Systematic Review and Meta-Analysis

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Prognostic significance of long intergenic non-protein-coding RNA 511expression in malignant tumors

A systematic review and meta-analysis

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Abstract

Background: A growing number of studies have suggested that the Long intergenic noncoding RNA 00511 (*LINC00511*) is aberrantly expressed in multiple malignancies and is related to patient survival. Herein, we conducted a systematic review and meta-analysis to comprehensively evaluate the prognostic significance of *LINC00511* in human malignancies.

Methods: Eligible studies published by March 11, 2020 were identified in 4 electronic databases including PubMed, EMBASE, Web of Science, and the Chinese National Knowledge Infrastructure. Hazard ratios and 95% confidence intervals (CIs) were used to evaluate the prognostic significance of *LINC00511* expression in malignant tumors. The association between *LINC00511* expression and cancer clinicopathologic features were assessed using Odds ratios (ORs) and CIs.

Results: A total of 13 studies, comprising 1,053 patients, were included in the meta-analysis. The calculated hazard ratio was 2.00 (95% CI: 1.59–2.52, $P < .000$), suggesting that higher *LINC00511* expression could predict poorer overall survival in patients with malignancies. Additionally, our statistical analysis indicated that elevated *LINC00511* expression closely associated with bigger tumors (OR = 2.92, 95% CI 1.65–5.18, $P < .000$), higher incidence of lymph node metastasis (OR = 3.46, 95% CI 2.11–5.66, $P < .000$) and distant metastasis (OR = 2.40, 95% CI 1.14–5.05, $P = .02$), poorer differentiation (OR = 1.55, 95% CI 1.11-2.16, $P = .01$), as well as more advanced TNM stage (OR = 3.90, 95% CI 2.70–5.63, $P < .000$).

Conclusions: High *LINC00511* expression may predict unfavorable prognosis in patients with malignancies. It should be further explored as a potential prognostic and therapeutic biomarker for human cancer.

Abbreviations: CC = cervical cancer, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, LINC00511 = lncRNA long intergenic non-protein-coding RNA 511, OC = ovarian cancer, OR = odds ratio, OS = overall survival.

Keywords: long intergenic non-protein-coding RNA 511, long non-coding RNA, prognosis, tumor

1. Introduction

Malignant tumors are the major cause of death globally, representing a severe public health problem with its incidence and mortality rapidly rising in recent years.[1] In 2018, 18.1 million newly diagnosed cancer cases and 9.6 million cancer-associated deaths were reported.[2] Several diagnostic and therapeutic advances were reported in the past decades, but the 3- and 5-year survival rates of patients with malignancies remain unsatisfying.[3] Thus, it is imperative and urgent to identify new diagnostic biomarkers and therapeutic targets to improve the prognosis of these patients.

Long noncoding RNAs consist of more than 200 nucleotides RNA sequences[4] that were previously considered as genetic "junk." However, increasing evidence shows that many long noncoding RNA are dysregulated in tumor tissues and play a vital role in tumor progression, which suggests that they may serve as prognostic and therapeutic biomarkers for tumors.[5–7] The long intergenic noncoding RNA 00511 (*LINC00511*) was firstly identified in 2015 by Cabanski et al.[8] Subsequently, several studies reported that abnormal *LINC00511* expression was correlated with prognosis in patients with malignancies. Moreover, most studies suggested that *LINC00511* could act as an oncogene and its high expression was predictive of poor prognosis in various malignancies, such as cervical cancer

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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(CC),[9,10] ovarian cancer (OC),[11–13] hepatocellular carcinoma (HCC),[14–16] pancreatic cancer,[17] lung cancer,[18,19] breast cancer,[20–24] renal cancer,[25] and glioma.[26,27] Nevertheless, some studies also reported that *LINC00511* could be a tumor suppressor, with high *LINC00511* expression being associated with favorable prognosis of some cancer patients.[28]

To better understand the prognostic significance of *LINC00511* in human malignancies, we performed a comprehensive systematic review and meta-analysis. Additionally, we also explored the association between *LINC00511* expression and several clinicopathological features of cancer that are closely associated with prognosis.

2. Materials and methods

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] The ethical approval is not necessary, since this study is a review article.

2.1. Literature search

Relevant studies available by March 11, 2020, were selected upon a systematic review of the PubMed, EMBASE, Web of Science, and Chinese National Knowledge Infrastructure databases. The search strategy was established by the following keywords:

(i) (Long intergenic noncoding RNA 00511) or (LINC00511); and
(ii) (cancer) or (neoplasm) or (tumor) or (carcinoma) or (adenocarcinoma).
(iii) We also manually searched through the references to identify potentially eligible studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows:

(i) cohort studies that explored the association of *LINC00511* expression with overall survival (OS) or clinicopathological features of cancer;
(ii) *LINC00511* expression was detected using quantitative real-time PCR (RT-qPCR); and
(iii) Odds ratios (ORs) or hazard ratios (HRs), which assessed the relationship of *LINC00511* expression with OS or clinicopathological features, were presented directly or could be calculated indirectly.

The exclusion criteria were:

(i) studies performed only at the cellular level;
(ii) case reports, letters, reviews, or summaries of conferences or discussions;
(iii) studies that evaluated tumor specimens collected before radiotherapy or chemotherapy; or
(iv) sample size < 30. If 2 or more studies analyzed the same cohort of patients, the most recent or complete study was selected.

2.3. Data extraction and quality assessment

Two authors extracted data from all the selected studies in an independent manner and inconsistencies between them were resolved through discussion. The collected data were as followings: first author's name, year of publication, patient source, sample size, median age, gender, TNM stage, tumor size, cut-off value for high *LINC00511* expression, detection method, follow-up time, HRs with 95% confidence interval (CIs) (presented directly or obtained indirectly from Kaplan-Meier survival curve), ORs with 95% Cis, and analysis type. Methodological quality of the included studies was assessed using Newcastle-Ottawa Scale,[30] with the maximum score of 9. In our study, we considered a score ≥ 6 as high quality, as previously reported.[31]

2.4. Statistical analysis

Review Manager (RevMan) 5.3 software was used to calculate the HRs or ORs, whereas publication bias assessment and sensitivity analysis were performed by Stata 14 software. The predicted effect size was calculated using a random-effects model when there was significant heterogeneity among the included studies.[32] Otherwise, a mixed-effects model was adopted. Heterogeneity studies were assessed using the Q value and I^2 statistic values. A predicted HR >1 indicated that high *LINC00511* expression was closely associated with poor prognosis of patients with malignancy. Statistical differences were considered when P value in Q statistics was $< .05$ or I^2 was $> 50\%$. Publication bias was determined by Begg funnel plot.[32]

3. Results

3.1. Basic characteristics and information of eligible studies

The preliminary search yielded 179 potential studies from PubMed, EMBASE, Web of Science and Chinese National Knowledge Infrastructure databases. First of all, we removed duplicated records using EndNote X9 software with 73 studies left for further identification. Next, these 73 studies were carefully screened by the titles, abstracts, and full texts. Finally, a total of 13 eligible studies comprising 1053 cancer patients were included according to the inclusion and exclusion criteria in this meta-analysis[9,10,16,17,21,22,25,28,33–35] (Fig. 1). All the eligible studies were from China and reported the association between LINC00511 expression and OS. A total of 9 cancer types were referred in these included studies, including pancreatic ductal adenocarcinoma, CC, OC, glioma, OC, HCC, osteosarcoma, clear cell renal cell carcinoma, and lung cancer. Each eligible study was given no less than 6 points based on Newcastle-Ottawa Scale score system, which suggested that these studies were high-quality and proper for the synthesized analysis. The basic characteristics and information of the included studies were shown in Table 1.

3.2. Association between LINC00511 expression and OS

The association between *LINC00511 e*xpression and OS was explored in all the included studies with 1053 cancer. The HRs were synthesized using a random effect model due to the significant heterogeneity ($I^2 = 77\%$, $P = .000$). The synthesized HR was 2.00 (95% CI 1.59–2.52, $P < .000$) (Fig. 2), which indicated that increased *LINC00511* expression may predict unfavorable OS. To determine the prognostic significance of *LINC00511* expression in different cancer types, we conducted

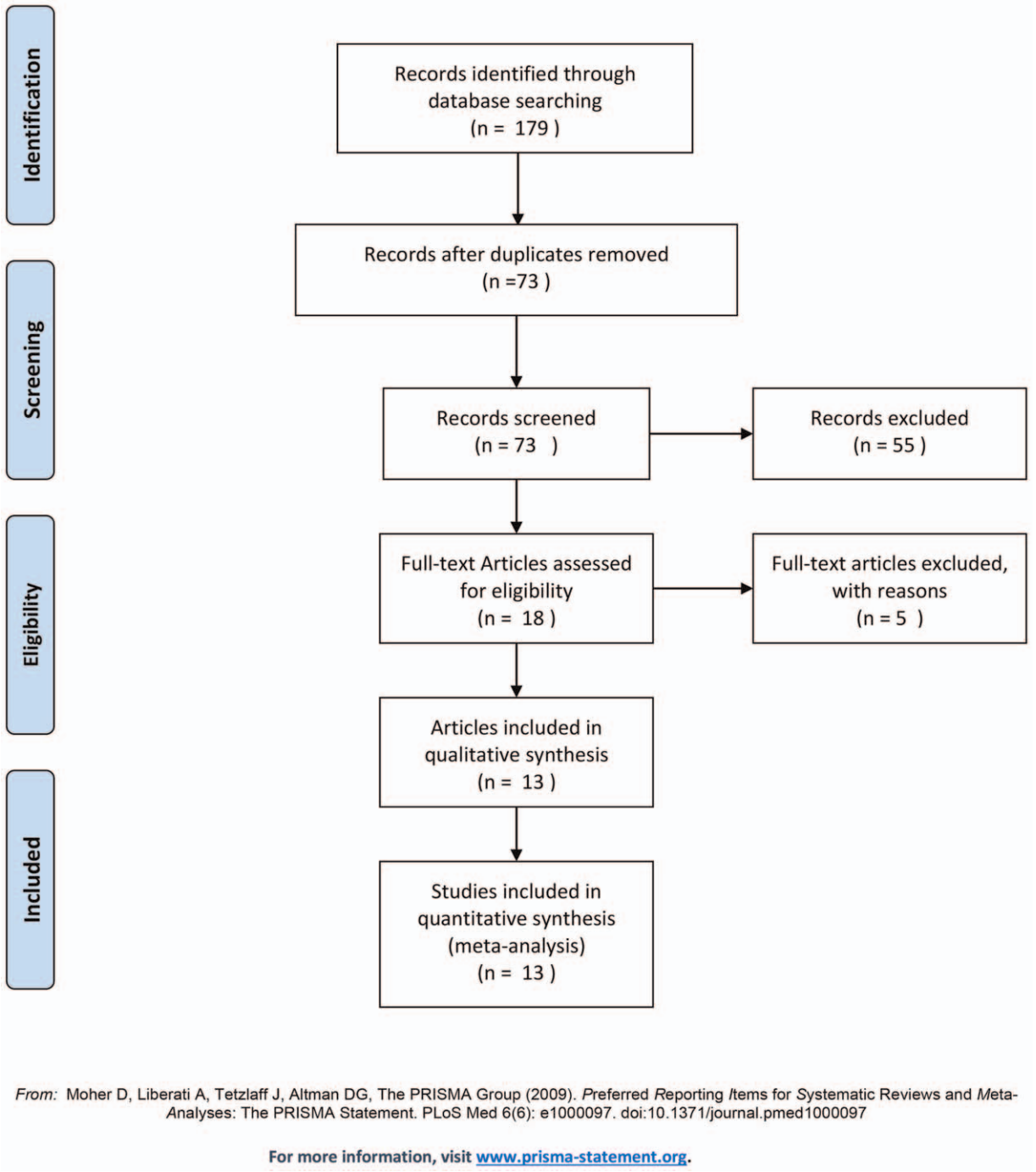

Figure 1. Flowchart illustrating the study selection process applied in the meta-analysis.

the subgroup analysis by malignancy type. As illustrated in Figure 3, higher *LINC00511* expression was associated with poorer OS in lung cancer, breast cancer, glioma, and CC. Additionally, the subgroup analysis by analysis type (univariate vs multivariate) showed that there was a tight relationship between high *LINC00511* expression and short OS regardless of analysis type (Fig. 4). This result implied that high *LINC00511* expression may be an independent prognostic factor in cancer patients.

3.3. Association between LINC00511 expression and clinicopathological features

Cancer clinicopathological features closely correlate with prognosis of patients, so we further explored the association between *LINC00511* expression and several clinicopathological features. As shown in Figure 5 and Table 2, the elevated *LINC00511* expression was closely associated with larger tumor size (OR = 2.92, 95% CI 1.65–5.18, $P < .000$), higher incidence of lymph node metastasis (OR = 3.46, 95% CI 2.11–5.66,

Table 1

The main characteristics of the eligible literatures included in the meta-analysis.

First author	Publication year	Region	Tumor type	Detection method	Cut-off value	Sample size	HRs (95% CIs) for OS	Analysis type	NOS score
Deng HH	2019	China	RCC	qRT-PCR	Median	49	1.43 (1.09-1.88)	Univariate	6
Du XL	2020	China	Glioma	qRT-PCR	Median	36	3.28 (1.33-8.09)	Univariate	6
Liu L	2019	China	BC	qRT-PCR	Median	98	1.67 (1.23-2.27)	Univariate	6
Lu GM	2018	China	BC	qRT-PCR	Median	39	1.57 (1.20–2.05)	Univariate	6
Mao BD	2019	China	CC	qRT-PCR	Median	84	1.44 (1.13–1.84)	Univariate	6
Qiao SC	2019	China	Osteosarcoma	qRT-PCR	Median	45	0.04 (0.00–0.29)	Univariate	6
Sun CC	2016	China	NSCLC	qRT-PCR	Median	124	7.19 (3.53–14.65)	Multivariate	7
Wang B	2019	China	Glioma	qRT-PCR	Median	82	2.53 (1.53–4.18)	Multivariate	7
Wang J	2019	China	OC	qRT-PCR	Median	80	1.76 (1.14–2.72)	Univariate	6
Wang RP	2019	China	HCC	qRT-PCR	Median	127	3.02 (1.22–7.48)	Multivariate	7
Yu CL	2019	China	CC	qRT-PCR	Median	92	2.90 (1.45–5.80)	Multivariate	7
Zhao XH	2018	China	PDAC	qRT-PCR	Median	140	2.26 (1.99–2.56)	Multivariate	7
Zhu FY	2019	China	NSCLC	qRT-PCR	Median	57	2.54 (1.05–6.17)	Univariate	6

BC = breast cancer, CC = cervical cancer, CIs = confidence intervals, HCC = hepatocellular carcinoma, HRs = hazard ratios, NOS = Newcastle-Ottawa Scale, NSCLC = non–small-cell Lung cancer, OC = ovarian cancer, OS = overall survival, PDAC = pancreatic ductal adenocarcinoma, RCC = renal cell carcinoma.

$P < .000$) and distant metastasis (OR = 2.40, 95% CI 1.14–5.05, $P = .02$), poorer differentiation (OR = 1.55, 95% CI 1.11–2.16, $P = .01$) as well as more advanced TNM stage (OR = 3.90, 95% CI 2.70–5.63, $P < .000$).

3.4. Publication bias assessment and sensitivity analysis

Begg test was conducted to assess the publication bias of this meta-analysis. As a result, no significant publication bias for OS ($P = .890$) was detected (Fig. 6A). The sensitivity analysis showed that sequential deletion of single study did not obviously alter the synthesized HRs for OS indicating that our synthesized analysis was stable and reliable (Fig. 6B).

4. Discussion

Growing evidence suggests that *LINC00511* may act as an oncogene and could be a prognostic biomarker for several malignancies. Nevertheless, the prognostic significance of *LINC00511* expression in cancer remains inconclusive. Most data suggested that increased *LINC00511* expression was significantly correlated with shorter OS. In contrast, some studies reported that *LINC00511* may be a tumor suppressor and that high *LINC00511* expression may correlate with favorable prognosis of cancer patients. Therefore, we performed this meta-analysis and systematic review of current literature to comprehensively evaluate the prognostic value of *LINC00511* in patients with malignant tumors. To the best of our knowledge, the present study is the first meta-analysis to evaluate the relationship between *LINC00511* expression and prognosis in patients with malignant tumors. A total of 13 eligible studies, comprising 1053 patients, were included in this meta-analysis. The results showed that higher *LINC00511* expression was significantly associated with worse OS. Additionally, our analyses indicated that high *LINC00511* expression was significantly correlated with larger tumor size, positive metastasis, low tumor differentiation, and advanced TNM stage. Notably, in our subgroup and sensitivity analyses, the calculated HR for OS did not fluctuate dramatically, indicating the robustness of our meta-analysis.

LINC00511 plays an important role in the progression of multiple malignancies, which may account for the prognostic significance of *LINC00511*. Liu et al.[21] and Lu et al.[22] reported that *LINC00511* contributed to the proliferation, stemness,

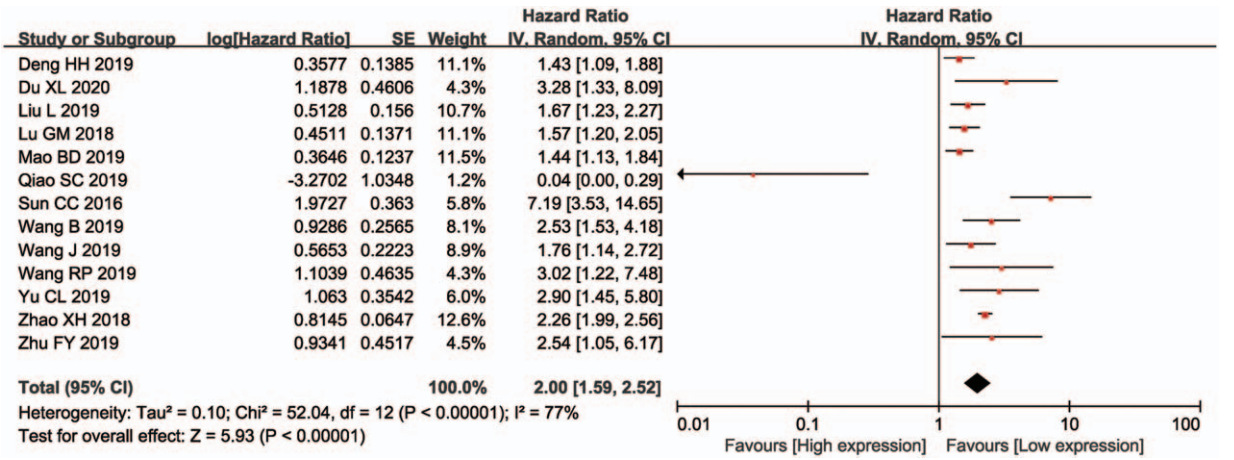

Figure 2. Forest plot for the association of *LINC00511* expression with overall survival (OS) in patients with malignancies.

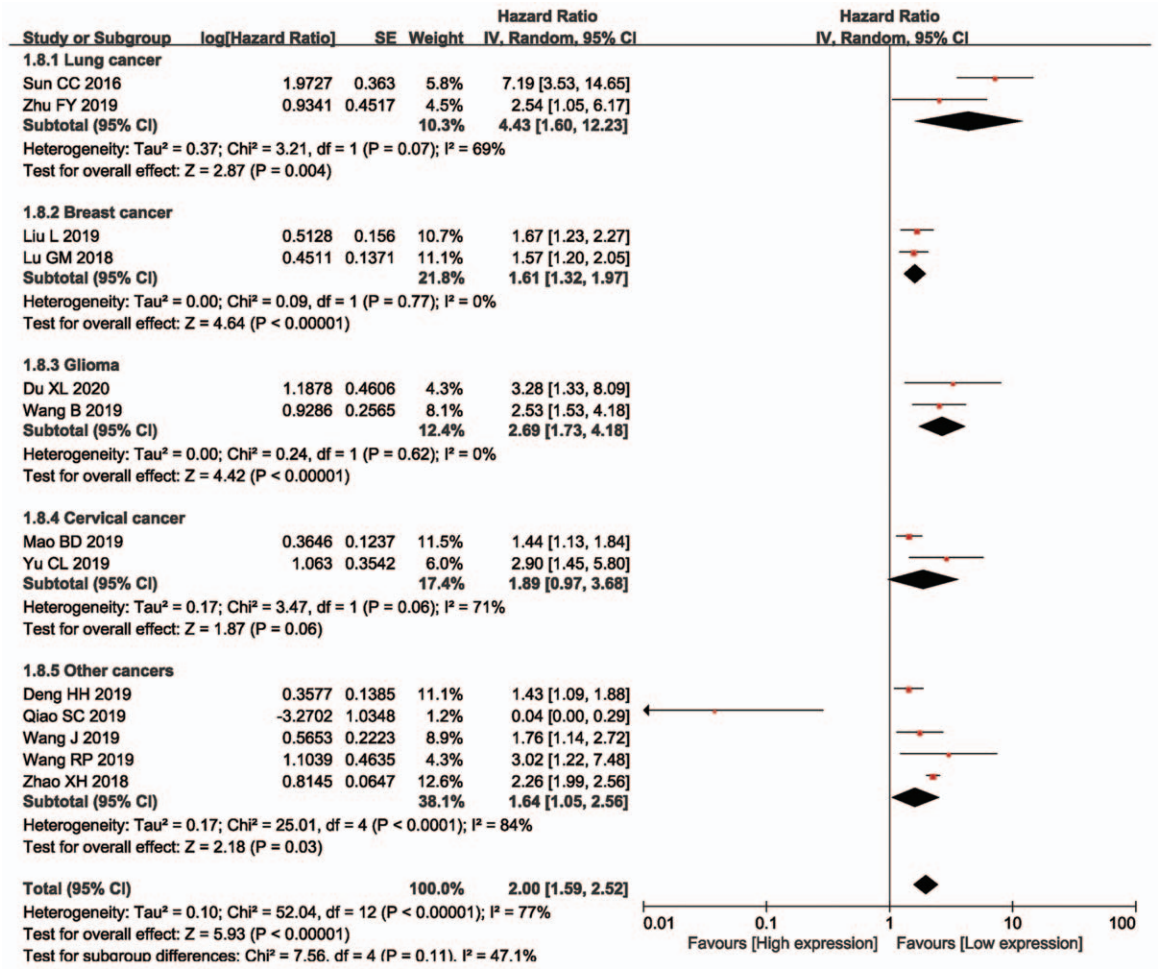

Figure 3. Subgroup analysis by tumor type of the association between *LINC00511* expression and overall survival (OS).

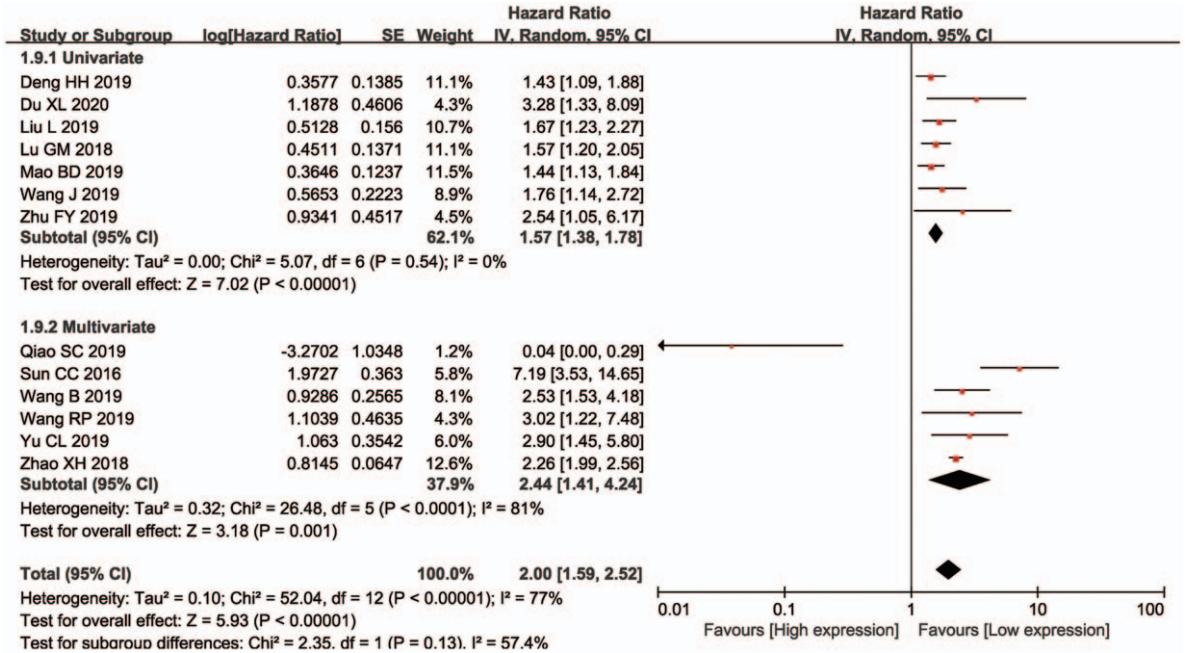

Figure 4. Subgroup analysis by analysis type of the association between *LINC00511* expression and overall survival (OS).

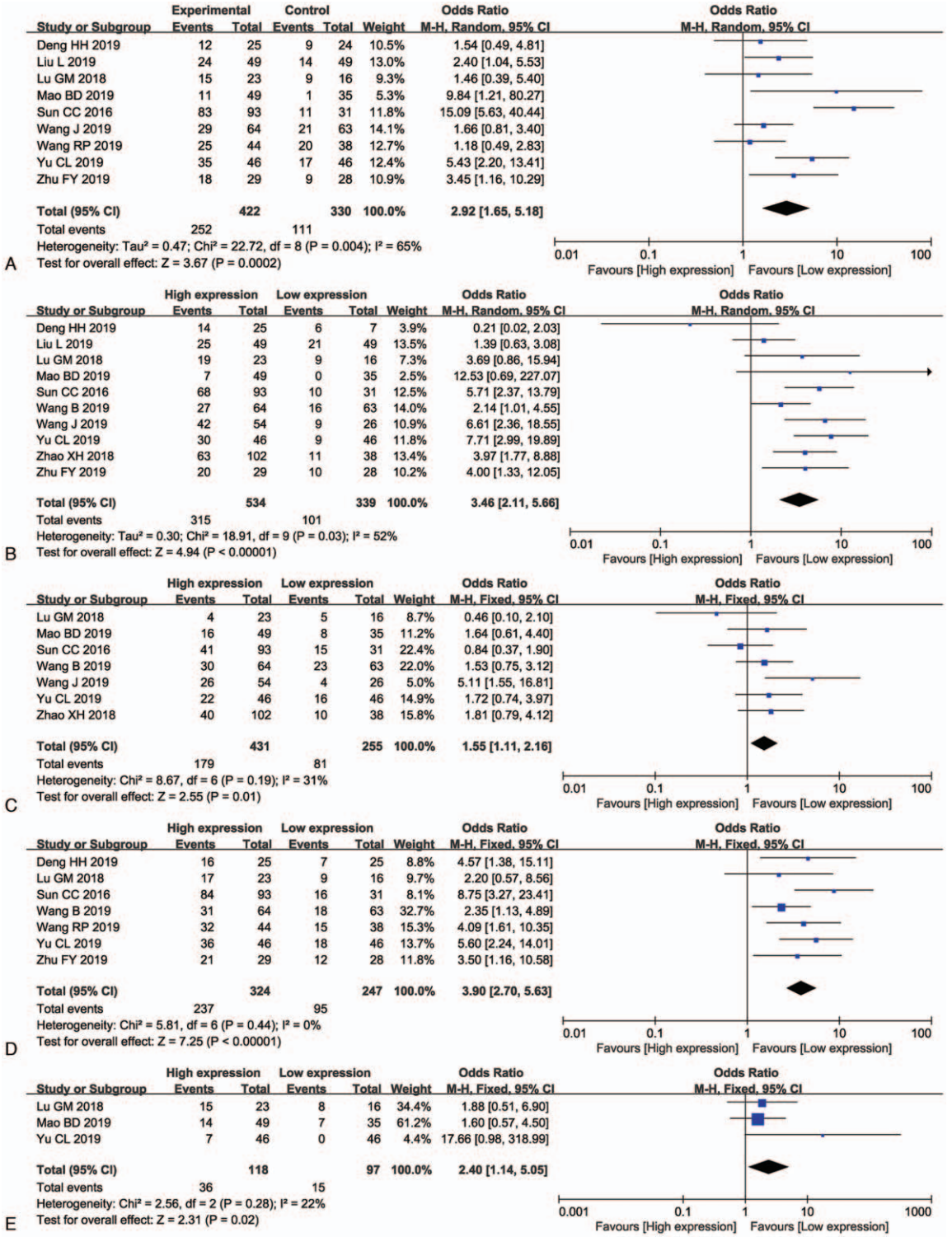

Figure 5. Forest plots for the correlation between *LINC00511* expression and clinicopathological characteristics of cancer. A: Tumor size; B: Lymph node metastasis; C: Tumor differentiation; D: TNM staging; E: Distant metastasis.

radio-resistance, and growth of breast cancer cells by inhibiting *miR-185-3p*. In HCC, *LINC00511* promoted the proliferation, colony formation, migration, and invasion of cancer cells by targeting *miR-424* and *miR-29c*, and regulating the *miR-195*/eyes absent homolog 1 axis.[14–16] Jiang et al[36] also suggested that silencing *LINC00511* would suppress the proliferation, migration, and epithelial-mesenchymal transition of lung cancer cells by modulating the PTEN/AKT/FOXO1 axis. Moreover, Li et al[37] found that overexpression of *LINC00511* enhanced the proliferation and invasion of glioma cells through inhibition of

Table 2

Association LINC00511 expression and clinicopathological characteristics of tumor patients.

Variable	No. of studies	No. of patients	ORs (95% CIs)	*P* value	Heterogeneity	
					I^2	*P* value
Tumor size (Larger vs Small)	9	752	2.92 (1.65–5.18)	<.01	65%	<.01
Lymph node metastasis (Positive vs negative)	10	873	3.46 (2.11–5.66)	<.01	52%	.03
Differentiation (Poor vs moderate/well)	7	656	1.55 (1.11–2.16)	.01	31%	.19
TNM stage (III/IV vs I/II)	7	571	3.90 (2.70–5.63)	<.01	0%	.44
Distance metastasis (Positive vs negative)	3	225	2.40 (1.14–5.05)	.02	22%	.28

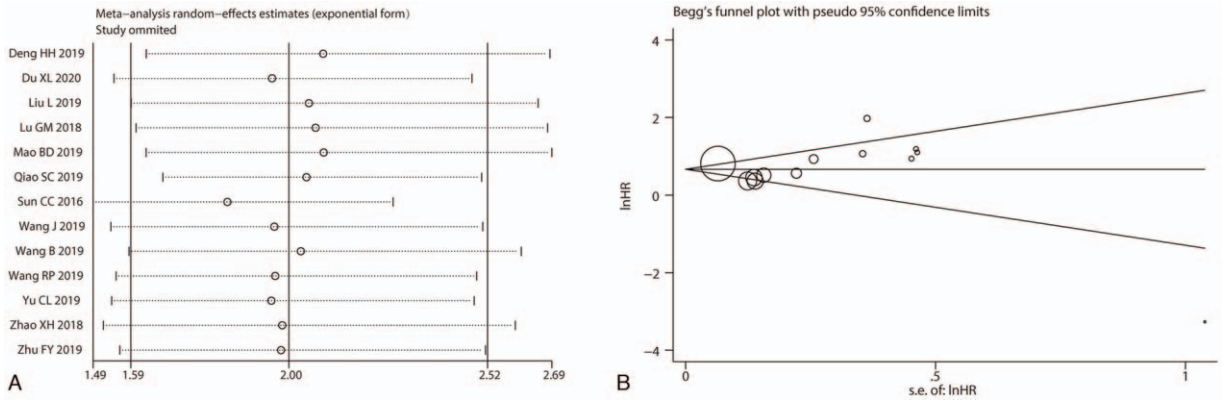

Figure 6. Sensitivity analysis and publication bias for overall survival (OS) in the meta-analysis. A: Sensitivity analysis; B: Begg funnel plots.

miR-124-3p and concomitant upregulation of cyclin D2.[37] In OC, *LINC00511* was found to interact with enhancer of zeste homologue 2 to repress P21 expression, thereby augmenting the viability and invasive ability of cancer cells.[16] Yu et al.[10] and Mao et al[9] also demonstrated that *LINC00511* could promote the proliferation, migration, invasion, and resistance to paclitaxel in CC cells by upregulating matrix metalloproteinase-9, P-glycoprotein, Bcl-2, and a multidrug resistance protein. In pancreatic cancer, overexpression of *LINC00511* could significantly contribute to tumor cell proliferation, migration, invasion, and angiogenesis via the *miR-29b-3p*/ vascular endothelial growth factor A axis.[17] In thyroid cancer, Chen et al.[37] revealed that *LINC00511* could bind to TATA-box binding protein-associated factor 1 to activate Janus kinase 2/signal transducer and activator of transcription 3 signaling pathway, which remarkably decreased the radio-sensitivity of malignant cells. In renal cell cancer cells, Deng et al[25] found that *LINC00511* was capable of promoting the proliferation, colony formation, in vitro invasion, and in vivo tumor growth, as well as inhibit apoptosis of cancer cells, by repressing the *miR-625* and consequently upregulating CCND1.[25] Collectively, these studies provide extensive evidences that *LINC00511* may act as an oncogene in human malignancies, which strongly supported the findings of our meta-analysis.

There are several limitations in our meta-analysis. First, significant inter-study heterogeneity was observed, which may have resulted in overestimation of the calculated effect size. Second, all the studies included in the analysis were conducted in Chinese populations; therefore the meta-analysis results may not fully reflect the cellular and molecular features of other ethnic populations. Third, we applied an indirect method to obtain HRs and 95% CI from the survival curves, which was likely accompanied by some operating errors, thereby leading to the overestimation of the association between *LINC00511* expression and prognosis in malignancies. Fourth, less than 2 studies reported the prognostic value of *LINC00511* in the same malignancy, so our predictive analysis of the association between *LINC00511* expression and prognosis in a particular type of malignancy may not be reliable, which may limit the prognostic value of *LINC00511* in human cancer. Lastly, there was significant publication bias in our meta-analysis. Usually, researchers tend to publish studies with positive results but not those with negative results, which may partially explain the publication bias.

In summary, high *LINC00511* expression may predict unfavorable prognosis in patients with malignancies and it should be explored as a potential prognostic and therapeutic biomarker for malignant tumors. More homogeneous studies enrolling multiracial populations are needed to further confirm our conclusions.

Author contributions

Ming Chen and Ping Qi performed literature search, identified the eligible studies and extracted the data independently. Wen-wen Jiang helped to resolve the disagreements in the literature assessment and data extraction, and conducted the statistical analysis. Besides, Ming Chen wrote the original manuscript and the other authors reviewed and corrected it. All the authors read and approved the final manuscript.

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