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Long noncoding RNA X-inactive specific transcript as a prognostic factor in cancer patients

A meta-analysis based on retrospective studies

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Abstract

Background/aims: Emerging evidence showed the long noncoding RNA X-inactive specific transcript (lncRNA XIST) may play a crucial role in various cancers. However, its prognostic value in cancer patients remains controversial. Therefore, we performed an in-depth meta-analysis to investigate the potential clinical value of lncRNA XIST as a prognostic marker for cancer patients.

Methods: A comprehensive literature search was performed from PubMed, Embase and the Cochrane Central Search Library by January 2018. Pooled hazard ratios (HRs) or odds ratios (ORs) with 95% confidence interval (95% CI) were calculated to evaluate the prognosis as well as clinicopathological parameters of XIST, respectively.

Results: A total of 18 retrospective studies with 1351 cancer patients were included. Current meta-analysis revealed that elevated lncRNA XIST expression was associated with poor overall survival (OS) (HR = 2.14, 95% CI = 1.26–3.64; $P = .005$) and disease free survival (DFS) (HR = 4.52, 95% CI = 1.42–14.37; $P = .011$). The clinicopathological parameters analysis demonstrated that increased XIST expression was significantly associated with tumor size (OR = 2.93, 95% CI = 2.24–3.84; $P < .001$), clinical stage (OR = 2.73, 95% CI = 1.62–4.58; $P < .001$) and lymph node metastasis (OR = 2.44, 95% CI = 1.74–3.42; $P < .001$). In addition, subgroup analysis based on cancer type revealed that lncRNA XIST expression correlated with distant metastasis in digestive cancer (OR = 2.90, 95% CI = 1.80–4.68; $P < .001$).

Conclusion: The current meta-analysis results indicated lncRNA XIST expression level could serve as a prognostic predictor and biomarker in multiple cancers.

Abbreviations: CI = confidence interval, DFS = disease free survival, GC = gastric cancer, HCC = hepatocellular carcinoma, HRs = hazard ratios, lncRNA = long noncoding RNA, NOS = Newcastle-Ottawa Scale, NSCLC = non-small cell lung carcinoma, ORs = odds ratios, OS = overall survival, XIST = X-inactive specific transcript.

Keywords: cancer, lncRNA, meta-analysis, X-inactive specific transcript

1. Introduction

Long noncoding RNA (lncRNA) is a kind of RNA without protein-coding function, which is identified more than 200 nucleotides in length.[1] Accumulating evidence have been showed lncRNA participated in a variety of biological and pathological processes and involved in a variety of human diseases, such as autoimmune disease, degenerative disease and cancer, etc.[2–4] Dysregulation of lncRNA in cancer may affect specific microRNAs or downstream genes expression, thus plays vital role in cancer initiation and progression.[5] To date, there are several lncRNAs have been identified as prognostic biomarkers in various cancers.[6–10]

The lncRNA X-inactive specific transcript (XIST) is derived from *XIST* gene, recently have been found differentially expressed in multiple cancers and influenced several aggressive phenotypes in tumor cells, such as non-small cell lung carcinoma (NSCLC),[11] gastric carcinoma,[12] nasopharyngeal carcinoma,[13] etc. And certain retrospective clinical studies investigated its expression in patient tumor samples, indicating that lncXIST may correlate with clinicopathological parameters and predict survival outcomes in cancer patients.[14,15] Nevertheless, discrepancies existed among different cancer types and patient number was limited. For instance, most of the studies revealed elevated expression of lncXIST promoted cancer progression and was associated with poor prognosis.[11–14] However, the study conducted by Du et al showed it may function as a tumor suppressor in prostate cancer.[16]

Therefore, a comprehensive systematic review and meta-analysis was performed based on eligible retrospective studies, aiming to precisely investigate the potential prognostic value of lncXIST for cancer patients.

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The authors declare that they have no competing interests.

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2. Materials and methods

2.1. Literature search strategy

We performed literature search using PubMed (ncbi.nlm.nih.gov/pubmed), Embase (embase.com) and the Cochrane Library (cochranelibrary.com) up to January 2018. Search terms used as follows: ("X inactive-specific transcript" OR "XIST" OR "long noncoding RNA XIST" OR "lncRNA XIST") AND ("cancer" OR "carcinoma" OR "tumor" OR "neoplasm"). Review articles and references of original studies were also searched by hand to find potential articles. This study protocol was conducted according to the PRISMA statement and approved by the institutional review board at Xiangya Hospital of Central South University.

2.2. Inclusion and exclusion criteria

Eligible studies should meet the following selection criteria. Inclusion criteria:

1. studies evaluated the association between lncRNA XIST and cancer patient samples;
2. prognosis outcomes or clinicopathologic features were reported;
3. sufficient information to estimate hazard ratio (HR) or odds ratio (OR) with 95% confidence interval (95% CI);
4. studies published in English.

Exclusion criteria:

1. article types including case report, review, conference abstract, editorial and letter, etc;
2. studies with insufficient data to estimate HR or OR with related 95% CI;
3. publications without clinical data.

2.3. Data extraction and quality assessment

Eligible articles were reviewed by 2 reviewers independently according to the above inclusion and exclusion criteria (Chen J and Yang X). Disagreement was resolved during a consensus with a third reviewer (Zu X). The following information was extracted: author name, publication year, country or region, patient number, study type, tumor type, gender, age, tumor size, clinical TMN stage, follow-up time, therapies, detecting methods for lncXIST, cut-off value, lymph node metastasis, distant metastasis, survival outcomes, such as overall survival (OS), and disease free survival (DFS). The HRs were obtained directly or indirectly from included articles according to the study of Tierney et al.[17] The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies.

2.4. Statistical analysis

The meta-analysis was performed using STATA 12.0 version software (Stata Corporation, College Station, TX). The pooled HRs with 95% CI were evaluated for OS, DFS. And pooled ORs with 95% CI were evaluated for gender, age, tumor size, tumor clinical stage, lymph node metastasis, and distant metastasis status. Subgroup analysis and sensitivity test were also performed. Statistical heterogeneity among studies was checked using a Chi-square-based Q test and I-squared value. A fixed-effects model was used if P value for the heterogeneity test was greater than .05; Otherwise, the random-effects model was used. Publication bias was evaluated by Egger and Begg test.[18,19] $P < .05$ was considered statistically significant.

3. Results

3.1. Study selection and characteristics

A total of 227 records were retrieved through databases and other sources. According to the inclusion and exclusion criteria, our present meta-analysis finally included 18 eligible retrospective studies with 1351 cancer patients (Fig. 1). Specifically, for prognostic evaluation, data was obtained from 12 studies on lncXIST expression and cancer patient OS and 3 studies on DFS. For clinicopathological parameters correlation, there were 12 studies on gender, 15 studies on age,

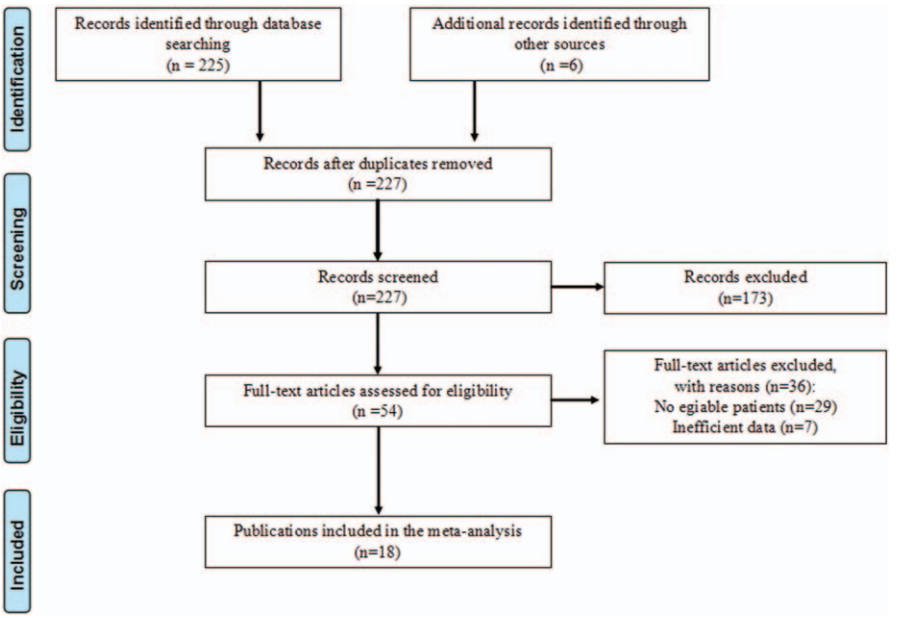

Figure 1. Flow chart of studies selection.

Table 1

Characteristics of studies in this meta-analysis.

Study	Year	Region	Study design	Cancer type	patient number	LncRNA XIST expression high/low (n)	tumor stage	Follow-up time (month)	Therapy	Detection method	Clinical Outcomes	Cut-off value	NOSscore	Reference
Tantai J et al	2015	China	Retrospective	NSCLC	32	21/11	I/II-III	NA	NA	qRT-PCR	NA	NA	6	[11]
Chen D et al	2016	China	Retrospective	Gastric cancer	106	54/52	I-II/III-IV	>100	surgery	qRT-PCR	OS	median	8	[12]
Fang J et al	2016	China	Retrospective	NSCLC	53	38/15	I/II-IV	NA	surgery	qRT-PCR	NA	fold ≥ 2.58	7	[20]
Song P et al	2016	China	Retrospective	Nasopharyngeal carcinoma	108	76/32	NA	>120	NA	qRT-PCR	OS	fold ≥ 2.31	7	[13]
Kobayashi R et al	2016	Japan	Retrospective	Cervical carcinoma	49	24/25	I-II/III-IV	44.1 (5.2 –142.1)	Chemo-radiation	qRT-PCR	OS	median	8	[21]
Chen D et al	2017	China	Retrospective	Colorectal cancer	115	58/57	I-II/III-IV	>100	surgery	qRT-PCR	OS	median	8	[22]
Song H et al	2017	China	Retrospective	Colorectal cancer	50	21/29	I-II/III-IV	60	surgery	qRT-PCR	DFS	NA	7	[23]
Ma L et al	2017	China	Retrospective	Gastric cancer	98	45/53	I-II/III-IV	>40	surgery	qRT-PCR	OS	NA	7	[15]
Du P et al	2017	China	Retrospective	Glioma	69	35/34	I-II/III-IV	36	surgery	qRT-PCR	OS	median	8	[24]
Sun W et al	2017	China	Retrospective	NSCLC	50	27/23	I-II/III-IV	NA	NA	qRT-PCR	NA	NA	7	[25]
Wei W et al	2017	China	Retrospective	Pancreatic cancer	64	32/32	I-II/III-IV	30	surgery	qRT-PCR	OS	median	8	[26]
Wu XL et al	2017	China	Retrospective	Esophageal squamous cancer	127	64/63	I-II/III-IV	>80	surgery	qRT-PCR	OS/DFS	median	8	[14]
Du Y et al	2017	China	Retrospective	Prostate cancer	62	37/25	I/II-III	>50	surgery	qRT-PCR	OS	NA	7	[16]
Xiao Y et al	2017	Ukraine	Retrospective	Colorectal cancer	120	63/57	NA	>70	Chemo-therapy	qRT-PCR	OS	median	7	[27]
Hu YY et al	2017	China	Retrospective	Bladder cancer	52	32/20	I-II/III-IV	>45	surgery	qRT-PCR	OS	NA	8	[28]
Xiong YY et al	2017	China	Retrospective	Bladder cancer	67	34/33	I-II/III-IV	NA	surgery	qRT-PCR	NA	median	7	[29]
Mo YC et al	2017	China	Retrospective	Hepatocellular carcinoma	88	38/50	NA	>40	surgery	qRT-PCR	DFS	NA	6	[30]
Zhang R et al	2017	China	Retrospective	Osteosarcoma	41	24/17	NA	60	surgery	qRT-PCR	OS	NA	7	[31]

DFS = Disease-free survival, NA = Not applicable, NOS = Newcastle-Ottawa Scale, NSCLC = non-small cell lung cancer, OS = overall survival, qRT-PCR = quantitative real-time reverse transcription polymerase chain reaction, XIST = X inactive-specific transcript.

14 studies on tumor size, 13 studies on clinical stage, 9 studies on lymph node metastasis, and 5 studies on distant metastasis. The main characteristics of the eligible studies were summarized in Table 1. For the quality assessment, the Newcastle-Ottawa Scale (NOS) score of individual cohort studies was ranged from 6 to 8 (Table 1).[11–16,20–31]

3.2. LncRNA XIST expression and cancer patients OS and DFS

There are 12 studies reported the association between lncRNA XIST expression and OS of 1011 cancer patients. There was a statistical heterogeneity between trials (I-squared = 67%; $P < .001$), so a random effects model was used in the analysis. Overall, high expression of lncRNA XIST was associated with poor OS (HR = 2.14, 95% CI = 1.26–3.64; $P = .005$). The subgroup analysis based on the cancer type revealed its expression correlated with OS in digestive system cancer (HR = 2.93, 95% CI = 1.91–4.49; $P < .001$) (Fig. 2A). And subgroup analysis based on the cut-off value of lncRNA XIST showed its expression associated with OS in median cut-off group (HR = 2.27, 95% CI = 1.17–4.40; $P = .015$) (Fig. 2B).

Three studies reported the association between lncRNA XIST expression and DFS of 265 cancer patients. There was a statistical heterogeneity between trials (I-squared = 72.5%; $P = .026$), so a random effects model was used in the analysis. Overall, high expression of lncRNA XIST was associated with poor DFS (HR = 4.52, 95% CI = 1.42–14.37; $P = .011$) (Fig. 2C).

3.3. LncRNA XIST expression and cancer patients clinicopathologic features

3.3.1. Gender. There are 12 studies reported the association between lncRNA XIST expression and gender of 904 cancer patients. There was no statistical heterogeneity between trials (I-squared = 0%; $P = .494$), so a fixed effects model was used in the analysis. Overall, no significant association was observed between expression of lncRNA XIST and gender difference (OR = 1.02, 95% CI = 0.77–1.34; $P = .907$).

3.3.2. Age. Fifteen studies reported the association between lncRNA XIST expression and age of 926 cancer patients. There was no statistical heterogeneity between trials (I-squared = 0%; $P = .751$), so a fixed effects model was used in the analysis. Overall, no significant association was observed between expression of lncRNA XIST and age (OR = 0.80, 95% CI = 0.62–1.02; $P = .074$). Since different cut-off values of age were described, we subsequently conducted subgroup analysis. Results showed lncRNA XIST expression was not associated with patient age in ≥ 60 y vs < 60 y group (OR = 0.74, 95% CI = 0.54–1.02; $P = .065$), ≥ 45 y vs < 45 y group (OR = 1.14, 95% CI = 0.69–1.88; $P = .613$) and other group (OR = 0.60, 95% CI = 0.31–1.15; $P = .121$), respectively.

3.3.3. Tumor size. There were 14 studies reported lncRNA XIST expression and tumor size with 1020 cancer patients. There was no statistical heterogeneity between trials (I-squared = 0%; $P = .668$), so a fixed effects model was used in the analysis. Overall, higher expression of lncRNA XIST was linked to larger tumor size (OR = 2.93, 95% CI = 2.24–3.84; $P < .001$). Since different cut-off values of tumor size were described, we subsequently conducted subgroup analysis. Results showed lncRNA XIST expression was associated with tumor size in ≥ 5 cm vs < 5 cm group (OR = 2.92, 95% CI = 2.07–4.13; $P < .001$) and ≥ 3 cm vs < 3 cm group (OR = 2.95, 95% CI = 1.91–4.55; $P < .001$), respectively (Fig. 3).

3.3.4. Clinical TMN stage. There were 13 studies reported lncRNA XIST expression and clinical TMN stage with 962 cancer patients. There was a statistical heterogeneity between trials (I-squared = 69.2%; $P < .001$), so a random effects model was used in the analysis. Overall, expression of lncRNA XIST

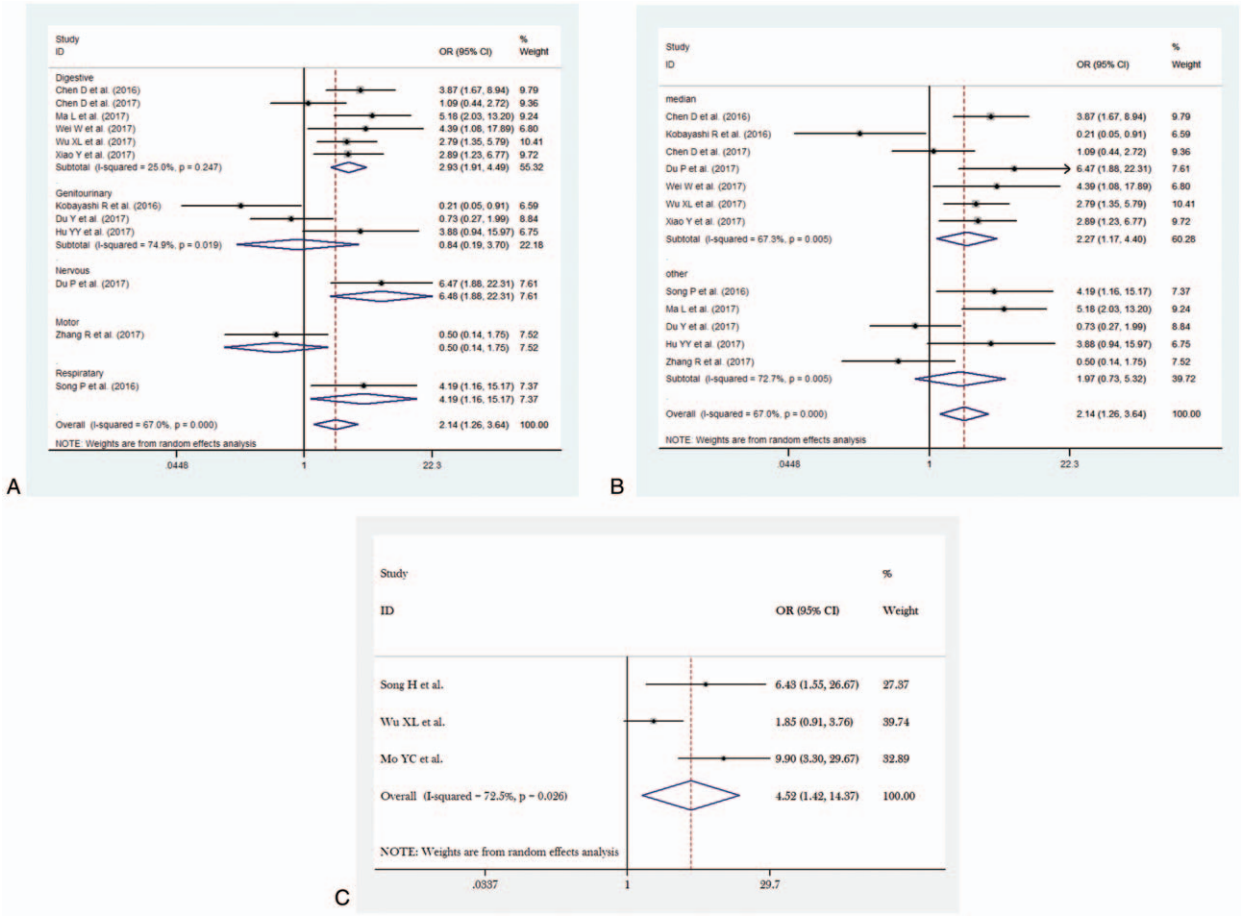

Figure 2. Forest plots of hazard ratios (HRs) for lncRNA XIST expression and prognosis in cancer. A: subgroup analysis of OS based on cancer type. B: subgroup analysis of OS based on expression cut-off value. C: DFS analysis. DFS = disease free survival, HRs = hazard ratios, lncRNA = long noncoding RNA, OS = overall survival, XIST = X-inactive specific transcript.

was associated with tumor clinical stage (OR = 2.73, 95% CI = 1.62–4.58; $P < .001$). Since different stage cut-off values were described, we subsequently conducted subgroup analysis. Results showed lncRNA XIST expression was associated with TMN stage in III–IV vs. I–II group (OR = 3.09, 95% CI = 2.06–4.62; $P < .001$). While, this association was not observed in the other group (OR = 1.65, 95% CI = 0.16–17.12; $P = .065$) (Fig. 4).

3.3.5. Lymph node metastasis. There were 9 studies reported lncRNA XIST expression and lymph node metastasis status with 619 cancer patients. There was no statistical heterogeneity between trials (I-squared = 0%; $P = .447$), so a fixed effects model was used in the analysis. Overall, expression of lncRNA XIST was associated with lymph node metastasis (OR = 2.44, 95% CI = 1.74–3.42; $P < .001$). Also, we conducted subgroup analysis based on cancer type. Results showed lncRNA XIST expression was associated with lymph node metastasis in digestive system group (OR = 2.62, 95% CI = 1.71–4.02; $P < .001$) and genitourinary system group (OR = 2.44, 95% CI = 1.74–3.42; $P = .004$), respectively. While, this association was not observed in the respiratory system group (OR = 1.50, 95% CI = 0.74–3.03; $P = .264$) (Fig. 5).

3.3.6. Distant metastasis. There were 5 studies reported lncRNA XIST expression and distant metastasis status with 397 cancer patients. There was a statistical heterogeneity between trials (I-squared = 82.7%; $P < .001$), so a random effects model was used in the analysis. Overall, expression of lncRNA XIST was not associated with distant metastasis (OR = 1.59, 95% CI = 0.55–4.63; $P = .393$). Subgroup analysis based on cancer type revealed that lncRNA XIST expression was associated with distant metastasis in digestive system group (OR = 2.90, 95% CI = 1.80–4.68; $P < .001$).

The detailed meta-analysis and subgroup analysis results for lncRNA XIST expression and cancer patient clinicopathological parameters are listed in Table 2.

3.4. Sensitivity analysis and publication bias

Sensitivity analysis was performed by exclusion of each single study to assess the stability of present pooled results. After removing those documents that led to heterogeneity, the overall HR or OR did not change significantly, so the current meta-analysis results were relatively stable (Fig. 6). Furthermore, Begg funnel plot and Egger regression test were performed to evaluate the publication bias. No evidence of publication bias was identified using Begg funnel plots (Fig. 7), which was further validated by Egger regression test ($P > .05$).

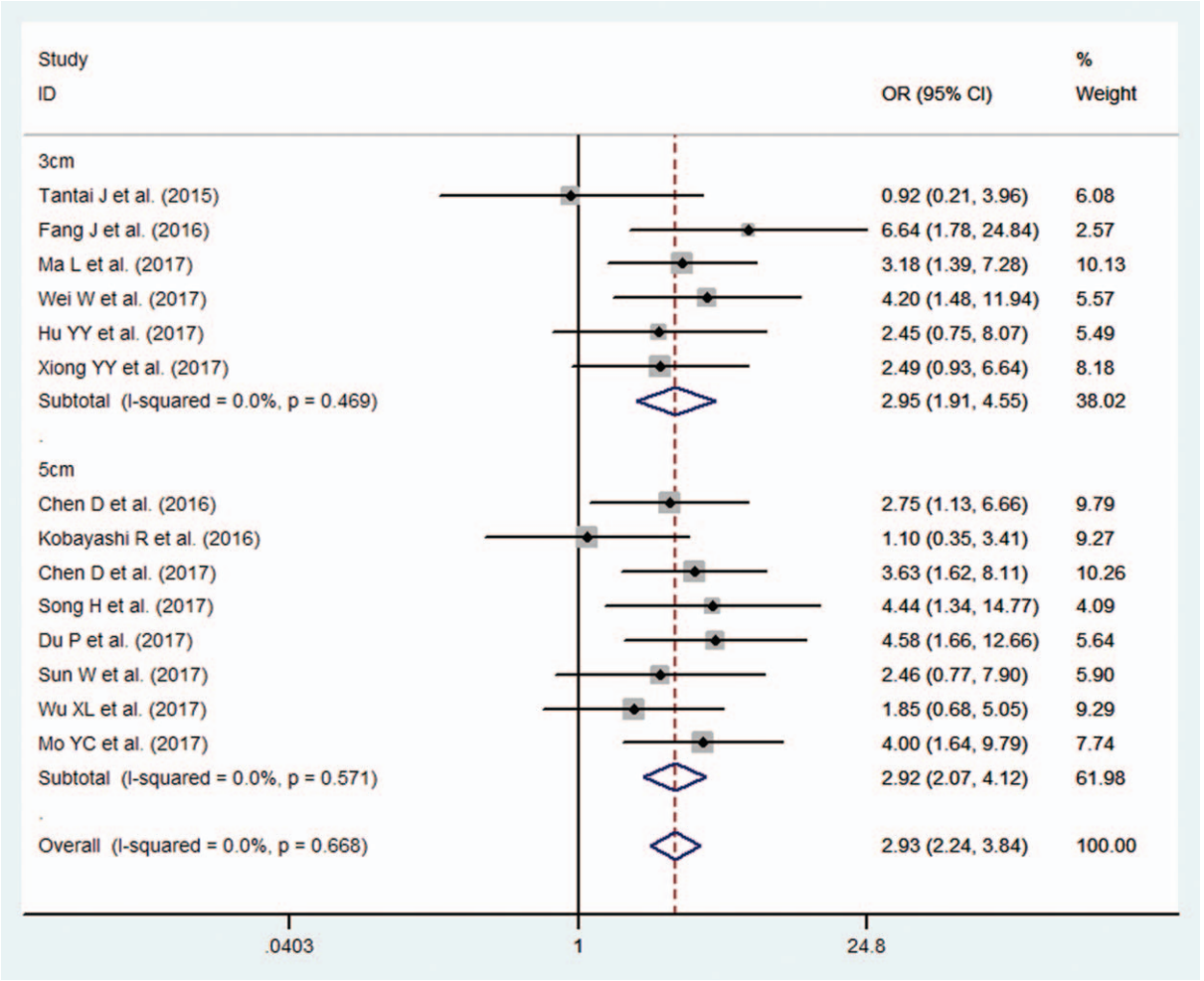

Figure 3. Forest plots of odd ratios (ORs) for lncRNA XIST expression and tumor size. lncRNA = long noncoding RNA, OS = overall survival, XIST = X-inactive specific transcript.

4. Discussion

Recent studies have provided novel insights into the functions and potential mechanisms of lncRNA XIST in cancer development. Yao et al found lncRNA XIST expression was up-regulated in glioblastoma cancer stem cells, knocking down this lncRNA exerted tumor-suppressive functions by up-regulating miR-152.[32] Several studies uncovered it may also influence the epithelial-mesenchymal transition (EMT) process in multiple cancers. Chen et al demonstrated it expedited metastasis by competing with miR-200b-3p to modulate the ZEB1 expression and boost EMT in colorectal cancer.[22] Zhuang et al revealed the lncXIST/miR-92b/Smad7 signaling axis promoted hepatocellular carcinoma (HCC) progression.[33] Zhang et al found lncXIST could promote gastric cancer (GC) progression through TGF-β1 via targeting miR-185.[34] Despite the ceRNA mechanisms, some studies dissected it may directly regulate protein expression or function. Fang et al showed lncXIST may act as an oncogene in non-small cell lung cancer (NSCLC) by epigenetically repressing KLF2 expression.[20] McHugh et al demonstrated it could silence transcription by directly interacting with SHARP, recruiting SMRT, activating HDAC3, and deacetylating histones to exclude Pol II across the X chromosome.[35] Tumor cell invasion and drug chemoresistance are 2 crucial problems for cancer therapeutics. In Du et al's study, they verified LnXIST could interact with miR-29c through DNA mismatch repair pathway to modulate the chemoresistance of glioma cell to temozolomide, which is one of the most commonly used drug in glioma chemotherapy.[24] Results from Sun et al showed Knocking down lncRNA XIST enhanced the chemosensitivity of NSCLC cells via suppression of autophagy. They provided preclinical evidence that the lncXIST/miR-17/autophagy pathway may be a promising target for patients with chemoresistant NSCLC.[25]

The in vitro and in vivo experiments demonstrated lncXIST may affect tumor progression in multiple potential pathways. In addition, several clinical sample surveys also confirmed these findings. Compared with para-carcinoma tissues, lncXIST aberrant expressed in tumor tissues, and its increased level was associated with shorter survival and poorer prognosis.[12–15,21–24,26–28,30,31] Further, overexpression of lncRNA XIST in tumor tissues associated with clinicopathological features in cancer patients.[11,12,20–23] However, this correlation seems

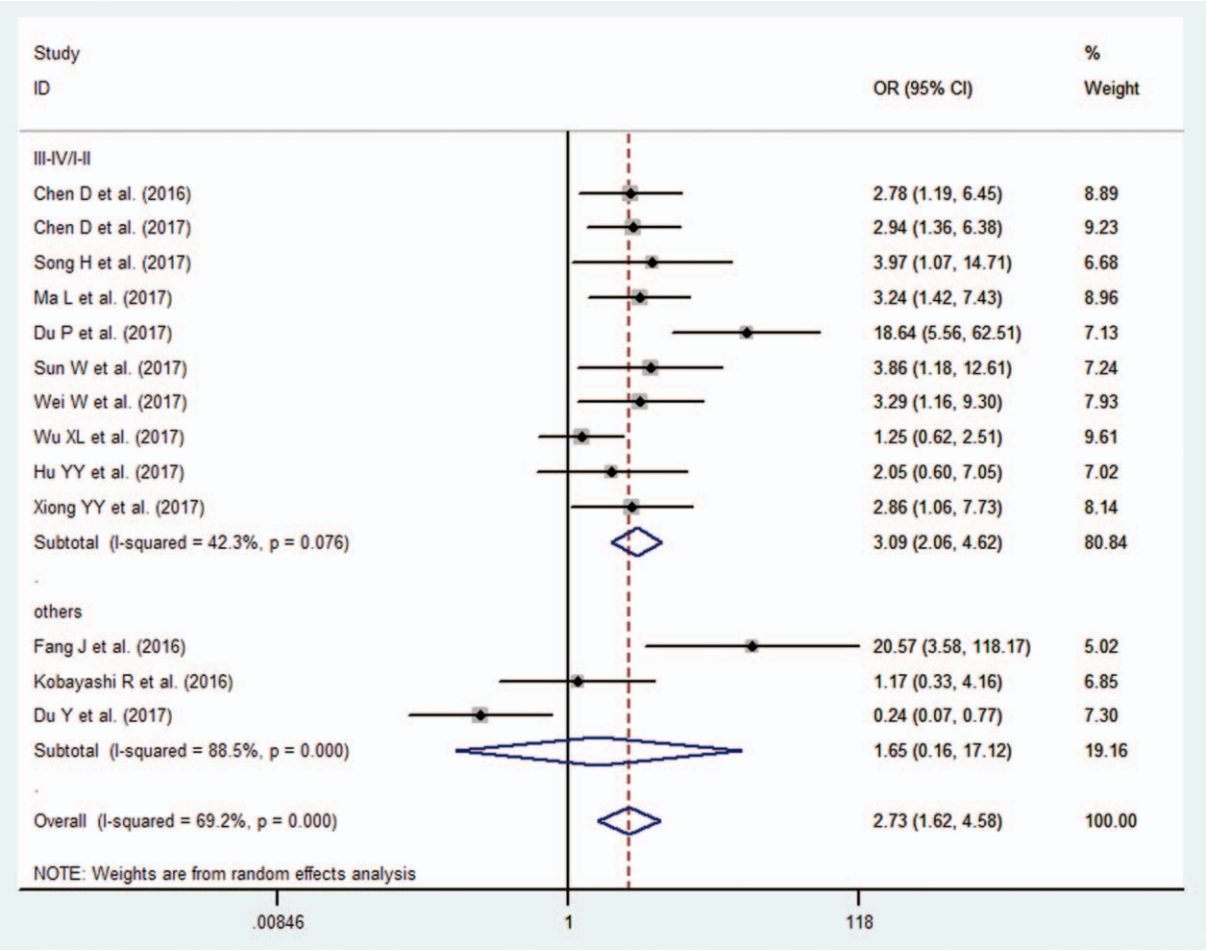

Figure 4. Forest plots of odd ratios (ORs) for lncRNA XIST expression and clinical TMN stage. lncRNA = long noncoding RNA, OS = overall survival, XIST = X-inactive specific transcript.

reversed in prostate cancer. Investigation from Du et al revealed lncXIST was down-regulated in prostate cancer specimens and low expression of XIST was correlated with poor prognosis and advanced tumor stage in prostate cancer patients.[16]

In this meta-analysis, we pooled data from a total of 18 retrospective eligible studies with 1351 cancer patients. Results revealed that high lncRNA XIST expression was an unfavorable prognostic factor in multiple cancer patients. For the survival analysis, high expression of lncRNA XIST was associated with poor OS (HR = 2.14, 95% CI = 1.26–3.64; $P = .005$). The subgroup analysis showed its expression correlated with OS in digestive system cancer (HR = 2.93, 95% CI = 1.91–4.49; $P < .001$) and median cut-off group (HR = 2.27, 95% CI = 1.17–4.40; $P = .015$). Also, high expression of lncRNA XIST was associated with poor DFS (HR = 4.52, 95% CI = 1.42–14.37; $P = .011$). The clinicopathological parameters analysis demonstrated that increased XIST expression was significantly associated with larger tumor size (OR = 2.93, 95% CI = 2.24–3.84; $P < .001$), higher clinical stage (OR = 2.73, 95% CI = 1.62–4.58; $P < .001$) and easier lymph node metastasis (OR = 2.44, 95% CI = 1.74–3.42; $P < .001$). In addition, subgroup analysis revealed that lncRNA XIST expression correlated with distant metastasis in digestive cancer (OR = 2.90, 95% CI = 1.80–4.68; $P < .001$). However, no significant association was observed between expression of lncRNA XIST and gender difference (OR = 1.02, 95% CI = 0.77–1.34; $P = .907$) as well as age (OR = 0.80, 95% CI = 0.62–1.02; $P = .074$).

Nevertheless, a comprehensive and in-depth meta-analysis was performed, there are several limitations should be considered. Firstly, several HRs were calculated based on data extracted from the survival curve, which may not be very accurate. Secondly, heterogeneity was observed in some analysis including OS, DFS, TMN stage and distant metastasis. Accordingly, subgroup analysis was performed to find potential associations. Thirdly, all included studies are retrospective and most of the studies are from China, some geographical factors may vary across different populations.

5. Conclusion

Our meta-analysis results revealed lncRNA XIST level served as a prognostic indicator in multiple cancers. Higher expression could predict cancer patient poor OS and DFS. Also, its expression correlated with tumor size, TMN stage and lymph node metastasis in multiple cancers as well as distant metastasis in digestive system cancer. Further clinical studies are still required and more mechanism researches are needed to explore the precise role of lncXIST in cancer.

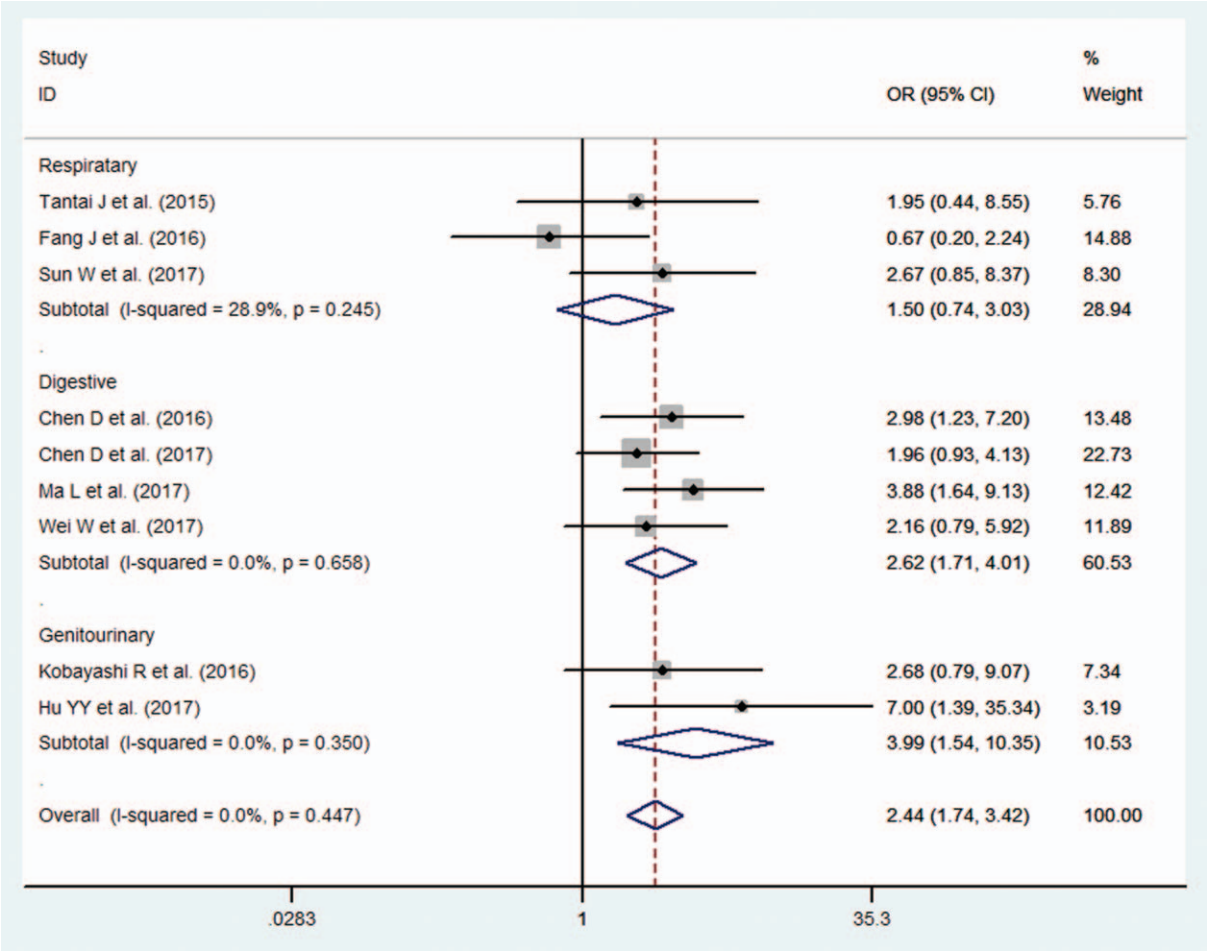

Figure 5. Forest plots of odd ratios (ORs) for lncRNA XIST expression and lymph node metastasis. lncRNA = long noncoding RNA, OS = overall survival, XIST = X-inactive specific transcript.

Table 2

Meta-analysis of the association between lncRNA XIST expression and clinicopathological parameters in cancer patients.

Clinicopathological parameters	Studies (n)	Total cases (n)	OR (95% CI)	*P* value	Heterogeneity		
					I^2 (%)	P_h	Model
Gender (Male vs Female)	12	904	1.02 (0.77–1.34)	.907	0	.494	Fix
Age (y)	15	926	0.80 (0.62–1.02)	.074	0	.751	Fix
≥ 60 vs < 60	8	530	0.74 (0.54–1.02)	.065	0	.667	
≥ 45 vs < 45	4	250	1.14 (0.69–1.88)	.613	0	.726	
others	3	146	0.60 (0.31–1.15)	.121	0	.603	
Tumor size (cm)	14	1020	2.93 (2.24–3.48)	<.001	0	.67	Fix
≥ 5 vs < 5	8	654	2.92 (2.07–4.13)	<.001	0	.571	
≥ 3 vs < 3	6	366	2.95 (1.91–4.55)	<.001	0	.469	
TNM stage	13	962	2.73 (1.62–4.58)	<.001	69.2	<.001	Random
III–IV vs I–II	10	798	3.09 (2.06–4.62)	<.001	42.3	.076	
others	3	164	1.65 (0.16–17.12)	.065	88.5	<.001	
Lymph node metastasis (Yes vs No)	9	619	2.44 (1.74–3.42)	<.001	0	.447	Fix
Respiratory System	3	135	1.50 (0.74–3.03)	.264	28.9	.245	
Digestive System	4	383	2.62 (1.71–4.02)	<.001	0	.658	
Genitourinary System	2	101	2.44 (1.74–3.42)	.004	0	.350	
Distant metastasis (Yes vs No)	5	397	1.59 (0.55–4.63)	.393	82.70	<.01	Random
Digestive system	4	335	2.90 (1.80–4.68)	<.001	0	.63	
Genitourinary system	1	62	0.17 (0.05–0.51)	.002	NA	NA	

CI = confidence interval, NA = Not applicable, OR = Odd ratio, P_h = *P* value of heterogeneity.

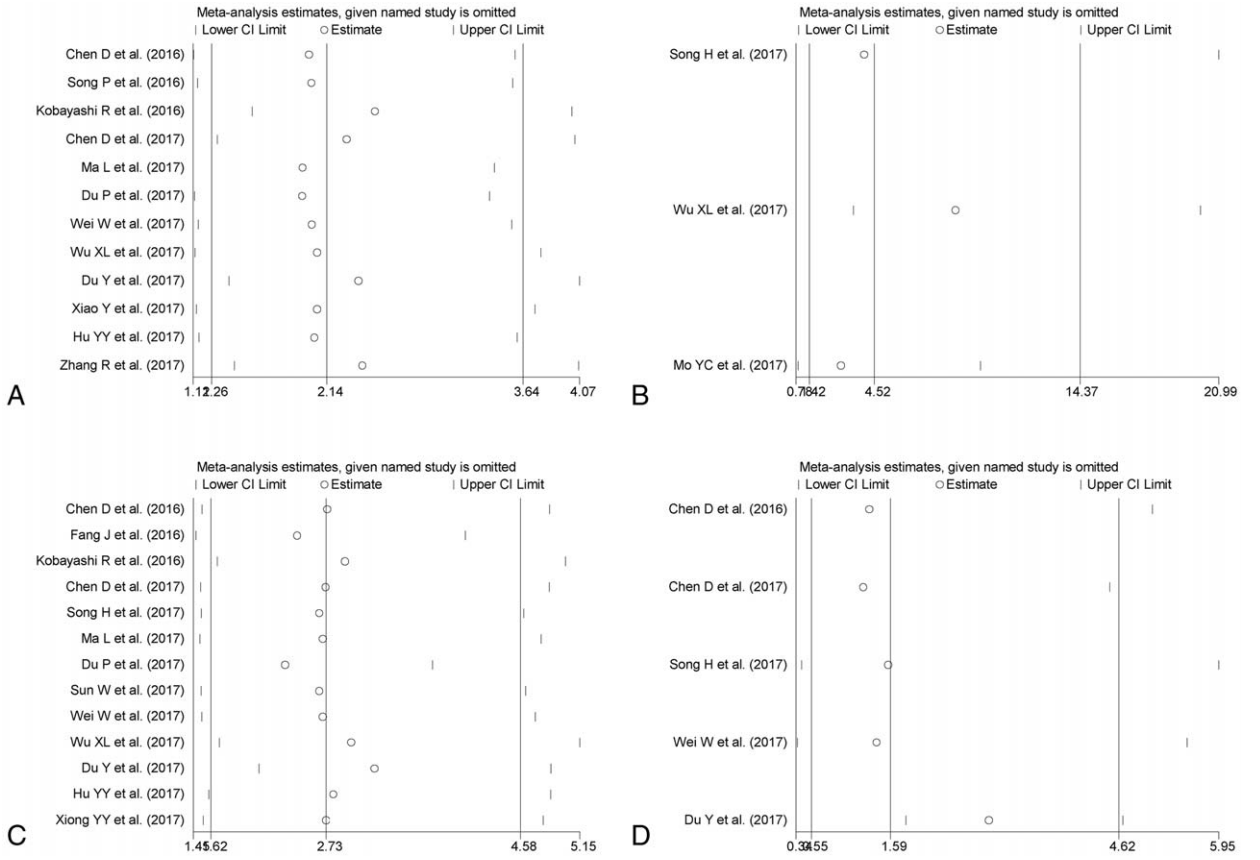

Figure 6. Sensitivity analysis for A: OS; B: DFS; C: TMN stage; D: Distant metastasis. DFS = disease free survival, OS = overall survival.

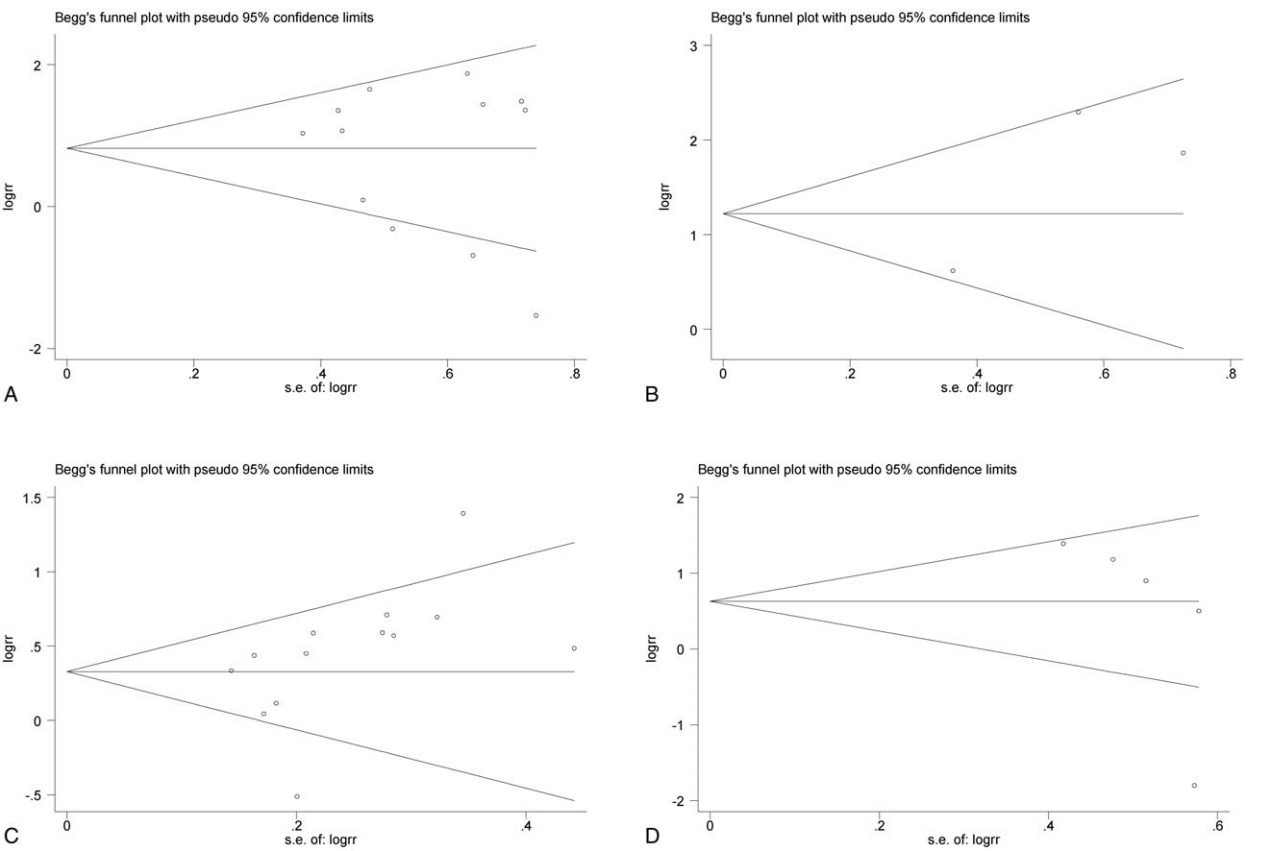

Figure 7. Begg funnel plot for potential publication bias. A: OS; B: DFS; C: TMN stage; D: Distant metastasis. DFS = disease free survival, OS = overall survival.

Author contributions

Conceptualization: Jinbo Chen, Xiong Yang, Xiongbing Zu.
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