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The clinical prognostic value of lncRNA LINC00473 in cancer patients

A meta-analysis

Yuanyang He, MD[a], Zheng Chen, MD[a], Jingyu He, MD[a,*]

Abstract

Background: LINC00473 is a promising long non-coding RNA. There is increasing evidence that SNHG7 is abnormally expressed in various tumors and is associated with cancer prognosis. However, identification of the effect of long non-coding RNA LINC00473 in tumors remains necessary.

Methods: Up to August 15, 2021, we searched electronic databases, including PubMed, Cochrane Library, EMBASE, Medline, and Web of Science. The results were evaluated by pooled odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: There weres 13 included literature totaling cancer patients involved in this meta-analysis. The aggregated results revealed that high expression of LINC00473 was significantly associated with unfavorable overall survival (HR = 1.66, 95% CI: 1.48–1.86, $P < .00001$), disease-free survival (HR = 1.59, 95% CI: 1.09–2.32, $P = .02$) in a variety of cancers. Additionally, increased LINC00473 expression was also correlated with tumor node metastasis stage ((III/IV vs I/II) OR = 4.67, 95% CI = 3.11–7.02, $P < .00001$), differentiation ((poor/moderately vs well) OR = 3.25, 95% CI = 1.41–7.50, $P = .006$), tumor size ((larger vs smaller) OR = 2.49, 95% CI = 1.26–4.91, $P = .03$), and lymph node metastasis ((positive vs negative) OR = 3.10, 95% CI = 2.13–4.51, $P = .008$) in patients with cancers. Besides, the Gene Expression Profiling Interactive Analysis dataset evaluated that LINC00473 was upregulated in a variety of tumors and predicted worse prognosis.

Conclusion: Our results of this meta-analysis demonstrated that high LINC00473 expression may become a potential target for predicting prognosis of human cancers.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, lncRNA = long non-coding RNA, LNM = lymph node metastasis, NOS = Newcastle–Ottawa Quality Assessment Scale, OR = odds ratio, OS = overall survival, SCC = squamous cell carcinoma.

Keywords: cancer, LINC00473, long non-coding RNA (lncRNA), overall survival (OS), prognosis

1. Introduction

Cancer is one of the major public health problems and the main leading cause of death around the world. The underlying molecular mechanism of cancer is still under exploration. According to the US statistics in 2018, about 17,353,500 new cancer cases and 609,640 cancer deaths expected, demonstrating that cancer remains a primary threat to public health and challenge.[1] However, it is still tough to identify the patients with early-stage cancer, which leads to that many cancer cases being diagnosed at the advance-stage with a dismal prognosis. So, early diagnosis and interventions play a much more prominent role in improving the overall survival (OS) of cancer patients.

Long non-coding RNAs (lncRNAs), longer than 200 nucleotides,[2] have no or limited capacity to encode proteins.[3] As we all know, lncRNAs perform molecular functions as prototypes of decoys, signals, guides and scaffolds in various categories of human cancers.[4–6] It has been established that the lncRNA's abnormal expression or dysfunction, including the sequence and spatial structure of abnormalities and abnormal interaction with binding proteins, are associated with the occurrence of a variety of diseases. For instance, cancer susceptibility candidate 11, a kind of lncRNAs, is regarded as a promotor in the progression of hepatocellular carcinoma, including oncogenesis, tumor development, and metastasis.[7] In gastric cancer, lncRNA SNHG7 has been found to be highly expressed and the improvement of expression means a worse prognosis.[8]

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Our study did not require an ethical board approval because it did not contain human or animal trials.

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Increasing evidence in the field of oncology has reported that lncRNAs are engaged in the signaling pathways of cancer via interactions with deoxyribonucleic acid, RNA, or proteins.[9] Thus, lncRNAs have a profound effect on the prognosis of cancer patients.[10]

LINC00473, located on chromosome 6q27, also called chromosome 6 open reading frame 176, can direct the posttranslational modification of nucleolus small-molecule RNA, which has an imperative value in the occurrence and progression of cancers.[11] There are plentiful studies from fundamental and clinical research to indicate that LINC00473 participates in tumorigenesis and could be a biomarker of poor prognostic in a variety of cancer types.[12,13] In colorectal cancer, the study of Wang et al reported that high expression of LINC00473 may be indicative of poor OS and the advanced clinical stage.[14] However, no systematic meta-analysis has been conducted to explain the relationship between LINC00473 and the prognostication of these cancers. In this paper, a meta-analysis is performed to formulate the clinical prognostic value of LINC00473 in cancer patients.

2. Materials and methods

2.1. Literature search

This meta-analysis pertaining to prognosis was conducted according to the guidelines of the Preferred Reporting Item for System Reviews and Meta-Analyses and the Meta-Analysis of Observational Studies in Epidemiology statement.[15] Our study did not require an ethical board approval because it did not contain human or animal trials. A comprehensive and systematic literature retrieval was performed. Two of the authors independently finished the search based on electronic databases including PubMed, Cochrane Library, EMBASE, Medline, and Web of Science to identify the relevant articles. The following terms selected for search were used: "LNC00473," "LINC00473," "chromosome 6 open reading frame 176," "tumor," "cancer," "carcinoma," "neoplasia," "neoplasm," and "prognosis." Our research was limited to English-language articles.

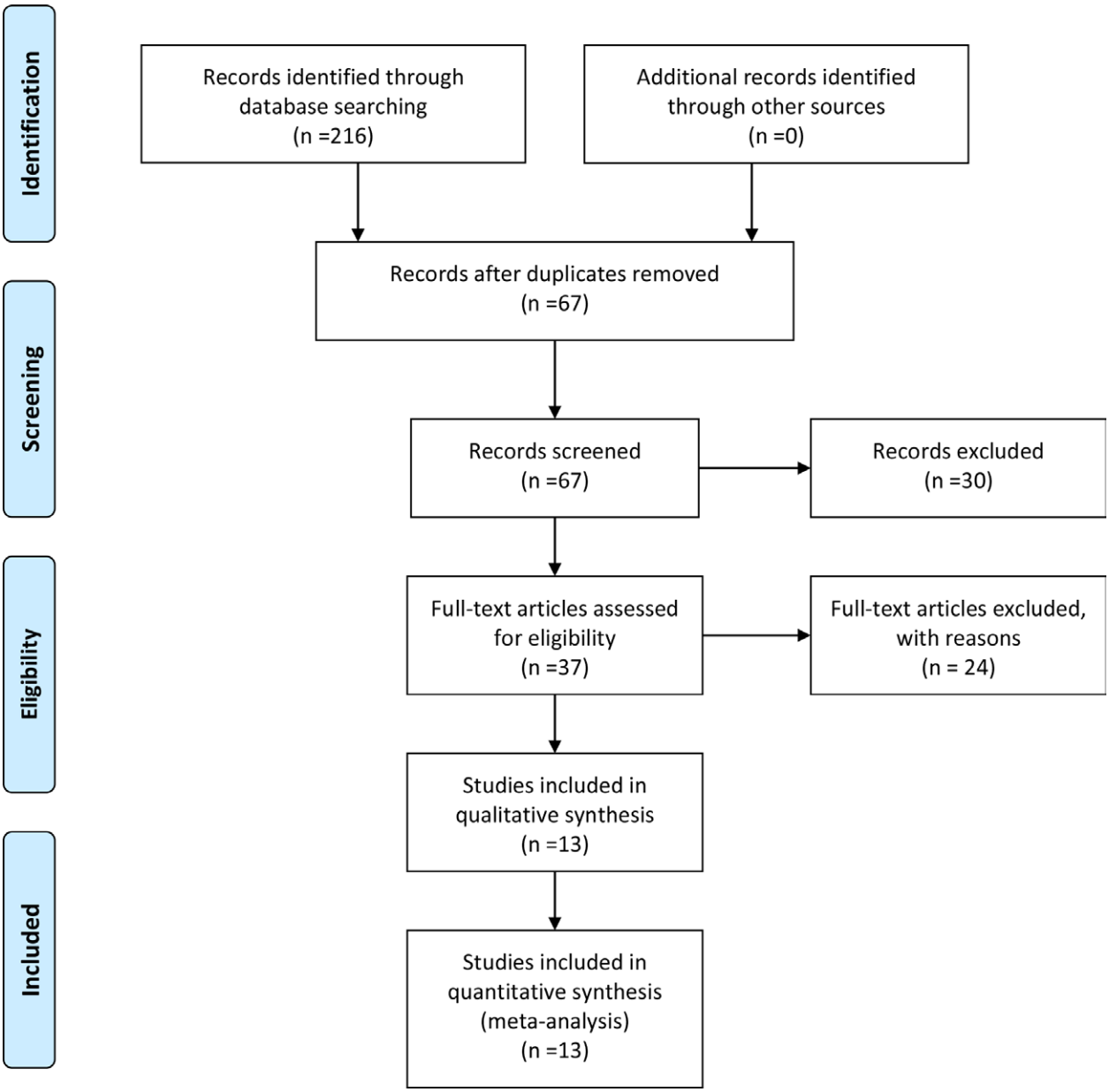

Figure 1. Flow diagram of the literature selection procedure in this meta-analysis.

2.2. Inclusion and exclusion criteria

All included researches depended on the Population, Intervention, Control, and Outcomes criteria: all articles were written and published in English and the LINC00473 expression must be detected in human cancer tissues by established molecular methods; to describe the correlation between the prognostic and clinicopathologic features of LINC00473 in patients with malignant tumor; and enough information to extract the pooled hazard ratio (HR) and 95% confidence interval (CI).

Exclusion criteria were: study data incomplete; duplicate publications; and non-human studies, letters, case reports, letters, review articles, and other studies without survival data.

2.3. Data extraction and quality assessment

Three authors extracted study data independently and reached a consensus. For all included studies, the following data were collected successively from each eligible literature: author, region, year of publication, tumor size, type of cancers, follow-up time, detection method and cutoff value, and total number of patients; clinicopathological characteristics including lymph node metastasis (LNM), distant metastasis, differentiation, depth of tumor invasion and tumor stage; the prognostic endpoints including OS; and survival curves.

We obtained HRs and 95% CIs from the univariate or multivariate analysis, or from the graph survival plot by using Engauge Digitizer V4.1 (http://digitizer.sourceforge.net/). The Newcastle–Ottawa Quality Assessment Scale (NOS) was performed to evaluate the quality of each eligible study and the score ranged from 0 (minimum) to 9 (maximum) points; a study with the NOS score >6 accounted were considered to be the high quality.

2.4. Statistical analysis

Review Manager (RevMan) 5.4 software (Cochrane Collaboration, Oxford, UK) and Stata SE 12.0 software (Stata Corporation, College Station, TX) were applied to analyze study data and construct the forest plot. $P < .05$ was considered to be statistically

Table 1

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

Study	Region	Tumor type	Sample size	TNM stage	LINC00473 expression		Cutoff value	Detection method	Outcome measure	NOS
					High	Low				
Bai et al 2019[16]	China	BRCA	122	I–IV	60	62	Median	qRT-PCR	OS	6
Niu et al 2018[17]	China	HCC	58	I–IV	26	32	Median	qRT-PCR	OS	7
Chen et al 2016[18]	China	NSCLC	469	I–IV	48	421	Median	qRT-PCR	OS	7
Qin et al 2020[19]	China	NSCLC	72	NA	38	34	Median	qRT-PCR	OS	8
Xu et al 2021[20]	China	NSCLC	58	NA	29	29	Median	qRT-PCR	OS	6
Zhang et al 2018[21]	China	GC	120	I–IV	60	60	Median	qRT-PCR	OS	6
Zhuo et al 2021[22]	China	GC	53	I–IV	27	26	Median	qRT-PCR	NA	7
Shi et al 2017[23]	China	CC	80	I–IV	40	40	Median	qRT-PCR	OS	8
Wang et al 2020[24]	China	Glioma	40	I–IV	17	23	Median	qRT-PCR	OS	8
Wu et al 2020[25]	China	CRC	157	NA	79	78	Median	qRT-PCR	OS, DFS	8
Chen et al 20218[26]	China	HCC	70	I–IV	35	35	Median	qRT-PCR	OS	7
Hao et al 2020[27]	China	PC	54	I–IV	27	27	Median	qRT-PCR	OS	6
Liu et al 2020[28]	China	ESCC	46	I–IV	24	22	Median	qRT-PCR	NA	6

BRCA = breast cancer, CC = cervical cancer, CRC = colorectal cancer, DFS = disease-free survival, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, LC = liver cancer, NA = not available, NOS = Newcastle–Ottawa Quality Assessment Scale, NSCLC = non-small cell lung cancer, OS = overall survival, PC = pancreatic cancer, PTC = papillary thyroid cancer, qRT-PCR = real-time quantitative reverse transcription polymerase chain reaction.

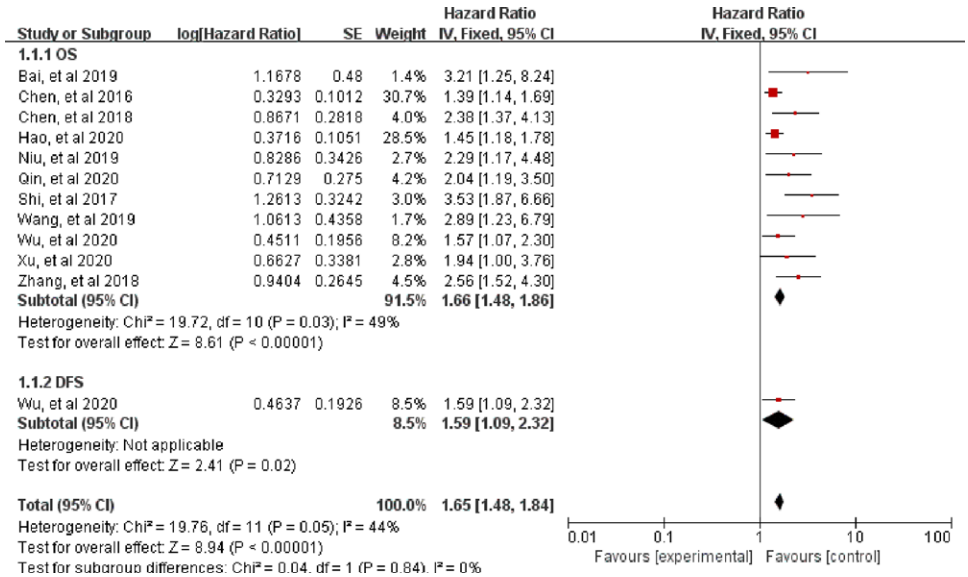

Figure 2. Forest plots of the included literatures evaluating the association between LINC00473 expression with overall survival (OS) and disease-free survival (DFS).

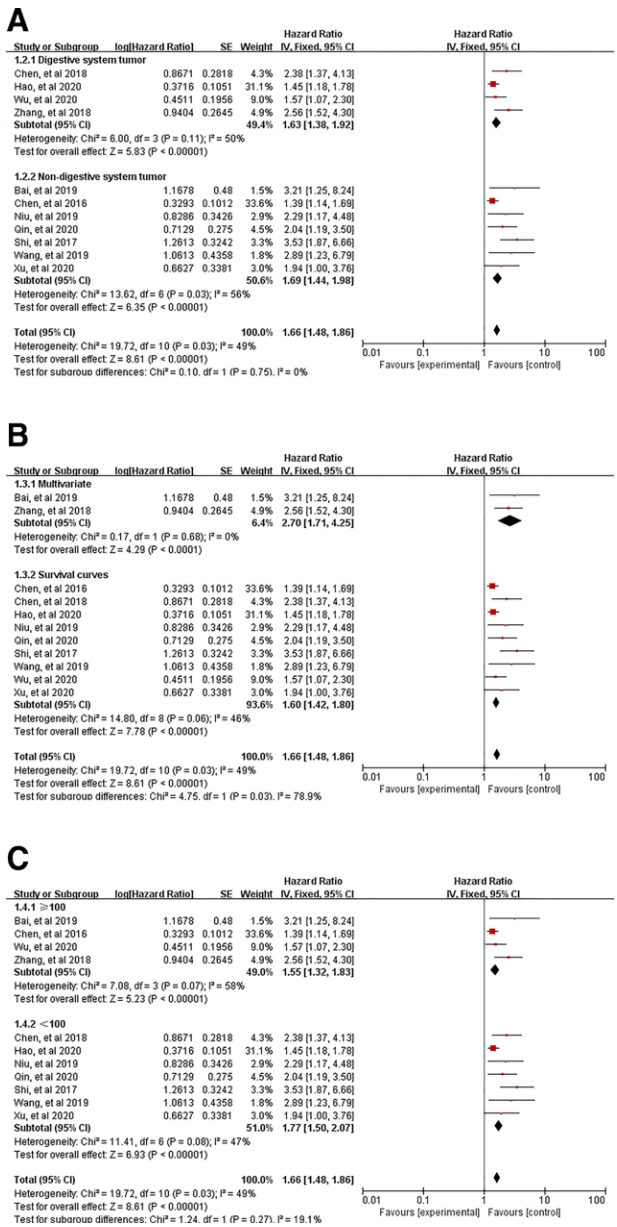

Figure 3. Forest plots of the included literatures evaluating the association between LINC00473 expression with overall survival: (A) stratified by analysis type, (B) the analysis method, and (C) stratified by sample size.

significant. Pooled HRs and 95% CIs were used to assess the association between LINC00473 expressions and clinical prognosis of the cancer patients. The LINC00473 expression with clinicopathological features was assessed by performing aggregated odds ratios (ORs) with 95% CIs. Heterogeneity among studies was quantified through using I^2 statistics. The fixed-effects model was picked in if $I^2 < 50\%$. Otherwise, the random-effects model was applied for data analysis. A subgroup and a sensitivity analysis were used when the heterogeneity between studies was significant and the source of heterogeneity failed to be identified ($I^2 > 50\%$). The assessment of publication bias was utilized by using Begg test.

3. Results

3.1. Characteristics and basic information of the included studies

After a systematic literature online search of published studies, we retrieved 216 relevant literature in total from electronic databases. After duplicates removal, a total of 67 studies were excluded. Further, after we thoroughly screened the title and abstract, 37 publications were subjected to be included. Through carefully assessment of the full texts, eventually, 13 literatures that had the publication date between 2016 and 2021 were enrolled in this meta-analysis, and the literature screening processes are shown in Figure 1. The total eligible literatures contained 1361 patients. In this meta-analysis, a variety of types of tumors were reported, including breast cancer,[16,17] non-small cell lung cancer,[18–20] gastric cancer,[21,22] cervical cancer,[23] glioma,[24] colorectal cancer,[25] liver cancer,[26] pancreatic cancer,[27] and esophageal squamous cell carcinoma (SCC).[28] The expression of LINC00473 was quantified with real-time fluorescent polymerase chain reaction in these included studies and the LINC00473 is an oncogene in different human cancers. The LINC00473 expressions were tested in tumor tissues. The median was selected as the cutoff value to distinguish between high expression and low expression of LINC00473. And 11 eligible literatures used OS to estimate patient survival. The detailed clinical characteristics of the 13 published literatures are summarized in Table 1. The NOS scores of all included researches were ≥6.

3.2. The expression of LINC00473 was significantly correlated with OS, disease-free survival (DFS)

After screening, 11 publications for OS including 1078 patients with cancer reported the HR and 95% CI were included in this meta-analysis. The fixed-effect model was used to calculate the pooled HR due to no significant heterogeneity between these literatures ($I^2 = 44\%$, $P = .05$). Obviously, the aggregated data elucidated that enforced LINC00473 expression levels were significantly correlated with poor OS in various carcinomas ((HR = 1.66, 95% CI: 1.48–1.86, P < .00001), and also with DFS (HR = 1.59, 95% CI: 1.09–2.32, $P = .02$) (Fig. 2), which means the cancer patients with high LINC00473 expression may result in a better prognostic outcome. Furthermore, to maximize the clinical relevance, we analyzed the subgroup meta-analysis stratified by cancer type, the analysis method and the sample size, suggesting that there was a considerable association between high LINC00473 expression and poor OS (Fig. 3).

3.3. Association between LINC00473 and clinicopathologic characteristics

In the 10 included eligible literatures that contained detailed clinicopathologic characteristics, we observed that the elevated expression of LINC00473 was positively involved in advanced tumor node metastasis stage ((III/IV vs I/II) OR = 4.67, 95% CI = 3.11–7.02, $P < .00001$), differentiation ((poor/moderately vs well) OR = 3.25, 95% CI = 1.41–7.50, $P = .006$), tumor size ((larger vs smaller) OR = 2.49, 95% CI = 1.26–4.91, $P = .03$), and LNM ((positive vs negative) OR = 3.10, 95% CI = 2.13–4.51, $P = .008$) (Fig. 4). Furthermore, in respect to other clinical parameters, including age, gender, and differentiation, no significant correlation was found between LINC00473 expression and them (Fig. 5). The detailed information was shown in Table 2.

3.4. Sensitivity analysis and publication bias

To test the impact of a single study to the overall results of OS, the sensitivity analysis was performed. The result was uncovered that the pooled HR was not altered by removing a study at a time, illustrating that the results were considerably stable and reasonable (Fig. 6A). Additionally, we conducted Begg test to assess publication bias of the included studies in this meta-analysis for OS; no statistically significant publication bias existed ($P = .083$) (Fig. 6B).

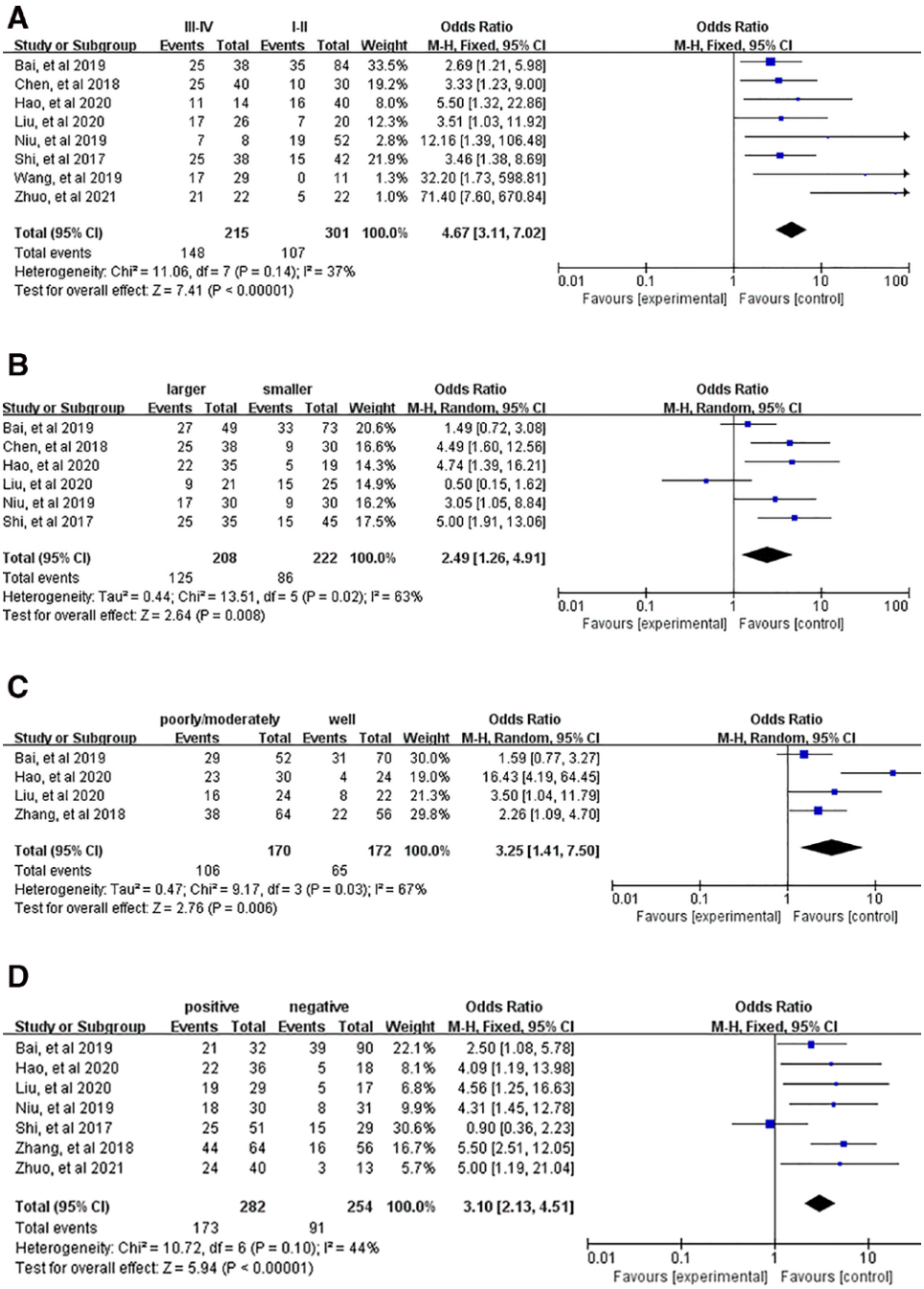

Figure 4. Forest plots of the included literatures evaluating the correlation between LINC00473 expression and clinicopathological characteristics. (A) TNM stage, (B) tumor size, (C) differentiation, and (D) lymph node metastasis. TNM = tumor node metastasis.

3.5. Validation of the results in Gene Expression Profiling Interactive Analysis (GEPIA) dataset

Furthermore, in order to validate our results, we conducted GEPIA dataset to analyze the expression of LINC00473 in multiple kinds of cancers. As depicted in Figure 7, we found that LINC00473 was more exposed in tumor tissue in patients with skin cutaneous melanoma (Fig. 7A). Moreover, the violin plot implicated that LINC00473 expression was also correlated with the clinical stage of human tumors ($P < .05$, Fig. 7B). In addition, we utilized survival plots in the GEPIA dataset to explore the association between LINC00473 expression and the clinical outcome of cancer patients. The results elucidated that increased LINC00473 expression has significantly negative effects on OS (Fig. 7C) and DFS (Fig. 7D), which were consistent with our consequences in this meta-analysis.

4. Disscusion

It is worth noting that lncRNAs have considerable implication in susceptibility of cancer and behave as a potential factor in predicting the prognosis of patients with malignant tumors at present.[29,30] An increasing number of studies demonstrated that lncRNA plays multiple and crucial roles in the initiation and biological processes of various carcinomas, which revealed the effect of lncRNA in cancer progression.[31] For instance, high expression of cancer susceptibility candidate 2 was markedly associated with OS in cancer patients and could promote tumor

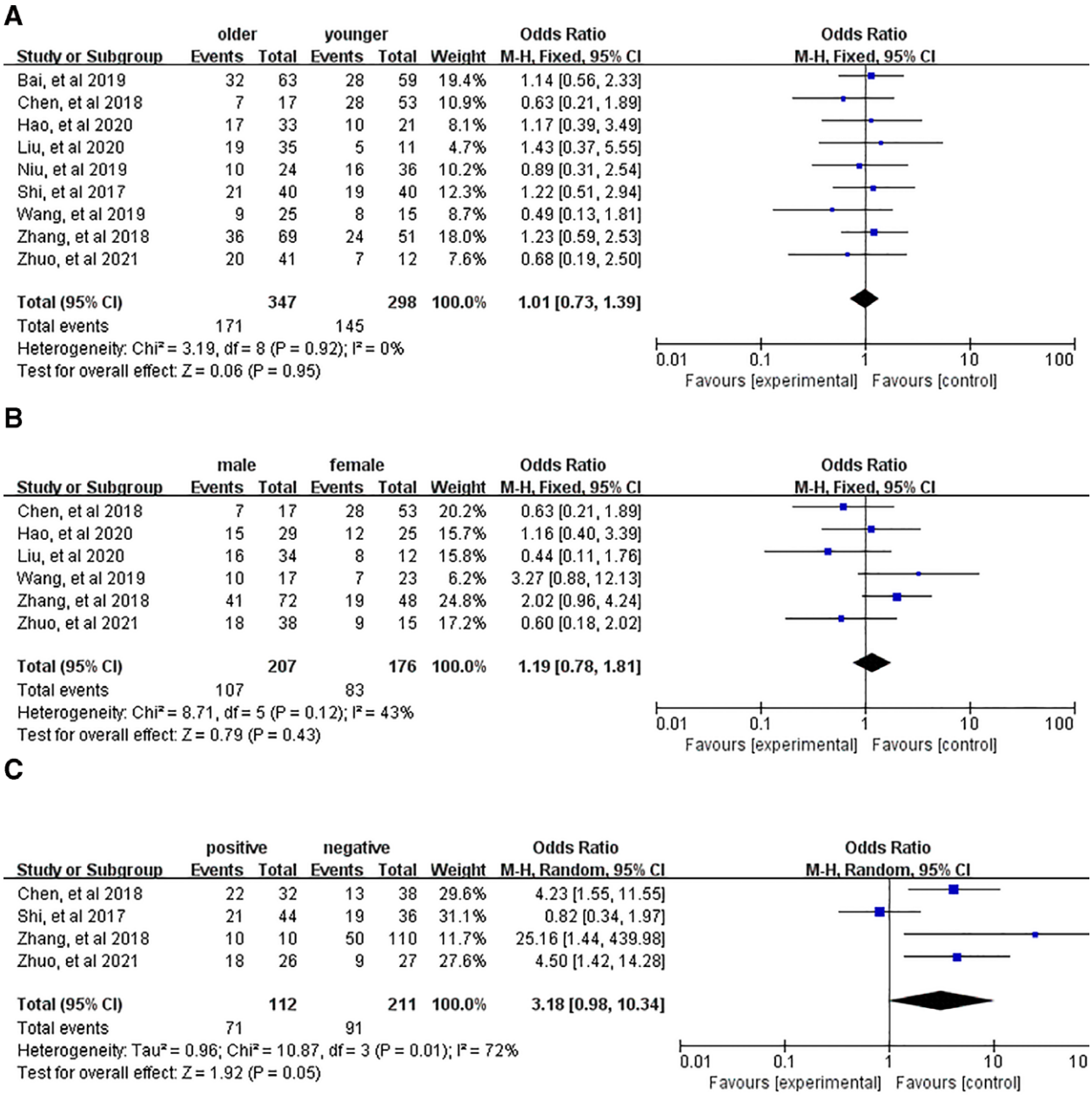

Figure 5. Forest plots of the included literatures evaluating the correlation between LINC00473 expression and clinicopathological characteristics. (A) Age, (B) gender, and (C) distant metastasis.

Table 2

Summary of correlation between LINC00473 expression and clinicopathological characteristics of cancers.

Clinicopathological parameters	Studies	Patients	OR (95% CI)	*P* value	Heterogeneity		
					I^2	*P* value	Model
Age (older vs younger)	9	645	1.01 (0.73, 1.39)	.95	0%	.92	Fixed
Gender (male vs female)	6	383	1.19 (0.78, 1.81)	.43	43%	.12	Fixed
Tumor size (larger vs smaller)	6	430	2.49 (1.26, 4.91)	**.008**	63%	.02	Random
Differentiation (poor/ moderately vs well)	4	342	3.25 (1.41, 7.50)	**.006**	67%	.03	Random
TNM stage (III + IV vs I + II)	8	516	4.67 (3.11, 7.02)	**<.00001**	37%	.14	Fixed
LNM (positive vs negative)	4	356	3.10 (2.13, 4.51)	**<.00001**	0%	.83	Fixed
DM (positive vs negative)	4	323	3.18 (0.98, 10.34)	.05	72%	.01	Random

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

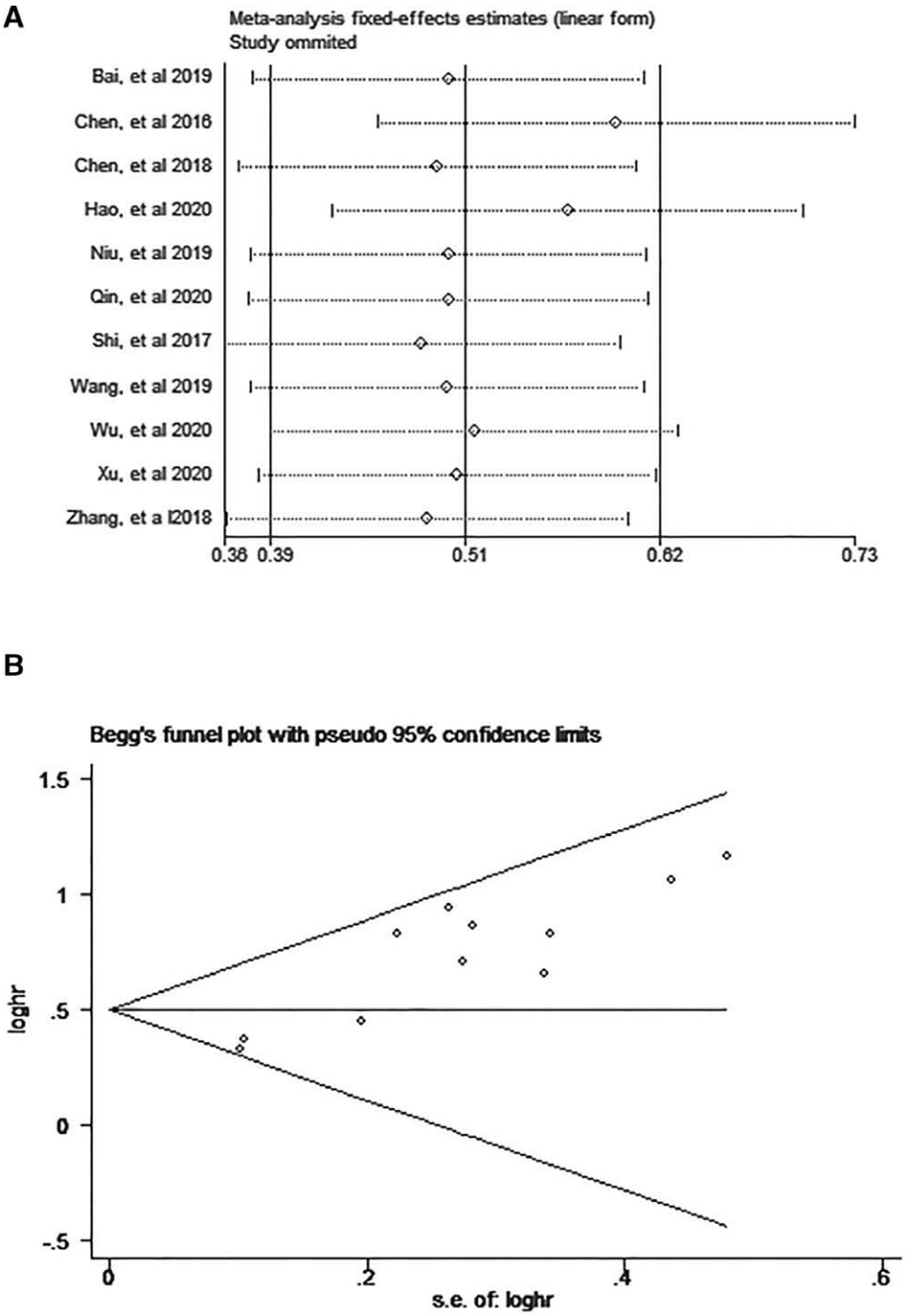

Figure 6. Sensitivity analysis and publication bias for OS in this meta-analysis. (A) sensitivity analysis, (B) Begg funnel plots. OS = overall survival.

growth and aggressiveness of cancer cells.[32] Thus, evolving evidence verified that lncRNA has the ability to provide a novel option for the prognosis assessment of cancer.[33]

LINC00473 has recently attracted the attention of a large group of researches. More and more studies indicated that the higher LINC00473 expression was positively associated with advanced clinical stage and its biological function is engaged in many processes in a variety of human cancers and diseases.[34–36] So better understanding the molecular mechanisms of the function of lncRNA in the progression of cancer is meaningful to improve the diagnosis and prognosis of cancer patients. In 2019, Zhou's study suggested that downregulated LINC00473 expression could inhibit the growth and migration of pancreatic cancer cells by enhancing the miR-195-5p-targeted downregulation of programmed death-ligand 1, which provide new strategies for the treatment of this kind of cancer.[37] Meanwhile, another study suggested that LINC00473 exerted a functional promoter in lung cancer through regulating the miR-1294/ROB1 axis.[38] Research by Huang also demonstrated that the oncogenes and tumorigenesis roles of LINC00473 are involved in cholangiocarcinoma growth and metastasis by regulating miR-506, which indicated that LINC00473 could be a molecular target for the treatment of cholangiocarcinoma.[39] Previous study confirmed that the Wnt/β-catenin signaling pathway is of significant importance to the migration and invasion of tumors.[40] What's more, Han's study recommended the downregulation of lncRNA

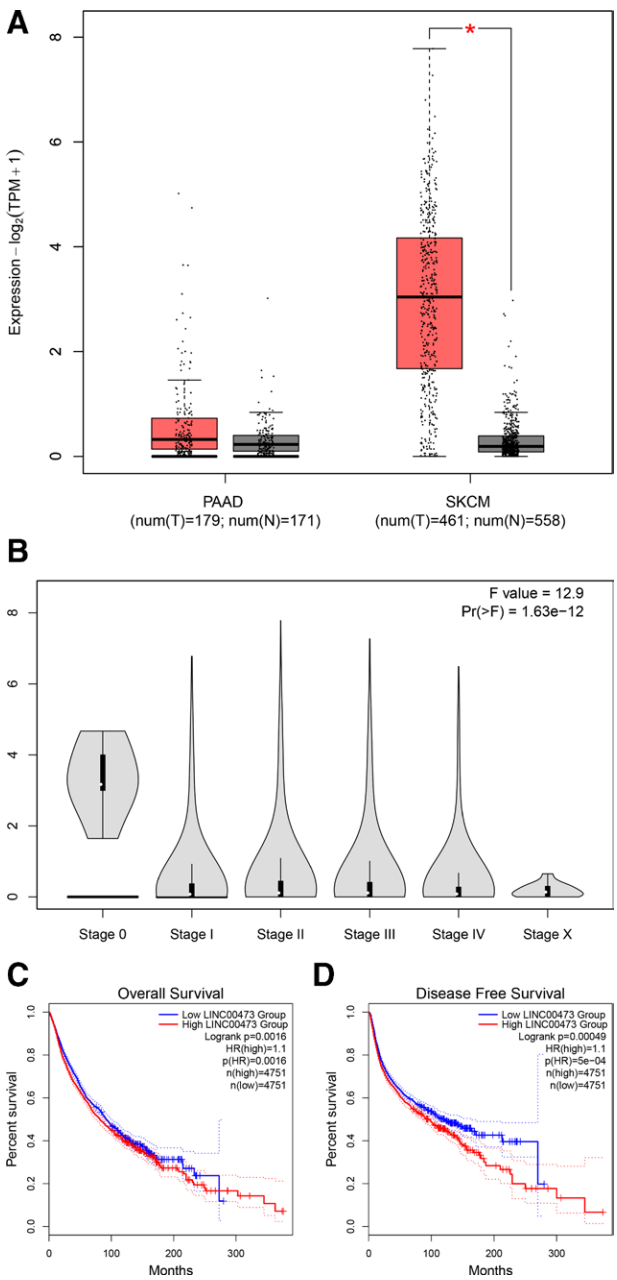

Figure 7. Validation of the role of lncRNA LINC00473 in human cancers in the GEPIA dataset: (A) the expression of LINC00473 in cancers and normal tissues, (B) violin plot of clinical stage of SNHG7 expression in human cancers, (C) overall survival plot of LINC00473, and (D) disease-free survival plot of LINC00473. GEPIA = Gene Expression Profiling Interactive Analysis, lncRNA = long non-coding RNA.

LINC00473 to attenuate the radioresistence of head and neck SCC cells through inhibiting Wnt/β-catenin signaling pathway.[40] A large body of evidence has demonstrated that LINC00473 might activate hepatocellular carcinoma progression by participating in signaling pathway of phosphatidylinositol-3-kinase/protein kinase B/the mammalian target of Rapamycin, which fortified cell proliferation, migration, invasion, and metastasis.[41] It is known to all that chemoradiotherapy is beneficial for the patients with advanced cancers. However, most of those patients are insensitive to chemoradiotherapy during the course of the late treatment. Thus, sufficient understanding of the underlying mechanism is helpful to improving the efficiency of treatment in those cancer patients. Recent study reported that LINC00473 enhanced radioresistance by activating the miR-374a-5p/SPIN1 axis in esophageal SCC.[42] In osteosarcoma, LINC00473 interactions with the transcript factor C/EBPβ led to impede chemoresistance, which provided a novel therapeutic method.[43] To sum up, it is urgent to explore the crosstalk between lncRNA LINC00473 and cancer clinical outcomes.

To date, in order to determine the prognostic value of LINC00473 in cancers, this is the first meta-analysis to comprehensively identify the relationship between LINC00473 expression and clinical outcomes of tumors. The pooled results indicated higher expression of LINC00473 signified worse OS and DFS, and the similar results are verified by the stratified analyses, which mean the 5-year mortality rate of cancer patients with high LINC00473 expression noticeably increased. Therefore, LINC00473 overexpression was positively correlated with dismal survival in cancer patients. In addition, collective studies also demonstrated that higher LINC00473 expression level was more exposed to worse clinicopathological outcomes, including tumor node metastasis stage, tumor size, differentiation, and LNM, which recommended that those patients had a significant propensity to invade surrounding tissues and metastasize to lymph nodes. Likewise, we conducted GEPIA online analyses to verify our results based on the cancer genome atlas dataset.

Recognizing, this paper has some limitations. Firstly, all included studies were conducted in Chinese population, which is best suitable for the clinical characteristics of Asian patients with tumors. Secondly, more literatures are needed to evaluate DFS and progression-free-survival. Thirdly, most HRs and 95% CIs were extracted via software reconstruction of Kaplan–Meier curves, which led to some bias inevitable. Finally, due to different types of cancer in these included literatures, the same gene is likely to be involved in different oncogenic mechanisms, which might make a difference to the prognostic role of expression of lncRNA LINC00473. Hence, increasing abundant studies are needed to avoid these various factors in the compound.

In conclusion, LINC00473 could emerge as a novel prognostic biomarker and an efficient therapeutic target. However, more prospective researches are required to further confirm the value of LINC00473 in cancers.

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Software: Jingyu He.
Supervision: Jingyu He.
Validation: Jingyu He.
Writing – original draft: Yuanyang He.
Writing – review & editing: Jingyu He, Jingyu He.

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