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Review Article

The clinicopathological and prognostic significance of X-inactive specific transcript overexpression in cancers: evidence from 11 case-control studies

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Abstract: Background: Recent studies have suggested that the lncRNA XIST plays an important role in cancer pathogenesis and clinical outcomes. The relationship between the level of lncRNA XIST gene expression and clinicopathological features, as well as its clinical value in cancer, remain inconclusive. Thus, we conducted a systematic review and a meta-analysis to assess the prognostic value of XIST on clinical outcomes in various cancers. Methods: 11 eligible articles were retrieved from PubMed, Embase, Web of Science, the Cochrane Library, CNKI, Scopus and the Wanfang databases, having been searched from their inceptions up through November 2, 2017. Pooled hazard ratios (*HRs*) with 95% confidence intervals (*CIs*) were used to evaluate XIST's prognostic value. The relationship between XIST expression and patients' clinicopathological features was estimated using pooled odds ratios (*ORs*) and their 95% *CIs*. Result: Data on 1053 patients from 11 articles were obtained between 2016 and 2017. The results demonstrated that elevated XIST expression was associated with poor overall survival (OS) (*HR*=1.61, 95% *CI* 1.24-2.08, I^2=57.2%, *Ph*=0.013) and disease-free survival (DFS) (*HR*=2.01, 95% *CI* 1.09-3.69) in various cancers. In addition, this meta-analysis showed that the up-regulation of XIST expression was significantly associated with TNM stage, lymph node metastasis, distant metastasis, and tumor size. Conclusions: This meta-analysis suggests that XIST may be a novel molecular marker for predicting numerous tumors. Upregulated XIST is correlated with a higher degree of tumor malignancy.

Keywords: Long noncoding RNA, XIST, cancer, prognosis, meta-analysis

Introduction

Although many strategies have been applied to the treatment of cancer, such as radiation therapy, chemotherapy, surgery, or a combination of these therapies, cancer remains the deadliest disease in the world [1]. Searching for suitable prognostic factors is an important issue for cancer post-therapy evaluation. Based on the development of high-resolution microarray technology and whole genome sequencing technology, long noncoding RNAs (lncRNAs) were increasingly observed in serum and used as sensitive markers for the early diagnosis and prognosis of cancer [2-6]. Long noncoding RNAs (lncRNAs) are a new class of RNA transcripts with more than 200 nucleotides. Most of the lncRNAs lack protein coding functions [7, 8] but involve, to some extent, molecular progress functions such as transcriptional regulation, differentiation, and apoptosis [9-13]. lncRNAs can serve as diagnostic biomarkers and therapeutic targets in cancer. For example, metastasis associated lung adenocarcinoma gene 1 (MALAT-1) is a potential marker in the diagnosis and prognosis of non-small cell lung cancer [14, 15]; LncRNA CCAT2 may be a new prognostic marker of cervical squamous cell carcinoma and a potential target for interventional therapy [16]; lncRNA HNF1A-AS1 acts as a regulator of

gastric cancer (GC), which may be a prospective novel biomarker and a target for the treatment of gastric cancer GC [17].

LncRNA XIST (X-inactive specific transcript), derived from the XIST gene, is the main regulator of X chromosome inactivation in mammals [18]. Increasingly, studies indicate that lncRNA XIST plays a key role in cell proliferation, differentiation and gene expression. It has been found that the dysregulation of the lncRNA XIST is associated with various cancers, including hepatocellular carcinoma [19], non-small cell lung cancer [20], glioblastoma [21] and breast cancer [22]. In addition, a number of studies have suggested that XIST expression is positively correlated with poor prognoses and the pathological outcomes of osteosarcoma, nasopharyngeal carcinoma, pancreatic cancer, and gastric cancer. Therefore, we performed a systematic review and a meta-analysis to examine the clinical outcomes and clinicopathological role of XIST expression in human cancers.

Methods

Search strategy

This analysis strictly followed by the preferred reporting items for systematic reviews and a meta-analyses standards (PRISMA) [23]. Systematic literature searches were conducted for eligible studies in PubMed, EMBASE, Web of Science, the Cochrane Library, CNKI, Wanfang, and the Scopus databases from their inceptions up to November 2, 2017. Medical Subject Headings were searched by inputting the following combinations of keywords: (XIST or X Inactive-Specific Transcript or long non-coding RNA XIST or lncRNA XIST) and (cancer or neoplasm or carcinoma or tumor) and (prognostic or prognosis or mortality or survival or outcome or recurrence). No language restriction was used. A manual selection of the relevant studies was carried out by reading the titles and summaries. This work was accomplished by two independent authors (YXL and XMC). Any disagreement was presented to the third independent author for a final decision (YNP).

Inclusion and exclusion criteria

Inclusion criteria: (1) studies in which the relationship between the XIST level and the prognosis or clinicopathological features was elevated; (2) studies that divided patients into high and low expression groups; (3) studies that provided sufficient information to estimate the hazard ratio (*HR*) or odds ratio (*OR*), and the 95% confidence intervals (*CIs*) for overall survival (OS), disease-free survival (DFS), or the clinicopathological parameters.

Exclusion criteria: (1) studies with overlapping or duplicated data; (2) letters, case reports, reviews, and animal studies; (3) studies that did not provide sufficient survival data; (4) studies that were not case-control studies.

Data extraction and quality evaluation

Two reviewers (YXL and XMC) selected articles and extracted data according to a standardized form independently. Any disagreement was resolved through a discussion with the third author (YNP). The following information was extracted from each study: the author's surname, year of publication, cancer type, number of patients, outcome measures, cut-off value of XIST expression, method of obtaining the *HR*, pathological data (such as gender, lymph node metastasis, differentiation, age, distant metastasis and TNM stage), *HR* with corresponding 95% *CIs* for OS, DFS. The *HRs* were extracted from multivariable priority or univariate analyses. Otherwise, *HRs* were estimated from Kaplan-Meier survival curves.

We used a modified Newcastle-Ottawa Assessment Scale (NOS) to assess the quality of primary studies (**Table 1**), which was a nine point assessment system including selection (0-4 points), comparability (0-2 points), exposure and outcome (0-3 points). Studies with a NOS score ≥6 were considered to be of high quality. Two authors (YXL and YNP) assessed this studies independently. Any discrepancy between authors was resolved by discussing it with a third author (XMC).

Statistical analyses

The HRs extracted from the eligible studies provided high v low comparisons of XIST expression. Therefore, an *HR*>1 suggested a poor prognosis, and an *HR*<1 suggested a good prognosis. The *HR* and 95% *CI* for OS and DFS were obtained directly from each study. For the article only providing Kaplan-Meier curves, data was extracted from the survival curves by using

Table 1. Main characteristics of all included studies

First author	Year	Country	Cancer type	Number	Stage	Analytical method	Cut-off	Survival analysis	Hazard ratio	Quality score
Chen	2016	China	GC	106	I-IV	qRT-PCR	median	OS	Reported	7
Ma	2016	China	GC	98	I-IV	qRT-PCR	NR	OS	SC	7
Song	2016	China	NPC	108	NR	qRT-PCR	2.31-fold	OS	SC	6
Wei	2017	China	PC	64	I-IV	qRT-PCR	Median	OS	Reported	6
Wu	2017	China	ESCC	127	I-IV	qRT-PCR	NR	OS DFS	Reported	7
Ma	2016	China	HCC	68	I-IV	qRT-PCR	Mean	OS	SC	7
Hui	2017	China	CRC	50	I-IV	qRT-PCR	NR	DFS	SC	6
Li	2017	China	OS	145	I-IV	qRT-PCR	NR	OS	SC	6
Cen	2017	China	CRC	115	I-IV	qRT-PCR	Media	OS	Reported	7
Hu	2017	China	Bladde	52	I-IV	qRT-PCR	Fold	OS	SC	6
Xiao	2017	Ukraine	CRC	120	NR	qRT-PCR	1.28-fold	OS	Reported	7

GC: gastric cancer; NPC: nasopharyngeal carcinoma; PC: pancreatic cancer; ESCC: esophageal squamous cell carcinoma; HCC: hepatocellular carcinoma; CRC: colorectal cancer; OS: osteosarcoma; qRT-PCR: quantitative reverse-transcriptase polymerase chain reaction; OS: overall survival; NR: not reported; SC: survival curve.

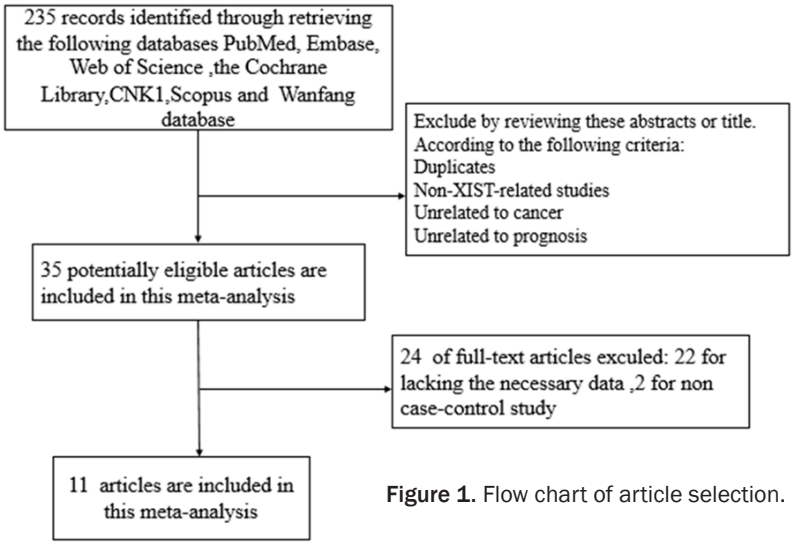

Figure 1. Flow chart of article selection.

Engauge Digitizer version 4.2. Tierney's method was used calculate the *HRs* and 95% *CIs* [24]. Odds ratios (ORs) and 95% CIs were used to evaluate the relationship between XIST overexpression and the clinicopathologic features. Combined HR and 95% CI were used to estimate the relationship between XIST and clinical outcomes.

Heterogeneity was analyzed by X^2-based Cochran Q test and Higgins I^2 statistic. I^2<25% for mild heterogeneity, 25%≤I^2<50% for moderate heterogeneity, I^2≥50% for significant heterogeneity. A *P* value <0.05 in combination with an I^2 value >50% were considered to be of significant heterogeneity. We used the random-effects model to estimate HR and 95% CI. A further analysis of heterogeneity was performed through a subgroup analysis. If there was no significant heterogeneity among these studies, the fixed-effects model was used. A sensitivity analysis was used to assess the stability of the results and to explore potential sources of heterogeneity by excluding each study individually. We investigated the publication bias using Begg's funnel plots and Egger's linear regression test. *P* values <0.5 were considered statistically significant [25, 26]. All the data were analyzed using STATA statistical software, version 12.0 (Stata Corporation, College Station, TX, USA).

Result

Search result

The detailed procedures of the literature retrieval are presented in **Figure 1**.

A total of 235 relevant articles were obtained: 41 from PubMed, 65 from Web of Science, 46 from Embase, 10 from Chinese National Knowledge Infrastructure (CNKI), 10 from Wanfang, and 62 from Scopus. 200 articles were exclud-

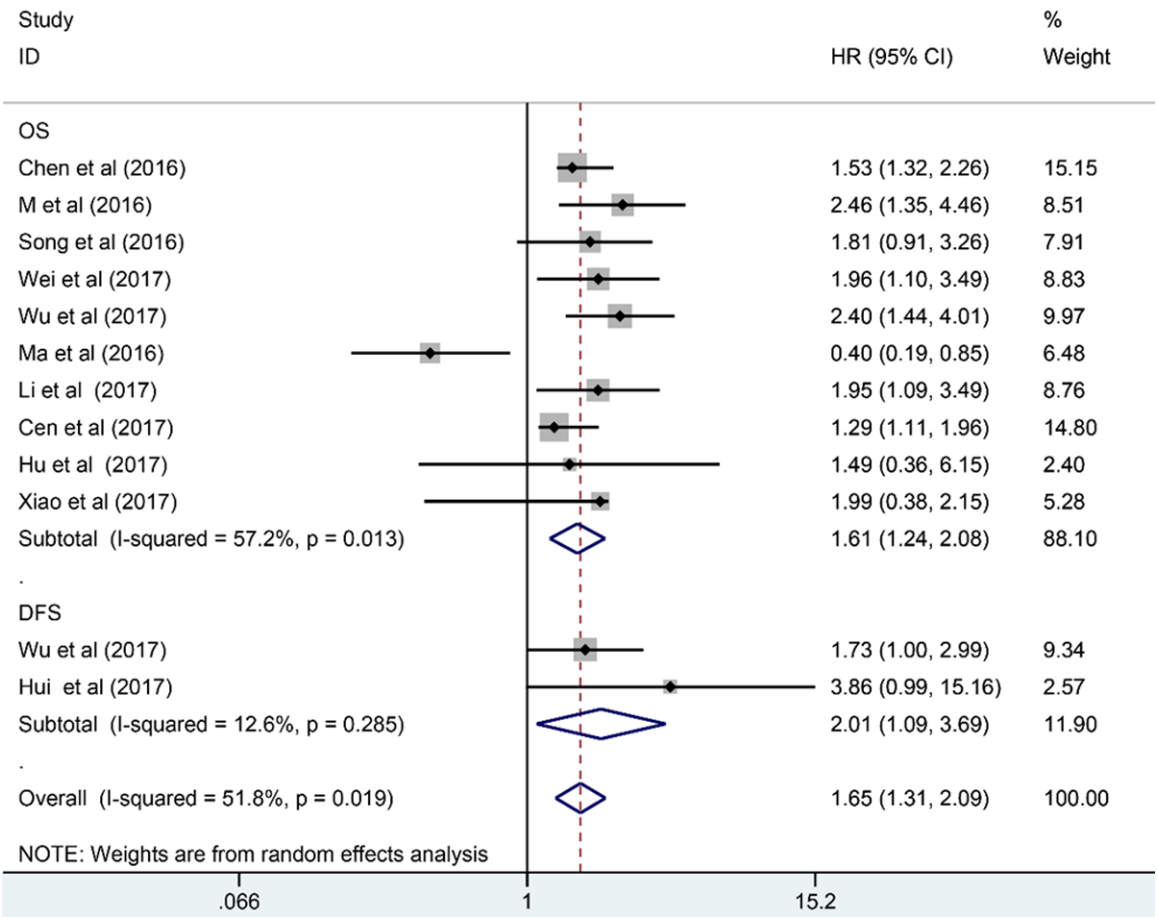

Figure 2. Forest plots for the association between XIST overexpression and the outcomes of cancer patients.

ed after reviewing their abstracts or titles. Furthermore, 22 articles were excluded for lacking necessary data, and 2 articles [27, 28] were excluded because they were non case-control studies, as determined by reading their full-texts. For one eligible non-full-text article, we contacted the corresponding author and asked for the missing data. In the end, 11 studies were included in our meta-analysis [29-39].

Characteristics of the literature

The main characteristics and the results of these 11 articles are summarized in **Table 1**. A total of 1053 patients from 11 articles were included. The sample size in these studies varied between 50 and 145. 9 cancer types were recorded in these 11 studies, including 2 cases of gastric cancer (GC), 1 of nasopharyngeal carcinoma (NPC), 1 of pancreatic cancer (PC), 1 of esophageal squamous cell carcinoma (ESCC), 3 of colorectal cancer (CRC), 1 of bladder cancer, 1 of osteosarcoma (OS), and 1 of hepatocellular carcinoma (HCC). Quantitative reverse transcription-PCR (qRT-PCR) was used to detect the XIST expressions in the tumor tissues and in their paired adjacent normal tissues. The cut-off values of the XIST expression level were examined using different methods, such as the mean value of XIST expression, the median value of XIST expression and 1.38-fold of XIST expression. HRs with the corresponding 95% CIs were directly extracted from 5 articles. The rest were calculated from the Kaplan-Meier Curves from the other 6 articles. The participants in 10 studies were Chinese, and 1 study was from Ukraine. There were 10 studies for OS and 2 for DFS. Various clinicopathological data were reported in the eight studies.

The relationship between XIST expression and OS

In these 11 included studies, 10 studies were conducted to investigate the relationship between XIST expression and OS in cancer patients. The random effect model was used be-

Table 2. Results of the subgroup analysis for overall survival

Categories	Studies	Number of patients	Randomized-effects model, Pooled HR (95% CI)	*P*-value	Heterogeneity	
					I^2 (%)	*Ph*
Overall survival	10	1003	1.61 (1.24-2.08)	0.000	57.2	0.013
Germ origion						
Endoderm	7	698	1.55 (1.11-2.15)	0.01	70.2	0.003
Ectoderm	1	108	1.81 (0.96-3.43)	0.068		
Mesoderm	2	197	1.88 (1.09-3.21)	0.022	0.0	0.731
Sample size						
≥100	6	721	1.6 (1.33-1.91)	0.0 00	9.4	0.356
<100	4	282	1.31 (0.56-3.09)	0.530	80.5	0.002
Cancer type						
No-digestive	3	305	1.85 (1.22-2.79)	0.003	0	0.939
Digestive	7	698	1.55 (1.11-2.15)	0.0 1	70.2	0.003

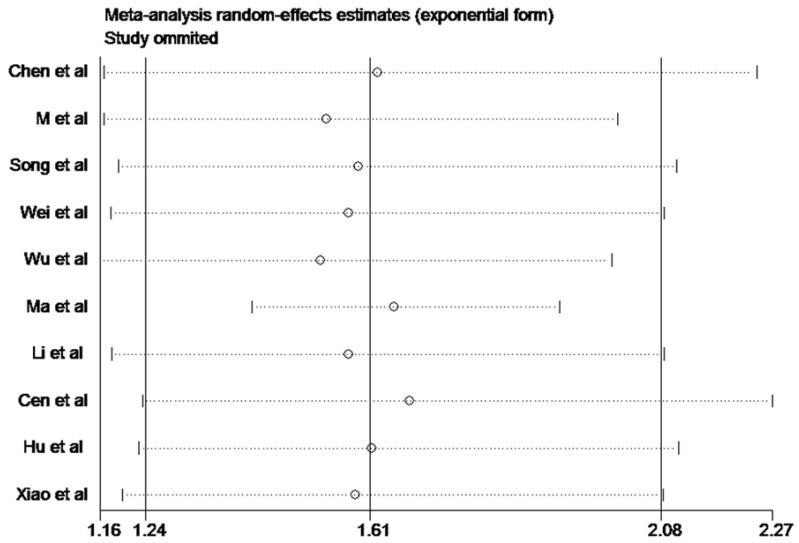

Figure 3. Sensitivity analysis of the relationship between lncRNA-XIST expression and OS.

cause of the significant heterogeneity (I^2= 57.2%, *Ph*=0.013) among these studies. The result showed that high XIST expression was positively associated with poor OS in human cancer (*HR*=1.24, 95% *CI* 1.24-2.08) (**Figure 2**). Subsequently, in order to reduce heterogeneity, a subgroup analysis was performed to further investigate the prognostic role of XIST, including tumor type, germ origin, and sample size (**Table 2**). A stratified analysis of cancer types indicated a significant prognostic effect of XIST on digestive (*HR*=1.55, 95% *CI*: 1.11-2.15) and non-digestive system cancers (*HR*=1.85, 95% *CI*: 1.22-2.79). Moreover, increased XIST expression was significantly associated with poor prognosis in these studies with sample size ≥100 (*HR*=1.6, 95% *CI*: 1.33-1.91). According to the source of tumor germ, high XIST expression was associated with poor survival in the endoderm (*HR* =1.55, 95% *CI*: 1.11-2.15), ectoderm (*HR*=1.81, 95% *CI*: 0.96-3.43) and mesoderm (*HR*=1.88, 95% *CI*: 1.09-3.21).

Sensitivity analysis

In order to examine whether the effect estimate was robust because of the sequential omission of individual studies, sensitivity analyses were performed. The conclusions remained similar when each study involved in this meta-analysis was deleted each time to reflect the impact of the rest of the data-set on the pooled HR. Notably, there was a substantial heterogeneity regarding the expression of XIST on OS (I^2=57.2%). However, deleting the article of Ma et al. [34] reduced the I^2 to 0% and did not change the prognostic significance. It is suggested that Ma's study was a source of heterogeneity (**Figure 3**).

Publication bias

Egger linear regression analysis and a Begg funnel plot analysis were used to evaluate the published offsets in this meta-analysis for OS.

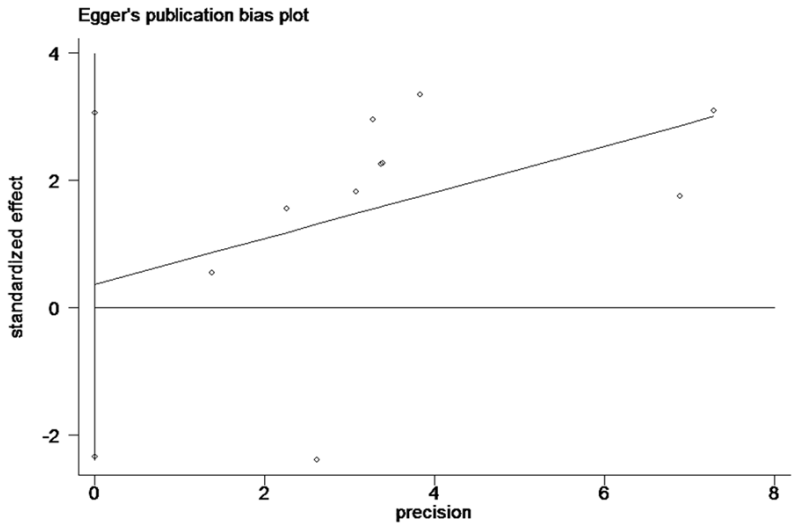

Figure 4. Egger's funnel plot for the assessment of publication bias for OS.

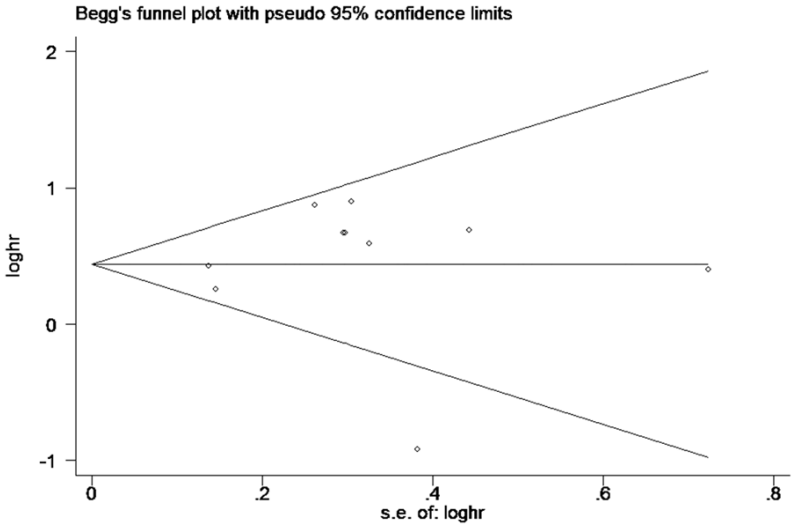

Figure 5. Begg's funnel plots of the included literature for OS.

The results of this Egger regression test showed no published bias for OS (t=0.31, P=0.761) (**Figure 4**). Similarly Begg funnel plots showed no publication bias in these studies (z=0.54, Pr>|z|=0.592) (**Figure 5**).

Association between lncRNA-XIST expression and DFS

In this meta-analysis, a total of 2 studies including 177 patients reported *HR*s for DFS. Overall, the upregulation of XIST was associated with an *HR* for DFS (*HR*=2.01, 95% *CI*: 1.09-3.69) (**Figure 2**).

Correlation between XIST expression and clinical characteristics

Eight studies reported the relationship between XIST and clinicopathological features such as TNM stage, age, gender, tumor size, lymph node metastasis, differentiation, and distant metastasis. The analysis result suggested that the overexpression of XIST was associated with advanced TNM stages (*OR*=2.57, 95% *CI*: 1.9-3.46, *P*=0.00), positive lymph node metastasis (*OR* =2.93, 95% *CI*: 1.58-5.43, *P*=0.00), positive distant metastasis (*OR*=2.79, 95% *CI*: 1.88-4.16, *P*=0.00), and tumor size (*OR*=2.98, 95% *CI*: 1.88-4.78, *P*=0.00). However, no significant correlation was found between XIST expression and gender, age, or differentiation (*P*>0.05). All these results are presented in **Table 3**.

Discussion

XIST belongs to a class of RNA molecules known as noncoding gene transcription (NCT), including noncoding RNA (ncRNA). XIST is involved in the development of malignant tumors through multiple mechanisms. More and more reports show that XIST acts as a promoter of cell proliferation and metastasis. Wei et al. reported that the expression of the XIST gene was enhanced in pancreatic cancer cells, and XIST promoted the proliferation of pancreatic cancer cells through miR-133/EFGR [32]. Jing et al. revealed that lncRNA-XIST knockdown inhibited NSCLC cell proliferation, migration and invasion. In addition, the carcinogenic effect of the XIST gene was partially mediated by the expression of EZH2 through epigenetic silencing of KLF2 [28]. Moreover, Yao et al. demonstrated that the knockdown of XIST

Table 3. The relationship between over-expressed lncRNA-XIST and clinicopathological parameters

Clinicopathological parameters	Number of studies	Number of patients	Model	Pooled OR (95% CI)	*P*-value	Heterogeneity	
						I^2 (%)	*P*-value
Gender (male/female)	8	757	Fixed	1.05 (0.78-1.41)	0.769	0.0	0.75
TNM stage (III-IV/I-II)	8	757	Fixed	2.57 (1.9-3.46)	0.000	0.0	0.57
Tumor size (≥5 cm/<5 cm)	4	398	Fixed	2.98 (1.88-4.78)	0.000	0.0	0.69
Lymph node metastasis (yes/no)	5	435	Random	2.93 (1.58-5.43)	0.001	50.1	0.09
Differentiation (poorly. others/well moderately)	3	378	Random	1.54 (0.57-4.14)	0.394	74.5	0.019
	4	398	Fixed	1.48 (0.97-2.25	0.07	46.4	0.133
Age (≥60/<60)	4	446	Fixed	0.8 (0.54-1.18)	0.256	19.5	0.292
Distant metastasis (yes/no)	5	480	Fixed	2.98 (1.88-4.78)	0.000	0.0	0.79

exerted a tumor suppressive function by reducing cell proliferation, migration, and invasion, as well as inducing apoptosis. These functions were achieved by up-regulating miR-152 in human glioblastoma [21]. Additionally, Mo et al. found that the XIST gene promoted cell cycle progression from the G1 phase to the S phase and protected cell apoptosis, leading to the growth of hepatic cells. They proposed that XIST was responsible for hepatoma cell proliferation, and XIST exerted its function through the mir-139-5p/PDK1 axis [34].

Recent studies have found that XIST expression is associated with cancer patients' prognosis. However, a wide range of studies were inconsistent and confusing due to their heterogeneity and small sample sizes. Therefore, this meta-analysis, which included 1053 patients from the 11 studies, was conducted to further investigate the relationship between clinicopathological features and the prognostic significance of XIST expression in various cancers. The results suggested that XIST overexpression is significantly associated with shorter OS, DFS, indicating that XIST could be considered a prognostic marker for cancer patients. Moreover, we performed a sensitivity analysis, and the result remained similar when a single study was removed each time. However, excluding Ma's study reduced the I^2 to 0%. The cut-off value for the XIST expression and the small sample size in this study might be the reasons for the heterogeneity. Thus we assessed the quality of this study with the Newcastle-Ottawa scale (NOS), which indicated that this case-control study was high quality and met the eligibility criteria. So we can't remove this study. Analyses stratified by sample size, germ of tumor origin, and cancer type did not alter the significant predictive value of XIST in OS from various cancers. Furthermore, we identified the relationship between XIST expression and pathological features, which suggested that elevated XIST expression was significantly correlated with tumor size, TNM stage, lymph node metastasis, and distant metastasis. None of the Begg's and Egger tests found a significant publication bias in the prognostic role of XIST in different types of cancer.

Several potential limitations still exist in this meta-analysis. First, the number of included patients and cancer types was relatively small. Second, the cut-off definition of high and low XIST expression was inconsistent in these studies, which may be one source of heterogeneity. Third, some studies did not provide *HR*s, which require the calculation or extraction of *HR*s and 95% *CI*s from the available data or from Kaplan-Meier curves. Furthermore, most of the patients included in this meta-analysis were from China. For this reason, the results we obtained may just be representative of the Chinese. Thus, more studies with larger sample sizes, high quality, different ethnic backgrounds and a uniform cut-off value are necessary to solidify the results in this study.

Conclusion

This meta-analysis revealed that the upregulation of lncRNA-XIST is associated with shorter OS and a potentially poorer DFS in human solid tumors. Furthermore, elevated lncRNA-XIST was significantly relevant to the clinicopathological features. In conclusion, lncRNA XIST may serve as a novel molecular marker of both prognosis and clinical pathology for cancer patients.

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Disclosure of conflict of interest

None.

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