

Prognostic value of long non-coding RNA ZEB1-AS1 in Chinese cancer patients

A Meta-analysis

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Abstract

Background: Aberrant expression of long non-coding RNA Zinc finger E-box binding homeobox 1 antisense 1 (lncRNA ZEB1-AS1) can be detected in numerous malignancies. Therefore, a meta-analysis had been carried out in this study, aiming to examine the prognostic value of lncRNA ZEB1-AS1 in malignancies.

Methods: Electronic databases, such as PubMed, OVID as well as Web of Science, had been systemically retrieved from inception to February 14th, 2019. Besides, the hazard ratios (HRs), together with the corresponding 95% confidence intervals (CIs), had also been analyzed for determining the association of lncRNA ZEB1-AS1 expression with the overall survival (OS) and recurrence-free survival (RFS). In addition, the pooled odds ratios (ORs) would also be computed using the Stata SE12.0 software for evaluating the relationship of lncRNA ZEB1-AS1 expression with pathological factors.

Results: A total of 21 original studies involving 1801 cancer patients had been enrolled into the current meta-analysis. As suggested by the pooled HR, high expression of lncRNA ZEB1-AS1 had displayed marked correlation with OS (HR = 2.16, 95% CI: 1.89–2.47) among cancer patients, and no significant heterogeneity was detected. Additionally, high expression of lncRNA ZEB1-AS1 was also markedly associated with RFS among cancer patients (pooled HR = 2.55, 95% CI: 1.61–4.03). Besides, the expression of lncRNA ZEB1-AS1 had displayed marked correlation with poor histological grade (PHG) (OR = 2.86, 95% CI: 2.11–3.87), high tumor stage (HTS) (OR = 3.81, 95% CI: 2.72–5.34) as well as lymph node metastasis (LNM) (OR = 3.33, 95% CI: 2.47–4.49). Additionally, no distinct asymmetry had been detected for RFS, PHG as well as HTS based on Begg funnel plot.

Conclusions: Taken together, high expression of lncRNA ZEB1-AS1 can predict the dismal OS, RFS, LNM, PHG, and HTS, indicating that lncRNA ZEB1-AS1 can be potentially used as a new biomarker to predict the dismal prognosis for cancer patients.

Abbreviations: BC = bladder cancer, B-LL = B-lymphoblastic leukemia, CRC = colorectal cancer, ESCC = esophageal squamous cell carcinoma, GAPDH = glyceraldehyde-3-phosphate dehydrogenase, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, HTS = high tumor stage, lncRNA ZEB1-AS1 = lncRNA Zinc finger E-box binding homeobox 1 antisense 1, LNM = lymph node metastasis, LTS = larger tumor size, NOS = Newcastle-Ottawa Scale, NSCLC = non-small cell lung cancer, OS = overall survival, OSC = osteosarcoma, PC = pancreatic cancer, PHG = poor histological grade.

Keywords: lncRNA, meta-analysis, neoplasm, prognosis, ZEB1-AS1

1. Introduction

Results from recent studies have demonstrated that the US has witnessed 609,640 cancer-related deaths as well as 1,735,350 newly diagnosed cancer cases in 2018.^[1] Unfortunately, the 5-year survival is quite low among a majority of malignancies;

thus, it is necessary to examine and develop the novel markers for the early diagnosis and prognosis of cancer, which can determine the survival.

Long non-coding RNAs (lncRNAs) are a class of the transcribed RNA molecules over 200 nucleotides in length, which lack the open reading frame.^[2] Specifically, they have

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participated in critical cellular processes determining tumorigenesis, such as epigenetic regulation, and regulation at transcriptional as well as post-transcriptional levels.^[3] Abnormal lncRNAs expression is detected in numerous cancer types,^[4–7] which can thereby serve as the potential markers for predicting cancer prognosis due to their involvements in the progression of cancers at various stages, such as cancer proliferation, invasion as well as metastasis.^[8,9] On this account, it is of crucial importance to identify the vital tumor-associated lncRNAs in tumorigenesis, which may be used as the promising biomarkers to predict cancer prognosis.

The lncRNA Zinc finger E-box binding homeobox 1 antisense 1 (lncRNA ZEB1-AS1), which is located on chromosome 10p11.22, is about 2535 nucleotides in length and has possessed 2 exons as well as 1 sandwiched intron.^[10] Originally, lncRNA ZEB1-AS1 is discovered in hepatocellular carcinoma (HCC), which is suggested to regulate the epithelial-mesenchymal transition (EMT) as well as cancer metastasis.^[11] Recently, lncRNA ZEB1-AS1 has been reported to be correlated with a variety of parameters related to tumor biology, such as metastasis as well as prognosis.^[12] Results from the above studies indicated that lncRNA ZEB1-AS1 is associated with certain value in predicting the prognosis for cancer patients. Additionally, no consensus has been reached about the value of lncRNA ZEB1-AS1 in predicting the prognosis for cancer patients. Thus, the current meta-analysis would be carried out, aiming to explore the value of lncRNA ZEB1-AS1 in predicting cancer prognosis through comprehensive analysis of data extracted from several literature.

1.1. Materials and methods

1.1.1. Literature collection. Electronic databases, including PubMed, OVID, as well as Web of Science, had been systematically retrieved from inception to February 14th, 2019, to search for studies reporting lncRNA ZEB1-AS1 as the potential marker in predicting the survival for cancer patients^[13,14] by 2 reviewers independently, according to the standard meta-analysis guidelines. Typically, the text word and MeSH strategies had been applied in literature retrieval, using the following terms, ‘ZEB1-AS1’, ‘ZEB1 antisense RNA 1’, ‘Zinc finger E-box binding homeobox 1 antisense 1’, ‘lncRNA ZEB1-AS1’, ‘lncRNA’, ‘noncoding RNA’, ‘long intergenic noncoding RNA’, ‘carcinoma’, ‘neoplasm’, ‘tumor’, ‘cancer’, ‘prognostic’, ‘prognosis’, ‘survival’ or ‘recurrence’. Notably, the retrieval strategy had been adjusted based on different databases for the sake of searching the maximum appropriate papers. Additionally, the reference lists from related articles would be manually retrieved to avoid omission of any eligible study. All related data had been analyzed on the basis of the previously published studies; as a result, no ethical approval or informed consent was necessary for this meta-analysis.

1.2. Study selection

All data extracted from articles had been assessed by 2 authors independently, so as to screen the relevant studies for the current meta-analysis. The study inclusion criteria of this meta-analysis would be shown below:

1. studies measuring the relationship of lncRNA ZEB1-AS1 expression with survival (or the clinicopathological factor) in several human tumors;

2. studies determining the lncRNA ZEB1-AS1 expression in human tumor tissues, in which patients would be divided based on the lncRNA ZEB1-AS1 expression level;
3. studies in which all tumors had been confirmed pathologically or histologically.

The study exclusion criteria were as follows:

1. reviews, letters, editorials, case reports or expert opinions;
2. studies written in non-English language or non-human studies;
3. studies with insufficient data listed in the study inclusion criteria; and
4. basic characterization studies on lncRNA ZEB1-AS1 alone.

1.3. Data extraction

Data had been collected from the enrolled studies and analyzed by 2 authors independently. Any disagreement between them in literature evaluation would be settled by the consensus with a third author. The collected data had included surname of the first author, publication year, country, tumor type, sample size, number of patients with large tumor size (LTS), number of patients with poor histological grade (PHG), number of patients with high tumor stage (HTS), number of patients with lymph node metastasis (LNM), threshold of lncRNA ZEB1-AS1 expression, HR as well as the corresponding 95% CIs regarding the up-regulated lncRNA ZEB1-AS1 expression for OS, reference gene of ZEB1-AS1, as well as the Newcastle-Ottawa Scale (NOS) score.

Moreover, the study quality would also be evaluated based on NOS score. Nine items had been determined in all studies, and each of them had been assigned a score of 1. Specifically, the total scores of each study were between 0 and 9, and a study with the score of ≥ 7 would be deemed to have high quality.

1.4. Statistical methods

The Stata version 12.0 software had been adopted for statistical analysis. Moreover, the inter-study heterogeneity would be detected through Q and I^2 tests, and a probability value of $I^2 \geq 50\%$ and $P < .1$ was indicative of the presence of significant heterogeneity.^[15] Thereafter, a random effects model or a fixed effects model would be chosen on the basis of heterogeneity analysis results. To be specific, a random-effects model would be selected in the presence of significant inter-study heterogeneity; otherwise, the fixed effects model would be selected. On the other hand, the underlying publication bias would be detected through Begg funnel plot. Besides, the pooled HRs as well as ORs would be collected from the published data. Specifically, the available HRs as well as the corresponding 95% CIs from the published literature would be used; however, when these data were not available from the studies, the HR values would be estimated based on the survival data collected from the Kaplan-Meier curve. OS would be computed according to the log HR as well as the standard error (SE) values.^[16] Moreover, the pooled odds ratios (ORs), together with the corresponding 95% CIs, would be utilized for evaluating the association of lncRNA ZEB1-AS1 expression with tumor parameters, such as LTS, LNM, histological (differentiation) grade as well as HTS.

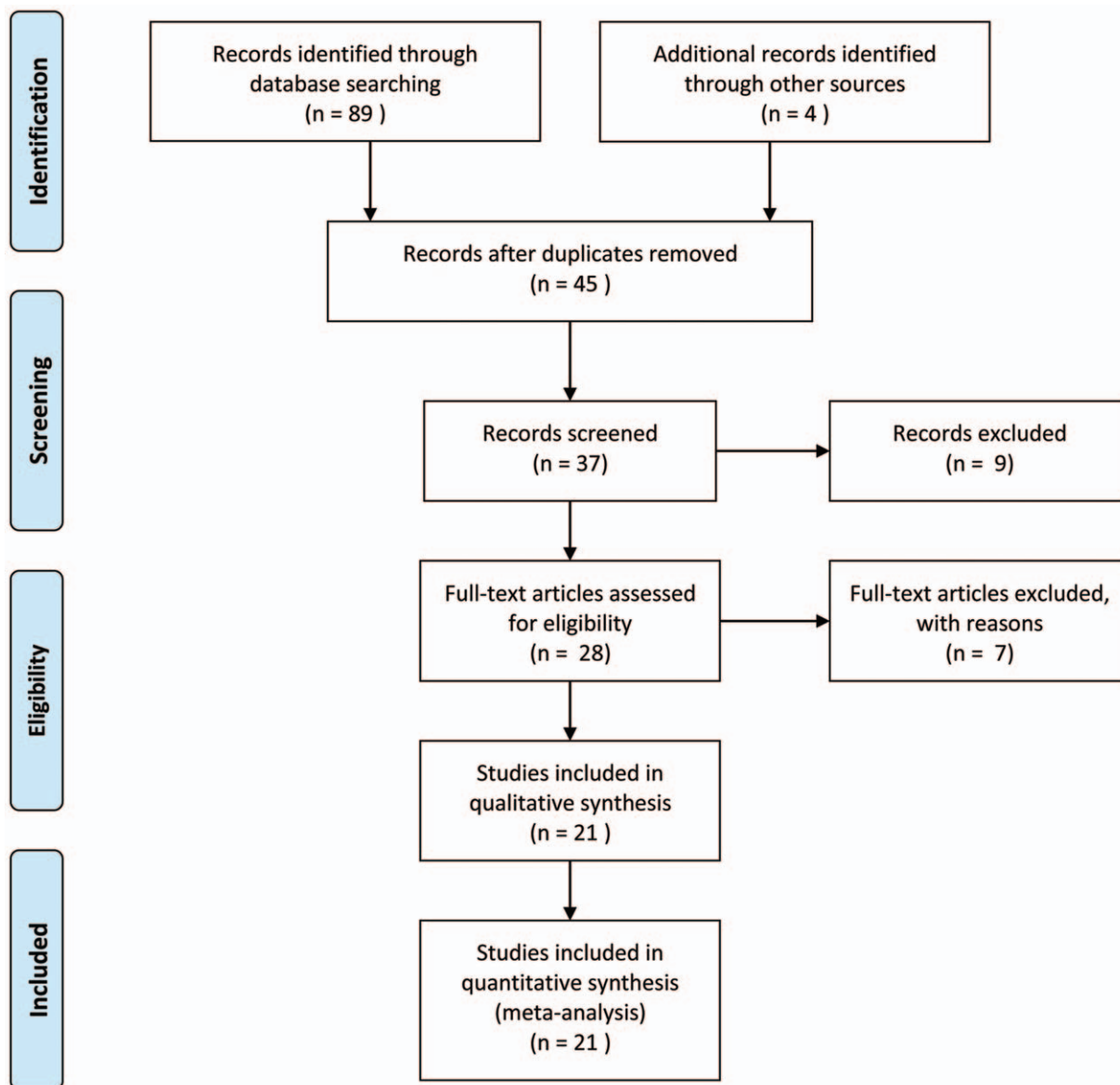


Figure 1. Flowchart showing the steps of literature search and selection criteria for the meta-analysis.

2. Results

2.1. Characteristics of the enrolled studies

The study screening process has been presented in Figure 1. Altogether 21 studies involving 1801 patients had been enrolled into this meta-analysis.^[10,11,17–35] Characteristics of the 21 enrolled studies are displayed in Table 1. The sample size in 13 studies was 30 to 183, with a mean of 85.8. All studies had been carried out in China, and published between 2015 and 2019. Four out of the 21 studies had concentrated on non-small cell lung cancer (NSCLC),^[21,23,24,34] 3 on gastric cancer (GC)^[22,27,35] and glioma,^[28,29,33] 2 on cervical cancer (CVC)^[17,19] and colorectal cancer (CRC),^[18,20] as well as 1 on hepatocellular carcinoma (HCC),^[11] bladder cancer (BC),^[25] osteosarcoma (OSC),^[26] pancreatic cancer (PC),^[10] esophageal squamous cell carcinoma (ESCC),^[30] B-lymphoblastic leukemia (B-LL),^[31] and

Melanoma,^[32] respectively. The expression level of lncRNA ZEB1-AS1 had been detected in all tumor specimens. Moreover, LNM, histological (differentiation) grade as well as HTS had been diagnosed pathologically.

2.2. High lncRNA ZEB1-AS1 expression was correlated with short OS

Cumulative meta-analysis had been carried out to detect the effect of ZEB1-AS1 expression on the OS for 1632 cancer patients recruited in 19 studies (Table 2). According to the statistical analyses, lncRNA ZEB1-AS1 expression was correlated with the OS for cancer patients (pooled HR = 2.16, 95% CI: 1.89–2.47, Fig. 2A). No significant inter-study heterogeneity had been detected in our study ($I^2 = 0.0\%$, $P_Q = .986$). Moreover, sensitivity analysis had also been conducted, which had verified the

Table 1

The basic information and data of all included studies in the meta-analysis. Note: The dashes represent no data.

Study	Year	Region	Tumor type	Sample size	lncRNA ZEB1-AS1 expression										Cut-off value	Reference gene	Method	NOS
					High expression					Low expression								
					Total	LTS	PHG	HTS	LNМ	Total	LTS	PHG	HTS	LNМ				
Cheng et al ^[17]	2018	China	CVC	106	59	29	25	38	44	47	15	12	17	21	Mean	GAPDH	PCR	8
Fu et al ^[18]	2017	China	CRC	108	54	38	47	22	-	54	23	36	11	-	Median	GAPDH	PCR	7
Gan et al ^[19]	2018	China	CVC	97	48	-	-	-	-	49	-	-	-	-	Median	GAPDH	PCR	6
Gong et al ^[20]	2017	China	CRC	63	31	6	14	20	24	32	9	8	24	13	Median	GAPDH	PCR	7
Jin et al ^[21]	2019	China	NSCLC	48	31	23	-	21	24	17	6	-	4	4	-	GAPDH	PCR	7
Li et al ^[11]	2016	China	HCC	102	51	23	-	13	-	51	20	-	11	-	Median	β-actin	PCR	7
Li et al ^[22]	2017a	China	GC	124	62	-	39	49	-	62	-	27	22	-	Median	GAPDH	PCR	8
Li et al ^[23]	2017b	China	NSCLC	122	49	23	-	26	26	73	19	-	14	24	-	GAPDH	PCR	7
Li et al ^[24]	2017c	China	NSCLC	68	34	10	-	18	15	34	17	-	6	4	Median	GAPDH	PCR	7
Lin et al ^[25]	2017	China	BC	55	37	23	27	15	2	18	11	5	2	0	-	GAPDH	PCR	6
Liu et al ^[26]	2016	China	OSC	50	25	12	-	8	-	25	5	-	1	-	Median	-	PCR	7
Liu et al ^[27]	2018	China	GC	75	42	17	29	31	36	33	19	13	12	20	*	GAPDH	PCR	8
Lv et al ^[28]	2016	China	Glioma	82	29	-	-	21	-	53	-	-	24	-	-	GAPDH	PCR	7
Meng et al ^[29]	2018	China	Glioma	100	59	-	-	-	-	41	-	-	-	-	-	GAPDH	PCR	6
Su et al ^[10]	2017	China	PC	114	57	-	-	54	-	57	-	-	33	-	-	GAPDH	PCR	6
Wang et al ^[30]	2015	China	ESCC	87	44	19	-	-	24	43	17	-	-	10	Median	GAPDH	PCR	8
Wang et al ^[31]	2017	China	B-LL	30	15	-	-	-	-	15	-	-	-	-	Median	GAPDH	PCR	6
Wang et al ^[32]	2019	China	Melanoma	46	23	-	-	15	18	23	-	-	7	8	Median	U6	PCR	7
Wei et al ^[33]	2018	China	Glioma	65	34	19	-	23	-	31	8	-	8	-	Median	GAPDH	PCR	6
Xie et al ^[34]	2018	China	NSCLC	183	97	69	66	57	27	86	53	34	26	17	Mean	GAPDH	PCR	8
Zhang et al ^[35]	2018	China	GC	76	38	13	30	25	15	38	18	24	14	6	Median	GAPDH	PCR	7

BC=bladder cancer, B-LL=B-lymphoblastic leukemia, CVC=cervical cancer, CRC=colorectal cancer, ESCC=esophageal squamous cell carcinoma, GAPDH=glyceraldehyde-3-phosphate dehydrogenase, GC=gastric cancer, HCC=hepatocellular carcinoma, HTS=high tumor stage, LNМ=lymph node metastasis, LTS=lager tumor size, NOS=Newcastle-Ottawa scale, NSCLC=non-small cell lung cancer, OSC=osteosarcoma, PC=pancreatic cancer, PHG=poor histological grade, PCR=polymerase chain reaction.

robustness of our results (Fig. 2B). Afterward, subgroup analyses had also been performed stratified according to cancer type, sample size, NOS score as well as the HR statistic method (Table 3, Fig. 3).

Taken together, our results suggested that lncRNA ZEB1-AS1 could serve as the independent factor for OS among cancer patients; besides, high lncRNA ZEB1-AS1 expression showed correlation with short OS.

Table 2

Survival data of studies included in the meta-analysis.

Study	Year	Country	Tumor type	Sample size	Method	Overall survival (OS)	HR statistic
Cheng et al ^[17]	2018	China	CVC	106	Multivariate	1.86 (1.045–3.312)	Survival curve
Fu et al ^[18]	2017	China	CRC	108	Multivariate	2.026 (1.493–2.748)	Data in paper
Gan et al ^[19]	2018	China	CVC	97	Multivariate	3.239 (1.799–9.989)	Data in paper
Gong et al ^[20]	2017	China	CRC	63	Multivariate	2.55 (1.10–5.90)	Survival curve
Jin et al ^[21]	2019	China	NSCLC	48	Multivariate	2.133 (1.035–4.086)	Data in paper
Li et al ^[11]	2016	China	HCC	102	Multivariate	2.25 (1.05–4.79)	Survival curve
Li et al ^[22]	2017a	China	GC	124	Multivariate	2.363 (1.410–3.962)	Data in paper
Li et al ^[23]	2017b	China	NSCLC	122	Multivariate	1.70 (1.12–2.57)	Survival curve
Li et al ^[24]	2017c	China	NSCLC	68	Multivariate	2.38 (1.23–4.59)	Survival curve
Lin ^[25]	2017	China	BC	55	NA	NA	NA
Liu et al ^[26]	2016	China	OSC	50	Multivariate	2.42 (1.055–5.552)	Survival curve
Liu et al ^[27]	2018	China	GC	75	Multivariate	2.280 (1.109–4.689)	Data in paper
Lv et al ^[28]	2016	China	Glioma	82	Multivariate	2.055 (1.384–4.462)	Data in paper
Meng et al ^[29]	2018	China	Glioma	100	Multivariate	2.47 (1.368–4.459)	Survival curve
Su et al ^[10]	2017	China	PC	114	NA	NA	NA
Wang et al ^[30]	2015	China	ESCC	87	Multivariate	2.371 (1.284–6.115)	Data in paper
Wang et al ^[31]	2017	China	B-LL	30	Multivariate	2.76 (1.0621–7.7124)	Survival curve
Wang et al ^[32]	2019	China	Melanoma	46	Multivariate	2.9 (1.27–6.62)	Survival curve
Wei et al ^[33]	2018	China	Glioma	65	Multivariate	2.983 (1.189–4.739)	Data in paper
Xie et al ^[34]	2018	China	NSCLC	183	Multivariate	1.704 (1.169–2.485)	Data in paper
Zhang et al ^[35]	2018	China	GC	76	Multivariate	3.06 (1.60–5.86)	Survival curve

NA represent no data.

BC=bladder cancer, B-LL=B-lymphoblastic leukemia, CVC=cervical cancer, CRC=colorectal cancer, ESCC=esophageal squamous cell carcinoma, GAPDH=glyceraldehyde-3-phosphate dehydrogenase, GC=gastric cancer, HCC=hepatocellular carcinoma, NOS=Newcastle-Ottawa scale, NSCLC=non-small cell lung cancer, OSC=osteosarcoma, PC=pancreatic cancer.

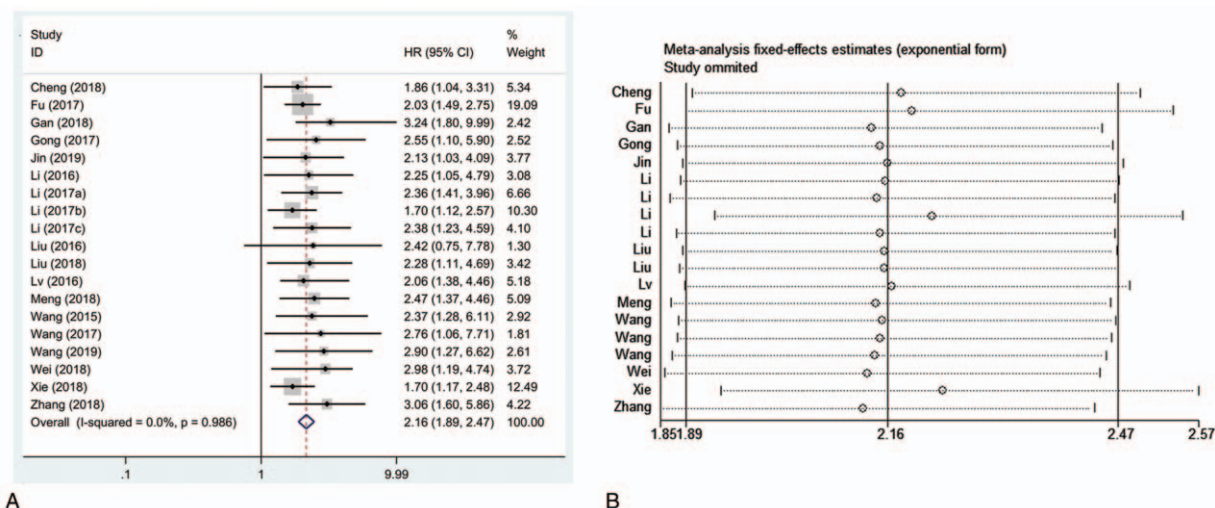


Figure 2. Forest plot (A) and sensitivity analysis (B) showing the association between OS and elevated lncRNA ZEB1-AS1 expression in cancer. lncRNA ZEB1-AS1 = lncRNA Zinc finger E-box binding homeobox 1 antisense 1.

2.3. High lncRNA ZEB1-AS1 expression was related to short RFS

Cumulative meta-analysis had also been performed to examine the effect of lncRNA ZEB1-AS1 expression on RFS for 215 cancer patients recruited in 3 eligible studies^[11,20,26] (Fig. 4). According to the statistical analyses, lncRNA ZEB1-AS1 expression was related to RFS (pooled HR=2.55, 95% CI: 1.61–4.03) for cancer patients. No significant inter-study heterogeneity had been detected in our study. Thus, these results revealed that lncRNA ZEB1-AS1 might serve as the independent factor for RFS of cancer patients; in addition, high lncRNA ZEB1-AS1 expression showed correlation with short RFS.

2.4. Association of lncRNA ZEB1-AS1 expression with LTS

Fourteen eligible studies involving 1208 cases had been analyzed, which suggested that lncRNA ZEB1-AS1 expression was closely correlated with LTS (Fig. 5). Moreover, significant

heterogeneities could be detected among studies ($I^2=60.8\%$, $P=.002$), so the random-effects model would be employed. In addition, the pooled OR, which was presented as high versus low lncRNA ZEB1-AS1 expression groups, had been calculated to be 1.45 (95% CI: 0.98–2.18; Fig. 5A). Furthermore, sensitivity analysis had also been carried out among all eligible studies; specifically, the OR of high versus low expression groups would be 1.89 (95% CI: 1.45–2.45) after removing 3 studies^[24,27,35] ($I^2=30.9\%$, $P_Q=.152$) (Fig. 5B–C).

No significant difference in the incidence of LTS was been detected between these 2 groups. Therefore, more studies would be required to verify the correlation of lncRNA ZEB1-AS1 with LTS among cancer patients.

2.5. High lncRNA ZEB1-AS1 expression was related to PHG

Eight of the enrolled studies involving 790 cancer patients had been analyzed. No significant inter-group heterogeneity was detected

Table 3
Subgroup analysis of overall survival by tumor type, sample size, NOS score and HR statistic method.

Subgroup analysis	No. of studies	No. of patients	Pooled HR (95% CI)	Heterogeneity	
				I ² (%)	P value
Total	19	1632	2.16 (1.89–2.47)	0.0	.986
cancer type					
Digestive system cancer	7	635	2.26 (1.84–2.77)	0.0	.963
Non-digestive system cancer	12	997	2.09 (1.75–2.49)	0.0	.894
Sample size					
Number ≥ 100	7	845	1.96 (1.65–2.32)	0.0	.893
Number < 100	12	787	2.53 (2.04–3.14)	0.0	.999
NOS score					
NOS=6	4	292	2.78 (1.92–4.03)	0.0	.957
NOS=7	10	765	2.13 (1.79–2.55)	0.0	.950
NOS=8	5	575	1.98 (1.56–2.52)	0.0	.834
HR statistic					
Survival curve	10	763	2.22 (1.80–2.74)	0.0	.926
Data in paper	9	869	2.11 (1.78–2.51)	0.0	.895

NOS=Newcastle-Ottawa scale.

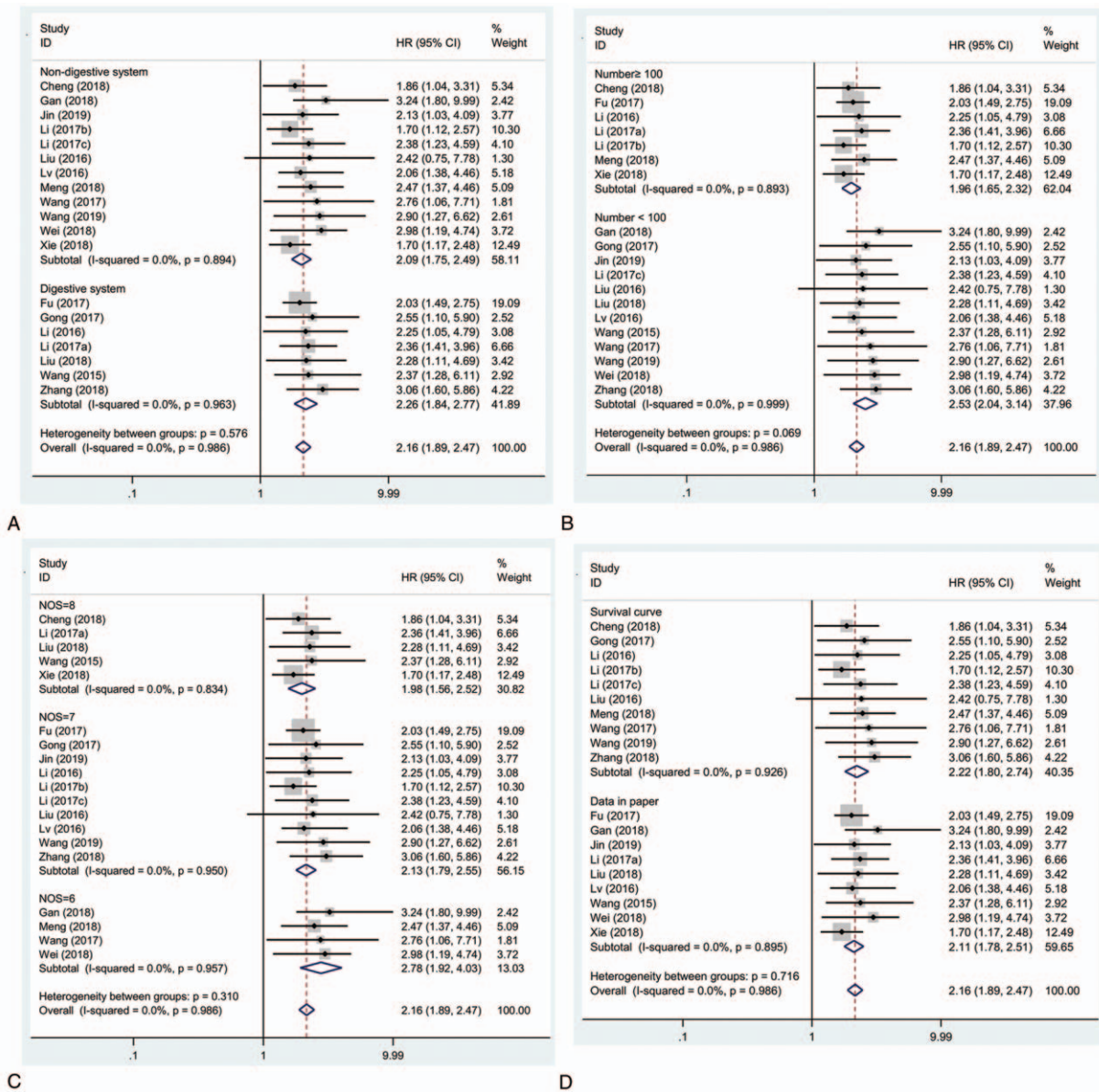


Figure 3. Forest plots of subgroup analysis for OS of patients with cancer: subgroup analysis by tumor type (A), sample size (B), NOS score (C) and HR statistic method (D). NOS = Newcastle-Ottawa Scale.

($I^2=0.0\%$, $P=.816$), so the fixed-effects model would be utilized to compute the pooled OR along with the corresponding 95% CI. According to our results, lncRNA ZEB1-AS1 expression was correlated with PHG (OR=2.86, 95% CI: 2.11–3.87; Fig. 6).

A significant difference could be detected in the incidence of PHG between the high and low lncRNA ZEB1-AS1 expression groups, revealing that cancer patients with high lncRNA ZEB1-AS1 expression were related to PHG.

2.6. High lncRNA ZEB1-AS1 expression was related to HTS

Seventeen eligible studies recruiting 1487 patients had been analyzed in the current meta-analysis, so as to detect the relationship of lncRNA ZEB1-AS1 expression with HTS. A significant inter-group heterogeneity had been detected ($I^2=$

44.3%, $P_Q=.029$); as a result, the random-effects model had been employed. Our findings suggested that the higher expression level of lncRNA ZEB1-AS1 was associated with the higher tumor grade, and the pooled OR was 3.81 (95% CI: 2.72–5.34; Fig. 7A). Notably, the above heterogeneity disappeared ($I^2=11\%$, $P_Q=.330$) when one study^[20] had been excluded from the sensitivity analysis, and the OR of high versus low expression group was 4.15 (95% CI: 3.25–5.31) (Fig. 7B–C). Consequently, our data indicated the significant correlation of high lncRNA ZEB1-AS1 expression with the elevated risk of incidence of HTS.

2.7. High lncRNA ZEB1-AS1 expression was related to LNM

Eleven of the enrolled studies involving 929 cancer patients had been analyzed. No obvious heterogeneity was detected ($I^2=10.0\%$,

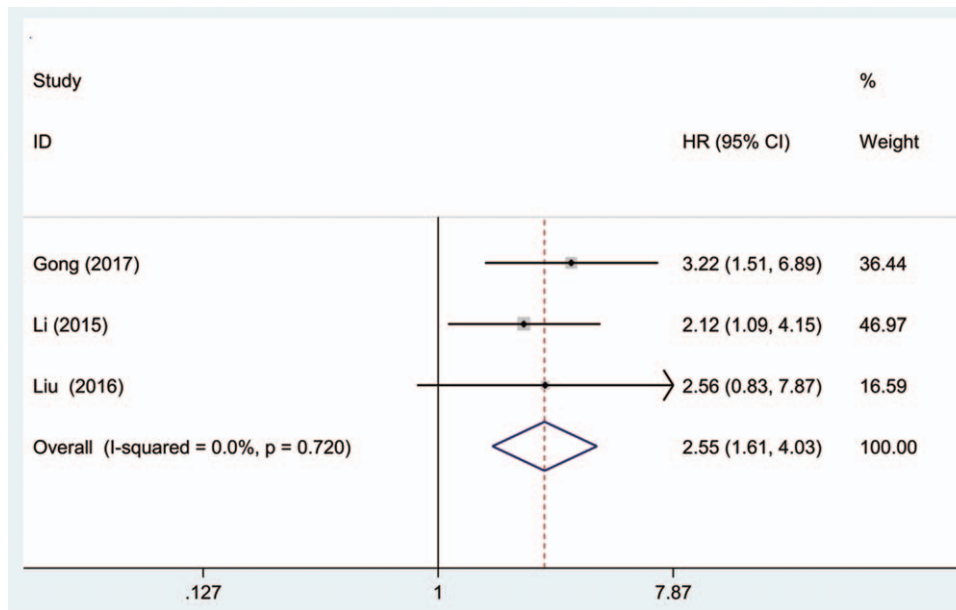


Figure 4. Forest plot showing the association between RFS, DFS and elevated lncRNA ZEB1-AS1 expression in cancer. LncRNA ZEB1-AS1 = LncRNA Zinc finger E-box binding homeobox 1 antisense 1.

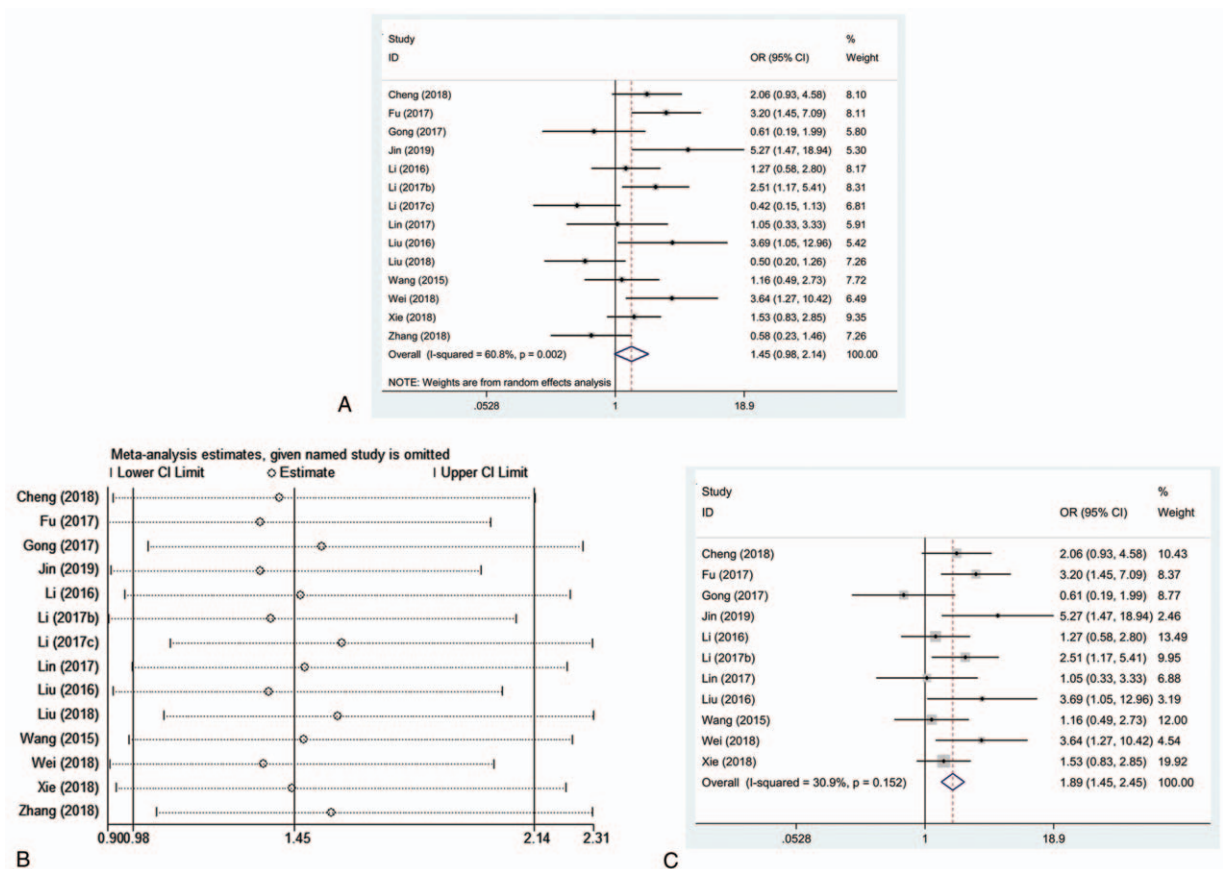


Figure 5. Forest plot (A) and sensitivity analysis (B–C) showing association between lncRNA ZEB1-AS1 expression levels and LTS. LncRNA ZEB1-AS1 = LncRNA Zinc finger E-box binding homeobox 1 antisense 1.

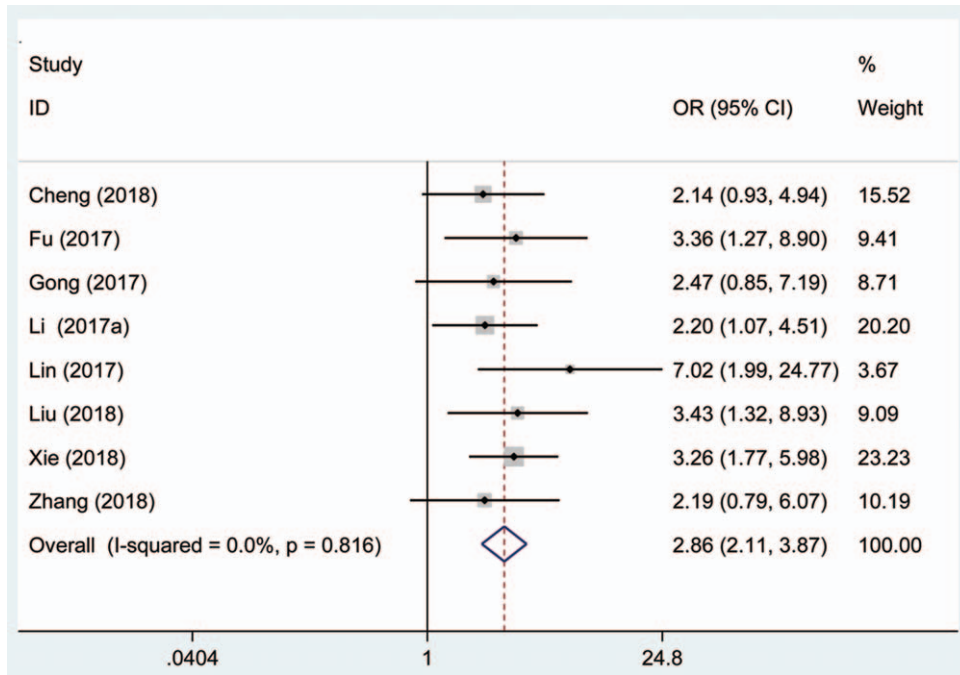
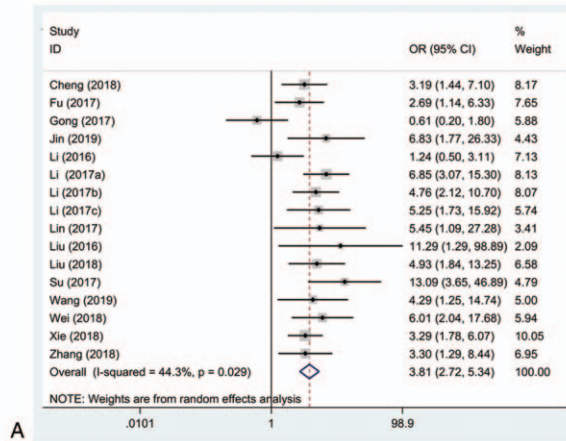
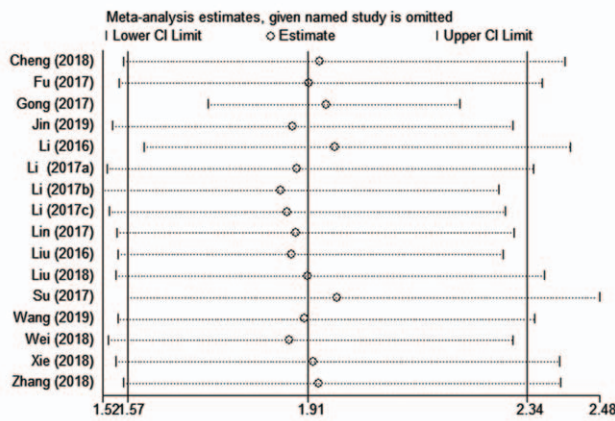


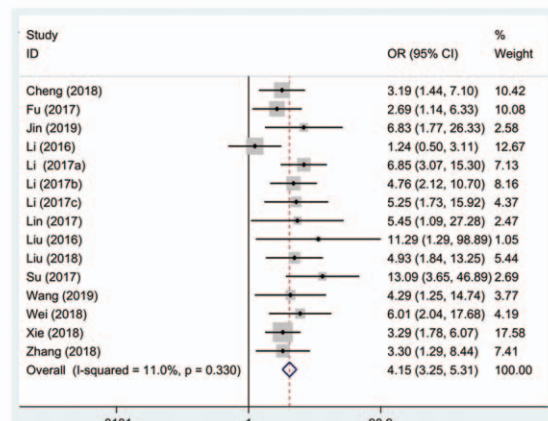
Figure 6. Forest plot showing association between lncRNA ZEB1-AS1 expression levels and PHG. lncRNA ZEB1-AS1 = lncRNA Zinc finger E-box binding homeobox 1 antisense 1.



A



B



C

Figure 7. Forest plot (A) and sensitivity analysis (B) showing meta-analysis of the role of lncRNA ZEB1-AS1 on HTS in the different types of cancer. lncRNA ZEB1-AS1 = lncRNA Zinc finger E-box binding homeobox 1 antisense 1.

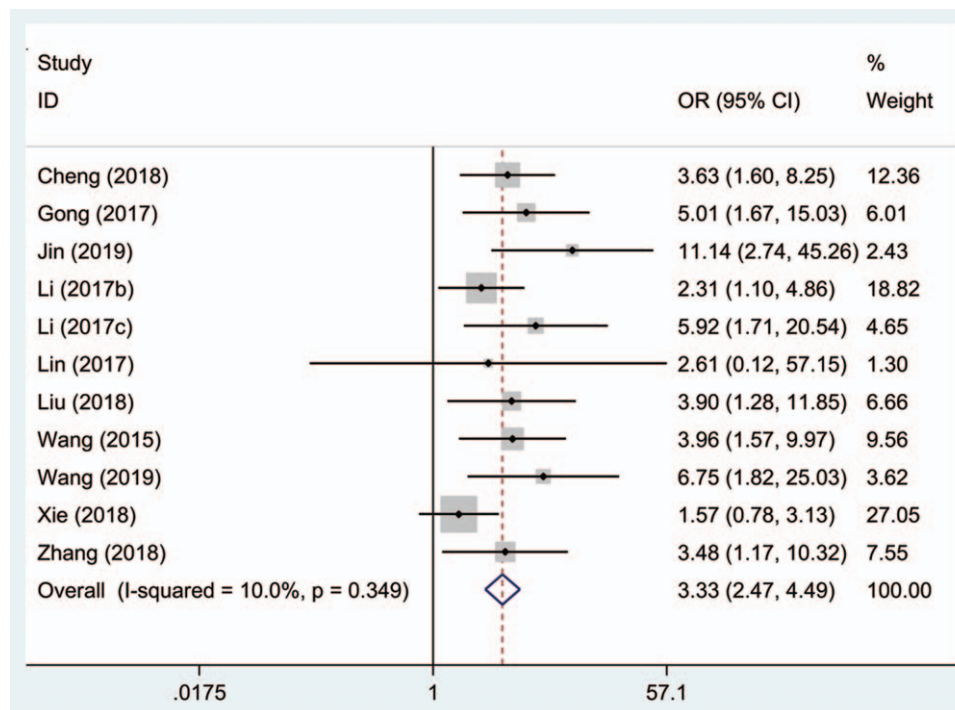


Figure 8. Forest plot showing association between lncRNA ZEB1-AS1 expression levels and LNM. lncRNA ZEB1-AS1 = lncRNA Zinc finger E-box binding homeobox 1 antisense 1.

$P = .349$); as a result, the fixed-effects model would be selected, with the pooled OR of 3.33 (95% CI: 2.47–4.49; Fig. 8). Such results suggested that high expression of lncRNA ZEB1-AS1 was associated with a higher risk of incidence of LNM among cancer patients; therefore, cancer patients with high expression level of lncRNA ZEB1-AS1 might be associated with a higher risk of incidence of LNM.

2.8. Publication bias

Furthermore, the possible publication bias would be evaluated using Begg funnel plot. As could be observed from Figure 9, there was no evidence suggesting significant asymmetry regarding RFS ($\text{Pr} > |z| = 1.000$), LTS ($\text{Pr} > |z| = 1.000$), PHG ($\text{Pr} > |z| = 0.536$) as well as HTS ($\text{Pr} > |z| = 0.091$). Nevertheless, there was obvious publication bias for OS ($\text{Pr} > |z| = 0.014$) as well as LNM ($\text{Pr} > |z| = 0.020$).

3. Discussion

Cancer has posted a leading threat to human health worldwide, and cancer morbidity has shown an increasing trend year by year.^[1] Finally, a majority of malignancies would develop metastases, including lymph node metastasis (LNM) as well as distant metastasis (DM). Specifically, the occurrence of metastasis is indicative of dismal poor prognosis, which can thereby serve as a key factor for predicting patient survival.^[36,37] Unfortunately, the underlying mechanism regarding metastasis is still largely unclear for most malignancies, while molecular biomarkers have been identified to exert crucial parts in the diagnosis, prognosis and treatment for cancer.^[38,39] On this account, it is of great significance to search for the novel molecular markers for the accurate prediction of tumor metastasis.

lncRNA ZEB1-AS1 has been identified in previous studies as a crucial oncogene in various types of human cancers, such as HCC, NSCLC, glioma as well as GC.^[10,11,17–35] Specifically, the expression of lncRNA ZEB1-AS1 has been up-regulated in glioma tissues, which may indicate an increased risk of brain cancer progression as well as the poorer OS.^[28] Additionally, Li suggested that GC patients with high expression level of lncRNA ZEB1-AS1 were associated with an elevated risk of the incidence of DM.^[22] Besides, Liu et al found that lncRNA ZEB1-AS1 had been up-regulated in osteosarcoma, which had predicted the dismal prognosis for osteosarcoma patients, and would enhance the proliferation as well as migration of osteosarcoma cells.^[26] Li et al^[23] had suggested the regulatory role of lncRNA ZEB1-AS1 in NSCLC, which might potentially serve as a new molecular marker indicating the prognosis as well as the therapeutic target for NSCLC. Gan et al^[19] discovered that the down-regulated lncRNA ZEB1-AS1 could block the p38MAPK signaling pathway in the meantime of suppressing CVC cell migration as well as invasion. Liu et al discovered that the down-regulated ZEB1-AS1 would evidently suppress the activity of the Wnt/ β -catenin signaling pathway among NSCLC patients.^[24] However, the effect of lncRNA ZEB1-AS1 on human cancer as a kind of molecular biomarker remains to be fully illuminated yet. Thus, the current meta-analysis aimed to examine the value of lncRNA ZEB1-AS1 in predicting the prognosis for cancer patients.

Specifically, a random-effects model or a fixed-effects model had been utilized for data analysis according to the heterogeneity analysis results. According to our findings, the up-regulated lncRNA ZEB1-AS1 expression was associated with a higher grade of cancer as well as dismal prognosis. Moreover, HRs upon Cox multivariate analyses would also be combined, which had suggested a significant difference in OS between the high and low

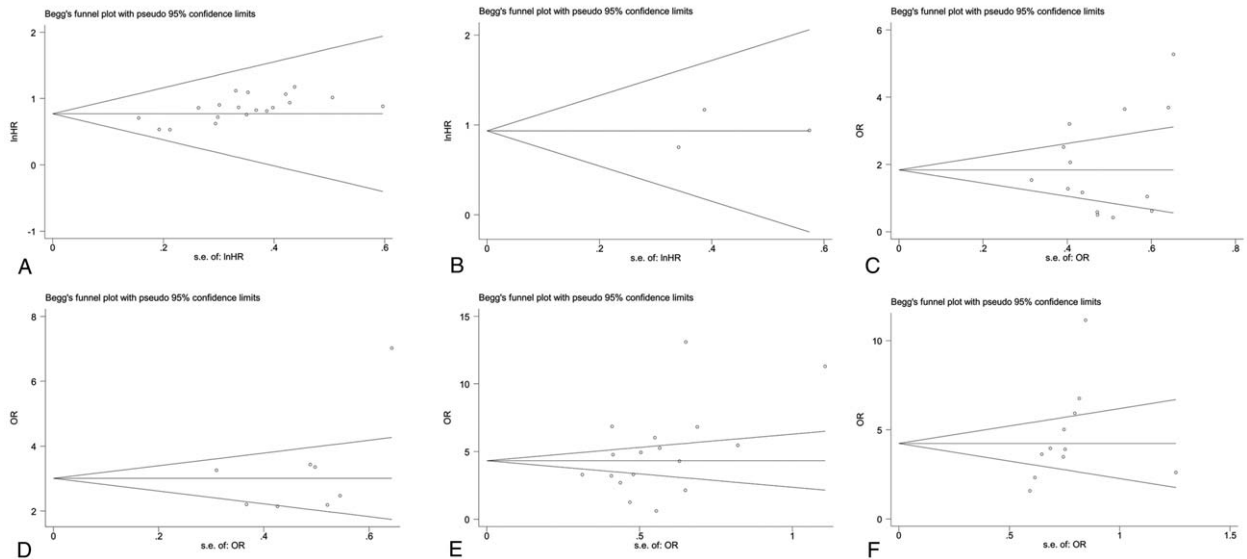


Figure 9. Funnel plot analysis to determine publication bias for the independent role of lncRNA ZEB1-AS1 on OS (A), RFS (B), LTS (C), PHG (D), HTS (E) and LNM (F) in cancers. HTS=high tumor stage, LNM = lymph node metastasis, LTS = larger tumor size, PHG=poor histological grade.

lncRNA ZEB1-AS1 expression groups (pooled HR=2.15, 95% CI: 1.81–2.55). Additionally, it was discovered that high expression of lncRNA ZEB1-AS1 had displayed marked correlation with dismal RFS and DFS among various cancer types. In addition, our results suggested that the up-regulated lncRNA ZEB1-AS1 expression had displayed correlation with PHG, HTS as well as LNM among various cancer types. Unfortunately, meta-analysis examining the relationship between the up-regulated lncRNA ZEB1-AS1 expression in cancer issues and DM was not carried out, due to the insufficiency of articles.

Nonetheless, certain limitations should be taken into consideration when interpreting our conclusions. First, all studies had been carried out in China, so our data might not be applicable globally. Second, few cancer types, as well as cancer cases, had been enrolled. Third, there were heterogeneities regarding the criteria for histological grade as well as tumor stage among studies. As a result, more well-designed studies with high quality should be performed to verify the role of lncRNA ZEB1-AS1 among various cancer types.

4. Conclusions

Taken together, high expression level of lncRNA ZEB1-AS1 is detected in numerous cancer types, which is related to the poor OS, RFS, LNM, PHG as well as HTS. Therefore, it can serve as a potential prognostic biomarker for cancer.

Author contributions

XZ and YHF search the electronic databases of Pubmed, OVID and Web of Science. XZ and YHF evaluated all of the included studies and extracted the data independently. WY and YL extracted and examined the data from the original articles independently. FW and YL resolved the disagreements in the literature assessment, and XZ was a major contributor in writing the manuscript.

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