Int J Clin Exp Med 2018;11(4):2940-2949
www.ijcem.com /ISSN:1940-5901/IJCEM0067511

Review Article

MALAT1 overexpression correlates with clinical progression and decreased survival in patients with esophageal cancer: a meta-analysis

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Received July 3, 2017; Accepted March 14, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is involved in tumor development and progression. Recent studies have shown that the MALAT1 expression may correlate with prognosis in esophageal cancer (EC). This study aimed to evaluate the prognostic value of MALAT1 in EC. A systematic literature search was conducted in PubMed, Embase, Web of Science, the China National Knowledge Infrastructure (CNKI) and Wanfang databases. Studies of the prognostic value of the MALAT1 in EC were included. Pooled hazard ratio (HR)/Odds Ratio (OR) and 95% confidence interval (95% CI) were calculated using fixed-effects/random-effects models. A total of five studies comprising 507 patients with EC were finally included. MALAT1 overexpression correlated significantly with poor overall survival (OS) (HR, 2.00; 95% CI, 1.14-2.86; $p < 0.001$), positive lymph node metastasis (LNM) (OR, 1.77; 95% CI, 1.04-3.00; $p = 0.04$) and worse tumor differentiation (OR, 2.06; 95% CI, 1.21-3.51; $p = 0.008$). No significant association was observed in gender (OR, 1.23; 95% CI, 0.78-1.93; $p = 0.37$) and depth of tumor (OR, 1.64; 95% CI, 0.37-7.34; $p = 0.52$). Upregulation of MALAT-1 correlated with clinical progression and decreased survival, therefore it might serve as a prognostic biomarker for EC.

Keywords: MALAT1, long noncoding RNA, esophageal cancer, prognosis

Introduction

Esophageal cancer (EC) is one of the most common malignancies in digestive tract. It is the fifth leading cause of cancer-related deaths in China, and the top eighth deadliest cancer worldwide [1, 2]. EC is classified in two major histological subtypes: squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) [3]. Although great progress has been made in clinical diagnosis and treatment for EC, most cases are diagnosed in the advanced stage, where prognosis remains unfavorable [4, 5]. Of note, there is a lack of specific prognostic biomarkers to guide clinical practice. Therefore, new molecular markers to predict the prognosis of EC are needed.

Long noncoding RNAs (lncRNAs) have attracted substantial attention in recent years [6, 7]. Evidence is increasing that lncRNAs are closely involved in tumorigenesis and progression of human tumors [8, 9]. They could function as tumor suppressor genes or oncogenes on multiple levels [10, 11]. Increasing numbers of cancer-related lncRNAs have been identified. Expression of some, including HOTAIR, H19, and UCA1, correlates with tumorigenesis, metastasis, and prognosis [12-14].

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1, also NEAT2), is a lncRNA comprising over 8,000 nucleotides. It was originally identified in non-small cell lung carcinoma [15]. MALAT1 is located on chromosome 11q13.1 [16, 17]. Recent studies have confirmed that MALAT1 serves important biological functions, including alternative splicing [18, 19], regulation of gene expression [20, 21], mediation of mRNA relocation [22], and chromosome modification [23]. MALAT1 is found aberrantly expressed in various cancer types, including thyroid cancer, breast cancer, gallbladder cancer, and esophageal cancer [24-

26]. Much evidence suggests that MALAT1 is involved in tumor development, and thus could be useful as a prognostic factor and therapeutic target [27-30]. Nevertheless, the prognostic value of MALAT1 in EC remains unclear, and has not yet been methodically analyzed. There is no specific meta-analysis assessing the prognostic impact of MALAT1 in EC. Therefore, we performed this meta-analysis by collecting relevant articles to clarify the prognostic significance and examine the pathological features of MALAT1 in EC.

Materials and methods

Search strategies

In order to access eligible articles for meta-analysis, a comprehensive literature searches were conducted in a number of databases: PubMed, Embase, Web of Science, the China National Knowledge Infrastructure (CNKI), and Wanfang database. The search interval was set from initiation to April 1, 2017.

The combination of the following search keywords was used: "Metastasis associated lung adenocarcinoma transcript 1" or "MALAT1" or "lncRNA MALAT1" or "long noncoding RNA MALAT1" or "NEAT2" or "nuclear-enriched abundant transcript 2", "esophageal tumor" or "esophageal neoplasm" or "esophageal cancer" or "esophageal squamous cell carcinoma" or "ESCC" or "EC", "pathological feature" or "pathology" or "prognosis" or "survival" or "clinical outcome". In addition, the references of relevant articles were manually searched.

Study selection

Inclusion criteria were as follows: (1) Patients included were diagnosed with esophageal cancer; (2) Studies reported the association between MALAT1 expression and overall survival (OS) or clinicopathologic features; (3) Patients were divided into two groups according expression of MALAT1 in tissue specimens; (4) Sufficient data were reported in order to calculate hazard ratio (HR) with 95% confidence intervals (CI) for survival rates, or odds ratios (ORs) with 95% CI for pathological features; (5) The studies were published in English or Chinese. Exclusion criteria were as follows: (1) Studies on cell lines or animals; (2) Studies with insufficient data for pathological features and overall survival; (3) Reviews, meta-analyses, case reports and duplicate articles.

Data extraction and quality assessment

Using standardized information-collection forms, the relevant data from all the included studies was extracted by two reviewers (QC and YHQ) independently. Any disagreements were resolved by discussion with a third reviewer (HJ). The extracted data included the following: first author's surname, publication year, country, sample size, tumor stage, follow-up period, MALAT1 expression, detection methods, clinicopathological features (gender, tumor invasion depth, histopathological grade, lymph node metastasis), cut-off value, HR, and corresponding 95% CI.

For studies providing detailed HRs and 95% CIs for survival, data were extracted directly. Otherwise, HRs were retrieved from Kaplan-Meier survival curves using the Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/).

The quality of all included studies was evaluated using the Newcastle-Ottawa quality assessment scale (NOS), which has a score ranging from 0 to 9 points. The higher the score, the lower the risk of bias.

Data synthesis and statistical analyses

Statistical analyses of HRs for OS were estimated using Stata statistical software version 12.0 (Stata Corporation, College Station, Texas, USA. ORs for clinicopathologic characteristics (gender, degree of differentiation, depth of tumor infiltration, and LNM) were calculated using RevMan5.3 software (Cochrane Collaboration).

Inter-study heterogeneity was assessed by the Chi square-based Q test and I^2 statistics. If the $P_Q < 0.05$ and $I^2 > 50\%$, a random-effects model was used to evaluate for heterogeneity. Conversely, if there was no obvious heterogeneity, a fixed-effects model was applied. All the *p* values were two-sided, and a statistically significant differences were defined as $p < 0.05$.

Results

Search results

Initially, 350 potentially relevant publications were returned by our search strategy. Among

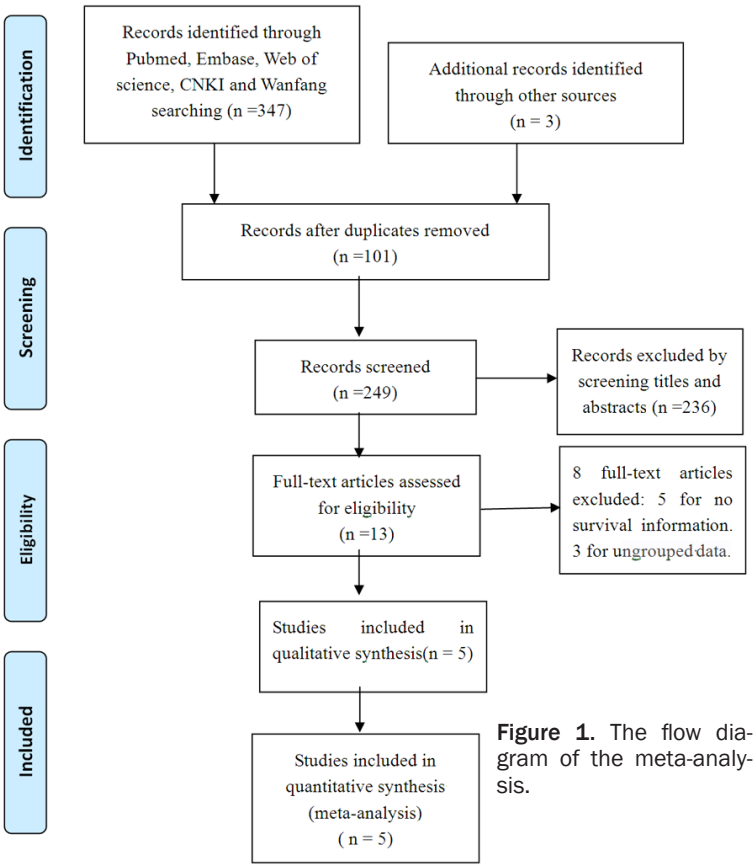

Figure 1. The flow diagram of the meta-analysis.

them, 101 were excluded for duplication. After screening titles and abstracts, 236 records were excluded. Thirteen relevant studies were selected for further evaluation, and eight articles were excluded after reviewing the full article. Finally, a total of five studies, including 507 EC patients, met all of the inclusion criteria [31-35]. The selection process is shown in **Figure 1**.

Characteristics of the included studies

Sample sizes of included articles ranged between 54-137 patients. All included studies were written in English and the participants were all from China. The publication period ranged from 2015 to 2016. Expression of MALAT1 in tissue samples was all measured by quantitative real-time polymerase chain reaction (qRT-PCR). All recruited patients had pathologically confirmed EC. Not all patients received chemotherapy or radiotherapy prior to surgery. The percentage of cancers with high MALAT1 expression ranged from 43.40% to 75.18%. Four studies reported an association between MALAT1 expression and OS [31, 33-35]. Two studies reported HRs and 95% CIs in multivariate analyses [31, 33]. The remaining two studies provided Kaplan-Meier survival curves [34, 35]. All included studies were grouped into higher and lower MALAT1 expression groups. In this meta-analysis, the quality of all included studies varied between 6 to 9, with a mean value of 7.4. Detailed patient characteristics are displayed in **Table 1**.

Meta-analysis

Correlation of MALAT1 expression and clinical characteristics: Three studies evaluated the association of MALAT1 expression and LNM.

Pooled HRs were significantly positive for high MALAT1 expression (OR, 1.77; 95% CI, 1.04-3.00; $p = 0.04$; **Figure 2**) without heterogeneity ($I^2 = 49\%$, $P_Q = 0.14$). There was a positive significant association between MALAT1 expression and tumor differentiation (OR, 2.06; 95% CI, 1.21-3.51; $p = 0.008$; **Figure 3**). The test for heterogeneity was not significant, so the fixed-effects model was used ($I^2 = 17\%$, $P_Q = 0.30$).

When we evaluated the correlation between MALAT1 expression and gender, the pooled ORs were not significant for high MALAT1 expression (OR, 1.23; 95% CI, 0.78-1.93; $p = 0.37$; **Figure 4**), without heterogeneity ($I^2 = 0\%$, $P_Q = 0.50$). No significant association was observed between high MALAT1 expression and depth of invasion (OR, 1.64; 95% CI, 0.37-7.34; $p = 0.52$; **Figure 5**), the random-effects model was applied ($I^2 = 80\%$, $P_Q = 0.03$).

Association between MALAT1 expression and overall survival of EC: Four studies reported the OS of 453 EC patients. No significant heterogeneity was found among studies ($I^2 = 0.0\%$, $P_Q = 0.487$), and a fixed-effects model was used. There was a significant association between high MALAT1 expression and poor OS in EC (HR, 2.00; 95% CI, 1.14-2.86; $p < 0.001$; **Figure 6**).

Table 1. Characteristics of the studies included in the meta-analysis

Author	Year	Country	Study design	No. of patients	High MALAT1 (n, %)	Gender (Male/Female)	Depth of invasion (T3-4/T1-2)	LNM (Yes/No)	Differentiation (Poor/Well + Moderate)	Survival analysis	Detection method	Cut-off value	NOS
Cao	2015	China	R	77	45, 58.4	H (35/10); L (22/10)	H (18/27); L (12/20)	H (16/29); L (11/21)	H (18/27); L (12/20)	OS	qRT-PCR	MALAT1/GAPDH	9
Hu	2015	China	R	54	25, 46.3	H (14/11); L (18/11)	NA	H (16/9); L (8/21)	H (19/6); L (22/7)	NA	qRT-PCR	cancer/normal ratio (1.5)	6
Huang	2016	China	R	133	99, 74.4	H (58/41); L (15/19)	NA	NA	H (56/43); L (11/23)	OS	qRT-PCR	NA	7
Wang	2016	China	R	106	46, 43.4	NA	NA	NA	NA	OS	qRT-PCR	Median value (0.2130)	7
Yao	2016	China	R	137	103, 75.2	H (70/33); L (24/10)	H (77/26); L (27/7)	H (51/52); L (13/21)	H (28/75); L (4/30)	OS	qRT-PCR	cancer/normal ratio (0.5)	8

R: retrospective cohort study; H: high expression; L: low expression; LNM: lymph node metastasis; OS: overall survival; qRT-PCR: quantitative real-time PCR; NA: not available.

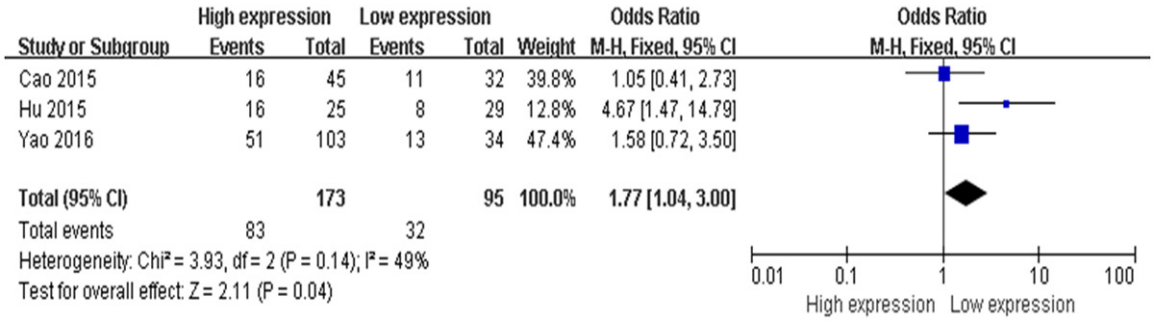

Figure 2. Forest plots for the association between MALAT1 expression and LNM. Three studies reported the association between MALAT1 and LNM, involving totally 268 EC cases. The fixed-effects model was applied to calculate the pooled OR with corresponding 95% CI because there was no significant heterogeneity among studies (I^2 = 49%, P_Q = 0.14). The pooled results showed that the patients with high MALAT1 expression tend to LNM (OR = 1.77, 95% CI: 1.04-3.00, p = 0.04).

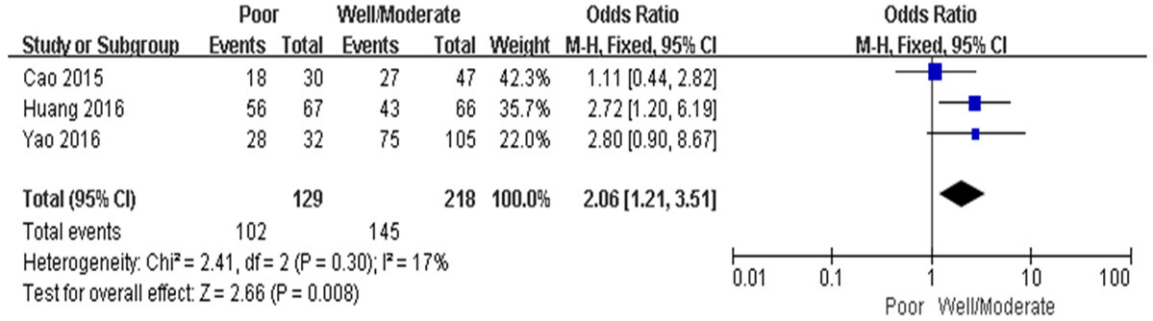

Figure 3. Forest plots for the association between MALAT1 expression and differentiation. Three studies reported the association between MALAT1 and differentiation, involving a total of 347 EC cases. The fixed-effects model was applied to calculate the pooled OR with corresponding 95% CI because there was no significant heterogeneity among studies (I^2 = 17%, P_Q = 0.30). The pooled results showed that the patients with high MALAT1 expression have poorer differentiation (OR = 2.06, 95% CI: 1.21-3.51, p = 0.008).

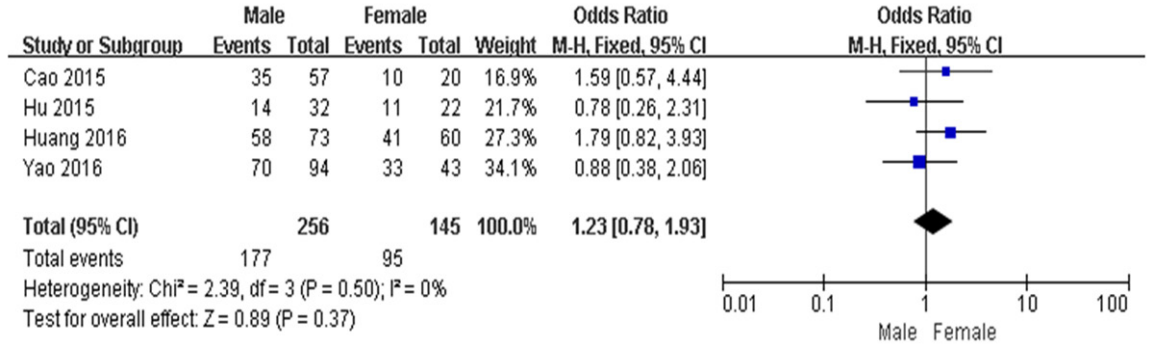

Figure 4. Forest plots for the association between MALAT1 expression and gender. Four studies reported the association between MALAT1 and gender, involving a total of 401 EC cases. The fixed-effects model was applied to calculate the pooled OR with corresponding 95% CI because there was no significant heterogeneity among studies (I^2 = 0%, P_Q = 0.50). The pooled results showed that there was no significant association between MALAT1 expression and gender (OR = 1.23, 95% CI: 0.78-1.93, p = 0.37).

Publication bias

For the meta-analysis of the association between MALAT1 expression and clinical parameters (LNM, tumor differentiation, gender and invasion depth), all of the funnel plots (**Figure 7**) were found to be approximately symmetric, which revealed there was no oblivious publica-

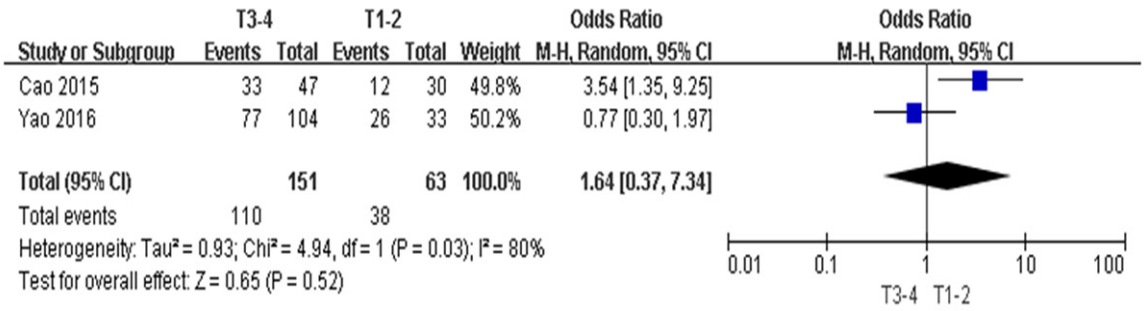

Figure 5. Forest plots for the association between MALAT1 expression and tumor invasive depth. Two studies reported the association between MALAT1 and depth of tumor invasion, involving 214 EC cases. The random-effects model was applied to calculate the pooled OR with corresponding 95% CI because there was significant heterogeneity across-studies (I^2 = 80%, P_Q = 0.03). The pooled results showed that there was no significant association between MALAT1 expression and tumor invasive depth. (OR = 1.64, 95% CI: 0.37-7.34, p = 0.52).

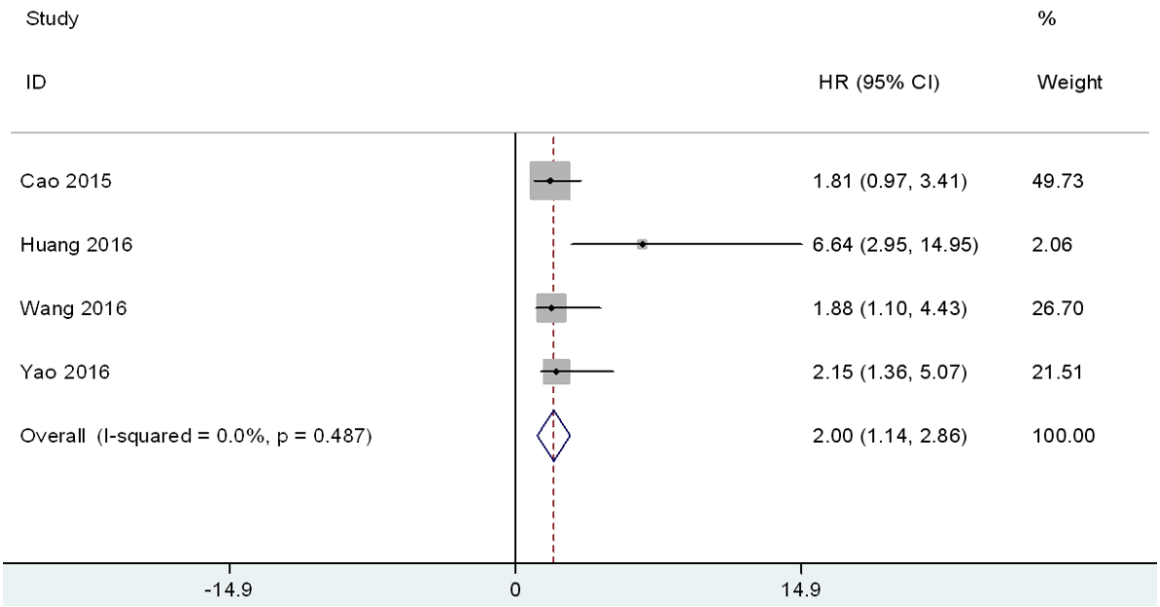

Figure 6. Forest plots for the association between MALAT1 expression and OS. Four studies reported the association between MALAT1 and OS, involving 453 EC patients. The fixed-effects model was applied to calculate the pooled HR with corresponding 95% CI because there was no significant heterogeneity among studies (I^2 = 0%, P_Q = 0.487). The pooled results showed that the cases with high MALAT1 expression had a poorer OS (HR = 2.00, 95% CI: 1.14-2.86, p < 0.001).

tion bias among studies. For the meta-analysis of the relationship between MALAT1 expression and OS, Begg's funnel plot (**Figure 8**) displayed that no significant publication bias was observed across studies, which was further confirmed in Begg's test (P > 0.05).

Discussion

MALAT1, is an emerging oncogene, that has been increasingly reported to be involved in various human diseases and cancers [36-37]. Like other oncogenic lncRNAs, MALAT1 contributes to tumorigenesis and progression. Expression of MALAT1 was found to be aberrant in a variety of tumors [38-39]. In EC tissues and cells, relative expression of MALAT1 was substantially higher compared with controls. Up-regulated expression of MALAT1 in EC was also related to some clinical characteristics and prognosis. Huang et al. [33] demonstrated that high MALAT1 expression was closely cor-

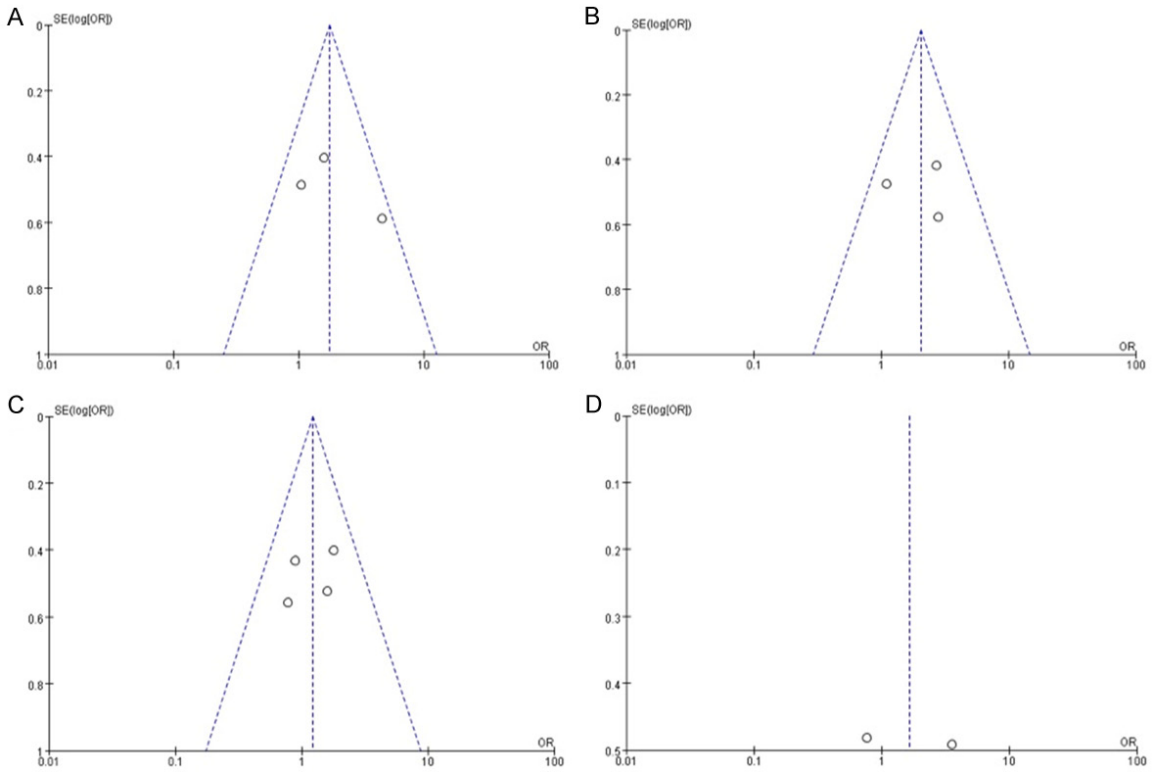

Figure 7. Funnel plots of publication bias test for LNM (A), tumor differentiation (B), gender (C) and invasive depth (D).

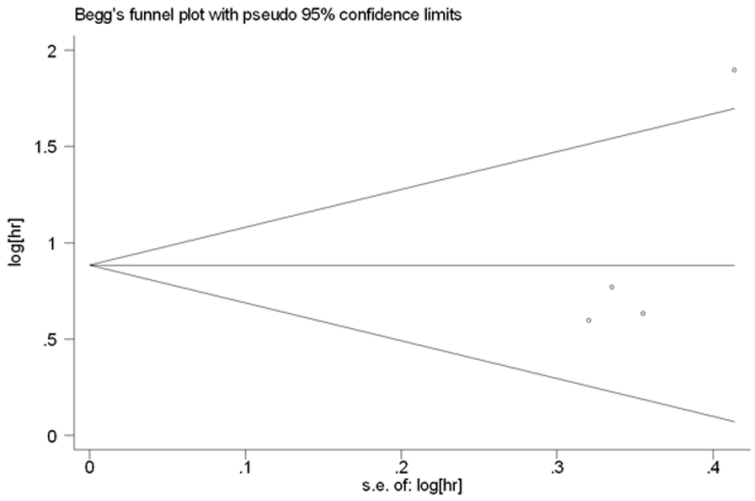

Figure 8. Begg's funnel plot of publication bias test for OS.

related with distant metastasis, poor tumor differentiation and shorter OS. Hu et al. [32] found that enhanced expression levels of MALAT1 was positively correlated with primary tumor size and LNM. Similarly, Wang et al. [34] found that MALAT1 expression was associated with LNM. However, Yao et al. [35] reported no significant association between MALAT1 expression and LNM. In another study by Cao et al. [31], MALAT1 expression was not related to LNM, TNM stage, or histological grade, but was significantly associated with tumor invasive depth. Furthermore, the patients with high expression of MALAT1 had a shorter DFS and OS. To the best of our knowledge, this is the first meta-analysis to investigate the relationship between MALAT1 expression and pathological features and OS in EC.

In our meta-analysis, five studies were analyzed to investigate the clinical relevance and prognostic value of MALAT1 in EC. We found that up-regulation of MALAT1 correlates with clinical progression and decreased survival in patients with EC. Compared with those with low

expression, patients with high MALAT1 expression have a shorter OS (HR, 2.00; 95% CI, 1.14-2.86; $p < 0.001$). We also explored the relationship between MALAT1 expression and clinicopathological parameters. We found that there is a significant association between MALAT1 expression and LNM (OR, 1.77; 95% CI, 1.04-3.00; $p = 0.04$) and tumor differentiation (OR, 2.06; 95% CI, 1.21-3.51; $p = 0.008$). This suggests that MALAT1 overexpression correlates with a higher risk of developing LNM and poorer histological differentiation. Expression of MALAT1 was not related to gender (OR, 1.23; 95% CI, 0.78-1.93; $p = 0.37$). No significant association was found between MALAT1 and tumor invasive depth (OR, 1.64; 95% CI, 0.37-7.34; $p = 0.52$). This result might be questioned because of the small number of included studies. Taken together, MALAT1 expression correlates with the development and progression of EC. It may act as a novel predictive factor for EC clinicopathology and prognosis.

The precise biological function and regulatory mechanism of MALAT1 in EC remains unclear. More study is needed to elucidate these mechanisms. However, several experimental studies have suggested that MALAT1 plays a pivotal role in the occurrence and development of EC. *In vitro* and *in vivo*, silencing MALAT1 expression impairs tumor proliferation, migration, and invasion. Conversely, enhanced expression of MALAT1 accelerates tumor growth, invasion, and metastasis. Hu et al. [32] found that MALAT1 functions as an oncogene by regulating EC growth via the ATM-CHK2 pathway. In animal and cell-line experiments, Wang et al. [34] found that MALAT1 promoted malignant transformation of ESCC by targeting β-catenin via Ezh2. They also found that MALAT1 might be a potential target for treatment of ESCC. Yao et al. [35] showed that knockdown of MALAT-1 decreased proliferation, enhanced apoptosis, and lead to cell cycle arrest at the G2/M phase. This is consistent with other previous studies [40].

There are several limitations in our meta-analysis. First, the number of included studies was relatively small. Second, the patients with EC in all included studies were from China. This might limit the applicability of our findings to other ethnic populations. Third, the cut-off values in included studies varied, as it is difficult to use a unified standard for high MALAT1 expression in tissues. In addition, studies with positive results are more likely to be published than those with negative results. Finally, other factors, such as age and postoperative therapy, may also affect the survival rate.

In conclusion, our meta-analysis provides strong evidence that elevated MALAT1 levels indicate poor prognosis for EC patients. MALAT1 expression correlates with clinical progression. It may have predictive potential for LNM and the degree of tumor differentiation in EC. Well-designed studies of larger samples and various ethnic groups are warranted to further confirm the prognostic and clinicopathological significance of MALAT1 in EC.

Disclosure of conflict of interest

None.

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