Long non-coding RNA XIST predicting advanced clinical parameters in cancer: A Meta-Analysis and case series study in a single institution (Review)

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Abstract. Dysregulated expression of long non-coding RNA X-inactive specific transcript (lncRNA-XIST) has been indicated in various cancer types. In the present study, a meta-analysis was conducted to evaluate the potential role of lncRNA-XIST in predicting the clinicopathological parameters of patients with cancer. Eligible studies were obtained through a systematic search of PubMed, Web of Science, Embase and the Cochrane Library, of articles published prior to January 2019. The combined odds ratio and 95% confidence interval were calculated to determine the association between lncRNA-XIST expression and patient outcome. In addition, 45 pairs of osteosarcoma (OS) tissues and adjacent healthy tissues from a single institution were analyzed for the expression of lncRNA-XIST, and its association with clinicopathological features; ultimately, a total of 1,869 cancer patients from 25 studies were assessed. The results demonstrated that high expression levels of lncRNA-XIST were significantly associated with lymphatic metastasis, larger tumor size, advanced cancer stage and distant metastasis. However, sex was not associated with lncRNA-XIST expression level. In the OS patient cohort, it was demonstrated that lncRNA-XIST was highly expressed in OS tissues, which negatively correlated with patient prognosis. The present study indicated that lncRNA-XIST may serve as a potential biomarker for advanced clinical parameters in human cancer.

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Introduction

Cancer is one of the leading causes of mortality worldwide (1). Although progress in cancer treatment has been achieved in previous decades, the prognosis for the majority of cancer types remains poor. Early diagnosis and treatment are important in improving the prognosis of patients with cancer. However, the sensitivity and specificity of the cancer markers used currently are not satisfactory (2). Therefore, novel molecular markers for predicting advanced cancer status and prognosis are required.

Although 70-80% of the human genome is transcribed into RNA, protein-coding sequences account for a small fraction of the total transcripts, indicating that the number of non-coding RNAs is increased compared with that of protein-coding genes (3-6). Specifically, long noncoding RNAs (lncRNAs) constitute a class of non-coding RNAs measuring >200 nucleotides in length, with no protein-coding capacity. These lncRNAs serve key roles in chromatin regulation, gene expression, growth, differentiation and development (7). Although the existence of lncRNAs has been known for some time, the term 'lncRNA' was not adopted until more recently. There are a large number of lncRNAs included in numerous databases, including LNCipedia (http://www.lncipedia.org) and the NONCODE database (http://www.noncode.org). As this number continues to increase, there are more opportunities to investigate the functions of these noncoding elements, particularly in association with cancer treatment and prognosis (8).

Accumulating evidence has suggested an oncogenic or tumor suppressive role for lncRNAs during tumorigenesis, in which numerous lncRNAs have been revealed to be dysregulated (9,10). lncRNA-X-inactive specific transcript (XIST)

was the first functional lncRNA identified to be responsible for X-chromosome inactivation (11). A growing body of data has revealed that lncRNA-XIST behaves in an oncogenic manner in colorectal (12), bladder (13) and gastric cancer (14), in addition to nasopharyngeal cancer (15) and osteosarcoma (OS) (16).

By contrast, XIST has been demonstrated to serve a tumor suppressor role in other studies (17-19). However, the majority of the data described so far is limited by discrete outcomes and small sample sizes. In recent years, several meta-analyses were conducted to evaluate the prognostic value of lncRNA-XIST in patients with cancer, and it was identified that the expression level of XIST was associated with overall survival, lymph node metastasis, distant metastasis and tumor stage (20-22). However, following these meta-analyses, a number of studies concerning XIST and cancer were published, with some describing contradicting conclusions (23,24). Therefore, we propose that an updated meta-analysis is required. In order to assess the value of lncRNA-XIST in predicting the progression of clinicopathological features in patients with cancer, a meta-analysis was conducted and a case series of 45 patients with OS was described.

Patients and methods

Search strategy. To identify the incidence of lncRNA-XIST expression in cancer, PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Web of Science (www.webofknowledge.com/), Embase (https://www.embase.com/) and the Cochrane Library (https://www.cochranelibrary.com/) databases were searched for articles published prior to January 2019, using the search terms 'long non-coding RNA' OR 'lncRNA,' AND 'cancer' OR 'sarcoma' OR 'carcinoma' OR 'neoplasm' OR 'malignancy', AND 'XIST'. Additionally, reference lists of associated reviews were searched to identify any potentially relevant studies. The inclusion criteria were as follows: i) The publication explored the relevance of lncRNA-XIST expression in human tumor tissues; ii) high and low lncRNA-XIST expression groups were defined, or the relevant data to categorize patients into these groups was present; and iii) the publication language was confined to English. The following articles were excluded from the study i) Reviews, editorials, meetings, abstracts and commentaries; ii) publications with no target data or relevant outcomes; and iii) duplicate studies.

The following basic information was extracted from each study using a standardized data collection method: i) First authors; ii) publication year; iii) study population; iv) sample size; v) tumor type; and vi) lncRNA-XIST detection method. If any essential information was not available from the original article, best efforts were made to contact the corresponding author to obtain the missing data. As summarized in Table I, all of the included publications were evaluated based on the critical checklist of the Dutch Cochrane Centre, as proposed by Meta-analysis of Observational Studies in Epidemiology (25).

Evaluation of clinical samples. A total of 45 (25 females and 20 males) paired OS tissues and adjacent healthy tissues from patients aged from 9-14 years (from January 2009 to September 2017), with no preoperative history of radiotherapy and/or chemotherapy were obtained from the Children's Hospital of Chongqing Medical University (Chongqing, China). The tumor and adjacent healthy tissues were obtained during biopsy/resection prior to chemotherapy. Staging was performed based on the Musculoskeletal Tumor Society staging system (26). Following resection, the tissues were immediately frozen in liquid nitrogen. The present study was performed with the approval of the Institutional Review Board of Children's Hospital of Chongqing Medical University. Written informed consent was obtained from the parents of all patients.

Total RNA was isolated with TRIzol® reagent (Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol and subjected to reverse transcription (RT) reactions using hexamers, dNTPs and M-MuLV Reverse Transcriptase (supplied with 10X Reaction Buffer) (New England BioLabs, Inc.). The thermocycling conditions of the RT polymerase chain reaction (RT-PCR) were as follows: 37˚C for 60 min, then at 95˚C for 1 min, followed by holding at 4˚C. The resultant cDNA products were diluted 10- to 100-fold and used as templates. RT-quantitative PCR (RT-qPCR) analysis was performed using the optimized touchdown qPCR protocol described previously by Zhang *et al* (27). Briefly, the SYBR Green qPCR reactions (Bio-Rad Laboratories, Inc.) were performed in triplicate, according to manufacturer's protocol, under the following thermocycler conditions: 95˚C for 3 min, followed by 95˚C for 20 sec and 66˚C for 10 sec for 4 cycles (decreasing by 3˚C per cycle); then 95˚C for 20 sec, 55˚C for 10 sec and 70˚C for 1 sec, for 40 cycles. The $2^{-\Delta\Delta Cq}$ method was used to determine the relative quantitation of lncRNA-XIST expression levels (28). The primer sequences used in were as followed: GAPDH forward, 5'-GTCAAGGCTGAGAACGGGAA-3'; GAPDH reverse, 5'-AAATGAGCCCCAGCCTTCTC-3'; lncRNA-XIST forward, 5'-GGTGGACATGTGCGGTCA-3'; and lncRNA-XIST reverse, 5'-CCTGCGGCAAAACCCAAC -3'.

Statistical analysis. All statistical analyses were performed using Stata 12.0 (StataCorp LP) and Revman5.2 software (Cochrane). The combined odds ratio (OR) and 95% confidence interval (CI) were used to determine the association between lncRNA-XIST expression level and clinical risk. The combined effect size was statistically significant when it did not overlap with 1. Heterogeneity across the studies was quantified using the I^2 statistic. A fix-effects model with the inverse variance method was conducted when the calculated I^2 <50% (29,30). If I^2 >50%, subgroup analysis was performed. Potential publication bias was assessed using Egger's bias indicator test with the linear regression method, respectively, and sensitivity analysis was also conducted. For analysis of the clinical samples, the patients were divided into two groups according to the expression level of lncRNA-XIST (the median expression level 2.4 was used as the cut-off). The χ^2 test was used to identify the differences between categorical variables, and the two-tailed Student's t-test was used for comparisons between groups. Overall survival was estimated with Kaplan-Meier method. $P<0.05$ was considered to indicate a statistically significant difference.

Quality assessment. The quality of each study was assessed using the Newcastle-Ottawa Scale (31), consisting of three

Table I. Characteristics of the studies included.

First author	Year	Country	Sample size	Ethnicity	Cancer type	Detection method	Quality assessment score	(Refs.)
Tantai	2015	China	32	Asian	NSCLC	qPCR	6	(32)
Kobayashi	2016	Japan	49	Asian	Cervical squamous cell carcinoma	qPCR	5	(19)
Fang	2016	China	53	Asian	NSCLC	qPCR	7	(33)
Chen	2016	China	106	Asian	Gastric cancer	qPCR	5	(34)
Li	2017	China	145	Asian	Osteosarcoma	qPCR	6	(35)
Chen	2017	China	115	Asian	Colorectal cancer	qPCR	8	(36)
Wei	2017	China	64	Asian	Pancreatic cancer	qPCR	7	(37)
Du	2017	China	69	Asian	Glioma	qPCR	7	(38)
Wang	2017	China	30	Asian	Glioma	qPCR	7	(39)
Song	2017	China	50	Asian	Colorectal cancer	qPCR	6	(12)
Ma	2017	China	98	Asian	Gastric cancer	qPCR	8	(14)
Mo	2017	China	88	Asian	Hepatocellular carcinoma	qPCR	7	(40)
Sun	2017	China	47	Asian	Cervical cancer	qPCR	6	(41)
Xiong	2017	China	67	Asian	Bladder cancer	qPCR	6	(42)
Sun	2017	China	50	Asian	NSCLC	qPCR	6	(43)
Du	2017	China	62	Asian	Prostate cancer	qPCR	7	(18)
Hu	2017	China	52	Asian	Bladder cancer	qPCR	7	(13)
Wu	2017	China	127	Asian	Esophageal squamous cell carcinoma	qPCR	6	(44)
Kong	2018	China	52	Asian	Hepatocellular carcinoma	qPCR	7	(45)
Yi	2018	China	140	Asian	Esophageal squamous cell carcinoma	qPCR	7	(46)
Liang	2017	China	73	Asian	Pancreatic carcinoma	qPCR	7	(47)
Sun	2018	China	120	Asian	Colon cancer	qPCR	7	(48)
Liu	2018	China	77	Asian	Thyroid cancer	qPCR	7	(49)
Hu	2018	China	30	Asian	Retinoblastoma	qPCR	6	(50)
Zhu	2018	China	52	Asian	Cervical cancer	qPCR	7	(51)

NSCLC, non-small cell lung cancer; NA, not available; qPCR, quantitative polymerase chain reaction.

parts: Selection; outcome; and comparability, with a score range of 0-9. A score ≥6 was considered to indicate high quality.

Results

Literature analysis. A total of 770 citations were retrieved from an initial online search for literature associated with lncRNA-XIST expression in cancer. A total of 644 citations were excluded following initial screening of titles and abstracts; of the remaining 125 candidate studies (which were reviewed in their entirety), 100 were also excluded. A total of 25 studies were included in the final analysis (Fig. 1).

Study characteristics. The characteristics of the final 25 articles are presented in Table I (12-14,18,19,32-51). These studies were published between 2015 and 2018, with sample sizes of between 31-146 patients. A total of 1,869 patients were divided into two groups (high and low expression of lncRNA-XIST) according to RT-qPCR results. The majority of the studies were conducted in China and the patients presented with the following 12 cancer types: Hepatocellular carcinoma; gastric cancer; pancreatic cancer; osteosarcoma; cervical cancer; bladder cancer; esophageal squamous cell carcinoma; glioma; colorectal cancer; non-small-cell lung cancer (NSCLC); thyroid cancer; retinoblastoma; and cervical cancer.

lncRNA-XIST expression and patient outcome. As outlined in Table II, the results demonstrated that high expression levels of lncRNA-XIST were associated with lymphatic metastasis (OR =2.32; 95% CI 1.81-3.00; P=0.028; Fig. 2), larger tumor size (OR=2.60; 95% CI 1.91-3.56; P=0.001; Fig. 3), advanced cancer stage (OR=2.97; 95% CI 2.15-4.09; P=0.001; Fig. 4) and positive distant metastasis (OR=2.07; 95% CI 1.24-3.47; P=0.001; Fig. 5). However, sex (OR=0.96; 95% CI 0.79-1.18; P=0.916) was not associated with lncRNA-XIST expression level (Fig. 6).

Table II. Primary outcome of X-inactive specific transcript expression on disease characteristics.

Disease characteristics	OR (95% CI)	Z-value	P-value	P_{het}	I^2 (%)	Egger's test	
						t	P-value
Lymph node metastasis (yes vs. no)	2.93 (2.09, 4.10)	6.27	<0.001	0.37	7	-0.47	0.65
Tumour size (bigger vs. smaller)	3.07 (2.40,3.92)	8.98	<0.001	0.16	26	-0.57	0.58
Stage (III/IV vs. I/II)	2.86 (1.85,4.42)	4.72	<0.001	0.00	64	1.89	0.08
Distant metastasis (yes vs. no)	1.76 (0.76,4.08)	3.59	<0.001	0.64	79	-1.77	0.15
Sex (female vs. male)	1.02 (0.79,1.30)	0.13	0.89	0.57	0	0.71	0.49

OR, odds ratio; CI, confidence interval; P_{het}, heterogeneity.

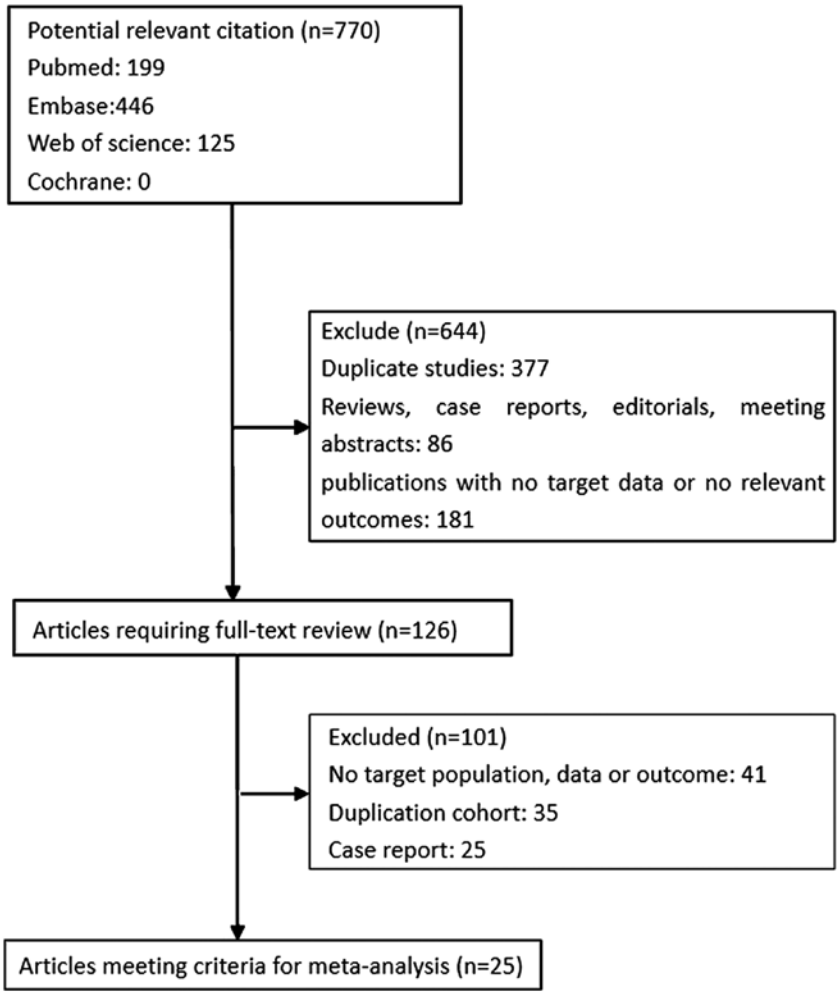

Figure 1. Flow diagram of meta-analysis process. A total of 644 publications were excluded following screening of titles and abstracts. Then, 25 eligible articles were identified to meet the criteria for the meta-analysis from the 126 relevant articles included in the full-text selection.

Publication bias and sensitivity analysis. The Egger linear regression test indicated a potential publication bias in the stage category (Table II). Next, sensitivity analysis was performed to evaluate the stability of the present study. Each parameter was excluded from the sensitivity analysis, and the results of our meta-analysis were consistent, indicating that the combined results were stable (Figs. S1-S5). Due to the marked heterogeneity observed, subgroup analysis was performed for distant metastasis, stage and tumor size. From the Figs. S6-S9, subgroup analysis results of cancer types, publication year, sample size and quality assessment for distant metastasis demonstrated that the levels of heterogeneity had not decreased, indicating that cancer types, publication year, sample size and quality assessment were not the source of heterogeneity. The

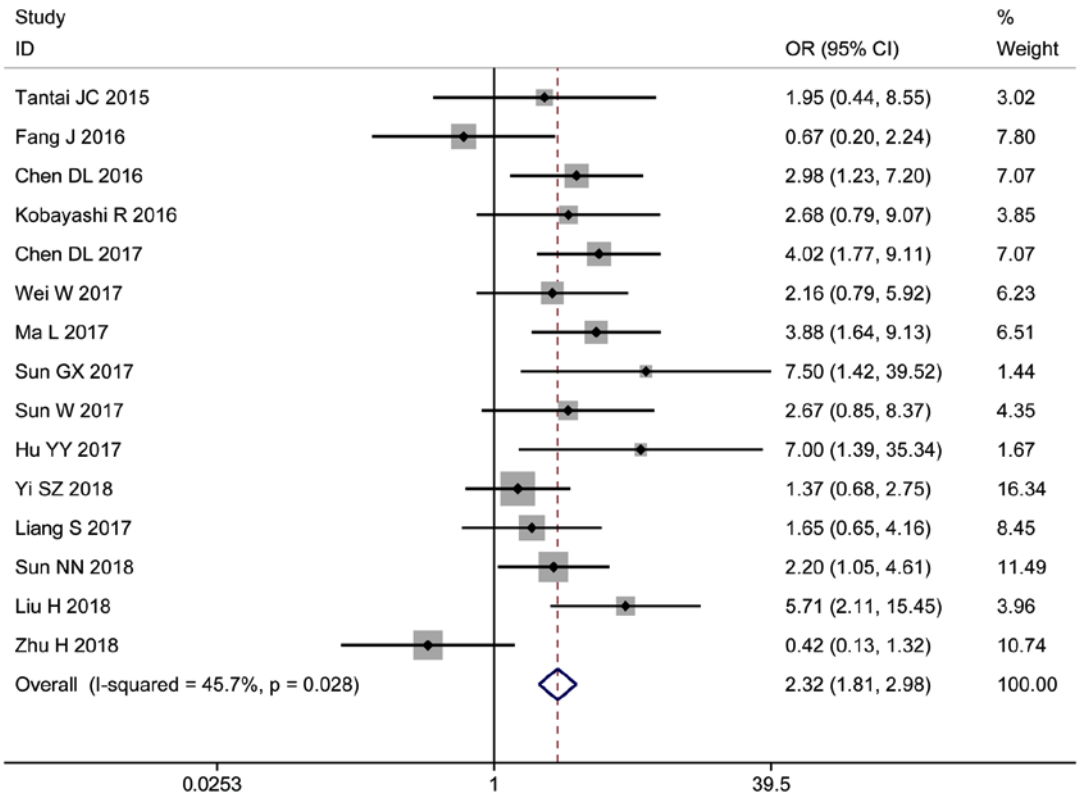

Figure 2. Forest plot studies investigating the association between long non-coding RNA X-inactive specific transcript and lymph node metastasis in a fixed effect model. OR, odds ratio; CI, confidence interval.

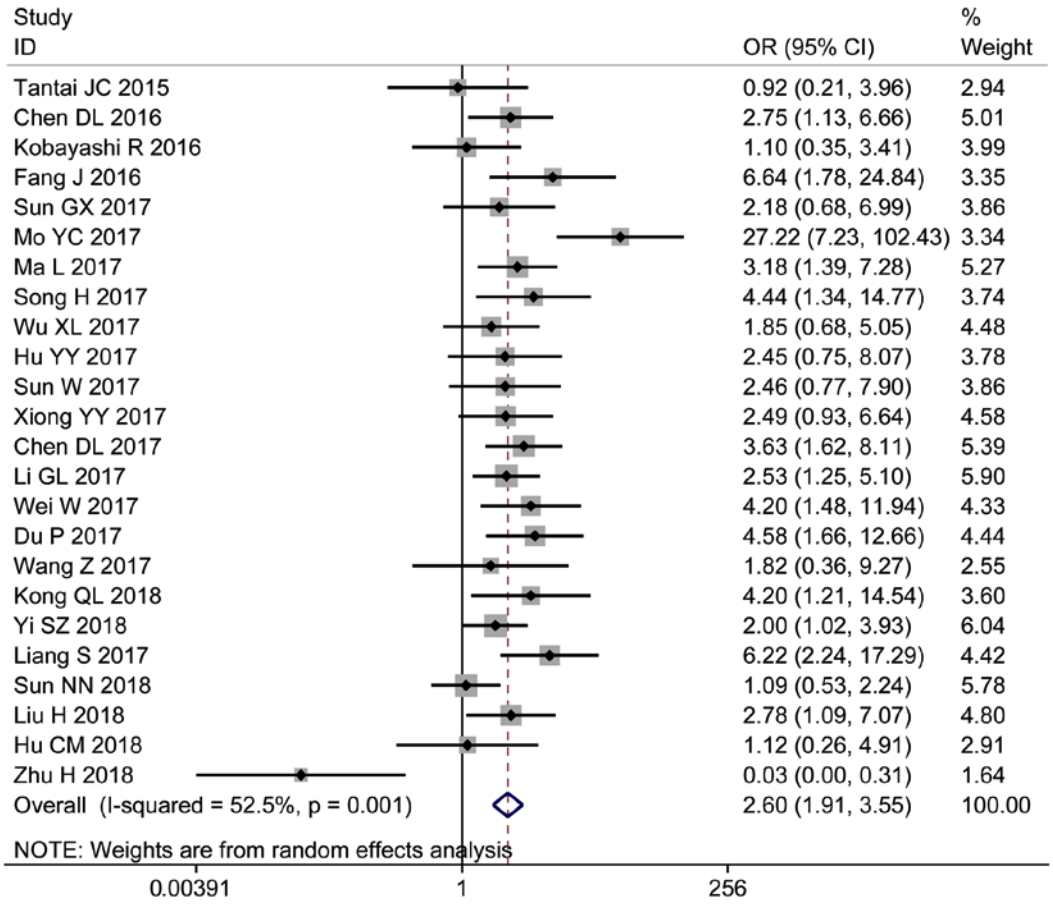

Figure 3. Forest plot of studies examining the association between long non-coding RNA X-inactive specific transcript and tumor size in a random effect model. OR, odds ratio; CI, confidence interval.

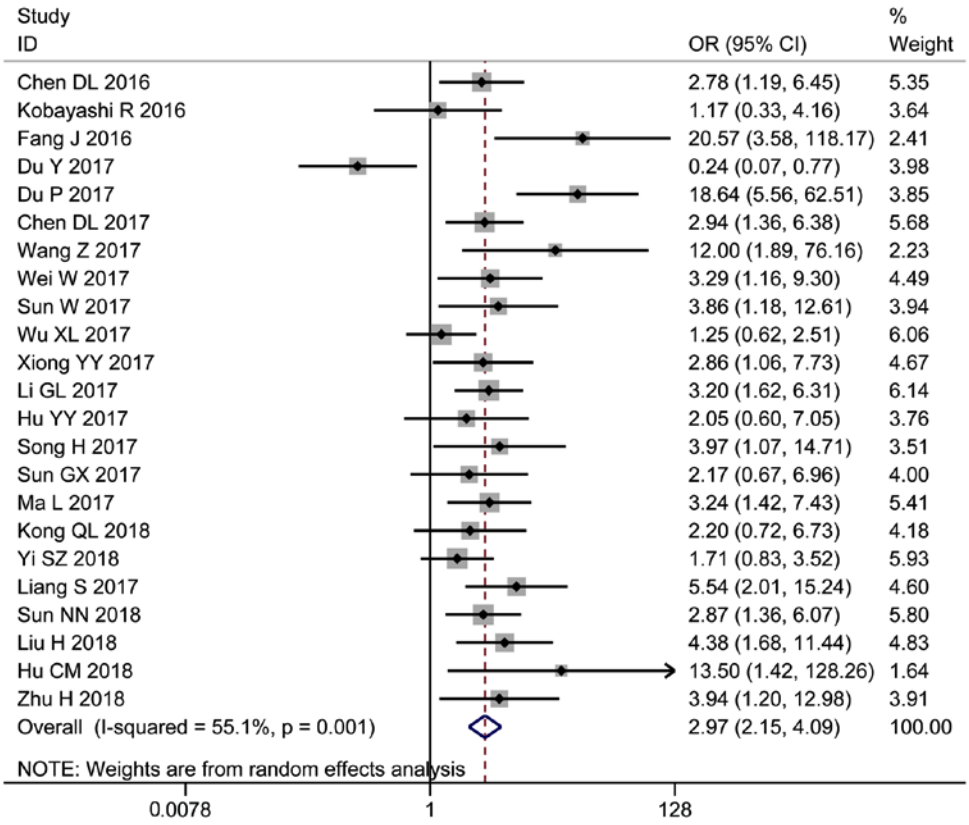

Figure 4. Forest plot of studies investigating the association between long non-coding RNA X-inactive specific transcript and disease stage in a random effects model. OR, odds ratio; CI, confidence interval.

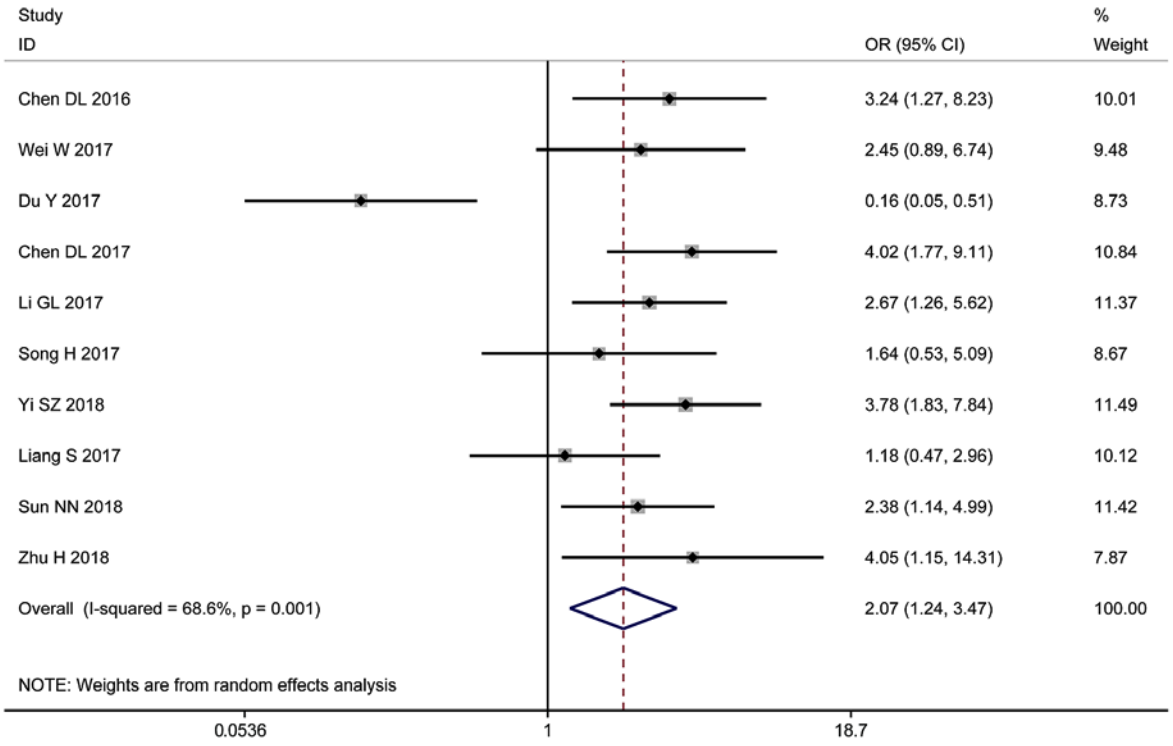

Figure 5. Forest plot of studies examining the association between long non-coding RNA X-inactive specific transcript and distant metastasis in a random effect model. OR, odds ratio; CI, confidence interval.

same results were identified in tumor size or stage subgroup analyses (Figs. S10-S17).

Quality assessment. The scores of the included studies ranged between 5-8, as determined using the Newcastle-Ottawa Scale.

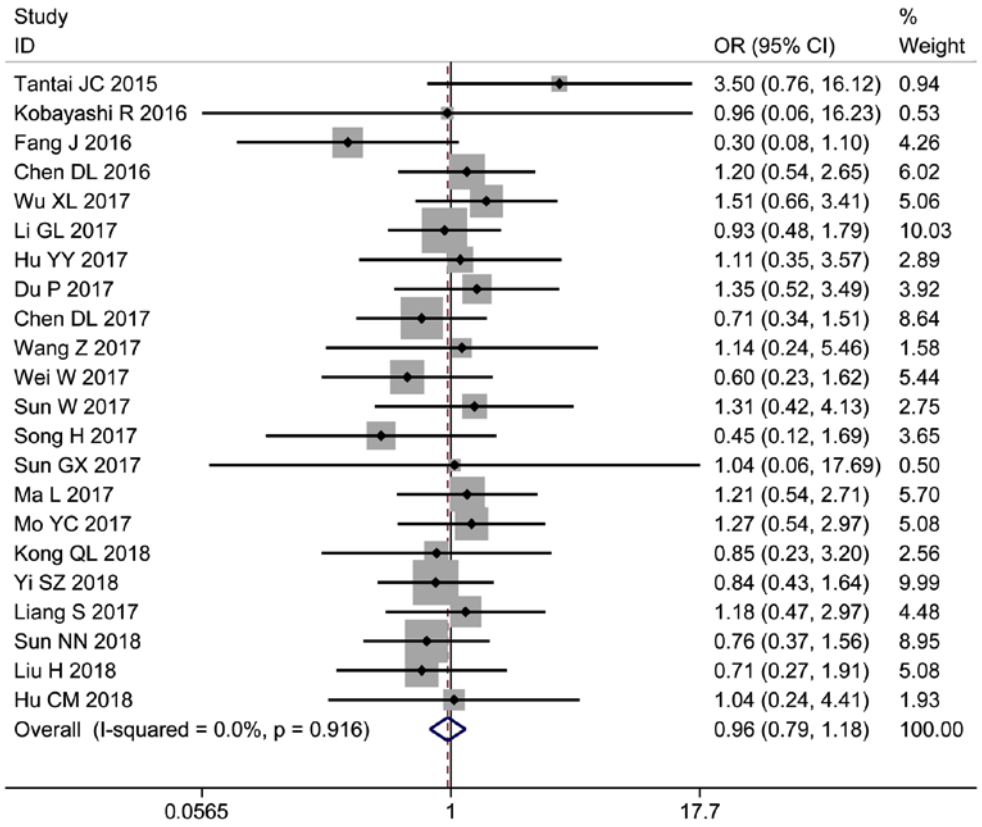

Figure 6. Forest plot of studies investigating the association between long non-coding RNA X-inactive specific transcript and sex in a fixed effect model. OR, odds ratio; CI, confidence interval.

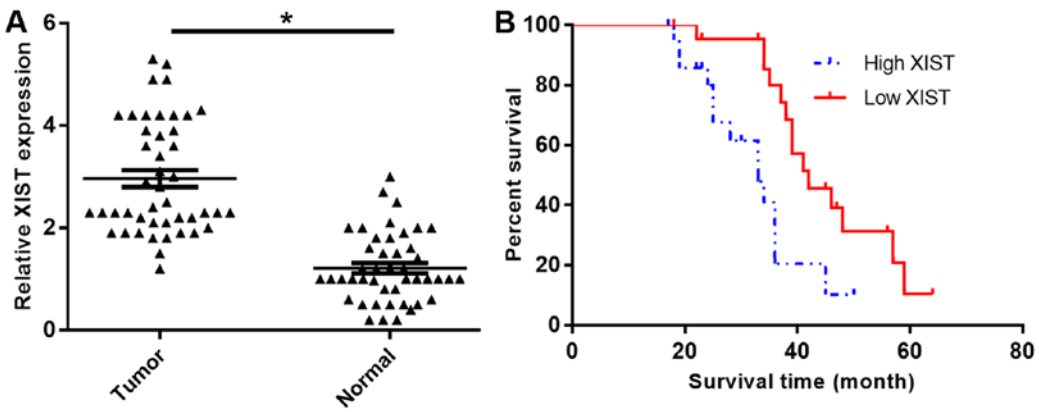

Figure 7. Validation of XIST role in the OS sample from the present study. (A) Reverse transcription quantitative polymerase chain reaction analysis demonstrated that the levels of XIST were significantly up-regulated in OS tumor samples compared with normal adjacent tissues. (B) Kaplan-Meier analysis indicated that high expression of XIST was inversely associated with overall survival in patients with OS. *P<0.05. OS, overall survival; XIST, X-inactive specific transcript.

The majority of the studies scored >7; 15 studies scored 7 and 2 studies scored 8 (Table I).

Clinical sample confirmation. To determine the role of lncRNA-XIST in patients with OS, expression levels were determined in the cancerous and adjacent healthy tissues of patients using RT-qPCR (Fig. 7A). The results revealed that lncRNA-XIST expression level was significantly upregulated in OS (Fig. 7A), and that high expression levels were inversely associated with patient overall survival (Fig. 7B). The potential association between lncRNA-XIST expression level and patient clinicopathological features was also evaluated (Table III). The results revealed that high lncRNA-XIST expression level correlated with advanced clinical stage and tumor size.

Discussion

Cancer is one of the leading causes of mortality worldwide (52). The identification of novel biomarkers is necessary for early diagnosis, and to improve the prognosis of patients with cancer. An increasing number of studies have suggested that lncRNAs are aberrantly expressed in various types of human cancer;

Table III. Correlations between clinicopathological features and the expression of XIST in osteosarcoma tissues.

Clinicopathological features	Number of patients	XIST expression		P-value
		High	Low	
Sex				
Male	22	12	10	0.87
Female	23	12	11	
Ages, years [Mean (SD)]		13.2 (2.4)	12.7 (2.9)	0.29
Histological type				
Osteoblastic	31	17	14	0.76
Chondroblastic	14	7	7	
TNM stage				
I, II	23	8	15	0.01
III	22	16	6	
Tumor size, cm				
<5	18	6	12	0.02
>5	27	18	9	

XIST, X-inactive specific transcript; TNM, tumor node metastasis.

furthermore, an association between lncRNA expression, pathophysiological features and patient survival has also been indicated, making lncRNAs promising biomarkers for cancer prognosis (53). It has also been demonstrated that lncRNAs may exert their functions via transcription and epigenetic regulation, as they also serve as scaffolds in the formation of ribonucleoprotein complexes (54). Various lncRNAs, including lncRNA-maternally expressed 3 (55), lncRNA-colon cancer associated transcript 2 (56) and lncRNA-HOX transcript antisense RNA (57) have been identified as novel indicators of poor prognosis in a number of types of human cancer.

Accumulating evidence implies a regulatory role for lncRNA-XIST, the earliest identified lncRNA, in various malignant tumors. Wei *et al* (37) demonstrated that lncRNA-XIST was involved in the proliferation, invasion, and epithelial-mesenchymal transition of cancer cells. Additionally, Wang *et al* (39) suggested that lncRNA-XIST promoted glioma cell proliferation by targeting microRNA-137. A study by Chen *et al* (34) indicated that high lncRNA-XIST expression levels were positively correlated with aggressive tumor phenotypes and prognosis in gastric cancer, and enhanced the functions of enhancer of zeste homolog 2. In nasopharyngeal carcinoma, abnormal expression of lncRNA-XIST was revealed to promote cell proliferation, partially by suppressing miRNA-34a-5p, and subsequently activating E2F transcription factor 3 (15). Small interfering RNA inhibition of lncRNA-XIST suppressed the proliferation, migration and invasion of NSCLC cells *in vitro*, and suppressed tumor growth *in vivo* (33). Based on these data, lncRNA-XIST may be a potential prognostic marker for patients with cancer (35-38).

Conversely, lncRNA-XIST may serve as a tumor suppressor in specific types of cancer. Kobayashi *et al* (19) revealed that increased expression levels of lncRNA-XIST were positively associated with favorable prognosis in cervical squamous cell carcinoma. In breast cancer, a decreased expression of lncRNA-XIST upregulated the phosphorylation of protein kinase B and inhibited tumor growth (17). Based on these contradictory results, the true value of lncRNA-XIST as a tumor marker remains to be determined. It is necessary to comprehensively evaluate the clinical significance of lncRNA-XIST. Therefore, meta-analyses were conducted to evaluate the prognostic value of lncRNA-XIST in patients with cancer. The study conducted by Hu *et al* (20) examined 9 studies with 853 patients with cancer, and identified that the expression level of lncRNA-XIST was markedly associated with overall survival, disease free survival, tumor type, lymph node metastasis, distant metastasis and tumor stage. Mao *et al* (21) identified 15 eligible studies containing 1,209 patients for inclusion in their meta-analysis; they observed that increased lncRNA-XIST expression levels in cancer tissues were associated with a poorer overall survival. In the study conducted by Liu *et al* (22), 15 studies with a total of 920 patients were included in the meta-analysis, and the results suggested that high lncRNA-XIST expression levels were associated with distant metastasis, tumor stage and poor prognosis. However, a number of contrasting studies were published concerning the role of lncRNA-XIST in cancer: In a recent study by Du *et al* (18), lncRNA-XIST served as a tumor suppressor in prostate cancer, its expression correlating with prognosis and tumor stage. In addition, Sun *et al* (23) identified that lncRNA-XIST regulated the microRNA-106b-5p/cyclin-dependent kinase inhibitor 1 axis to suppress tumor progression in renal cell carcinoma. Consequently, we proposed that an updated meta-analysis was required. In the present study, a comprehensive and detailed meta-analysis was conducted to investigate the association between lncRNA-XIST expression and the clinicopathological characteristics of patients with cancer. The analysis of 25 studies, including 1,869 cancer patients, indicated that high lncRNA-XIST expression level was significantly associated with lymphatic metastasis, larger tumor size, advanced stage

and positive distant metastasis, suggesting that increased lncRNA-XIST levels may be associated with advanced disease presentation. It should also be noted that the prognostic value of lncRNA-XIST may vary between different types of cancer. For example, the expression level of lncRNA-XIST was significantly associated with tumor size in all types of cancer in the included studies, with the exception of NSCLC and cervical squamous cell carcinoma.

As a number of the clinicopathological characteristics of cancer may be associated with the sex of the patients, and lncRNA-XIST is responsible for X-chromosome inactivation, it was speculated that there may be a sex-specific association between the expression of lncRNA-XIST and the features of different types of cancer. Although the results of the present study revealed no significant association between lncRNA-XIST expression and sex, this should be considered in future studies.

Following a review of the current literature, potential associations between clinicopathological features and the expression of lncRNA-XIST in OS tissues were determined. It was confirmed that lncRNA-XIST expression was upregulated in OS tissues, and that high expression levels were inversely correlated with the overall survival of patients with OS. Advanced staging and increased tumor size were closely associated with increased lncRNA-XIST expression levels. The results of the present study were consistent with the conclusions of meta-analysis, additionally highlighting the importance of lncRNA-XIST in human malignancies.

In the present study, a number of limitations should be considered. Only papers written in English were included. Additionally, the majority of the studies originated from China, therefore the results are largely representative of the Chinese population. Furthermore, the cut-off values for high and low expression levels of lncRNA-XIST differed between the studies. Also, due to the small number of studies comparing the expression of lncRNA-XIST with distant metastasis, the significance of certain data may have been limited by population size. Positive results were described in the majority of studies, whilst those with negative results were less likely to be published, which may be suggestive of a publication bias. Also, the association between lncRNA-XIST expression and the survival rates of patients was not determined. However, recent studies revealed that high expression levels were correlated with decreased overall and disease-free survival (20,22,58). The subgroup analysis did not identify a source of heterogeneity, although significant heterogeneity in distant metastasis, tumor size and stage was observed. More high-quality original studies are required to confirm the conclusions of the present study.

Given the aforementioned limitations, the present study supports the hypothesis that the upregulation of lncRNA-XIST expression may be considered a credible predictive factor for advanced clinicopathological features in human cancer. In the future, large-scale and multicenter studies are required to confirm these results, and to validate the clinical significance of lncRNA-XIST expression in human cancer.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

CY and JT conceived and designed the study, acquired data, and drafted the manuscript. CD and CY performed the acquisition of data and analyzed the data. XH and KW acquired data.

Ethics approval and consent to participate

The present study was performed with the approval of the Institutional Review Board of Children's Hospital of Chongqing Medical University. Written informed consent was obtained from the parents of all patients.

Patient consent for publication

Written informed consent was obtained from the parents of all patients.

Competing interests

All authors declare that they have no competing interests.

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