

LncRNA LOXL1-AS1 expression in cancer prognosis

A meta-analysis

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Abstract

Background: Several studies showed that LncRNA LOXL1 antisense RNA 1 (LOXL1-AS1) is overexpressed in a variety of cancers and plays a role as an oncogene in cancer. The present meta-analysis aims to elucidate the relationship between LOXL1-AS1 expression and prognosis and clinicopathological features among cancer patients.

Methods: PubMed, Web of Science, Cochrane Library, and EMBASE database were comprehensively and systematically searched. Pooled odds ratios (ORs) and hazard ratios with a 95% confidence interval (CI) were employed to assess the relationship between LOXL1-AS1 expression and clinical outcomes and clinicopathological features in cancer patients.

Results: The present study finally enrolled 8 studies which included 657 cancer patients. The combined results indicated that the overexpression of LOXL1-AS1 was significantly associated with shorter overall survival (pooled hazard ratio = 1.99, 95% CI 1.49–2.65, $P < .00001$). Meanwhile, regarding clinicopathology of cancer patients, the upregulation of LOXL1-AS1 expression was closely related to lymph node metastasis (yes vs no OR = 4.01, 95% CI: 2.02–7.96, $P < .0001$) and distant metastasis (yes vs no OR = 3.04, 95% CI: 1.82–5.06, $P < .0001$), respectively.

Conclusion: High expression of LOXL1-AS1 in some cancers predicts shorter overall survival, distant metastasis, and lymph node metastasis. LOXL1-AS1 shows great promise as a prognostic biomarker in cancer patients.

Abbreviations: CI = confidence interval, HRs = hazard ratios, LOXL1-AS1 = LncRNA LOXL1 antisense RNA 1, ORs = odds ratios, OS = overall survival.

Keywords: cancer, LncRNA LOXL1-AS1, meta-analysis, prognosis

1. Introduction

Nowadays, cancer is 1 of the leading causes of death worldwide and has become a serious public health problem.^[1] Despite numerous improvements in cancer diagnosis and treatment, there are still 19.3 million new cases of cancer and 10.0 million cancer deaths worldwide in 2020.^[2] The lack of sensitive prognostic biomarkers is thought to be a significant contributor to this situation.^[3] Therefore, there is still a need to develop new prognostic biomarkers to predict the prognosis and treatment efficiency in cancer patients.

Therefore, there remains an urgent need to develop new prognostic biomarkers for predicting the prognosis and treatment efficiency in cancer patients.

LncRNAs play a vital role in the development of various cancer cells by interacting with DNA, mRNA, non-coding RNAs,

and proteins to exert their regulatory roles and to act as functional molecules, such as signaling molecules, decoys, scaffolds, and guides.^[4] It has been shown that many LncRNAs are aberrantly expressed in tumors and can play the role of oncogenes or tumor suppressor genes in a variety of tumors.^[5,6] In addition, an increasing number of studies have identified the great potential of LncRNAs as useful markers for diagnosis and prognosis of cancer.^[7,8]

LncRNA LOXL1 antisense RNA 1 (LOXL1-AS1), a newly discovered LncRNA, is involved in a great number of biological behaviors of cancer cells, such as proliferation, migration, invasion, apoptosis, chemoresistance, et cetera.

LOXL1-AS1, a newly discovered LncRNA, is involved in a great number of biological behaviors, including proliferation, migration, invasion, apoptosis, and chemoresistance, of cancer cells. For instance, Wu et al^[9] found that LOXL1-AS1 expression

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was elevated in colorectal cancer tissues and cell lines compared to paracancerous tissues and normal cells, respectively, and the inhibition of LOXL1-AS1 expression led to a loss of proliferation, migration, and invasion capacity of colorectal cancer cells. Long et al^[10] reported that LOXL1-AS1 is involved in the proliferation and cell cycle of prostate cancer. In addition, abnormally high expression of LOXL1-AS1 was found in a variety of tumors, such as osteosarcoma,^[11] epithelial ovarian cancer,^[12] gastric cancer,^[13,14] thymic epithelial tumors,^[15] endometrial cancer,^[16] liver cancer,^[17–19] cholangiocarcinoma^[20] and cervical cancer.^[21–23] And more notably, LOXL1-AS1 has been shown to have the potential as a prognostic biomarker in a variety of tumors. due to a number of limitations of existing studies, such as small sample sizes and discrete outcomes, a meta-analysis was conducted to examine the prognostic value of LOXL1-AS1 in various cancers.

2. Methods

2.1. Publication search

Web of Science, PubMed, Embase, and Cochrane Library were used for literature search, up until April 15, 2022. The search strategy which was used in PubMed is as follows: (((“Neoplasms”[Mesh]) OR (((((((((((((((Tumor[Title/Abstract]) OR (Neoplasm[Title/Abstract])) OR (Tumors[Title/Abstract])) OR (Neoplasia[Title/Abstract])) OR (Neoplasias[Title/Abstract])) OR (Cancer[Title/Abstract])) OR (Cancers[Title/Abstract])) OR (Malignant Neoplasm[Title/Abstract])) OR (Malignancy[Title/Abstract])) OR (Malignancies[Title/Abstract])) OR (Malignant Neoplasms[Title/Abstract])) OR (Neoplasm, Malignant[Title/Abstract])) OR (Neoplasms, Malignant[Title/Abstract])) OR (Benign Neoplasms[Title/Abstract])) OR (Benign Neoplasm[Title/Abstract])) OR (Neoplasms, Benign[Title/Abstract])) OR (Neoplasm, Benign[Title/Abstract])) AND (((Hepatocellular carcinoma upregulated EZH2-associated long non-coding RNA[Title/Abstract]) OR (Long noncoding RNA HEIH[Title/Abstract])) OR (lncRNA HEIH[Title/Abstract])) OR (HEIH[Title/Abstract])) AND (((((((clinical outcome[Title/Abstract]) OR (outcome[Title/Abstract])) OR (prognosis[Title/Abstract])) OR (prognostic[Title/Abstract])) OR (survival[Title/Abstract])) OR (diagnosis[Title/Abstract])) OR (clinicopathological[Title/Abstract])). Search strategies are used in accordance with the different databases.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: study subjects are human cancer patients; the association between LOXL1-AS1 expression and available survival data and clinical histological features were provided; cancer patients were divided into a low and a high expression group according to the expression level of LOXL1-AS1. Exclusion criteria were as follows: reviews, letters, conference reports, and animal studies; studies without available overall survival (OS) data or clinicopathological parameters; duplicate publications.

2.3. Data extraction and quality assessment

Zhaoyuan Chen and Huaqiang Zhou independently examined each eligible study and extracted the data. Data and information extraction of enrolled articles were as follows: family name of the 1st author, year of publication, cancer type, country, sample size, sample source, number of patients, detection methods, study endpoints, follow-up times, outcome measures, and clinicopathological parameters. If the COX regression model is used with both univariate and multivariate analysis, multivariate analysis is preferred due to its higher accuracy in explaining the confounding factors. If the hazard ratios (HRs) and 95%

confidence intervals (CIs) or OS were not available in the articles, the data were extracted from Kaplan–Meier survival curves indirectly.^[24] The Newcastle–Ottawa scale was used to assess the quality of the included articles, and the article with a score ≥ 6 was considered to be of high quality.

2.4. Statistical analysis

STATA software version 11.0 (Stata, College Station, TX) and Review Manager software version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) were used to analyze all the data extracted from the included studies. HRs and 95% CIs were combined to evaluate the relationships between LOXL1-AS1 expression and survival outcomes. Pooled odds ratios (ORs) and 95% CIs were employed to assess the relationship between LOXL1-AS1 expression and clinical parameters. Heterogeneity in the meta-analysis was analyzed by the I^2 test and Q tests. There is no significant heterogeneity when $I^2 < 50\%$ or $P > .05$ and a fixed effects model was utilized; otherwise, a random effects model was chosen. The publication bias was evaluated by the Egger and Begg funnel plot, and sensitivity analysis was performed to examine the robustness of the results. $P < .05$ were recognized as statistical significance.

3. Results

3.1. Study selection and characteristics

The selection process of the literature is detailed in Figure 1. A total of 99 articles were obtained by filtering from the 4 databases. After completing the elimination of duplicates and irrelevant study topics, the titles, abstracts, and full texts of these studies were further read and 8 articles were finally included in our Meta-analysis. All included studies were from China and contained a total of 657 patients, sample sizes ranged from 38 to 185, and were published between 2019 and 2021. A total of 8 types of cancer were involved: including osteosarcoma,^[11] epithelial ovarian cancer,^[12] gastric cancer,^[13] thymic epithelial tumors,^[15] endometrial cancer,^[16] liver cancer,^[17] cholangiocarcinoma,^[20] and cervical cancer.^[21] Quantitative reverse transcription PCR (RT-qPCR) was used to detect LOXL1-AS1 expression in all included studies and all included tumor patients were divided into a high and a low expression group according to the difference in LOXL1-AS1 expression. None of the articles had a Newcastle–Ottawa scale score below 6, and thus all the included articles can be considered of high quality. This study

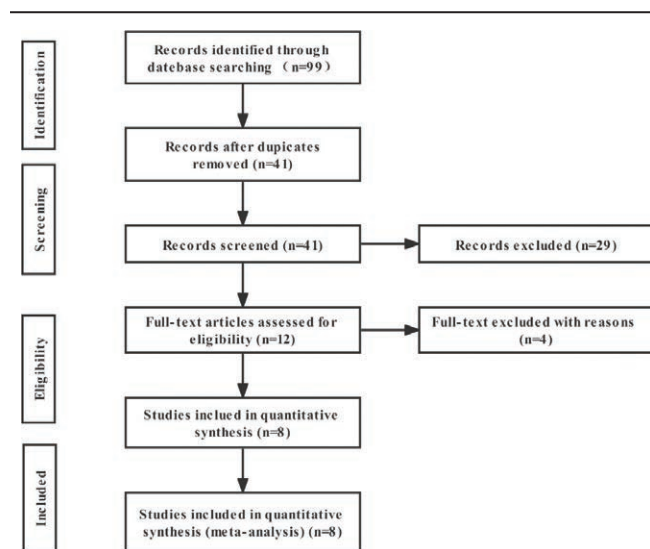


Figure 1. Literature screening and study selection process flow diagram.

has been registered on the PROSPERO website with an account number CRD42022355616. The characteristics of all eligible articles are shown in Table 1.

3.2. Association between LOXL1-AS1 expression and prognosis

To assess the value of LOXL1-AS1 expression in the prognosis of cancer patients, a cumulative meta-analysis was performed. A total of 8 articles containing 657 patients were included. No statistically significant heterogeneity in these studies ($I^2 = 0\%$, $P = .96$), and therefore, a fixed effects models were used. The pooled HR was 1.99 (95% CI: 1.49–2.65, $P < .00001$) (Fig. 2), indicating that the OS of the LOXL1-AS1 high expression group was significantly worse than that of the LOXL1-AS1 low expression group. This suggests that high expression of LOXL1-AS1 is promising as a marker for predicting poorer OS in cancer patients. In addition, subgroup analysis was used to further validate the prognostic value of LOXL1-AS1 based on the classification of tumor type, HR estimation method, sample type, and sample size. The results showed that high expression of LOXL1-AS1 in each subgroup still could predict poor prognosis (Table 2 and [Figure S1, Supplemental Digital Content, <http://links.lww.com/MD/I202>], which illustrates the Forest plot for the relation between LOXL1-AS1 expression and OS based on subgroup analysis.).

3.3. Associations between LOXL1-AS1 expression and clinicopathological parameters

The OR and 95% CI were used to assess the relationship between LOXL1-AS1 expression and clinicopathological

features. As shown in Figures 3 and 4 and Table 3, patients with high LOXL1-AS1 expression tended to higher susceptibility to lymph node metastasis (yes vs no OR = 4.01, 95% CI: 2.02–7.96, $P < .0001$) and distant metastasis (yes vs no OR = 3.04, 95% CI: 1.82–5.06, $P < .0001$). However, there was no significant correlation between LOXL1-AS1 expression and age (old vs young OR = 0.70, 95% CI: 0.48–1.02, $P = .06$), gender (male vs female OR = 1.31, 95% CI: 0.73–2.36, $P = .37$), tumor size (large vs small OR = 1.56, 95% CI: 0.78–3.11, $P = .21$), and TNM stage (III/IV vs I/II OR = 1.52, 95% CI: 0.40–5.77, $P = .53$) (Table 3 [Figure S2, Supplemental Digital Content, <http://links.lww.com/MD/I203>], which illustrates the Forest plot for the relation between LOXL1-AS1 expression and clinicopathological characteristics).

3.4. Publication bias and sensitivity analysis

The Begg and Egger test were used to evaluate the publication bias of the LOXL1-AS1 and OS, the result suggested that no significant publication bias was found (Egger test: $P = .916$ and Begg test: $P = .902$), and the results of Egger and Begg funnel plot also support this conclusion (Fig. 4a and b). In addition, the sensitivity analysis, by removing any of the included articles, showed that the change in HR was not significant, suggesting that the results are robust. (Fig. 4c).

4. Discussion

There is growing evidence that LncRNAs are intimately involved in almost all aspects of cellular physiological and pathological processes. In recent, the role of LncRNAs in cancer is being

Table 1
Characteristics of enrolled studies in this meta-analysis.

First author	Year	Cancer	Country	Expression (low/high)	Sample size	Sample source	Detection methods	Study endpoints	Follow time (months)	HR availability	NOS score
Chen	2019	OS	China	63/63	126	Tissue	RT-qPCR	OS	72	multivariate analysis	8
Liu	2020	EOC	China	93/92	185	blood	RT-qPCR	OS	60	multivariate analysis	9
Sun	2019	GC	China	42/42	84	Tissue	RT-qPCR	OS	60	K-M curve	7
Wang	2021	TETs	China	35/35	70	Tissue	RT-qPCR	OS	60	K-M curve	7
Yang	2020	EC	China	18/32	50	Tissue	RT-qPCR	OS	40	K-M curve	7
Yu	2021	LC	China	19/19	38	Tissue	RT-qPCR	OS	60	K-M curve	7
Zhang	2019	CCA	China	30/34	64	Tissue	RT-qPCR	OS	60	multivariate analysis	8
Zhang	2021	CC	China	20/20	40	Tissue	RT-qPCR	OS	60	K-M curve	9

CCA = cholangiocarcinoma, CC = cervical cancer, EC = endometrial cancer, EOC = epithelial ovarian cancer, GC = gastric cancer, HR = hazard ratio, K-M curve = Kaplan-Meier survival curve, LC = liver cancer, NOS = Newcastle–Ottawa scale, OS = osteosarcoma, TETs = thymic epithelial tumors, RT-qPCR = quantitative reverse transcription PCR.

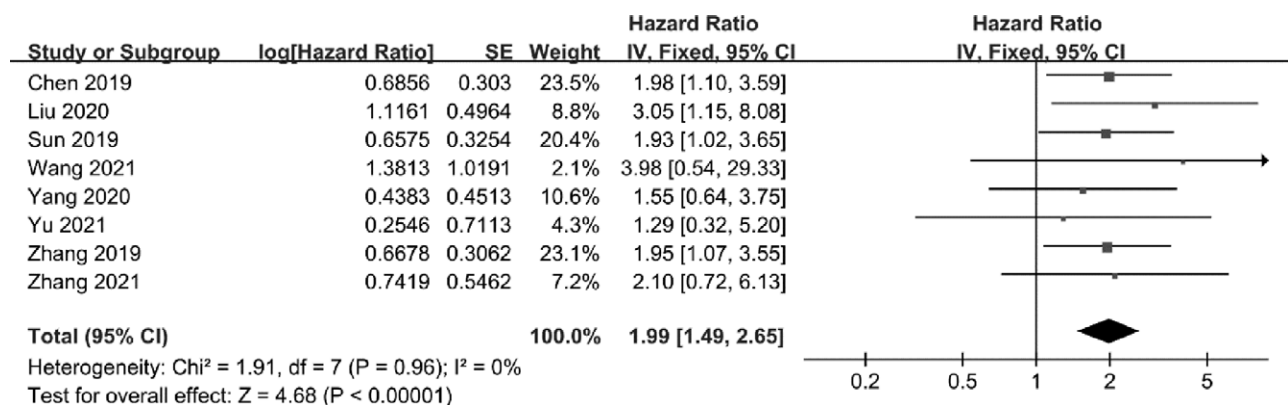


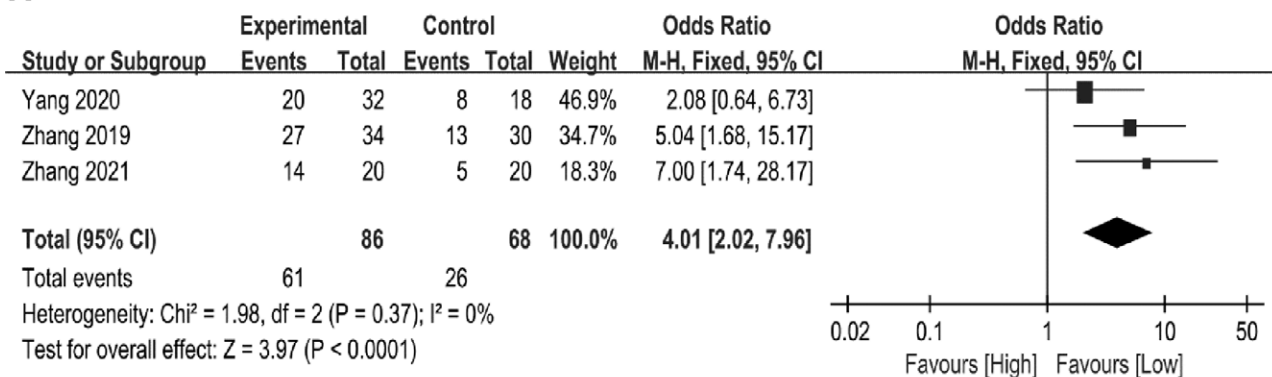
Figure 2. Forest plot for the relation between LOXL1-AS1 expression and OS based on different types of cancers. OS = overall survival.

Table 2
Subgroup analysis for the association between LOXL1-AS1 expression and OS.

Subgroups	No. of studies	No. of patients	Pooled HR (95% CI)	PHet	I ² (%)	P value
Cancer type						
Digestive system	3	186	1.87 [1.23, 2.84]	0.86	0	.003
Reproductive system	3	275	2.10 [1.20, 3.68]	0.60	0	.009
Others	2	196	2.10 [1.19, 3.71]	0.51	0	.01
HR estimation method						
Indirectly	5	282	1.85 [1.20, 2.85]	0.90	0	.005
Directly	3	375	2.11 [1.43, 3.11]	0.72	0	.0002
Sample type						
Cancer tissue	7	472	1.91 [1.41, 2.58]	0.98	0	<.0001
Blood sample	1	185	3.05 [1.15, 8.08]	NA	NA	.02
Sample size						
≥70	4	465	2.16 [1.46, 3.19]	0.79	0	.0001
<70	4	192	1.80 [1.17, 2.76]	0.92	0	.007

HR = hazard ratio, OS = overall survival.
Reproductive system, Female reproductive system.

A



B

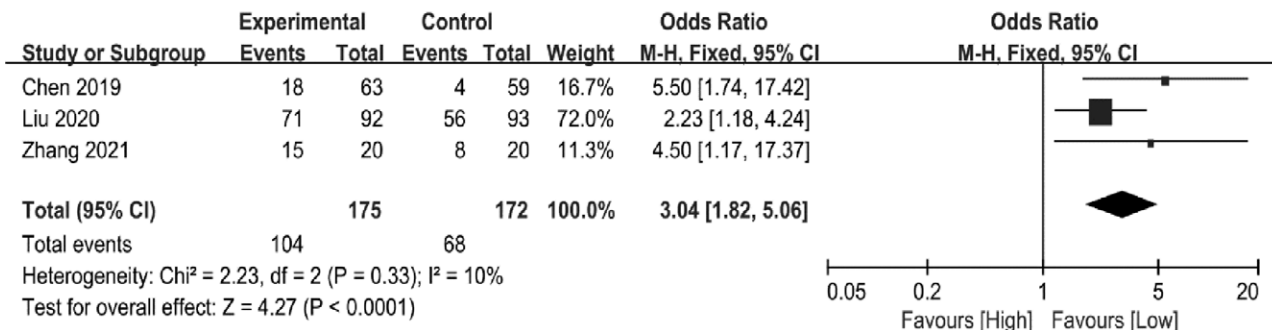


Figure 3. Forest plot for the relation between LOXL1-AS1 expression and clinicopathological characteristics; a, LM; b, DM. DM =distant metastasis, LM = lymph node metastasis.

revealed at an accelerated pace. LncRNAs have been reported to be involved in a variety of malignant biological behaviors of tumor cells, such as proliferation,^[25] migration,^[26] apoptosis,^[27] drug resistance,^[28] and radiotherapy tolerance.^[29] Notably, a large number of LncRNAs demonstrated potential value in predicting tumor prognosis.^[30]

LOXL1-AS1 is a LncRNA that encodes on the opposite strand of the lysine oxidase-like 1 (LOXL1) gene. Recently, the dysregulation of LOXL1-AS1 has been found in many tumors, and aberrant expression of LOXL1-AS1 resulted in a variety of oncogenic processes. Feng et al^[18] found that LOXL1-AS1 expression was upregulated in hepatocellular carcinoma cells and the knockdown of LOXL1-AS1 inhibited hepatocellular carcinoma cell proliferation, migration, and invasion, but induced apoptosis by modulating miR-3614-5p/YY1 axis. Moreover, Chen et al^[11] demonstrated that the deficiency of LOXL1-AS1

significantly impeded osteosarcoma cell proliferation, migration, and invasion by suppressing PI3K-AKT pathway. Liu et al^[31] found that LOXL1-AS1 could regulate the proliferation and migration ability and inhibit apoptosis of pancreatic cancer cells by competing with SEMA7A to bind miR-28-5p. As for glioma, the depletion of LOXL1-AS1 suppressed cell viability, migration, invasion, and vasculogenic mimicry ability by sponging miR-374b-5p and upregulating MMP14 expression in glioma cells.^[32] Therefore, the mechanism of LOXL1-AS1 function in cancer is complex and more research is still needed to thoroughly explore the biological mechanisms of LOXL1-AS1 in different types of cancer.

To further identify the role of LOXL1-AS1 in different cancers, a meta-analysis was performed to elucidate the impact of aberrant LOXL1-AS1 expression levels on the prognostic value and clinicopathologic features of cancer patients.

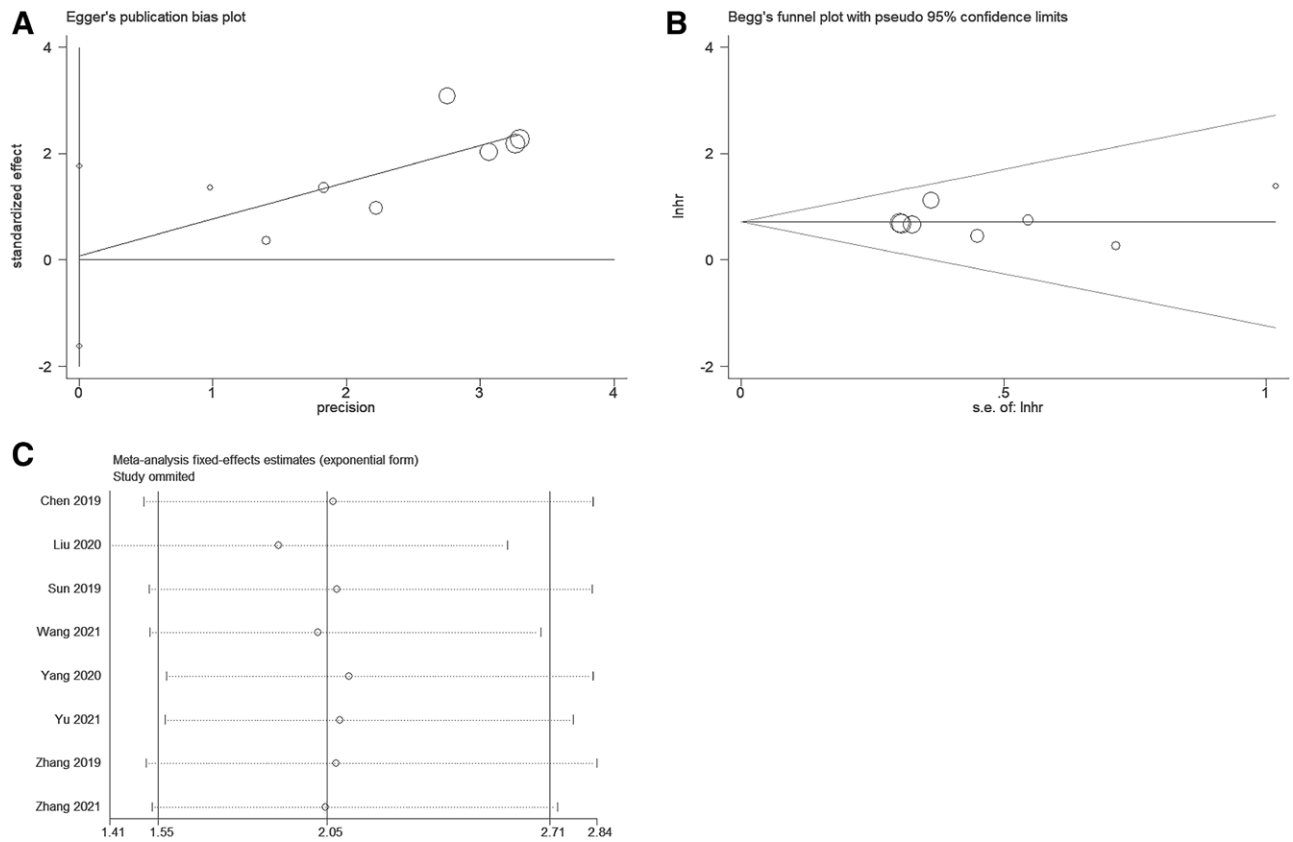


Figure 4. Egger funnel plot, Begg funnel plot and Sensitivity analysis for the evaluation of potential publication bias in the impact of LOXL1-AS1 on OS; (a) Egger funnel plot; (b) Begg funnel plot; (c) sensitivity analysis. LOXL1-AS1 = LncRNA LOXL1 antisense RNA 1, OS = overall survival.

Table 3
Meta-analysis results for the association between LOXL1-AS1 expression and clinicopathological characteristics.

Variables	Studies (n)	Patient (n)	Pooled OR (95% CI)	PHet	P (%)	P	Model
Age (old: young)	5	465	0.70 [0.48, 1.02]	0.28	21	.06	Fixed
Gender (male: female)	2	190	1.31 [0.73, 2.36]	0.73	0	.37	Fixed
Tumor size (large: small)	5	465	1.56 [0.78, 3.11]	0.02	65	.21	Random
Distant metastasis (yes: no)	3	347	3.04 [1.82, 5.06]	0.33	10	<.0001	Fixed
Lymph node metastasis (yes: no)	3	154	4.01 [2.02, 7.96]	0.37	0	<.0001	Fixed
TNM stage (III/IV: I/II)	4	339	1.52 [0.40, 5.77]	0.0002	85	.53	Random

fixed = fixed-effect model, LOXL1-AS1 = LncRNA LOXL1 antisense RNA 1, OR = odds ratio, PHet = P(Heterogeneity), Random = random-effect model.

A total of 8 studies including 8 tumor types with a total of 657 patients were enrolled in the present Meta-analysis. The combined results unveiled that high expression levels of LOXL1-AS1 are associated with poor survival prognosis in a variety of tumors, and similar results were obtained in further subgroup analysis. Meanwhile, overexpression of LOXL1-AS1 can increase the risk of Lymph node metastasis and distant metastasis in cancer patients. However, there was no significant correlation between LOXL1-AS1 expression with age, gender, tumor size, and TNM stage. Taken together, the high expression of LOXL1-AS1 has great clinical prognostic value for tumor patients, and which might bring some valuable guidance to the clinical diagnosis and treatment of tumors.

Nevertheless, there are still some limitations of our present Meta-analysis: HR and its corresponding 95% CI values were obtained indirectly in a part of the included literature, which may cause some errors; All of the included cancer patients were from China, so the applicability of the

conclusions obtained from this study is limited; We did not obtain enough samples in a specific cancer type to study further, so more studies are needed in the future to validate our conclusions.

5. Conclusions

In summary, the present study shows that high LOXL1-AS1 expression may lead to shorter OS in cancer patients and is associated with lymph node metastasis and distant metastasis in cancer patients. Therefore, LOXL1-AS1 is expected to be a prognostic marker for a variety of cancers, and the prognostic value of LOXL1-AS1 in various types of tumors will be further tested in the future through larger sample sizes, broader population sources, and standardized clinical trials.

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Writing – review & editing: Xuhua Wang, Zhaoyuan Chen, Huaqiang Zhou, Jiaquan Luo.

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