# Prognostic and clinicopathological role of long non-coding RNA ZFAS1 in various carcinomas

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## ABSTRACT

**Accumulating evidence indicated that the lncRNA zinc finger antisense 1(lncRNA ZFAS1) expression was increased in various cancer patients. We performed a meta-analysis to determine the relationship between lncRNA ZFAS1 expression and overall survival (OS) of patients with malignant tumors. A comprehensive, computerized literature search was conducted in PubMed, Medline, Ovid, Cochrane Library and Web of Science database up to June 15, 2017. Eight eligible studies with a total of 747 cancer patients were included. The results indicated the high expression of lncRNA ZFAS1 was associated with lymph node metastasis (LNM) (OR = 2.44 CI 95 %:1.21-4.91, *p* = 0.012)), distant metastasis (DM) (OR = 3.46 CI 95 % :1.26-9.55, *p* = 0.016), TNM stage (OR = 2.80 95% CI: 1.42–5.50, *p* = 0.003), and poor outcome (HR = 1.52 95% CI: 1.24–1.87, *p* < 0.001) in both gastrointestinal and non-gastrointestinal cancer patients. In conclusion, this meta-analysis showed that lncRNA ZFAS1 associated with clinicopathological features and poor OS in different type of cancers and lncRNA ZFAS1 might serve as a novel molecular marker for predicting outcome in human cancers.**

## INTRODUCTION

With the continuous development of medical technology and diagnostic level, cancer is still a major public health problem and a leading cause of death worldwide. According to the Bureau of Disease Control of China, about 4, 292, 000 Chinese patients had been diagnosed cancer, with 2.8million patients were dead from cancer in 2015 [1]. Although encouraging progress in treatment for cancer has been achieved, the 5-year survival rate remains low and the majority of patients die due to late diagnosis and metastases [2–3]. Therefore, it is urgent to found more reliable and efficient biomarkers for cancer metastasis and prognosis.

Long non-coding RNAs (lncRNAs) are a newly defined class of ribonucleic acid molecules which transcript with the length of > 200 nucleotide that do not encode proteins [4]. These lncRNAs act as key players in imprinting genomic loci, allosterically regulating enzymatic activity and shaping chromosome conformation which can also lead to the regulation of cell differentiation, proliferation, migration and invasion [5–7]. Dysfunction of these lncRNAs has been strongly associated with various biological processes including cell growth regulation, differentiation, apoptosis and tumorigenesis. LncRNA HOTAIR was identified as a candidate tumor promotor involved in various malignancies [8]. Recent evidence indicated the downregulated lncRNA BANCR could promote the proliferation of colorectal cancer cells, which served as tumor suppressor in colorectal cancer [9]. Although altered lncRNAs expression has been found in various types of malignancies, the functions of the majority of lncRNAs in malignancies remains unknown. Thus further studies are needed to elucidate their etiologic involvement in cancer.

LncRNA zinc finger antisense 1 (ZFAS1) is a transcript antisense to the 5' end of the gene ZNFX1( zinc finger NFX1-type containing 1) which was first discovered in breast cancer by Marjan E et.al [10]. Askarian Amiri et.al found that lncRNA ZFAS1 was upregulated in mammary gland and repressed in breast tumors [11]. The silencing of lncRNA ZFAS1 in breast tumor cells resulted in an increased cellular proliferation and differentiation which suggested that lncRNA ZFAS1 might act as a tumor suppressor gene in breast cancer [10]. However, there were opposite findings that elevated lncRNA ZFAS1 occurred in gastric cancer, hepatocellular carcinoma and glioma. The function of lncRNA ZFAS1 in cancer cells might be cell type-dependent [12–20]. Therefore, we need a systematical and comprehensive meta-analysis to explore whether overexpression of ZFAS1 in tumor are related to worse outcome.

In the present study through gathering available evidence, we carried out a meta-analysis combining available evidences to evaluate the prognostic value of lncRNA ZFAS1 expression in cancer patients, aiming to provide more theoretical supports for targeted regimens.

## RESULTS

### Study characteristics

According to the inclusion and exclusion criteria, 747 patients from 8 eligible studies were included in this meta-analysis [12–19]. The screening process was shown in Figure 1. The mean patient sample size was 96.86 (range from 46 to 173). All of the studies were conducted in China, which were published between 2015–2017. Among the 8 included studies, one focused on ovarian cancer, one on colonic cancer, one on non-small cell lung cancer, one on gastric cancer, two on glioma, one on hepatocellular carcinoma, one on pancreatic cancer and one on colorectal cancer (Table 1). All the diagnosis of lymph node metastasis (LNM), distant metastasis (DM), and TNM stage assessments was based on individual pathology.

### Association between the lncRNA ZFAS1 expression level and OS

In this meta-analysis, data of pooled HR and 95 %CI of overall survival were collected with 747 patients from 8 eligible studies. Because there was no obvious statistical heterogeneity across-studies ($I^2 = 0$, $P = 0.585$), the fixed-effects model was applied. Analysis showed the pooled HR for the high lncRNA ZFAS1 expression group versus the low expression group was 1.52 (95% CI: 1.24–1.87, $p < 0.001$, Figure 2). As for the non-gastrointestinal cancer the HR was 1.79 (95% CI: 1.18–2.71, $p = 0.002$) while the gastrointestinal cancer was 1.50 (95% CI: 1.16–1.94, $p = 0.007$). Therefore, our data demonstrated that lncRNA ZFAS1 was an independent OS factor among cancer patients and its high expression was associated with shorter OS in non-gastrointestinal cancer and gastrointestinal cancer.

### The analysis of lncRNA ZFAS1 expression and clinicopathologic characteristics of cancer

We pooled all the clinicopathological data from these eligible studies to do further meta-analysis for the association between lncRNA ZFAS1 expression level and clinicopathological parameters. As shown in Table 2, we observed that high lncRNA ZFAS1 expression were not associated with age (1.020, 95% CI:0.695-1.496, $p = 0.921$, random-effect), gender (0.914, 95% CI:0.613-1.365, $p = 0.662$, random-effect). Interestingly, high lncRNA ZFAS1 expression was significantly associated with certain phenotypes of tumor aggressiveness, such as advanced TNM stage (pooled OR = 2.80 , 95% CI: 1.42–5.50, $p = 0.003$, random-effect, Figure 3A), both gastrointestinal tumors (OR = 2.67, 95% CI:0.93–7.65, $p = 0.068$, random-effect) and non-gastrointestinal tumors (OR = 3.16, 95% CI:1.85-5.41, $p < 0.001$, random-effect) showed their association between the TNM stage and lncRNA ZFAS1 expression. The same result were also found in positive lymph node metastasis (pooled OR = 2.44 CI 95 % 1.21-4.91, $p = 0.012$; random-effect, Figure 3B). As a result of the subgroup analysis, lncRNA ZFAS1 and LNM were associated in both gastrointestinal tumors (OR = 4.10, 95% CI:2.15–7.83, $p < 0.001$, random-effect) and non-gastrointestinal tumors (OR = 1.60, 95% CI:0.62-4.10, $p = 0.331$, random-effect). In addition , the meta-analysis showed that the increased lncRNA ZFAS1 expression level was significantly associated with distant metastasis 3.46 (CI 95 % 1.26-9.55, $p = 0.016$, fixed-effect, Figure 3C),. Because of the insufficient data for other clinicopathological parameters (such as tumor location, family history of cancer), the relationship between elevated lncRNA ZFAS1 expression and these clinicopathological parameters were not processed for the meta-analysis.

### Sensitivity analysis

Sensitivity analysis showed that the pooled HRs were not materially influenced by any single study in the overall meta-analysis results in Figure 4. When each study was excluded sequentially, we didn't find the results were significantly altered each time.

### Publication bias

Begg's funnel plot and test were conducted to assess publication bias of the literature. The funnel plots of the OS analysis that based on lncRNA ZAFS1 expression were almost symmetric, as shown in Figure 5. In addition, The Egger's test did not display obvious publication bias for the HR evaluations of OS (Begg's test, $t = –0.25$, $p = 0.805$)

**Table 1: Basic characteristics of all studies included in the meta-analysis**

| Author | Year | Country | Sample size | Cancer type | TNM(I/II,VS III/IV) | ZFAS1 Expression | | Follow up (Month) | Method | Variance Analysis | Outcomes | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | high | low | | | | | |
| | | | | | | total | total | | | | | |
| **Bairong Xia** | 2016 | China | 60 | Ovarian cancer | 26/34 | 30 | 30 | 80 | RT-PCR | Multivariate analysis | OS | 6 |
| **Changyi Fang** | 2016 | China | 73 | Colorectal cancer | 48/25 | 36 | 37 | 120 | RT-PCR | Multivariate analysis | OS | 6 |
| **Fengmei Tian** | 2016 | China | 173 | NSCLC | 92/81 | 85 | 88 | 70 | RT-PCR | Multivariate analysis | OS | 8 |
| **Fengqi Nie** | 2016 | China | 54 | Gastric cancer | 24/30 | 27 | 27 | 40 | RT-PCR | Multivariate analysis | OS | 7 |
| **Kai Gao** | 2016 | China | 46 | Glioma | – | 23 | 23 | 50 | RT-PCR | Multivariate analysis | OS | 6 |
| **Tao Li** | 2015 | China | 113 | Hepatocellular carcinoma | 76/37 | 57 | 56 | 40 | RT-PCR | Multivariate analysis | OS | 7 |
| **Weili Wang** | 2016 | China | 159 | Colorectal cancer | 71/87 | 79 | 80 | 100 | RT-PCR | Multivariate analysis | OS | 6 |
| **Qiaoli Lv** | 2017 | China | 69 | Glioma | – | 27 | 42 | 48 | RT-PCR | Multivariate analysis | OS | 6 |

**Table 2: Meta-analysis results for the associations of over-expressed lncRNA-ZFAS1 with clinicopathological parameters**

| Clinicopathological parameters | No. of studies (*n*) | No. of patients | Pooled OR | *p*-value | Heterogeneity ($I^2$) |
|---|---|---|---|---|---|
| Age | 6 | 632 | 1.02, (0.70–1.50) | 0.921 | 28.8 |
| Gender | 5 | 572 | 0.91, (0.61–1.37) | 0.662 | 26.6 |
| TNM stage | 6 | 642 | 2.85, (1.57–5.16) | 0.001 | 69.1 |
| Lymph node metastasis | 5 | 460 | 2.44, (1.21–4.91) | 0.012 | 67.9 |
| Distant metastasis | 2 | 213 | 3.46, (1.26–9.55) | 0.016 | 0 |

## DISCUSSION

LncRNAs are transcripts longer than 200 nucleotides with little or no protein coding function [21]. In recent years, elegant studies had shown that lncRNAs could regulate gene expression at different levels and widely participate in various physiological processes, including nuclear import, alternative splicing, and epigenetics. [15, 22–24]. Interestingly, the aberrant expression of lncRNAs were widely involved in tumor progression, such as proliferation, cell cycle, invasion and metastasis. Until now, the functions of the majority of lncRNAs are still not fully understood. As novel kind of biomarkers, lncRNAs have significant potential for cancer diagnosis and accuracy prognostic prediction [25].

LncRNA zinc finger antisense 1 (ZFAS1) is a transcript antisense to the 5' end of the gene Znfx1 which was first discovered in breast cancer. Previous study suggested that lncRNA ZFAS1 which harbored C/D-box snoRNAs could function independently of the snoRNAs and repressed the proliferation and differentiation in human breast cancer [10]. Numerous studies have tried to explore the biological function and mechanism of lncRNA ZFAS1 on oncogenesis and development in different cancer types. In addition, Wang et.al suggested that the upregulated lncRNA ZFAS1 in CRC might be involved in p53 and CDK1/cycliB complex-dependent cell cycle control and apoptosis [18]. Moreover, emerging evidence indicated that the upregulated lncRNA ZFAS1 promoted tumor metastasis of both HCC and ovarian cancer cell through miR-150-dependent manner [14]. Nie et al. also revealed that lncRNA ZFAS1 could mediate the carcinogenic effects in GC partially through silencing the KLF2 and NKD2 expression by binding with PRC2 and LSD1 [19]. Epithelial-Mesenchymal Transition (EMT) was mentioned in one study that the author suggested that lncRNA ZFAS1 induce EMT by elevating ZEB1 expression [12].

Up to now, the aberrant of lncRNA ZFAS1 was found in various malignancies, including gastric cancer, glioma, breast cancer, hepatocellular carcinoma, and

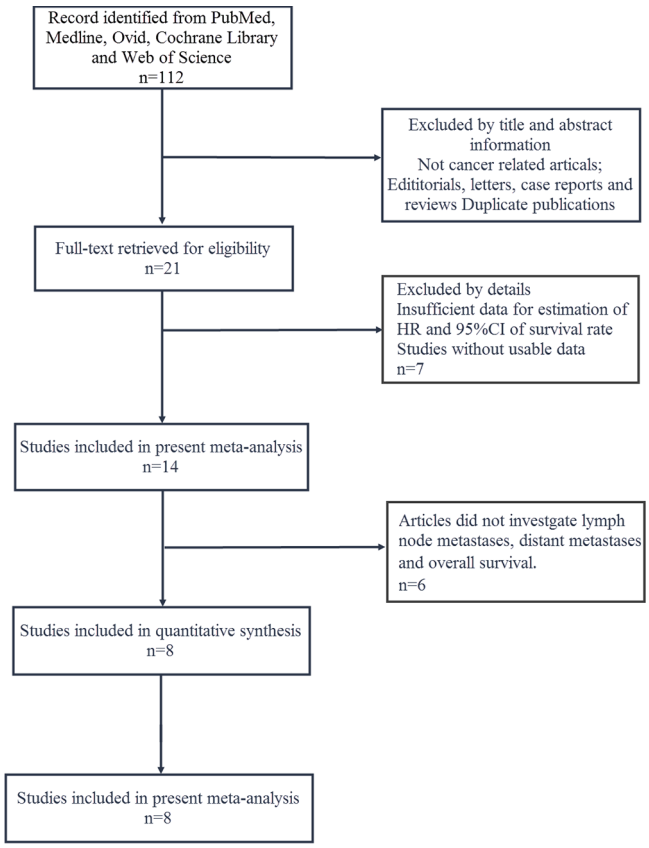


**Figure 1: Flowchart indicated the process of literature retrieval and selection.**

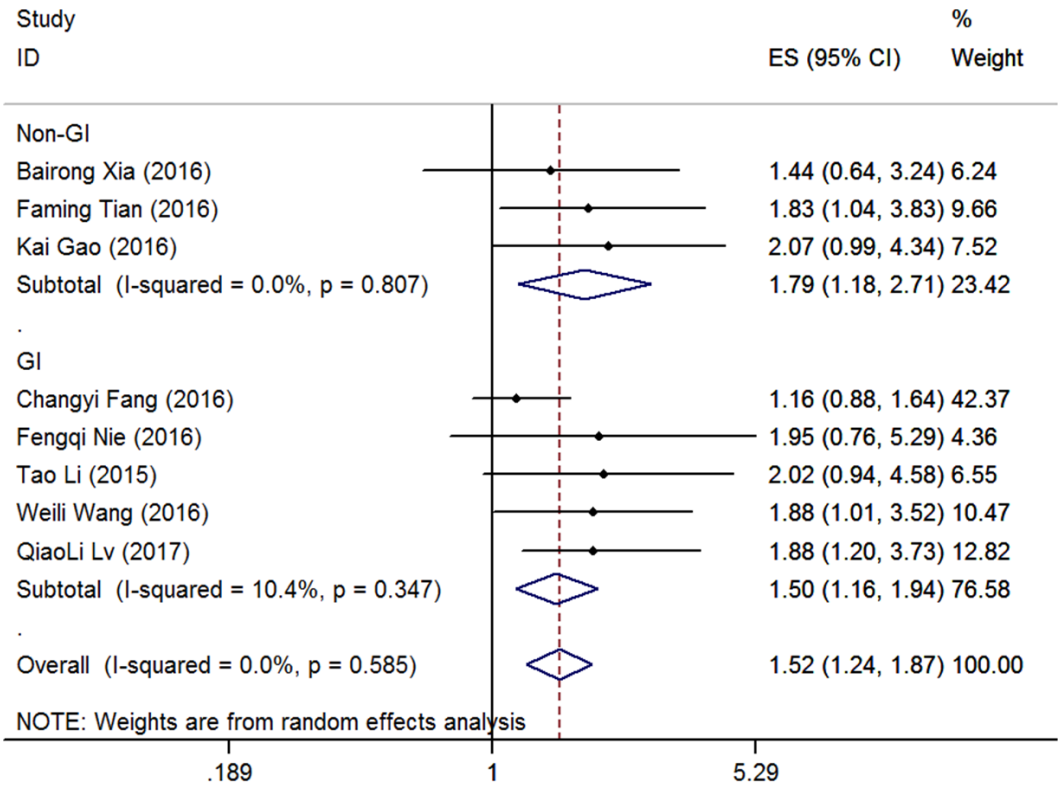


**Figure 2 : Meta-analysis of the pooled HRs of OS in different cancer types.**

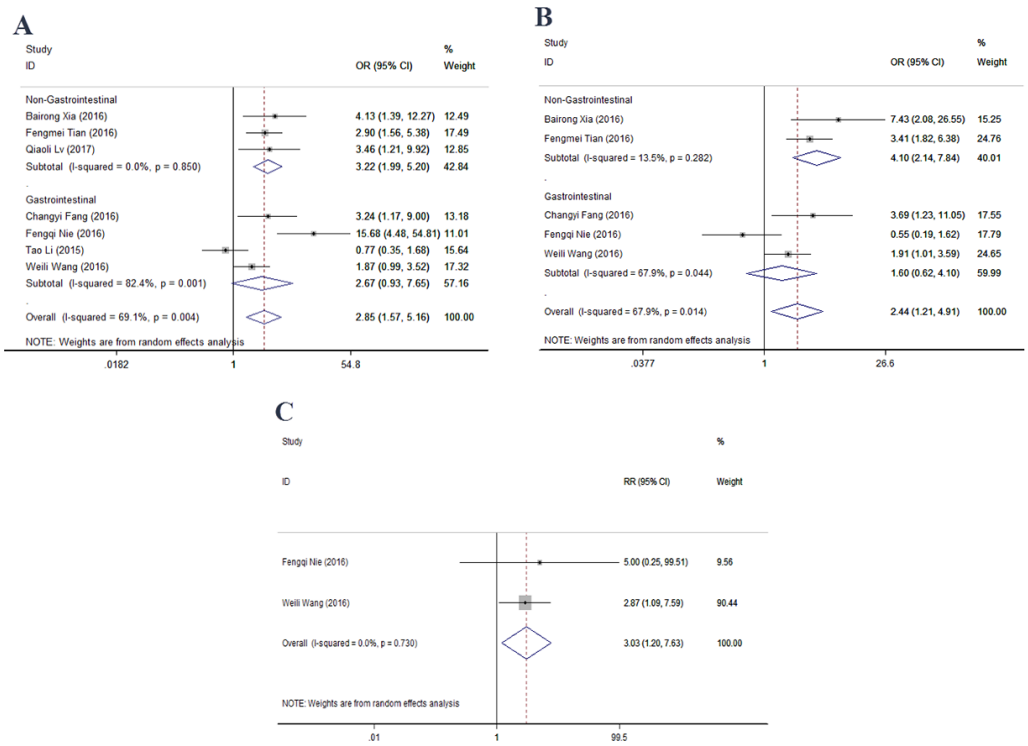


**Figure 3: Forest plot for the association between lncRNA ZFAS1 expression levels with TNM (A), LNM (B) and DM (C).**

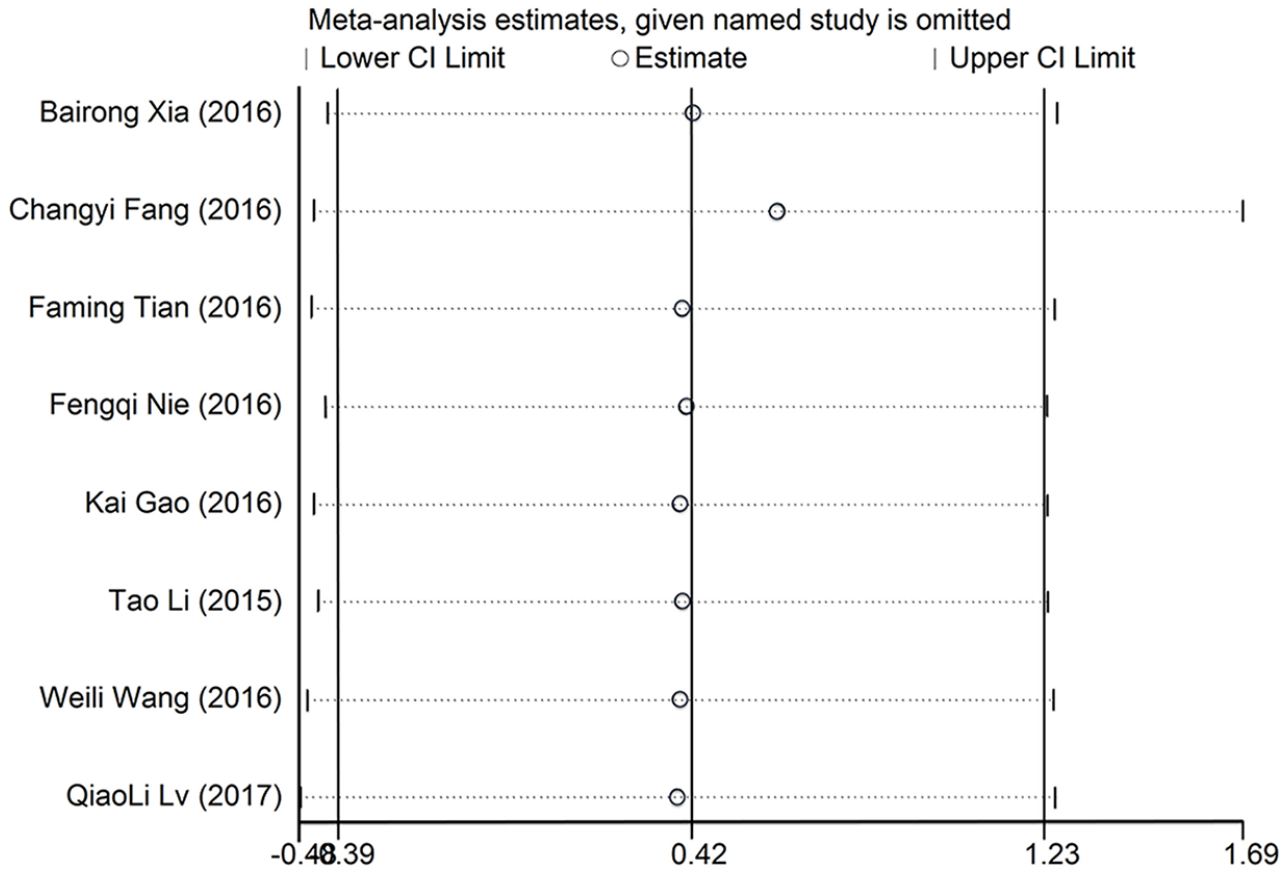


**Figure 4: Result of sensitivity analysis in OS group.**

NSCLC, indicating that lncRNAs were critical players in various cancers [13–15, 26]. The crucial association with LNM, TNM and OS might indicate that lncRNA ZFAS1 could function as a potential biomarker of prognosis in various cancers. However, the role of lncRNA ZFAS1 in cancer remained unclear, therefore, we use a meta-analysis to explore the prognostic value of lncRNA ZFAS1 in various types of malignancies.

In our present study, a significant association was observed between lncRNA ZFAS1 and OS in cancer patients (HR = 1.52 95% CI: 1.24–1.87, $P$ = 0.000). In subgroup analysis, a significant association between lncRNA ZFAS1 and OS in gastrointestinal system cancer patients (HR = 1.50, 95% CI: 1.16–1.94, $p$ = 0.002), and non-gastrointestinal system cancer patients (HR = 1.79, 95% CI: 1.18–2.71, $p$ = 0.007) was observed. These results implied the expression levels of ZASF1 could be used to predict the OS in both gastrointestinal or non-gastrointestinal cancers patients.

TNM stage is also a potential factor that plays crucial roles in cancer outcome. Numerous studies revealed that the expression of lncRNAs such as UCA1, BANCR, MALAT-1, associated with patients' clinical stage. We found that the lncRNA ZFAS1 expression had a significant association with TNM stage. Both gastrointestinal cancers and non-gastrointestinal cancers had supported the conclusion. However, heterogeneity was observed among the included studies especially in the subgroup analysis of gastrointestinal cancers in TNM stage. Lymph node metastasis was rarely occurred in hepatocellular carcinoma which might partially explain the inter-study heterogeneity in gastrointestinal cancer subgroup analysis of the TNM stage. As for the other cancers, in the case of lymph node metastasis, a significant association was observed in non-gastrointestinal cancers and gastrointestinal cancers. In addition, two studies reported the correlation between the lncRNA ZFAS1 expression level and DM, and high lncRNA ZFAS1 expression was obviously related to a high risk of DM. It is quite obvious that higher expression of lncRNA ZFAS1 was correlated with shorter OS, higher occurrence probability of LNM and advanced TNM stage in both gastrointestinal cancers and non-gastrointestinal cancers. These results suggested that lncRNA ZFAS1 might serve as a biomarker for both prognosis and clinical pathology. By performing the sensitivity and bias analysis, our meta-analysis did not draw different conclusions from the pooled estimates which in another word confirmed our relatively results.

However, there are still some limitations in the present meta-analysis that need to be emphasized. First of all, only 8 studies of Chinese population were analysis in this meta-analysis, therefore our data might just represent district population instead of the global population, the population bias, as well as the small sample size negatively affected the reliability of our study. Secondly, the cut-off value of lncRNA ZFAS1 expression differed in different types of cancer which lead to the increase of heterogeneity. The inaccurate cutoff values might affect the evaluation of lncRNA ZFAS1 as a prognostic biomarker. Thirdly, most of the included studies didn't report the negative result. The heterogeneity in our meta-analysis made us have to use random-effects model in some suspects, during to several

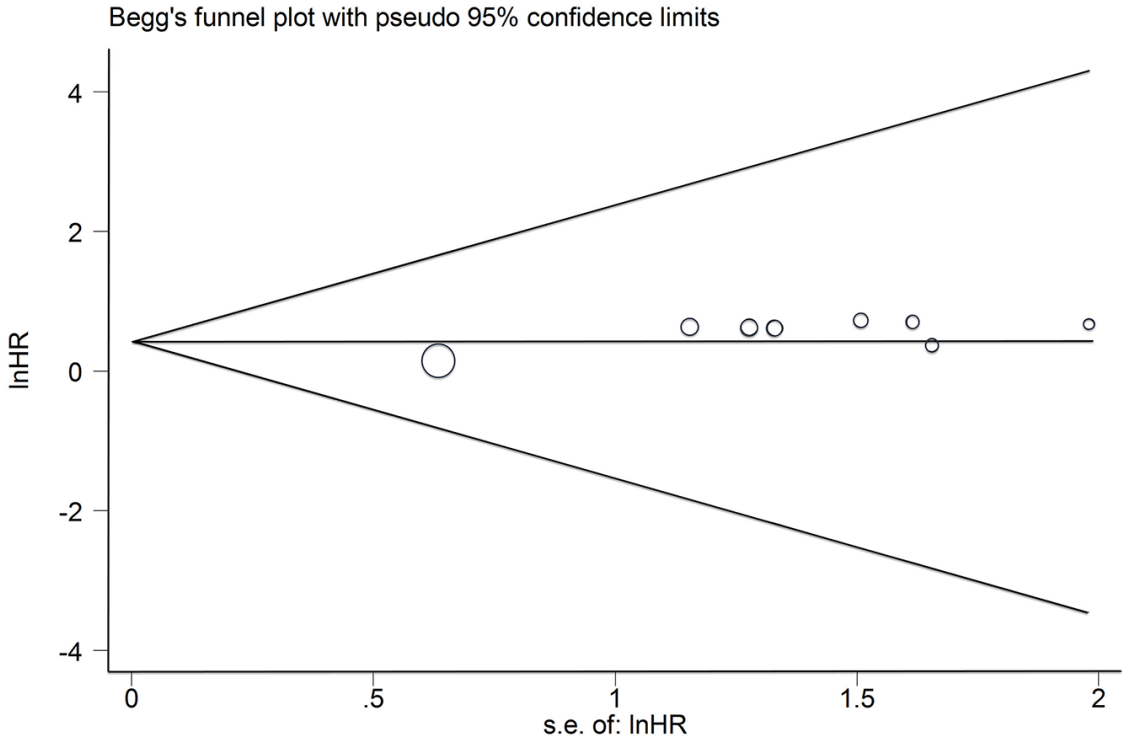


**Figure 5: Funnel plot analysis of potential publication bias in OS group (Bgger's test).**

potential sources of heterogeneity among the original studies. The different characteristics of included patients such as gender, age, tumor grade, stage, follow-up time in these studies might be the main reason. Otherwise, the different cancer types especially in non-gastrointestinal cancers were also related to the heterogeneity.

In conclusion, our study demonstrated that the prognostic values of lncRNA ZFAS1 expression varied in different types of cancer, which high levels of lncRNA ZFAS1 was associated with poor prognosis in various types of malignancies. Considering the limitation of present analysis, this conclusion should be regarded cautiously. Further study of larger sample size and different ethnic populations are still need to be addressed, as well as to explore more effective therapy strategies.

## MATERIALS AND METHODS

### Literature search strategy

We searched the online databases like PubMed, OVID, and Web of Science for eligible studies, with combinations of the following keywords: "zinc fnger antisense 1 OR ZFAS1 OR lncRNA ZFAS1"; (all fields) AND "tumor OR tumour OR neoplasm OR cancer OR carcinoma" (all fields) AND "prognosis OR prognostic OR survival OR outcome" (all fields). The articles were published up to 2017 June 15. We did not set any advanced limitations. The reference lists of full-text articles were also screened to avoid omitted studies. Two authors conducted the search independently (Rui Ren and Qiaoming Zhi).

### Inclusion and exclusion criteria

Literatures were considered eligible if they met the following criteria: (1) patients were grouped according to the expression levels of lncRNA ZFAS1;(2) expression of lncRNA ZFAS1 in human cancer tissues was investigated; (3) associations between lncRNA ZFAS1 and overall survival (OS) were described. While exclusion criteria are as the following: (1) studies without sufficient data; (2) duplicate publications; (3) case reports, letters, conference abstracts and expert opinions.

### Data extraction

Data extraction was performed from eligible articles by two investigators (Rui Ren and Qiaoming Zhi). The information extracted was as follows: first author surname, publication year, country, tumor type, sample size, number of patients with the expression of lncRNA ZFAS1, lncRNA ZFAS1 HR and 95% CI for OS, and lncRNA ZFAS1 detection method. If any disagreement emerged, it will be discussed and judged by a third investigator (Daiwei Wan).

Multivariate analysis were considered to be prior to univariate analysis if the result of OS was provided in the studies. For only Kaplan-Meier curve was provided, the survival data was extracted with Engauge Digitizer version 4.1 [27]. The quality of each study was assessed independently by two researchers according to the NOS [28]. For quality assessment, scores ranged from 0 (lowest) to 9 (highest), and studies with scores of 6 or more were rated as high quality.

### Statistical methods

Cochran's Q test and Higgins I-squared statistic were used to measure the heterogeneity across eligible studies. We used the fixed effects model when heterogeneity between studies included was not obvious($p > 0.05$), while the random effects model was applied if there was significant heterogeneity($p < 0.05$). Odds Ratios(ORs) and their 95% CIs were used to evaluate the LNM, DM and TNM stage. Hazard Ratios(HRs) and 95%CI were used to summarize the overall survival. Moreover, publication bias was assessed by Bgger's test. All the statistical analyses were conducted via Stata SE12.0 software (StataCorp, College Station, TX, USA).

## CONFLICTS OF INTEREST

The authors declared that there is no conflicts of interests regarding the publication of this paper.

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