

# Prognostic role of the long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 in various cancers: A meta-analysis

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**Abstract.** Several studies have investigated the correlation between the expression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and cancer prognosis, with inconsistent results. Therefore, a meta-analysis was conducted to identify the potential correlation after pooling data from eligible studies. PubMed/Medline, Web of Science and The Cochrane Library electronic databases were searched for eligible studies on the prognostic role of MALAT1 in cancer, from inception to January, 2015. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to summarize the effect. A total of 1,198 patients from 10 studies were included in the analysis. The results suggested that MALAT1 expression was significantly associated with overall survival (HR=2.07, 95% CI: 1.67-2.56), disease-free survival (HR=2.60, 95% CI: 1.69-4.00) and recurrence-free survival (HR=3.28, 95% CI: 1.52-7.09). MALAT1 was also found to be significantly associated with tumor size (P=0.013). Overall, MALAT1 expression may be considered as a potential prognostic factor for cancer patients.

## Introduction

The Human Genome Project demonstrated that ≥90% of the human genome is actively transcribed to RNA, but <2% of the RNA encodes proteins (1,2). Long non-coding RNAs (lncRNAs) are non-protein-coding RNA molecules longer than 200 nucleotides, which in the past had been simply dismissed as transcriptional ‘noise’ (3). lncRNAs are highly conserved throughout mammalian evolution, including in

humans. In addition, lncRNAs have been shown to be aberrantly expressed in various diseases, including cancer (4). It has been reported that lncRNAs are associated with a spectrum of biological processes, such as gene regulation at the transcriptional and post-transcriptional levels, chromatin modification and epigenetics, protein activity modulation and protein localization (5,6). In fact, lncRNAs have been recognized as hallmarks of the onset and development of various types of cancer (7,8).

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), an 8.1-kb lncRNA transcribed from the 52 nuclear-enriched transcript 2, was one of the first cancer-associated lncRNAs to be identified. In terms of its association with cancer, MALAT1 has been shown to be oncogenic and is overexpressed in several types of cancer (9-13). As regards its function, MALAT1 is localized to nuclear speckles and has been associated with a number of cancer-related processes, such as alternative splicing and cell cycle regulation (14-17).

Recent clinical studies have demonstrated that increased expression of MALAT1 is correlated with poor prognosis in various types of cancer. Furthermore, MALAT1 in different human cancers is significantly correlated with certain clinicopathological characteristics, such as cancer differentiation, depth of invasion and lymph node metastasis (9,18-26). However, a number of these studies are limited by their small size and single-center design. Therefore, a meta-analysis was performed to elucidate the prognostic value of MALAT1 in human cancer.

## Materials and methods

**Search strategy and selection criteria.** The present meta-analysis was performed in line with the guidelines of the Meta-analysis of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses groups (27,28). The PubMed/Medline, Web of Science and The Cochrane Library databases were systematically searched (up to January, 2015) for articles assessing the prognostic value of MALAT1 in various types of cancer. The key words and related Medical Subject Headings for lncRNA, MALAT1, cancer, prognosis, death and survival were used.

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**Key words:** metastasis-associated lung adenocarcinoma transcript 1, cancer, clinicopathological characteristics, prognosis, meta-analysis

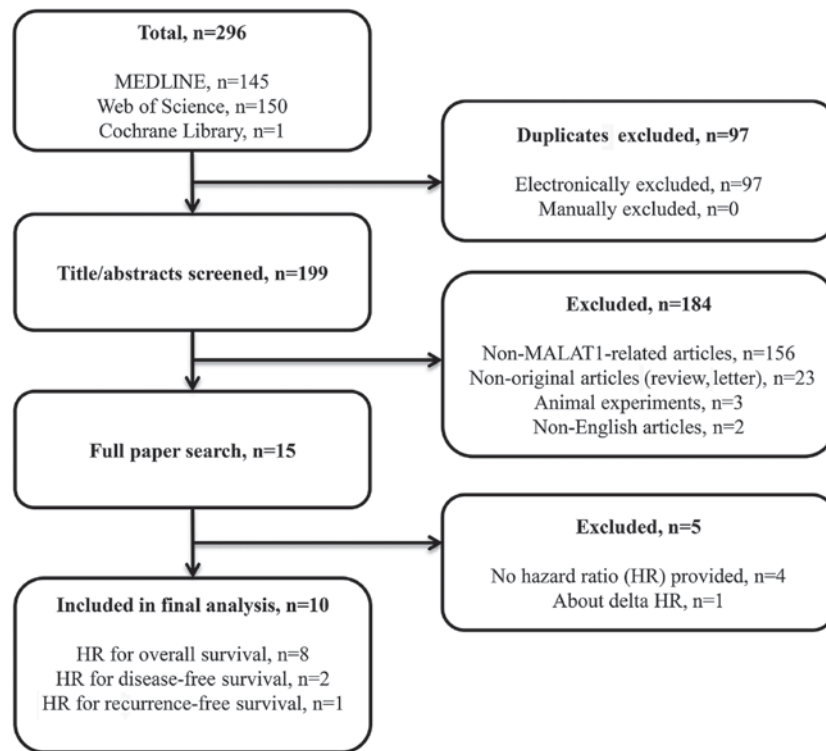


Figure 1. Flow chart of identification process for eligible studies. MALAT1, metastasis-associated lung adenocarcinoma transcript 1.

In addition, experts were consulted, the reference lists of retrieved articles were reviewed, and the ‘see related articles’ links were searched for key publications in PubMed. In addition, the authors of the articles were contacted if necessary.

The inclusion criteria for the present analysis were as follows: i) Studies investigating the prognostic role of MALAT1 in patients with various types of cancer; ii) providing enough information to estimate hazard ratio (HR) and 95% confidence interval (CI) for overall survival (OS), disease-free survival (DFS) or recurrence-free survival (RFS); and iii) studies conducted on adults and published in English. Duplicate studies, non-original articles and animal experiments were excluded. Two reviewers (J.Y. and X.Y.Z.) independently scanned all titles and abstracts identified during the search. In addition, we obtained full-text reports of articles that indicated or suggested eligibility, resolving disagreements on exclusion through consensus adjudication. Finally, a total of 10 studies were included in the analysis (14,18-26).

**Data extraction and quality assessment.** Data were independently extracted by two investigators (J.Y. and X.Y.Z.) trained to interpret information to ensure homogeneity in data collection and entry. These data included name of first author, year of publication, demographic characteristics of the patients included in the study (number, age, gender and ethnicity), cancer characteristics (tumor type, tumor size, differentiation, invasion, lymph node metastasis and stage), study design (specimen, measuring method, cut-off point defining high MALAT1 expression and follow-up period) and survival analysis. HRs were preferentially extracted from multivariate or univariate analyses; if these were not available, Engauge 4.0 was used to calculate HRs and corresponding 95% CIs.

Study quality was rated by the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (29), in which the quality of the selected study was determined by 8 questions in 3 domains: selection (0-4 points) and comparability (0-2 points) of the study groups, and ascertainment of the outcome of interest (0-3 points). Based on previous recommendations, studies with 5 points were considered to be of high quality. The two aforementioned investigators independently evaluated the quality of each study. Disagreements were resolved by consensus.

**Statistical analysis.** Estimates of odds ratios (ORs) and HRs were weighted and pooled using the generic inverse-variance (30). ORs with 95% CIs were used to estimate the association between MALAT1 expression and clinicopathological characteristics. Pooled HRs with 95% CIs were used to estimate the prognostic role of MALAT1 in various cancers.  $I^2$  was calculated as a measure of statistical heterogeneity, with values of 25, 50 and 75% representing mild, moderate and severe heterogeneity, respectively. Random-effects models were applied in cases with significant heterogeneity. Stratified analyses were conducted to assess potential confounder contribution to heterogeneity. In addition, publication bias was investigated using Begg's funnel plots and Egger's linear regression test. Analyses were performed with STATA statistical software, version 12.0 (Stata Corporation, College Station, TX, USA). The results were considered significant at two-sided P-value of 0.05.

## Results

**Characteristics of included studies.** A total of 296 articles were identified during the electronic search through

Table I. Main characteristics of all eligible studies.

Authors, year (Refs.)	Region	Tumor type	Sample size	Method	Cut-off point	Follow-up (months)	Outcome measures	Survival analysis	Method score	Quality
Zheng <i>et al.</i> , 2014 (18)	China	Colorectal cancer	146	RT-qPCR	Median	56.2, 11-72.8	OS, DFS	U, M	a,b	6
Schmidt <i>et al.</i> , 2011 (9)	Germany	NSCLC	222	ISH	50%	38	OS	U, M	a,b	7
Fan <i>et al.</i> , 2014 (19)	China	Bladder cancer	95	RT-qPCR	Median	5-30	OS	U	b	4
Liu <i>et al.</i> , 2014 (20)	China	Pancreatic ductal adenocarcinoma	45	RT-qPCR	Mean	1-36	OS	U, M	a	7
Lai <i>et al.</i> , 2012 (21)	China	Hepatocellular carcinoma	112	RT-qPCR	NR	1-36	RFS	U, M	a	8
Shen <i>et al.</i> , 2015 (22)	China	NSCLC	78	RT-qPCR	Mean	NR	DFS	U	b	5
Pang <i>et al.</i> , 2014 (23)	China	Pancreatic cancer	126	RT-qPCR	Median	5-60	OS	U, M	a	7
Zhang <i>et al.</i> , 2014 (24)	China	Clear-cell renal cell carcinoma	106	RT-qPCR	Mean	3-60	OS	U, M	a	7
Okugawa <i>et al.</i> , 2014 (25)	USA	Gastric cancer	150	RT-qPCR	0.985	1-60	OS	U	a	7
Ma <i>et al.</i> , 2015 (26)	China	Glioma	118	RT-qPCR	Median	5-60	OS	U, M	a	7

<sup>a</sup>HRs obtained directly from publication. <sup>b</sup>HRs extracted from Kaplan-Meier curves. RT-qPCR, reverse transcription quantitative polymerase chain reaction; ISH, *in situ* hybridization; NR, not reported; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; U, univariate analysis; M, multivariate analysis; HR, hazard ratio; NSCLC, non-small-cell lung cancer.

PubMed/Medline, Web of Science and The Cochrane Library. Duplicates, animal experiments, non-MALAT1-related studies, non-English articles, and studies lacking data on the association of MALAT1 expression with prognosis were excluded, leaving 10 eligible studies to be included in this meta-analysis (Fig. 1). The characteristics of the included studies are summarized in Table I. All the studies were published from 2011 onwards. The participants in 8 studies were Chinese and in the other 2 studies German and American. Various types of cancers were recorded, including colorectal, non-small-cell lung and bladder cancer, pancreatic ductal adenocarcinoma, hepatocellular carcinoma, pancreatic cancer, clear cell renal cell carcinoma, gastric cancer and glioma. The expression level of MALAT1 was detected by reverse transcription quantitative polymerase chain reaction or *in situ* hybridization (ISH). The sample size ranged between 45 and 222 patients. There were 8 studies for OS, 2 for DFS and 1 for RFS. HRs with the corresponding 95% CIs were extracted from univariate analysis and Kaplan-Meier curves in 10 studies, and from multivariate analysis in 7 studies. The NOS scores of 90% of the included studies were  $\geq 5$ .

**MALAT1 expression and clinicopathological characteristics.** The main results of the association between MALAT1 expression and clinicopathological characteristics are summarized in Table II. The results demonstrated that MALAT1 was not associated with clinicopathological parameters such as age, gender, differentiation, depth of invasion, lymph node metastasis, distant metastasis or tumor stage, but was significantly associated with tumor size (HR=2.70, 95%CI: 1.23-5.92, P=0.013).

**OS.** A total of 8 studies including 1,008 patients reported HRs for OS. Of the 8 eligible studies, one (12.5%) reported a non-statistically significant HR (i.e., the 95% CIs crossed 1). A forest plot of all studies is presented in Fig. 2. It was suggested that increased MALAT1 expression predicted a poor outcome for OS (HR=2.07, 95% CI: 1.67-2.56, P=0.000). There appeared to be no heterogeneity between the HRs of MALAT1 among these studies ( $I^2=0.0\%$ , P=0.488). However, subgroup analysis was also conducted to investigate the association between HRs and these variables, including type of cancer, region of subjects, sample size, analysis methods and quality scores (Table III). Stratified analysis by cancer type indicated a significant prognostic effect of MALAT1 for digestive (HR=1.86, 95% CI: 1.37-2.53) and non-digestive system cancers (HR=2.28, 95% CI: 1.70-3.07). Although the differences in HRs between subjects from China (HR=2.33, 95% CI: 1.79-3.03) and Western countries (HR=1.66, 95% CI: 1.16-2.37) was not statistically significant (P=0.134), high MALAT1 expression in Chinese subjects was associated with numerically higher HR values. Moreover, the HRs were significant for studies including <110 subjects (HR=2.67, 95% CI: 1.69-4.23) as well as those with >110 subjects (HR=1.93, 95% CI: 1.52-2.45). When different analysis methods were considered, MALAT1 was a strong prognostic marker by univariate (HR=1.83, 95% CI: 1.81-2.85) as well as multivariate (HR=2.15, 95% CI: 1.68-2.73) analyses. In addition, when performing subgroup analyses stratified by quality score, increased MALAT1 expression was significantly

Table II. Main results of the meta-analysis of the association between MALAT1 and clinicopathological characteristics.

Clinical parameters	No. of studies	Fixed-effects model		Random-effects model		Heterogeneity (I <sup>2</sup> ) (%)
		Pooled HR (95% CI)	P-value	Pooled HR (95% CI)	P-value	
Age (young vs. elderly)	7	1.03 (0.77-1.38)	0.854	1.03 (0.76-1.39)	0.850	0.0
Gender (male vs. female)	7	0.62 (0.85-1.15)	0.289	0.87 (0.57-1.33)	0.511	41.4
Tumor size (small vs. large)	6	2.46 (1.77-3.41)	0.000	2.70 (1.23-5.92)	0.013	79.8
Differentiation (high/moderate vs. poor)	4	1.27 (0.80-2.00)	0.309	1.25 (0.79-1.98)	0.336	0.0
Depth of invasion (T1/2 vs. T3/4)	3	1.88 (1.18-3.01)	0.008	2.16 (0.93-5.02)	0.075	63.7
Lymph node metastasis (absent vs. present)	5	1.85 (1.30-2.63)	0.001	2.04 (0.94-4.45)	0.073	76.6
Metastasis (absent vs. present)	3	2.422 (1.09-5.37)	0.029	3.47 (0.36-33.21)	0.280	73.3
Stage (I/II vs. III/IV)	4	1.24 (0.84-1.84)	0.277	1.54 (0.56-4.29)	0.407	82.3

MALAT1, metastasis-associated lung adenocarcinoma transcript 1; HR, hazard ratio; CI, confidence interval.

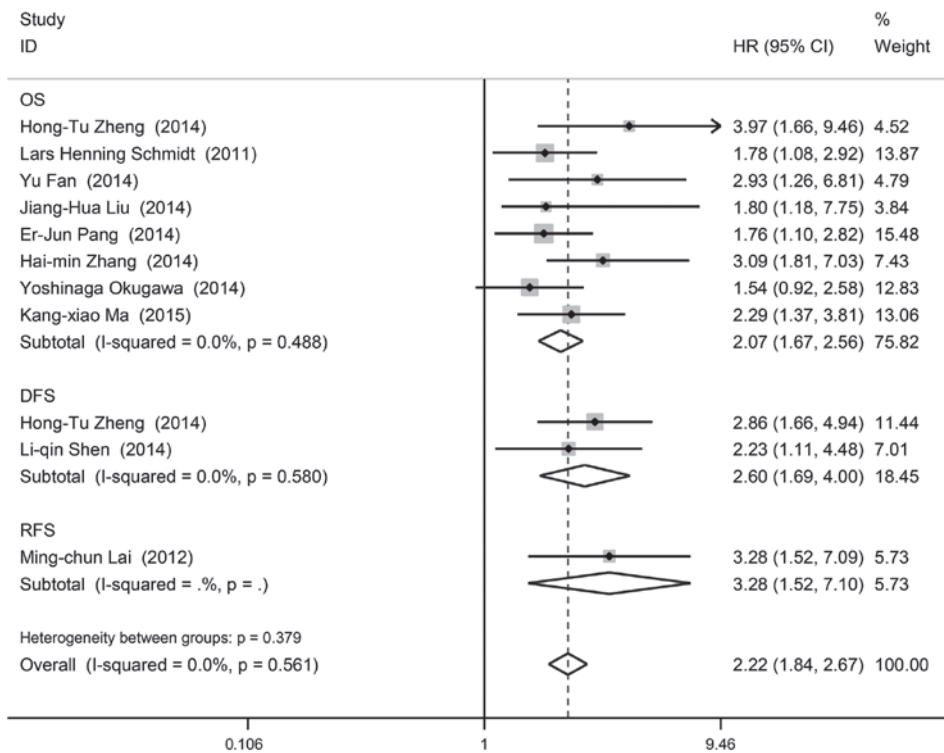


Figure 2. Forest plots for the association between MALAT1 and prognosis in cancer patients by the fixed-effects model. The grey squares indicate the value of OR and the size of the square is inversely proportional to its variance. The horizontal lines represent the 95% CIs of the ORs. The white diamonds represent the pooled results. MALAT1, metastasis-associated lung adenocarcinoma transcript 1; CI, confidence interval; OR, odds ratio.

associated with poor prognosis in the studies with a score of <7 (HR=3.40, 95% CI: 1.85-6.22), as well as in those with a score of  $\geq 7$  (HR=1.93, 95% CI: 1.54-2.42).

Begg's funnel plots and Egger's linear regression tests were applied to evaluate publication bias. The shape of the funnel plot exhibited no significant asymmetry (Fig. 3). Subsequently, Egger's test also indicated no evidence of publication bias (P=0.174).

**DFS and RFS.** A total of 2 studies including 224 patients reported HRs for DFS (Table III). Overall, upregulation

of MALAT1 was associated with an HR for DFS of 2.60 (95% CI: 1.69-4.00). In addition, 1 study including 112 patients reported HRs for RFS (Table III). High MALAT1 expression also predicted a poor clinical outcome for RFS (HR=3.28, 95% CI: 1.52-7.09).

## Discussion

As a novel molecular basis, the study of lncRNAs has focused on their role in cancer pathogenesis and prognosis, providing a new insight into cancer therapeutic strategy (31,32). This

Table III. Main results of the pooled analysis.

Survival	Variables	No. of studies	No. of patients	P <sup>s</sup> <sup>a</sup>	Fixed-effects model		Random-effects model		Heterogeneity	
					Pooled HR (95% CI)	Pz <sup>b</sup>	Pooled HR (95% CI)	Pz <sup>b</sup>	I <sup>2</sup> (%)	Ph <sup>c</sup>
OS	All	8	1,008		2.07 (1.67-2.56)	0	2.07 (1.67-2.56)	0	0.00	0.488
	Type of cancer			0.345						
	Digestive	4	467		1.86 (1.37-2.53)	0	1.89 (1.35-2.65)	0	14.20	0.321
	Non-digestive	4	541		2.28 (1.70-3.07)	0	2.28 (1.70-3.07)	0	0.00	0.559
	Region			0.134						
	China	6	636		2.33 (1.79-3.03)	0	2.33 (1.79-3.03)	0.005	0.00	0.542
	Western countries	2	372		1.66 (1.16-2.37)	0.005	1.66 (1.16-2.37)	0.005	0.00	0.691
	Sample size			0.221						
	<110	3	246		2.67 (1.69-4.23)	0	2.67 (1.69-4.23)	0	0.00	0.638
	≥110	5	762		1.93 (1.52-2.45)	0	1.93 (1.52-2.46)	0	1.40	0.399
	Analysis method			0.541						
	Univariate	2	245		1.83 (1.81-2.85)	0.007	1.94 (1.06-3.55)	0.032	38.50	0.202
	Multivariate	6	763		2.15 (1.68-2.73)	0	2.15 (1.68-2.73)	0	0.00	0.486
Quality score			0.087							
<7	2	241		3.40 (1.85-6.22)	0	3.40 (1.85-6.22)	0	0.00	0.623	
≥7	6	767		1.93 (1.54-2.42)	0	2.07 (1.67-2.56)	0	0.00	0.658	
DFS	All	2	224		2.60 (1.69-4.00)	0	2.60 (1.69-4.00)	0	0.00	0.58
RFS	All	1	112		3.28 (1.52-7.09)					

<sup>a</sup>P-value for subgroup differences. <sup>b</sup>P-value for z test. <sup>c</sup>P-value for heterogeneity; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.

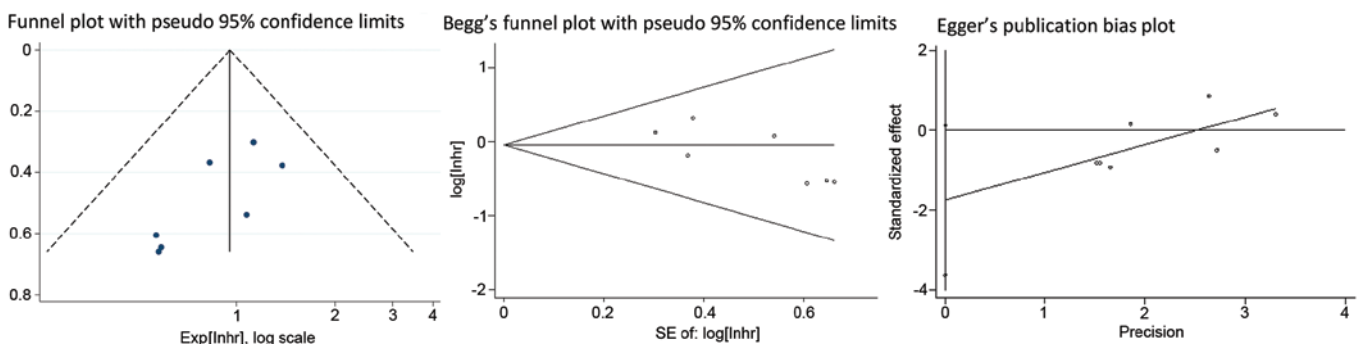


Figure 3. Begg's and Egger's funnel plots of the included literature for OS. The middle line represents the summary estimate, whereas the sloping lines represent the expected 95% CIs. OS, overall survival; CI, confidence interval; SE, standard error.

meta-analysis was conducted to investigate the effect of lncRNA MALAT1 on tumor prognosis.

A meta-analysis of 10 studies including 1,198 cancer patients was undertaken. We found that increased MALAT1 expression was significantly associated with poorer OS, DFS and RFS, indicating that MALAT1 may be a promising prognostic marker for cancer patients. Moreover, the significant association was retained among various cancer type subgroups and across different regions, sample sizes, analysis methods and quality scores. Our subgroup analysis by region revealed that the abnormal expression of MALAT1 was strongly correlated with poor prognosis in China, as well as in Western countries. There was a trend for the association of high

MALAT1 expression with worse OS to be more significant in the more sensitive and accurate multivariate studies compared with univariate analysis; however, the magnitude of its effect on OS was lower in the subgroup with >100 participants and in that with a quality score of >7. This contradiction indicates that more studies including more participants are required. In addition, we identified an association between MALAT1 and clinicopathological characteristics, which demonstrated that high MALAT1 expression was significantly correlated with tumor size in the random-effects model and TNM stage in the fixed-effects model. Both Begg's and Egger's tests revealed no significant publication bias regarding the prognostic role of MALAT1 in different types of cancer.

The mechanisms underlying the association of high MALAT1 expression and poor outcome of cancer patients are poorly understood. The results of this study may suggest the following mechanisms as being potentially involved in the prognostic effect of MALAT1 on carcinogenesis: MALAT1, acting as an oncogene, has been reported to be involved in the modulation of cellular processes leading to tumor occurrence, development, metastasis and drug resistance (13,22,25,33,34). MALAT1 is retained in the nucleus and controls sequestration of the paraspeckle proteins PSP1, p54, and factors linked to A-I editing, which are implicated in mRNA nuclear retention (35); in addition, it has been proven to participate in the phosphatidylinositol 3-kinase/Akt (36), extracellular signal-regulated kinase/mitogen-activated protein kinase (37) and Wnt/ $\beta$ -catenin (38) pathways. Downregulating MALAT1 by short hairpin RNA in the CaSki cervical cancer cell line led to a decrease of apoptosis-inhibited gene Bcl-2 and Bcl-xL expression and an increase of apoptosis-promoted proteins caspase-3 and -8, and Bax (6). Consistently, silencing of the lncRNA MALAT1 by the microRNA (miR)-101 and miR-217 was shown to inhibit the proliferation, invasion and migration of esophageal squamous cell carcinoma cells (39).

Certain limitations in this study should be acknowledged. First, the number of included studies and the number of included patients per study was relatively small. Second, only summarized data rather than individual patient data could be abstracted. Third, we only included studies reporting HRs and survival curves; consequently, the excluded publications reporting on the prognostic value of MALAT1 may lead to bias. Fourth, the cut-off values of defining the specimens as positive or negative in terms of MALAT1 expression in cancer patients differed among these studies. Fifth, certain HRs could not be directly obtained from the primary studies, requiring calculation or extraction of the HR estimates from the survival curves. Sixth, non-original English articles were excluded from our analysis, which may also introduce bias. Therefore, additional studies with larger sample sizes, high quality, different ethnic background and same cut-off value are required to draw a more definitive conclusion.

In conclusion, increased MALAT1 expression is associated with adverse survival in several types of cancer, and MALAT1 may serve as an effective prognostic cancer biomarker. Therefore, investigating the levels of MALAT1 expression in the clinical setting is a promising approach to identifying patients who require more intimate care and may enable personalized medical follow-up.

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