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The prognostic value of long non-coding RNA H19 in various cancers

A meta-analysis based on 15 studies with 1584 patients and the Cancer Genome Atlas data

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Abstract

Background: Recent studies have shown that long noncoding RNA (lncRNA) H19 is aberrantly expressed in various cancers. However, the prognostic significance of H19 in cancer patients remains to be elucidated. Here, we designed and conducted a meta-analysis to evaluate the prognostic value of this lncRNA for malignant solid neoplasms.

Methods: Relevant publications were collected from PubMed, Cochrane Library, Web of Science, and Embase databases. The relevant survival data of patients with H19-associated cancers were downloaded from The Cancer Genome Atlas (TCGA) project. Statistically significant relationships between H19 expression levels and overall survival were analyzed by hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

Results: A total of 15 studies with 1584 patients were ultimately included for this literature meta-analysis. An elevated level of H19 expression was found to be negatively correlated with the overall survival (OS) (HR = 1.62, 95% CI = 1.36–1.93, $P < .001$) in various cancers. Abnormal H19 expression was also positively correlated with poor tumor differentiation ($P < .0001$), more advanced clinical stage ($P < .0001$), earlier lymph node metastasis ($P < .0001$), and earlier distant metastasis ($P < .05$). The relationship between elevated H19 expression and overall survival was further validated by a TCGA dataset consisting of 7462 cancer patients (HR = 1.12, 95% CI = 1.03–1.22, $P < .05$).

Conclusion: Our study indicates that H19 expression is closely relevant to clinical outcome and suggests that lncRNA H19 could be a crucial prognostic biomarker for certain carcinoma types.

Abbreviations: CCA = cholangiocarcinoma, CI = confidence interval, CP = clinicopathological characteristic, CRC = colorectal cancer, DM = distant metastasis, EMT = epithelial-mesenchymal transition, GC = gastric cancer, HR = hazard ratio, LNM = lymph node metastasis, NOS = Newcastle-Ottawa quality assessment scale, NSCLC = non-small cell lung cancer, OS = overall survival, TC = thyroid cancer, TCGA = the Cancer Genome Atlas.

Keywords: cancer, H19, meta-analysis, overall survival, prognosis

1. Introduction

Because of high incidence and mortality rates, cancer has undeniably become a significant threat to public health in the modern world. In 2018, researchers predicted that there will be about 1,735,350 new cases of cancer and 609,640 deaths in the United States alone.[1] Though there have been substantial advances in diagnosis and treatment methods, the 5-year survival rate of various human cancers still remains low in general.[2] This

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HY and SL have contributed equally to this work.

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is due to the fact that most patients are diagnosed at an advanced stage of cancer development. Therefore, it is urgent to search for new prognostic cancer markers to earlier and better characterize metastasis, the specific clinical stage, and prognosis of different carcinomas.

Long noncoding RNAs are RNA transcripts that have >200 nucleotides in length but do not encode proteins. Because lncRNAs have no function in protein translation, they were previously considered as transcriptional noises. However, it has now become better understood that lncRNAs instead have various roles in regulating gene expression.[3,4] Recently, accumulating evidence has indicated that certain lncRNAs are dysregulated in various types of cancer. Moreover, a series of studies have reported that lncRNAs are involved in a variety of physiological and pathological processes, such as cell proliferation, migration, apoptosis, as well as the progression of carcinogenesis.[5–9] lncRNAs in general are thought to be promising as independent biomarkers for diagnosis and prognosis in human cancers.[10–12]

lncRNA H19, one of the earliest detected maternally imprinted genes, is approximately 2.3 kb nucleotides in length and located on human chromosome 11p15.5.[13] lncRNA H19 is normally expressed in almost all fetal tissues, though there is a large reduction in the expression level after birth.[14] However, H19 is overexpressed in a variety of cancers, including gastric cancer (GC),[15,16] non-small cell lung cancer (NSCLC),[17,18] colorectal cancer (CRC),[19–22] thyroid cancer (TC),[23] cholangiocarcinoma (CCA),[24] melanoma.[25] H19 can also regulate the expression of genes that promote tumor progression[26] and abnormal levels of H19 may increase the risk of various malignancies. Nevertheless, the prognostic value of H19 remains unclear, because previous studies were conducted with narrow constraints as well as small sample sizes. Hence, we gathered a larger set of eligible studies and performed this quantitative meta-analysis to further clarify the prognostic value of H19 in different types of carcinomas.

2. Materials and methods

2.1. Literature search

PubMed, Embase, Cochrane Library, and Web of Science databases were comprehensively searched from their inception up to November 2018 for eligible literature. The search terms used were as follows: ("Long non coding RNA H19" OR "Long Noncoding RNA H19" OR "long non-coding RNA H19" OR "lncRNA H19" OR "H19") AND ("prognosis" OR "prognoses" OR "prognostic" OR "outcome" OR "survival") AND ("neoplasia" OR "neoplasm" OR "tumor" OR "cancer" OR "tumour" OR "carcinoma"). The references of this original set of articles were reviewed for additional eligible literature.

2.2. Inclusion and exclusion criteria

Inclusion criteria are as follows: patients divided into "high H19" and "low H19" groups based on their H19 expression levels; patients with tumors explicitly confirmed by pathological or histological examinations; all supplementary information necessary to extract or calculate the HRs and corresponding 95% CIs or clinical features; studies published in the English language; case–control studies.

Exclusion criteria are as follows: studies published in non-English languages; duplicate studies and studies without sufficient genotype information; studies without other essential data for further research; reviews, letters, editorials, expert opinions, conference abstracts, and similarly categorized other writings.

2.3. Data extraction

Two investigators reviewed and extracted the following relevant information from all enrolled articles independently: first author (s); publication year; country where study was performed; tumor types; numbers of cases and controls; follow-up time; method to assess H19 expression; number of patients in each the "high" and "low" H19 expression groups; cut-off values for "high" versus "low" H19; the hazard ratios (HRs) of H19-associated cancers and their 95% CIs. The patient outcome data was directly extracted from multivariate or univariate analyses. Any disagreement regarding data extraction was resolved by a third investigator.

2.4. Quality assessment

The quality of all included studies was assessed using the Newcastle-Ottawa quality assessment scale (NOS). Studies with score ≥6 were considered to be of sufficient quality to include in the meta-analysis.

2.5. Public data and tools

Pan-cancer RNA sequencing (RNA-Seq) and outcome data of various cancers were downloaded from http://kmplot.com/analysis/index.php?p=service&cancer=pancancer_rnaseq. The patients were divided into high and low H19 expression groups according to the median value of H19 expression. Survival was analyzed using the HR and 95% CI, which were shown in the Kaplan–Meier plots.

2.6. Statistical analysis

Statistical analysis was performed by using Stata SE12.0 and RevMan5.3 software. Cochrane Q-test and I^2 statistics were utilized to determine the heterogeneity among all the studies. For $P > .05$ and $I^2 < 50\%$, meaning the inexistence of heterogeneity among studies, the fixed-effects model would be adopted to analyze the results. Otherwise, the random-effects model would be adopted. The stability of consequences was examined by a sensitivity analysis. Begg bias test and a funnel plot, with significance level $P < .05$, were used to evaluate the existence of statistically significant publication bias.

3. Results

3.1. Study selection and study characteristics

As shown in the Fig. 1, a total of 962 relevant articles in line with our search strategy were collected from the databases. After the duplications were removed, 560 articles remained. Through careful evaluation of the titles, abstracts, and publication types, 506 records were excluded because they did not pertain to human cancer or were not original research papers (exclusions include: letters, case reports, editorials, reviews, and expert opinions). The full texts of the remaining 38 publications were further examined, and 23 studies were excluded due to lack of data pertaining to distinct high and low H19 expression groups or lack of adequate

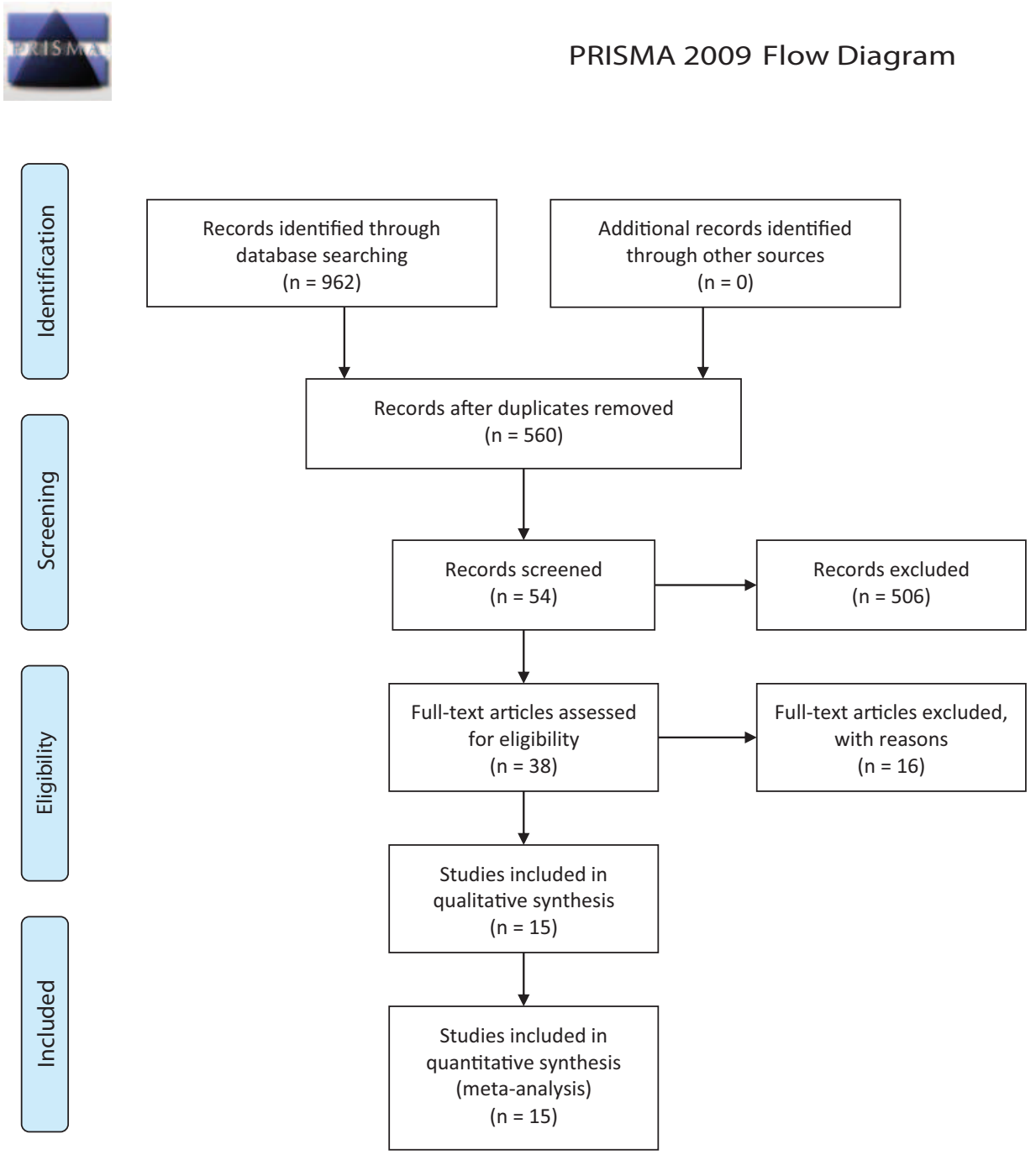

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Figure 1. PRISMA flow diagram. Flow diagram of articles search and selection.

information for calculating the HR and 95% CI for survival rate. Ultimately, 15 articles with 1584 patients were determined to be eligible for the meta-analysis. The primary clinical characteristics and survival data of the patients from included studies were summarized in Tables 1 and 2. These articles were published between 2014 and 2018 with sample sizes ranging from 24 to 214. Fourteen of the included articles were from China and 1 article was from Korea, and all the articles were published in English. There were 9 different types of cancers in these papers, with 4 studies focusing on colorectal cancer, 2 on gastric cancer, 2 on non-small cell lung cancer, 2 on melanoma, and 1 each on hepatocellular carcinoma, renal cell carcinoma, gallbladder

Table 1

Survival data of studies included in the meta-analysis.

Author, year	Country	Type	Method	Cut-off	Sample size (High/Low)	Outcome	Hazard ratios (95% CI)	Analysis	Follow-up (months)	NOS score
Er-Bao Zhang, 2014	China	GC	RT-PCR	Mean	80 (40/40)	OS	1.137 (1.005–1.287)	M	60	8
J. S. Chen, 2016	China	GC	RT-PCR	Median	128 (64/64)	OS	1.959 (0.966–3.973)	M	40	8
Erbao Zhang, 2016	China	NSCLC	RT-PCR	Median	70 (35/35)	OS	1.087 (1.048–1.128)	M	60	8
Xiao-Jun Ge, 2018	China	NSCLC	RT-PCR	T/C = 1.5	76 (35/41)	OS	NA	NA	60	6
Dong Han, 2016	China	CRC	RT-PCR	≥3-fold	83 (48/35)	OS	1.433 (1.239–1.786)	M	48	7
Shan-Wen Chen, 2017	China	CRC	RT-PCR	≥4-fold	96 (53/43)	OS	4.028 (1.332–12.183)	M	60	7
Dayong Ding, 2018	China	CRC	RT-PCR	Median	185 (125/60)	OS	3.506 (2.09–5.85)	M	60	8
Chang-feng Li, 2018	China	CRC	RT-PCR	Median	214 (133/81)	OS	3.968 (2.58–6.10)	M	50	8
Wenkang Luan, 2018	China	Melanoma	RT-PCR	NA	30 (15/15)	OS	NA	NA	60	6
Gaofeng Shi, 2018	China	Melanoma	RT-PCR	Median	82 (42/42)	OS	NA	NA	60	6
Zongguo Yang, 2015	Korea	HCC	NA	NA	240	OS	1.025 (0.955–1.101)	U	120	6
L. Wang, 2015	China	RCC	RT-PCR	≥3.8-fold	92 (42/50)	OS	3.894 (1.872–8.014)	M	60	7
Shou-Hua Wang, 2016	China	GBC	RT-PCR	≥Median ratio	24 (13/11)	OS	NA	NA	40	6
Na Liu, 2017	China	TC	RT-PCR	≥3.58	131 (95/36)	OS	2.268 (1.274–4.032)	M	60	7
Yi Xu, 2017	China	CCA	RT-PCR	Mean	56 (31/25)	OS	NA	NA	60	6

CCA = cholangiocarcinoma, CRC = colorectal cancer, GBC = gallbladder cancer, GC = gastric cancer, HCC = hepatocellular carcinoma, M = multivariate analysis, NA = not available, NSCLC = non-small cell lung cancer, OS = overall survival, RCC = renal cell carcinoma, TC = thyroid cancer, U = univariate analysis.

Table 2

The characteristics of included studies in the meta-analysis.

					H19 expression													
					High								Low					
Author	Year	Region	Cancer type	Sample size	Total	M	Elder	BTS	PHG	LNM	DM	HTS	Total	M	Elder	BTS	PHG	LNM	DM	HTS
Zhang et al	2014	China	GC	80	40	24	24	NA	NA	32	NA	31	40	23	19	NA	NA	18	NA	13
Chen et al	2016	China	GC	128	64	41	NA	35	NA	35	2	34	64	38	NA	33	NA	24	1	14
Zhang et al	2015	China	NSCLC	70	35	21	12	28	32	23	NA	NA	35	25	21	19	29	18	NA	NA
Ge et al	2018	China	NSCLC	76	35	15	22	11	NA	NA	NA	NA	41	17	26	16	NA	NA	NA	NA
Han et al	2016	China	CRC	83	48	20	19	NA	36	24	20	31	35	20	17	NA	16	20	20	14
Chen et al	2017	China	CRC	96	53	21	31	13	11	NA	15	28	43	21	26	8	2	NA	4	14
Ding et al	2018	China	CRC	185	125	77	60	67	NA	NA	NA	73	60	29	27	22	NA	NA	NA	25
Li et al	2018	China	CRC	214	133	65	55	NA	58	NA	90	120	81	47	38	NA	21	NA	28	49
Luan et al	2018	China	melanoma	30	15	8	NA	NA	NA	NA	NA	NA	15	9	NA	NA	NA	NA	NA	NA
Shi et al	2018	China	melanoma	82	42	28	22	NA	NA	28	27	NA	42	21	16	NA	NA	18	15	NA
Yang et al	2015	Korea	HCC	240	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wang et al	2015	China	RCC	92	42	26	20	16	NA	15	9	NA	50	31	20	28	NA	4	2	NA
Wang et al	2016	China	GBC	21	13	4	4	5	NA	9	NA	9	11	2	7	9	NA	2	NA	3
Liu et al	2017	China	TC	131	95	35	NA	70	NA	56	NA	64	36	8	NA	17	NA	13	NA	16
Xu et al	2017	China	CCA	56	31	15	12	17	21	21	NA	27	25	10	14	6	16	11	NA	14

BTS = big tumor size, CCA = cholangiocarcinoma, CRC = colorectal cancer, DM = distant metastasis, GBC = gallbladder cancer, GC = gastric cancer, HCC = hepatocellular carcinoma, HTS = high TNM stage (III/IV), LNM = lymph node metastasis, M = male, NSCLC = non-small cell lung cancer, PHG = poor histologic grade, RCC = renal cell carcinoma, TC = thyroid cancer.

carcinoma, thyroid cancer, and cholangiocarcinoma. The expression levels of H19 were detected by Quantitative Real-Time Reverse Transcription PCR in all studies except the study from Yang et al,[40] where the method used was not defined. Patients in these studies were divided into high and low H19 expression groups. The diagnosis of differentiation degree, lymph node metastasis (LNM), distant metastasis (DM), and TNM stage was based on pathological examination. The survival data were manually extracted from the specific values found in these articles.

3.2. Correlation between H19 expression and overall survival

In 10 of the 15 studies, HRs and 95% CIs of overall survival (OS) were directly collected and used to assess the relationship between lncRNA H19 expression and OS in human cancers. Then, a random-effect model was performed to estimate the pooled HRs and 95% CIs ($I^2 = 90\%$, $P < .01$). The result clearly demonstrates that high H19 expression is an unfavorable factor for overall survival outcome in human carcinomas (HR = 1.62, 95% CI = 1.36–1.93, $P < .001$) (Fig. 2).

3.3. Correlation between H19 expression and clinicopathological characteristics

Fourteen studies with 1347 patients were included in the meta-analysis of clinicopathological characteristics (CPs). Results showed that high H19 expression levels were positively correlated with poor tumor differentiation (OR = 2.41, 95% CI = 1.59–3.66, $P < .001$, fixed effect), more advanced clinical

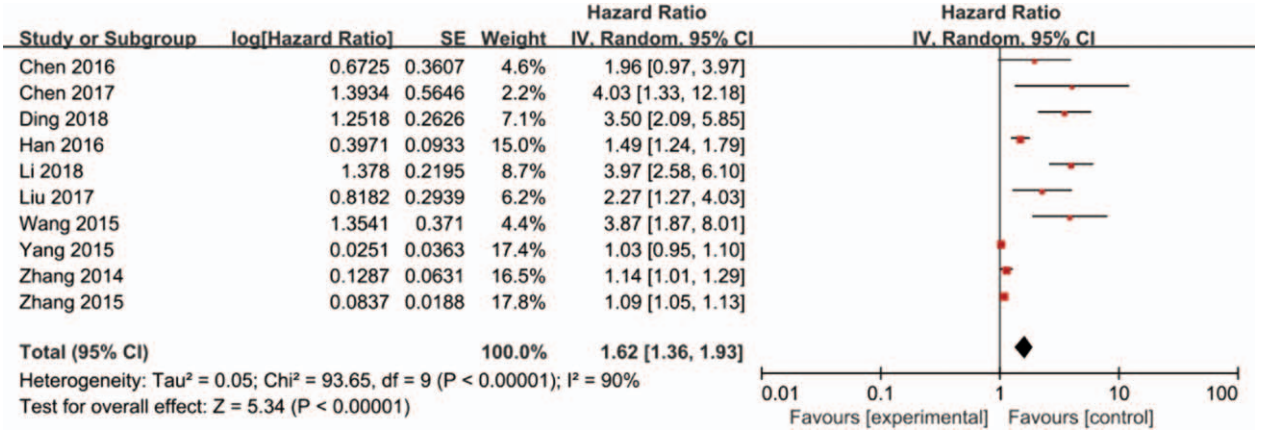

Figure 2. Forest plot for the association between H19 expression and overall survival (OS) rate in included published studies.

stage (OR = 3.39, 95% CI = 2.56–4.48, $P < .001$, fixed effect), earlier lymph node metastasis (OR = 2.38, 95% CI = 1.75–3.24, $P < .001$, fixed effect), and earlier distant metastasis (OR = 2.53, 95% CI = 1.16–5.55, $P < .05$, random effect) (see Figure S1, http://links.lww.com/MD/D536, Supplemental Content, which showed the correlation of H19 expression levels with poor tumor differentiation, more advanced clinical stage, earlier lymph node metastasis, and earlier distant metastasis, respectively). However, there was no apparent correlation in sex (OR = 1.05, 95% CI = 0.84–1.31, $P = .66$, fixed effect), age (OR = 0.91, 95% CI = 0.71–1.16, $P = .45$, fixed effect), or tumor size (OR = 1.37, 95% CI = 0.80–2.35, $P = .25$, random effect) (Table 3).

3.4. Validation of the results using TCGA dataset

In order to further evaluate the connection between the H19 expression level and OS in various cancers, we examined the H19 expression in 20 categories of cancers using data from The Cancer Genome Atlas (TCGA). The expression levels of H19 were upregulated in different types of cancers, including but not limited to: bladder cancer, breast cancer, cervical squamous cell carcinoma, esophageal cancer. Seven thousand four hundred sixty two patients from 20 independent datasets were divided into high and low expression groups on the basis of the median H19 level. The fixed effects model was used because of no heterogeneity among these TCGA datasets ($I^2 = 0\%$, $P = .53$). As shown in Fig. 3, the result confirmed that patients from the high H19 expression group had a shorter overall survival time than those from the low H19 expression group across cancer types (HR = 1.12, 95% CI = 1.03–1.22, $P = .01$).

3.5. Sensitivity analysis and publication bias

In consideration of obvious heterogeneity found in the meta-analysis of OS ($P < .001$, $I^2 = 90\%$), we conducted a sensitivity analysis to explore the impact of individual studies on the composite results. The pooled HR was influenced most significantly by the study from Zhang et al[18] (Fig. 4), suggesting that this study accounts for most of the heterogeneity. In addition, we observed the cut-off value of the H19 expression levels was not consistent among included studies, and the follow-up time was not exactly 60 months in some studies. Furthermore, the sample sizes were different. All these factors could have contributed to the heterogeneity.

Begg and Mazumdar rank correlation test, Egger regression, and funnel plots were applied to evaluate for potential publication bias in our meta-analysis. The results indicated that there was no obvious publication bias across the included studies in terms of CPs ($P > .05$) (see Figure S2, http://links.lww.com/MD/D537, Supplemental Content, showing no obvious publication bias). With regard to OS, Begg funnel plot is shown, and the results from Begg test ($P = .283$) and Egger test ($t = 4.7$, $P = .002$) indicated that this particular analysis likely contains publication bias (Fig. 5A). Consequently, we conducted a trim and fill analysis with the random-effects model. A statistically significant difference between the H19 levels and OS was observed according to the pooled analysis of 10 included studies (HR = 0.473, 95% CI: 0.298–0.648, $P < .001$, random effect) (Fig. 5B). Five imputed unpublished studies were also included in the study, for the purpose of acquiring a symmetrical funnel plot. The pooled analysis, integrated with the hypothetical studies, revealed no statistical significance in the relationship between H19

Table 3

The meta-analysis results for the association between LncRNA H19 expression and clinical parameters.

Variables	Included studies	Patients(n)	OR 95% CI	P	I^2	Model
Gender (male vs female)	14	1347	1.05 (0.84, 1.31)	.66	5%	Fixed
Age (older vs younger)	11	1058	0.91 (0.71, 1.16)	.45	21%	Fixed
Tumor size (large vs small)	9	858	1.37 (0.80, 2.35)	.25	68%	Random
Differentiation (poor vs moderate/well)	5	519	2.41 (1.59, 3.66)	<.001	0%	Fixed
TNM stage (III/IV vs I/II)	9	997	3.39 (2.56, 4.48)	<.001	20%	Fixed
Lymph node metastasis (yes vs no)	9	746	2.38 (1.75, 3.24)	<.001	43%	Fixed
Distant metastasis (yes vs no)	6	695	2.53 (1.16, 5.55)	.02	69%	Random

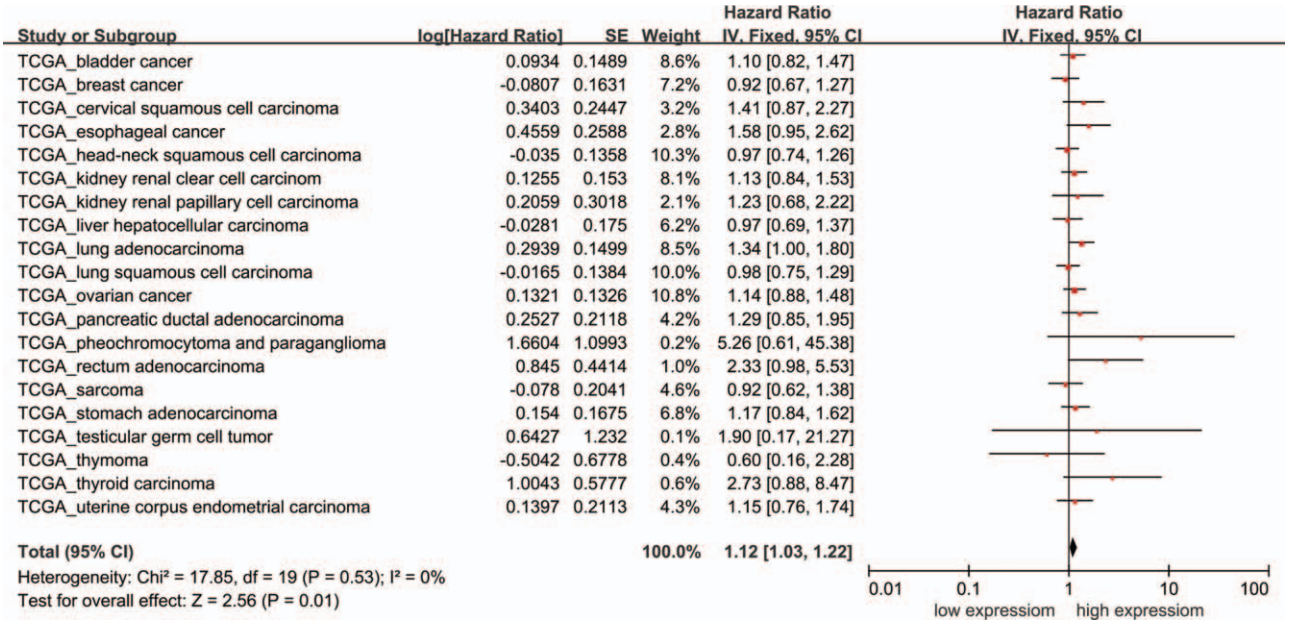

Figure 3. Forest plot for the association between H19 expression and overall survival (OS) rate in the TCGA dataset. TCGA = the Cancer Genome Atlas.

expression levels and OS (corrected HR = 1.147, 95% CI: 0.949–1.385, $P = .155$, random effect).

4. Discussion

Accumulating scientific evidence has revealed that lncRNAs are aberrantly expressed in various cancers.[27] To date, a great number of lncRNAs, including CASC2,[28] HNF1A-AS1,[29] PANDAR,[30] and ROR,[31] have been reported as potential prognostic biomarkers in human carcinomas. Similarly, H19 has been reported to be overexpressed specifically in different cancers, identifying it as a promising research target. Furthermore, previous publications have suggested that high H19 expression levels are highly correlated with worse clinical outcomes over time in human cancers. Although the prognostic value and clinicopathologic significance of H19 levels in cancer patients have been explored by some researchers, inconsistent results were found for some clinical parameters and the limitations of some of these studies are obvious. For example, it was previously found that H19 levels were associated with patients' age, but there was no correlation with lymph node metastasis in NSCLC.[18] Yet completely opposite results were reported in renal cell carcinoma.[32] Also, some previous articles

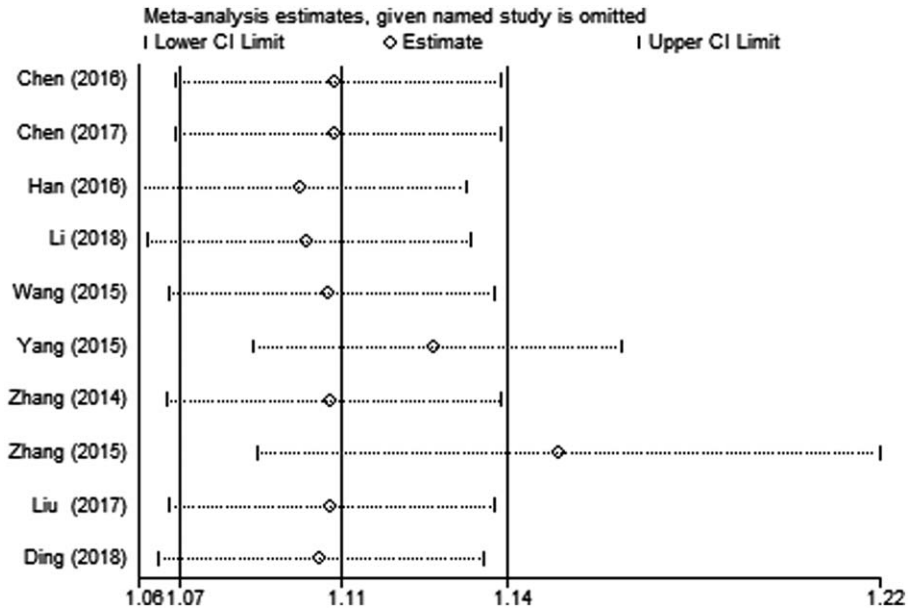

Figure 4. The sensitivity analysis for meta-analysis of OS. OS = overall survival.

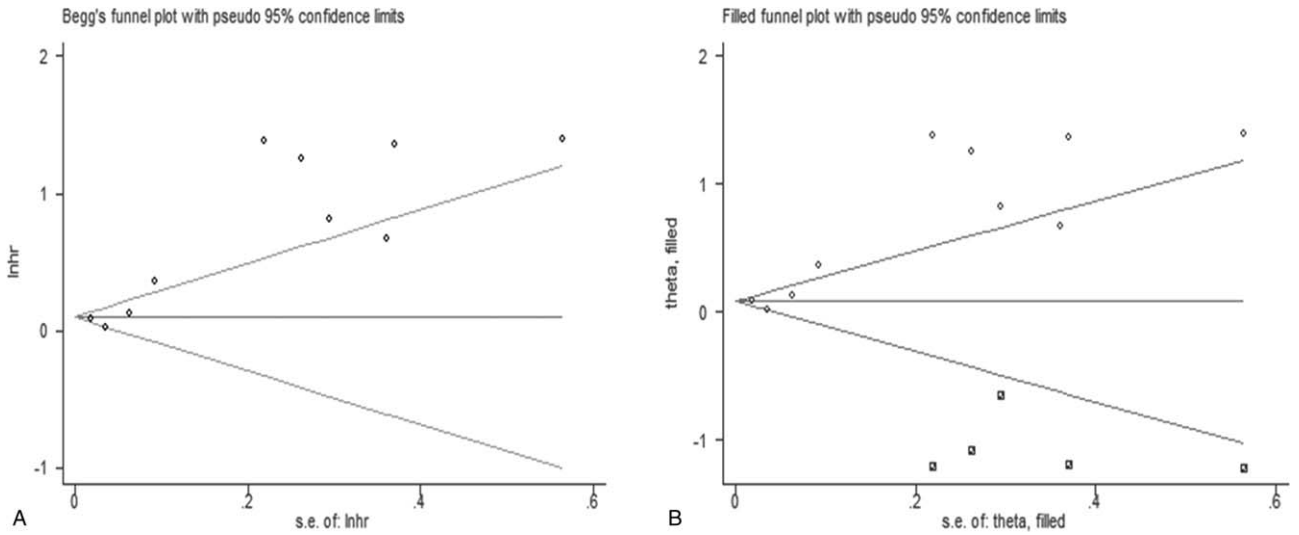

Figure 5. The detection of publication bias for meta-analysis of OS. (A) Begg funnel plot; (B) filled funnel plot. OS = overall survival.

only presented a Kaplan–Meier curve, rather than specific HR values. Finally, the sample sizes in several studies were too small to draw reliable conclusions from.[33,34] Therefore, we performed this meta-analysis to more comprehensively examine the prognostic value of H19 expression in various types of cancers.

Through the data extracted from past publications and the TCGA dataset, we found that upregulated lncRNA H19 expression was positively correlated with poor prognosis and clinicopathological features in patients with malignant tumors. Our findings suggest that overexpression of H19 could be an adverse indicator for the clinical outcome of cancer patients. Though it has been previously reported that patients categorized with high H19 expression had a worse prognosis as compared with those with low H19 expression,[35] that study only focused on the scientific literature, and some survival data were indirectly extracted from Kaplan–Meier curves. Unlike their study, our research analyzed a large survival dataset from TCGA to examine the correlation between H19 expression and OS. Moreover, all the survival data in our study was directly extracted from the set of included articles, instead of indirectly inferred. In addition, for the first time, we examined the prognostic significance of H19 expression levels in thyroid cancer, bladder cancer, pancreatic ductal adenocarcinoma, and other types of tumors, which was absent from previous meta-analysis. Finally, we found that H19 expression levels were positively correlated with poor tumor differentiation, more advanced clinical stage, earlier lymph node metastasis, and earlier distant metastasis, though no correlation with patient's age, sex, and tumor size. Notably, the significant correlation between H19 expression levels and distant metastasis was not observed in the previous meta-analysis. This inconsistent conclusion was possibly a result of our different sample sizes. Our effort includes more studies and more patients, as compared with previous work, in order to reduce the impact of any individual study's sampling errors, biases, and noise.

Despite previous studies testifying that lncRNA H19 was involved in the process of tumorigenesis and progression of human solid tumors, the underlying mechanism remains elusive. It is known there is a negative association between H19 and miR-17, and H19 can promote NSCLC cell invasion and metastasis via the miR-17/STAT3 axis.[36] Moreover, it has been found that upregulated H19 contributes to the occurrence of the epithelial-mesenchymal transition (EMT) process by targeting miRNA-203, which participates in the proliferation and invasion of NSCLC cells.[17] These results suggest that H19 may be a valuable prognostic biomarker and potential target for gene therapy in patients with NSCLC. It has also been reported that H19 mediates carcinogenesis by facilitating the RAS-MAPK signaling pathway in colorectal cancer.[37] H19 might serve as a competitive endogenous RNA to regulate the expression of its target gene HOXA10 by competing with miR-612, thus further promoting the progression of endometrial cancer.[38] A recent study showed that the H19/miR-29-3b/PGRN/Wnt signaling pathway participated in the pathogenesis of the EMT process, suggesting that the components of this signaling pathway could be potentially used as diagnostic biomarkers or therapeutic targets for colorectal cancer.[22] Another study reported that H19 was involved in the process of TGF-β-induced EMT by functioning as a ceRNA of miR-370-3p, indicating that the H19-miR-370-3p axis could be a potential molecular target to inhibit EMT in ovarian cancer.[39] In summary, lncRNA H19 is involved in the cell proliferation, migration, and invasion in various cancer,[7–9] and more relevant research should be conducted to elucidate the underlying mechanism of H19 with respect to its prognostic value for cancers.

The highlights of our meta-analysis are as follows: although previous studies have evaluated the clinicopathologic significance and prognostic value of H19 level in various cancers, this study is the first meta-analysis that combined data from published articles with a large TCGA dataset. Moreover, only the 10 studies that directly reported the specific value of the HR and 95% CI were included into our OS meta-analysis, and 5 other studies that only provided survival curves were excluded, thus reducing potential interference from human factors. Nonetheless, a few limitations do exist in this meta-analysis. First, except for 1 article from Korea,[40] all the included patients were from China, thus the conclusions are largely only applicable to those of East-Asian ethnicity. Second, cut-off values for high and low H19 expression, the age of patients, as well as tumor size were

inconsistent in different studies, consequently resulting in some heterogeneity. Third, the limited sample of patients and the number of included studies, though larger than previous efforts, could still result in errors and biases within the results. Fourth, the significant heterogeneity among included studies also might make our conclusions unreliable. Fifth, we uncovered potential publication bias in our study, which, we speculate, was caused by the sample size limitations and heterogeneity of the included literature. We speculate another possible cause could be the fact that articles with positive outcomes are easier to publish in modern journals. Therefore, in order to further and better validate our results, more studies with improved experimental design and larger sample sizes remain in demand.

5. Conclusion

This meta-analysis demonstrates that high H19 expression is closely related to shorter overall survival, poor tumor differentiation, more advanced clinical stage, earlier lymph node metastasis, and earlier distant metastasis in various types of cancers. Therefore, the expression level of H19 holds powerful prognostic value as an independent biomarker for human carcinoma.

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