

The clinical prognostic value of lncRNA LINC00675 in cancer patients

A meta-analysis

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Abstract

A newly discovered long non-coding RNA (lncRNA) is associated with the progression of a variety of tumors. The purpose of this meta-analysis is to explore further the relationship between clinicopathological features and the prognostic value of LINC00675 in cancers.

We searched the various database, including PubMed, Web of Science, Cochrane Library, Embase together with Wanfang, and China National Knowledge Infrastructure for articles on LINC00675 and clinicopathological characteristics and prognosis of patients with cancers before February 20, 2020. According to the inclusion and exclusion criteria, the studies that meet the criteria were systematically collected through search keywords. The Newcastle Ottawa document quality assessment system was used to evaluate the quality of documents. The required data from literature were extracted, and the hazard ratio (HR), odds ratio (OR), and 95% confidence interval (CI) were calculated using stata12.0 software and RevMan5.3 software.

A total of 5 studies covering 462 patients were included in this meta-analysis to evaluate the prognostic value of LINC00675 in cancers. Our results showed that high LINC00675 expression was significantly correlated with poor overall survival (OS) (HR = 1.60, 95% CI: 1.23–2.08, $P = .0005$). Additionally, upregulated expression of LINC00675 was significantly associated with tumor node metastasis stage (OR = 1.74, 95% CI: 1.18–2.58, $P = .006$) and distant metastasis (OR = 2.22, 95% CI: 1.21–4.08, $P = .01$).

Our study suggests that LINC00675 could be used as a biomarker to evaluate the prognosis of cancer patients. More studies to further confirm that the clinical value of LINC00675 in cancers will be required.

Abbreviations: DM = distant metastasis, lncRNA = long non-coding RNA, LNM = lymph node metastasis, NOS = Newcastle–Ottawa Quality Assessment Scale, OS = overall survival, qRT-PCR = quantitative real-time fluorescent polymerase chain reaction.

Keywords: cancer, LINC00675, long non-coding RNA, overall survival, prognosis

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1. Introduction

Cancer has become a major and complex public issue and the incidence is gradually increasing worldwide, which resulted in the high mortality and morbidity worldwide.^[1,2] Furthermore, the clinical characteristics of most cancers are in the advanced stage at the time of diagnosis,^[3] limiting the utility of therapy, so the route of treatment is mainly based on the cancer staging, the features, and status of patients. It is well established that immunotherapy has received great attention because of its effectiveness in some cancers in current years,^[4] and it has also been reported that the use of dendritic cells (DCs) vaccine is beneficial for advanced hepatocellular carcinoma (HCC) patients.^[5] However, despite the advanced and improved treatment strategies of surgery, radiotherapy, immunotherapy, and chemotherapy for cancer patients, and it has been reported that the 5-year rate remains dismal, especially for high-grade cancers.^[6,7] Moreover, there is a lack of effective biomarkers to accurately predict the prognosis of cancer, limiting the treatments for cancer. Thus, more efforts should be made to found novel predictable biomarkers for cancer.

Accumulating researches have demonstrated that long non-coding RNAs (lncRNAs) with the dysfunction of protein-coding and the length over 200 nucleotides plays an imperative role in the different biological processes of cancer, including cell proliferation, differentiation, invasion, migration, and metastasis via regulating gene expression, indicating a large amount of

noncoding RNAs have potential biological impacts and can be established as tumor inhibitors or oncogenes.^[8–11] Recently, lncRNAs have gained enormous attention and are reported to be associated with the progression of several cancers.^[12,13] The results of emerging studies have shown that the expression extents of lncRNA TUG-1,^[14] lncRNA PCAT-1,^[15] and lncRNA ZEB1-AS1^[16] have been associated with clinicopathological features and prognosis of numerous cancers. In addition, it has been reported that serum Metadherin mRNA expression was involved in tumor prognosis and could be suggested as a non-invasive biomarker for colorectal cancer patients.^[17] Muhammad et al found that the role of HOX transcript antisense RNA (HOTAIR) overexpression is crucial for survival outcomes and clinical parameters of chronic myeloid leukemia, suggesting that HOTAIR can be recognized as a new and valuable prognostic biomarker for chronic myeloid leukemia,^[18] meanwhile circulating miR-146a can predict early response to imatinib treatment in patients with chronic myeloid leukemia.^[19] Another study revealed that octamer-binding transcription factor 4 (Oct4) plays an important role in the progression and prognosis of patients with gastric carcinoma (GC).^[20] Moreover, another research found that high-temperature-required protein A2 (HtrA2) is a potential biomarker for the diagnosis of breast cancer.^[21] The results of recent literatures have proposed that LINC00675 is related to clinicopathological features and prognosis of various cancer patients via participating in cancer cells proliferation and invasion.^[22,23] All these results provide evidences that lncRNAs may serve as novel prognostic biomarkers and therapeutic targets in human tumors.^[24,25]

LINC00675 belongs to the lncRNA family, and is also known as TMEM238L. It is a long intergenic non-coding RNA that is found on the region 17p13.1-p12 of the human chromosome. According to previous study, lncRNA Linc00675 has been proved to prevent the metastasis of gastric cancer cells through contributing to vimentin collapse and being downregulated in human gastric cancer, identifying as a tumor suppressor gene.^[26] However, it has been shown that LINC00675 expression in pancreatic ductal adenocarcinoma was 672 times higher than normal pancreatic tissues and functioned to facilitate the progression of pancreatic cancer cell proliferation and invasion.^[27] It has also been reported that LINC00675 can inhibit the proliferation, invasion and migration of colorectal cancer (CRC) cells, and predict the prognostication of CRC.^[22] Based on those findings, we speculated that high expression levels of LINC00675 are involved in clinicopathological features such as tumor size, lymph node metastasis (LNM), differentiation, tumor node metastasis (TNM) stage, distant metastasis (DM), and prognosis.

Due to inadequate information, there have been no reports with regard to the prognostic value of LINC00675 in patients with cancer. We, therefore, conducted this meta-analysis to investigate the relationship between LINC00675 and clinicopathological characteristics and prognosis for cancer patients.

2. Materials and methods

2.1. Literature search

This meta-analysis was performed on the basis of the guidelines for reporting systematic reviews and meta-analyses.^[28] A comprehensive literature search was independently performed by 2 investigators (Hao Hua and Jie Wang) without restriction to regions, publication types, or languages. The primary sources

were the electronic databases of PubMed, Web of Science, Cochrane Library, Embase. The last search time was prior to February 20, 2020. The search terms were included: “LINC00675” AND “Tumor” OR “Cancer” OR “Carcinoma” OR “Neoplasia” AND “Survival” OR “Outcome” OR “Predict”. Any discrepancy was solved by consultation of a researcher, not involved in the initial procedure. The relevant literature was manually searched for additional eligible articles.

2.2. Inclusion and exclusion criteria

We used the following inclusion criteria to screen published articles:

1. the exposure of interest was LINC00675;
2. the outcomes of interest were the overall survival and clinicopathological parameters of various cancers;
3. providing the hazard ratio (HR) estimates and their 95% confidence interval (CI) or reporting available data for calculation of the HR estimates and 95% CIs;
4. the link between LINC00675 expression and cancer patients prognosis was investigated;
5. patients were divided into high and low LINC00675 expression groups.

Exclusion criteria were the following:

1. studies without adequate data to calculate the relevant estimates for further analysis;
2. the subjects were cell or animal experiments, letters, case reports, reviews, or duplicate publications.

2.3. Data extraction

Two investigators (Pingyong Zhong and Tinggang Mou) separately extracted relevant information from each eligible study, and any discrepancies were resolved through discussion, and an agreement was achieved by a third investigator (Pan Liu). The following data were extracted: name of the first author, publication year, country; Patients' characteristics: cancer type, number of patients, expression pattern, follow-up duration, gender, age, tumor size, differentiation, LNM, DM, and TNM stage, HR and the corresponding 95% CI for the expression LINC00675 of cancer patients for OS. HRs with corresponding 95% CIs were directly extracted if it was reported in multivariate analyses. If unavailable, the HR estimates were extracted from the graphical survival plots through Engauge Digitizer V4.1 software according to Tierney method.^[29]

2.4. Quality assessment

Two reviewers independently applied the Newcastle-Ottawa Scale (NOS) criteria to assess the quality of included studies. The NOS consists of 3 factors: patient selection, comparability of the study groups, and outcome assessment. The overall scores range from 0 to 9, which was allocated to each study except randomized control trials (RCTs). Studies with a NOS ≥ 5 were considered to be of high quality.

2.5. Statistical analysis

All statistical analyses in this meta-analysis were performed using STATA software, version 12.0 (STATA, College Station, TX),

and RevMan5.3 (Cochrane community) software. A two-sided P value of .05 or less was considered significant, or opposite. HR and 95% CI to be assessed was beneficial for determining the relationship between LINC00675 and OS. ORs and 95% CIs were evaluated for determining the relationship between LINC00675 and clinicopathological features, including the gender, tumor size, differentiation, LNM, and TNM stages. If $HR > 1$, there was a significant connection between LINC00675 overexpression with poor survival. If $HR < 1$, then it indicated that high LINC00675 expression marked a trend toward long survival.

Heterogeneity between studies was assessed by using the Chi Squared-based Q test^[30] and calculating I^2 values.^[31] The random-effects model was conducted when the value of I^2 was over 50%. In contrast, the fixed-effects model was used with a

value of less than 50% of I^2 . By constructing a funnel plot and Begg test, the possible publication bias is shown. Sensitivity analysis was used to evaluate the stability of the synthesis results.

3. Results

3.1. Included literatures

As shown in Figure 1, a total of 107 articles were identified through the systematic electronic databases search and manual searching relevant reference lists. However, among them, a total of 68 studies were excluded after duplicates, and 23 articles were excluded for the following reason: unrelated articles through screening title and abstract, leaving 16 eligible articles were assessed for full text review. We further excluded 11 articles because of insufficient data. Finally, a total of 5 selected studies

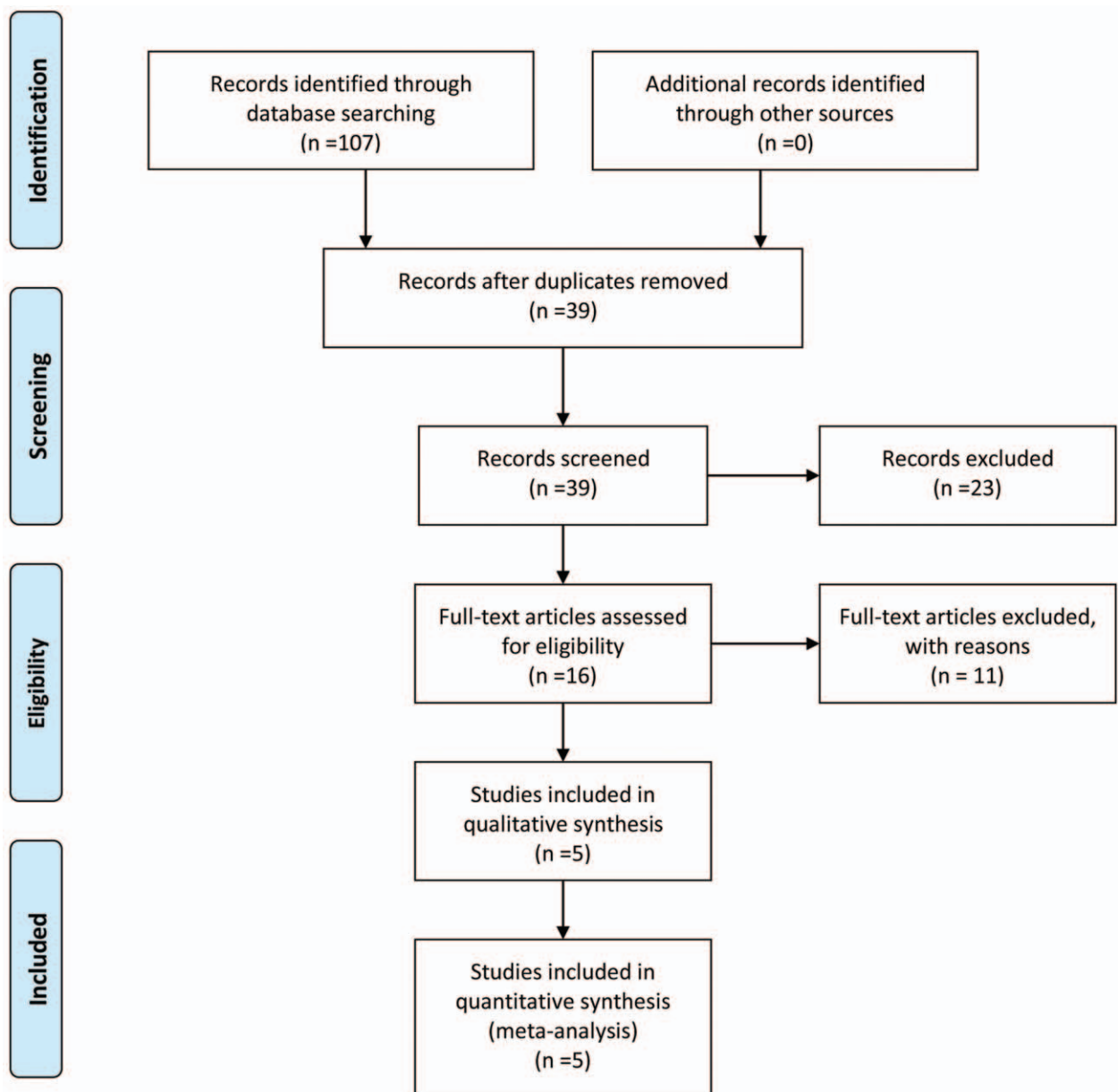


Figure 1. Flow diagram of the literatures selection procedure in this meta-analysis.

Table 1
The main characteristics of the included studies in the meta-analysis.

Study	Region	Tumor type	Sample size	TNM stage	LINC00675 expression		Cut-off value	Detection method	Outcome measure	NOS
					high	low				
Zeng, et al 2017 ^[26]	China	GC	45	I-IV	22	23	Median	qRT-PCR	OS	7
Ma, et al 2018 ^[32]	China	CC	66	I-IV	33	33	Median	qRT-PCR	OS	7
Zhong, et al 2018 ^[33]	China	ESCC	143	I-IV	70	73	Median	qRT-PCR	OS	6
Li, et al 2018 ^[23]	China	glioma	118	I-IV	59	59	Median	qRT-PCR	OS	7
Li, et al 2015 ^[27]	China	PDAC	90	I-IV	45	45	Median	qRT-PCR	OS	6

CC = cervical cancer, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, NA = not applicable, OS = overall survival, PDAC = pancreatic ductal adenocarcinoma, qRT-PCR = real-time quantitative polymerase chain reaction.

for our meta-analysis.^[2,3,26,27,32,33] All of the selected articles contained 462 patients were published in English with the posted time ranged from 2015 to 2018. All of the individuals included in the article are from china. The expression of LINC00675 was detected by quantitative real-time fluorescent polymerase chain reaction (qRT-PCR) in all studies. To distinguish the expression of LINC00675 by high and low levels, the cut-off value was used. The clinical outcomes were also recorded for OS. The major characteristics of all included articles were summarized in Table 1.

3.2. The expression of LINC00675 was significantly correlated with OS

Included studies comprising 462 patients recorded the relationship between lncRNA LINC00675 and OS. The fixed-effect model was used for analysis owing to small heterogeneity among the studies ($I^2=14\%$, $P=.32$). The synthetic results proposed that high expression of LINC00675 in cancer tissues has shown promising performance in poor OS in cancers (HR=1.60, 95% CI: 1.23–2.08, $P=.0005$) (Fig. 2). The patients with high LINC00675 expression had a worse OS than the patients with low expression of LINC00675. These results indicate that LINC00675 might be a factor for predicting the prognosis of cancer patients.

3.3. Relationship between LINC00675 and clinicopathological features

The relationship between LINC00675 expression and TNM stage was assessed in all the included studies. The pooled results indicated that elevated expression of LINC00675 was related to advanced TNM stage (III/IV vs I/II, OR=1.74, 95%CI=1.18–2.58, $P=.006$) (Fig. 3A), and the fixed effects model was selected

to estimate due to the inconspicuous heterogeneous. Furthermore, in terms of the association between LINC00675 and DM, the analysis results of 3 studies revealed that the patients with LINC00675 overexpression were more vulnerable to induce DM (OR=2.22, 95%CI: 1.21–4.08, $P=.01$), as shown in Figure 3B. However, there were no significant differences between LINC00675 expression and gender (OR=0.78, 95% CI: 0.53–1.16, $P=.23$), differentiation (OR=1.40, 95% CI: 0.59–3.31, $P=.44$), LNM (OR=1.15, 95% CI: 0.37–3.15, $P=.81$), tumor size (OR=1.35, 95% CI: 0.49–3.71, $P=.56$), and age (OR=1.09, 95% CI: 0.76–1.56, $P=.65$) (Fig. 4A–E). All these informations are presented in Table 2.

3.4. Publication bias and sensitivity analysis

The publication bias of the meta-analysis was assessed according to Begg test. The result indicated that no significant publication bias had an effect on the analysis of OS ($Pr > |z| = 0.808$) (Fig. 5). Additionally, as shown in Figure 6, the result for sensitivity analysis for OS was negative, revealing that our results were relatively robust. The sensitivity analysis revealed that the pooled HR was not significantly affected by eliminating any single study, indicating that the results were relatively robust.

4. Discussion

To the best of our knowledge, numerous cancers are characterized by a difficult early diagnosis and poor prognosis. The majority of patients are at a high risk of advanced stage at the time of diagnosis, which means that tumors have spread to nearby or distant organs, tissues, or lymph nodes, leading to poor prognosis. Therefore, reliable novel biomarkers for predicting the diagnosis and prognosis of cancer patients are indispensable.

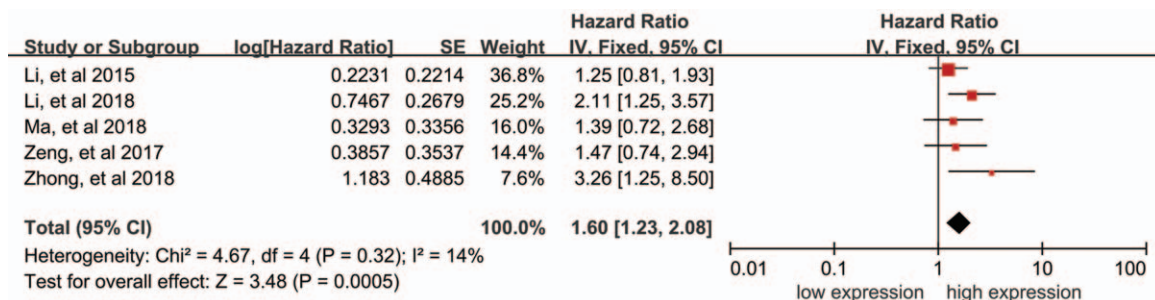


Figure 2. Forest plots of the included literatures evaluating the association between LINC00675 expression with overall survival (OS).

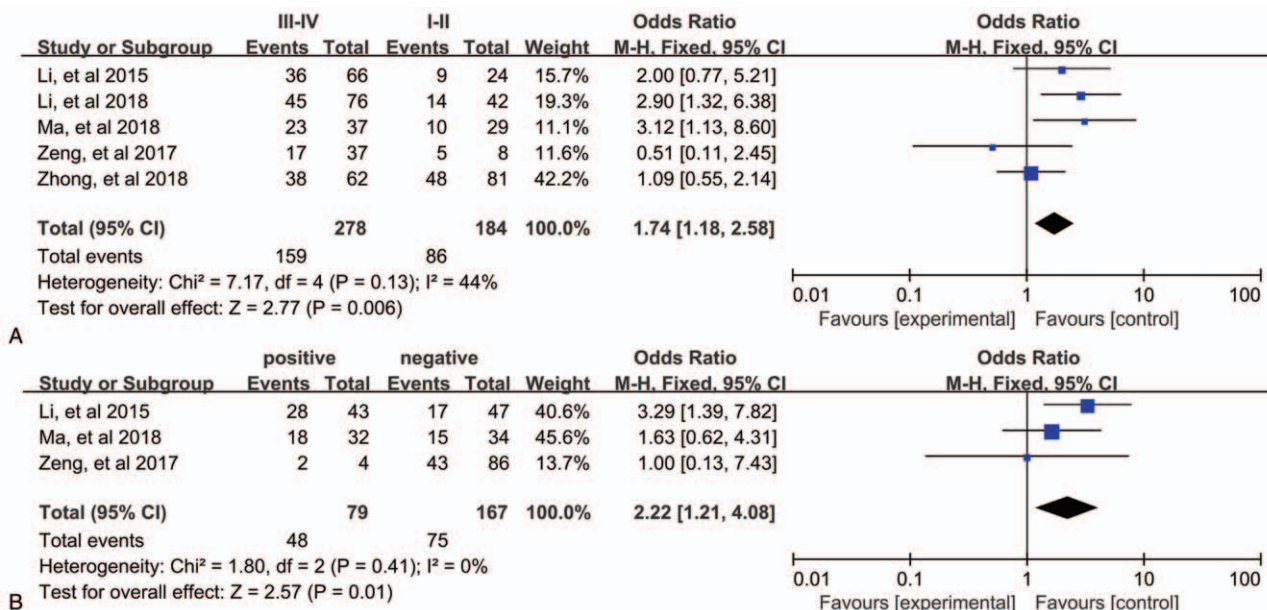


Figure 3. Forest plots of the included literatures evaluating the correlation between LINC00675 expression and clinicopathological characteristics. A: TNM stage; B: distant metastasis.

Recently, lncRNAs are recognized as noninvasive predictors in human cancers. Among them, there has been great interest in LINC00675 because accumulating studies have reported that LINC00675 may represent a vital determinant for the clinical outcome of various carcinomas.^[26] Due to limited numbers of sample in most studies, more evidence is required about the prognostic role of LINC00675 that provides sufficient data for further analysis.

As far as we know, this is the first meta-analysis providing comprehensive insights into the exact role of LINC00675 in patient survival and clinicopathological parameters. In the present study, we acknowledged that elevated LINC00675 level was significantly associated with inferior overall survival in various cancers, indicating that LINC00675 could be used as a functional indicator for the prognosis of cancers, with the possibility of supporting new therapies. In terms of clinicopathological features, we also found that the high LINC00675 expression group is more vulnerable to induce the high risk of DM and advanced TNM status than those in the low LINC00675 expression group. These data indicate a significant difference between LINC00675 overexpression and the incidence of DM and high TNM stage, signifying that increased LINC00675 expression has a positive effect on advanced cancer features. However, no obvious relationships were found between the high LINC00675 expression and gender, tumor size, differentiation, LNM, and age.

The underlying mechanisms of the relationship between abnormal LINC00675 expression and poor clinical prognosis in cancers are complex and need to be clarified. There are several possible explanations for accounting this significant connection. Previous studies have demonstrated that LINC00675 is markedly involved in cancer cell proliferation and migration by promoting the activity of the Wnt/ β -catenin signaling pathway to activate downstream, targets c-myc and cyclin D1.^[34,35] In cervical

cancer, Ma et al confirmed that LINC00675 has a negative impact on cell proliferation, migration, and invasion via treating GSK-3 β inhibitor LiCl.^[32] LINC00675 promotes cell proliferation by enhancing the activity of the p53 signaling pathway.^[36] Li et al demonstrated that TRIP6 was regulated to be beneficial for the effect of LINC00675. Silencing on inhibiting glioma cell proliferation, migration, and invasion.^[23] Another study reported^[27] that not only inhibition of LINC00675 can reduce cell proliferation and invasion by regulating its expression in SW1990 and miacpa-2 cell lines, but also knockdown of LINC00675 resulted in S phase arrest in pancreatic cancer cells, which may improve the response to gemcitabine therapy to an excellent prognosis of cancer undoubtedly. However, this result needs to be further explored.

Similar to other meta-analyses, there are several limitations in our meta-analysis. First, only English language reports have been involved. All the included studies were from China so that we may have missing data from important studies published in other languages, therefore, the conclusions represent the Chinese population. Second, all the included studies were retrospective, and the sample size was relatively small, larger cancer patients and all aspects of cancers should be included in future studies. Additionally, the studies included in this analysis were insufficient, especially in views of subgroup analysis. Thus, potential publication bias is very likely to exist, despite the lack of evidence from our statistical tests. At last, some HRs of OS were extracted from the Kaplan–Meier curves or available data rather than being reported directly, leading to latent errors.

5. Conclusions

In summary, our meta-analysis has revealed a significant relationship of the elevated expression of LINC00657 with poor survival and clinical outcomes in different types of cancer,

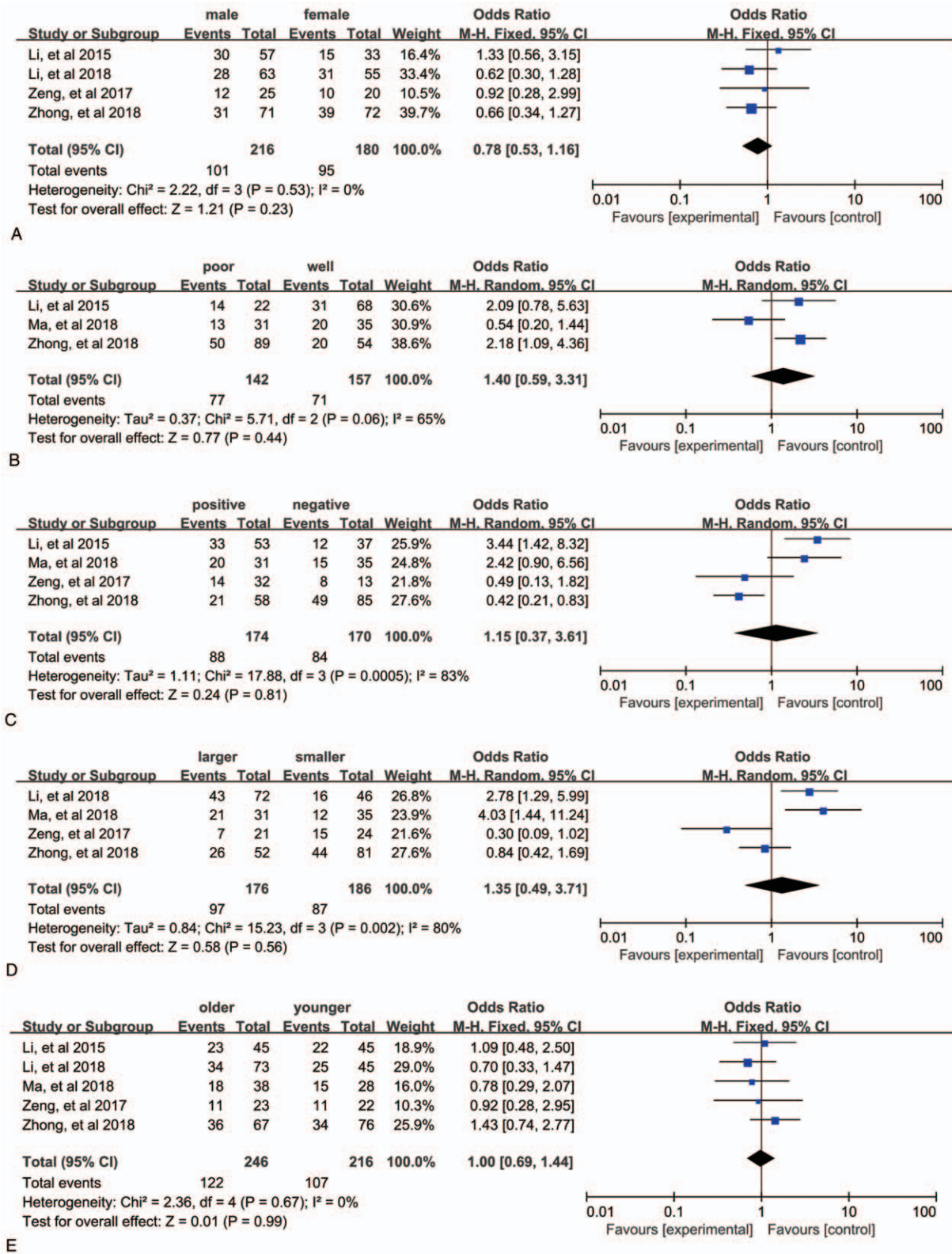


Figure 4. Forest plots of the included literatures evaluating the correlation between LINC00675 expression and clinicopathological characteristics. A: gender; B: differentiation; C: tumor size. D: lymph node metastasis; E: age.

Table 2

Summary of the relationship between LINC00675 over-expressed and clinicopathological parameters.

Clinicopathological parameters	Studies	Patients	OR (95% CI)	P value	Heterogeneity		
					I ²	P value	Model
Age (older vs younger)	5	462	1.00 (0.69, 1.44)	.99	0%	.67	Fixed
Gender (male vs female)	4	396	0.78 (0.53, 1.16)	.23	0%	.53	Fixed
Tumor size (larger vs smaller)	4	362	1.35 (0.49, 3.71)	.56	80%	.002	Random
Differentiation (poor vs well)	3	299	1.40 (0.59, 3.31)	.44	65%	.06	Random
TNM stage (III+IV vs I+II)	5	462	1.74 (1.18, 2.58)	.006	44%	.13	Fixed
LNM (Positive vs Negative)	4	344	1.15 (0.37, 3.69)	.81	83%	.0005	Random
DM (Positive vs Negative)	3	246	2.22 (1.21, 4.08)	.01	0%	.41	Fixed

95% CI = 95% confidence interval, DM = distant metastasis, LNM = lymph node metastasis, OR = odds ratio, TNM = tumor node metastasis.

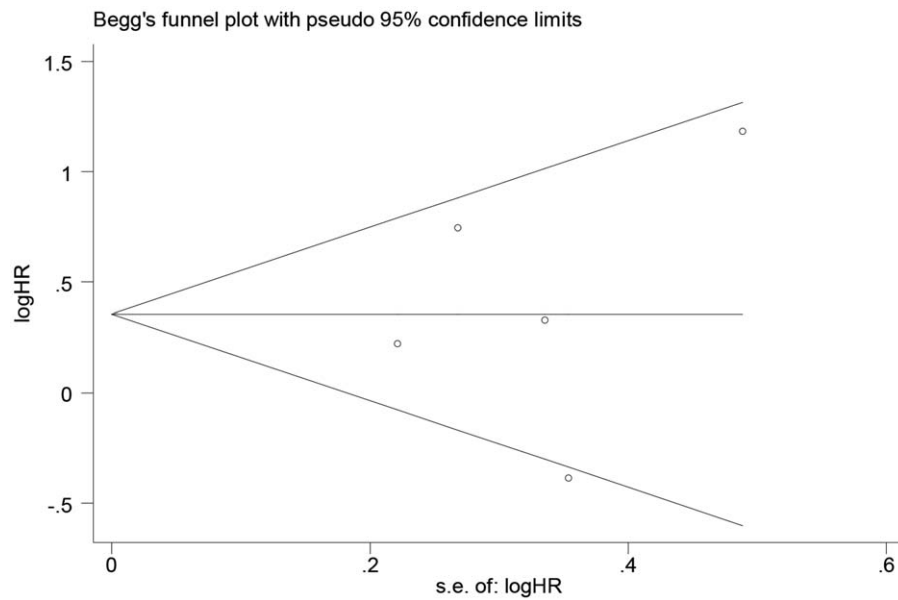


Figure 5. Begg funnel plot of publication bias on the correlation between LINC00675 expression and OS.

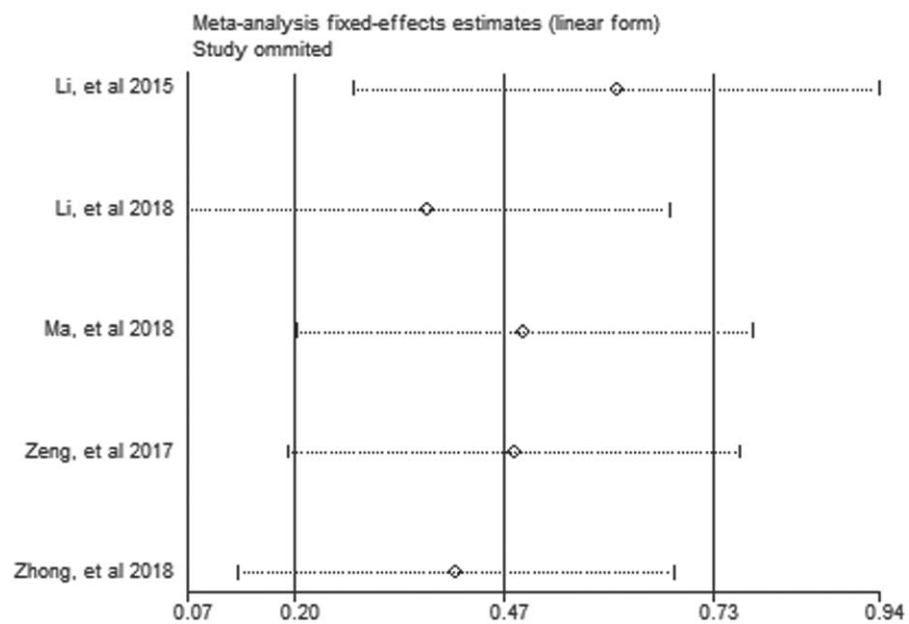


Figure 6. Sensitivity analysis for OS in this meta-analysis.

indicating that LINC00675 could act as a potential and practical prognostic biomarker. However, on account of the limitations of the present meta-analysis, it is essential to conduct more Large-scale and well-designed multicenter studies to clarify the prognostic value of LINC00675 in cancers.

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Project administration: Fei Xie.

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Supervision: Fei Xie.

Writing – original draft: Hao Hua.

Writing – review & editing: Hao Hua.

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