Erping Xu.

Visualization: Fujiao Duan.

Writing – original draft: Xiaona Xu.

Writing – review & editing: Guanghui Niu.

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