Correlation of increased *MALAT1* expression with pathological features and prognosis in cancer patients: a meta-analysis

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ABSTRACT. Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) has been identified as a potential cancer biomarker, yet the mechanism by which it influences the development of cancer remains unknown. In this study, we aimed to correlate *MALAT1* expression with pathological features and prognosis in cancer patients. Several databases were searched using combinations of keywords relating to *MALAT1* and cancer. After selection of relevant cohort studies according to strict criteria, a meta-analysis was conducted. Twelve studies were analyzed, involving 958 cancer patients. Elevated *MALAT1* expression was associated with poor prognosis and larger tumors [prognosis: hazard ratio = 3.11, 95% confidence interval (CI) = 1.98-4.23, P = 0.000; tumor size: odds ratio (OR) = 0.40, 95%CI = 0.21-0.74, P = 0.003]. However, no connection with histological grade, T-stage, lymph node (LN) metastasis, or distant metastasis was established (all P > 0.05). A correlation between increased

expression and poor prognosis was observed in the large and small sample-size subgroups (all P< 0.05), as was a relationship with large tumor size (OR = 0.30, 95%CI = 0.13-0.71, P = 0.006). Expression was correlated with T-stage and distant metastasis in the small sample-size subgroup (all P < 0.05), but no association was detected regarding histological grade, LN metastasis in either subgroup (all P > 0.05). Our findings demonstrate that elevated *MALAT1* expression correlates with large tumor size, advanced tumor stage, and poor prognosis, and might therefore be utilized to evaluate clinical pathological features and prognostic out come for cancer patients.

Key words: *MALAT1*; Protein expression; Cancer; Pathological features; Prognosis; Meta-analysis

INTRODUCTION

Cancer, with its potential to develop in any organ or location in the human body, is considered a malignant disease owing to the fact that cancerous cells grow at an abnormal speed within tissues (Yamashita and Wang, 2013; Lapunzina et al., 2014). Due to the diversity of cancer types, signs and symptoms differ between tumors (Axon, 2006; Astin et al., 2011). Cancer has long been recognized as a serious threat to human health (Leong and Ng, 2014). For example, lung cancers are the fifth most common cause of death worldwide of any disease, and gastric cancer has been categorized as the second most common cause of cancer-related death worldwide (Okugawa et al., 2014). Despite the application of significant systematic and sensitive medical care, the prognosis for patients with certain cancers remains poor, owing to unavoidable invasion and metastasis (Pang et al., 2015; Zhang et al., 2015). Therefore, medical research has focused on identifying factors that contribute to poor cancer prognosis (Yan et al., 2008; Gao et al., 2011). In recent years, long noncoding RNAs (lncRNAs) have been implicated in regulating the growth and apoptosis of human cells, and thus may contribute to carcinogenesis (Zhang et al., 2015). As a classic lncRNA, metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) has been reported as a potential factor associated with unfavorable cancer prognosis (Dong et al., 2015; Pang et al., 2015).

MALAT1, also known as NEAT2, is approximately 8000 nucleotides in length and has been shown to be commonly expressed in humans (Tripathi et al., 2010; Zhang et al., 2015). It has previously been demonstrated that this lncRNA is capable of interacting with the demethylated form of chromo box homolog 4 (*CBX4*, also known as *PC2*), and that such interaction can regulate the re-localization of genes controlling growth. In addition, *MALAT1* has been found to localize to subnuclear structures, areas of active or silent gene expression, and thus may be able to activate expression by interfering with the assembly of coactivator complexes (Gutschner et al., 2013). Recently, it has been proposed that *MALAT1* expression may be involved in the progression and prognosis of various cancers, including pancreatic and colorectal malignancies (Zheng et al., 2014; Pang et al., 2015). Some reports also indicate that its differential expression may be linked with metastasis and recurrence of certain cancers (Liu et al., 2014; Zhang et al., 2015). These proposals may be based on the fact that *MALAT1* is able to control the activity of the transcription factor E2F1, which plays a key role in cell cycle progression and tumorigenesis (Tripathi et al., 2013; Zheng et al., 2014). Moreover, *MALAT1* has been observed to enhance the proliferation and migration of human cells by mediating the expression of pre-mRNA, demonstrating effects conducive to metastasis and transformation in tumor cells (Lai et al., 2012). When *MALAT1* expression

is knocked down, migration and invasion cell processes are repressed and G2/M cell-cycle arrest and cell apoptosis can subsequently be induced (Pang et al., 2015). Therefore, expression of this lncRNA can be seen to be correlated with the clinical features and prognosis of certain cancers. Nevertheless, recent studies related to its role in carcinogenesis have generated conflicting results (Okugawa et al., 2014; Zheng et al., 2014; Ma et al., 2015; Zhang et al., 2015). Therefore, in this meta-analysis we endeavored to evaluate the effect of *MALAT1* expression on clinical pathological features and prognosis in various cancers.

MATERIAL AND METHODS

Literature search

Relevant studies published as of April 2015 were retrieved using Embase, PubMed, EBSCO, Ovid, and Web of Science databases, as well as manual searching. No restriction was placed on geographic origin, but publication language was limited to Chinese or English. The search strategy involved a combination of keywords related to *MALAT1* and cancer. The following search terms were used in combinations of keywords and free words: ("long non-coding RNA, human" OR "*MALAT1*" OR "metastasis associated lung adenocarcinoma transcript 1" OR "*MALAT-1*" OR "*NEAT2*") and ("cancer*" OR "tumor*" OR "tumour*" OR "carcinoma*" OR "neoplas*" OR "malignan").

Inclusion and exclusion criteria

The following inclusion criteria were taken into account when collecting published articles for the present study: 1) patient diagnoses were confirmed and no restriction was placed on cancer type; 2) data included sex, age, tumor size and stage, World Health Organization differentiation grade, metastasis status, and overall survival (OS); 3) the study focus should consist of the relationship between *MALAT1* expression and the clinical pathological features and prognosis of cancers; and 4) the investigation should be in the form of a cohort study. Articles that did not meet the above criteria were excluded. In addition, studies were excluded if they: 1) consisted of abstracts only; 2) were case reports; 3) were based on animal models or cell lines; (3) were duplicate publications (only the most recent or complete study was included); or 4) provided insufficient information relating to our topic of interest.

Data extraction and quality assessment

Descriptive information related to the key focus of this article was collected using a standard form containing the following fields: first author name, year of publication, country/ethnicity, cancer type(s), sample size, age, sex, tumor size, differentiation grade, tumor stage, metastasis status, and OS. The above data were extracted from each study by two independent researchers, to reduce the probability of selection bias and strengthen the reliability of this meta-analysis. Disagreement regarding the inclusion of data was settled by consultation with a third investigator.

We assessed risk of bias by examining the random sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessment), and selective outcome reporting used in each trial (Higgins and Green, 2011). Two authors (X.S. Shi and J. Li) independently assessed the included studies and rated each as having low, high, or unclear risk of bias.

Statistical analysis

Statistical calculation was performed with Stata statistical software version 12.0 (StataCorp, College Station, TX, USA). Odds ratios (ORs) and hazards ratios (HRs) with 95% confidence intervals (95%CIs) were estimated using fixed- or random-effects models to evaluate the association between *MALAT1* expression and the clinical pathological features and prognosis of cancers. AZ-test was employed to assess the significance of the pooled effect size (Chen et al., 2012) and forest plots were generated to display between-group comparisons of HRs and ORs with 95%CIs. The *Q* (Jackson et al., 2012) and I^2 tests were applied to assess between-study heterogeneity (Peters et al., 2006). When values of P value < 0.05 or I^2> 50% revealed significant heterogeneity, the random-effects model was implemented. The fixed-effects model was employed in all other cases (Zintzaras and Ioannidis, 2005). Sensitivity analysis was used to determine whether the removal of a single study influenced the overall outcome. Funnel plots and Egger's linear regression test were carried out to assess publication bias, thereby ensuring the reliability of our results (Egger et al., 1997; Sterne and Egger, 2001). Two-tailed tests were conducted, with P < 0.05 signifying statistical significance.

RESULTS

Selection of eligible studies

The initial search yielded 227 articles and after screening titles and abstracts, 168 citations were excluded. Fifty-nine potentially relevant articles were selected for full-text review (Figure1). Finally, 12 primary studies, including 958 patients, met the inclusion criteria (Ji et al., 2003; Lai et al., 2012; Cho et al., 2014; Liu et al., 2014; Okugawa et al., 2014; Zheng et al., 2014; Dong et al., 2015; Hirata et al., 2015; Li et al., 2015; Ma et al., 2015; Pang et al., 2015; Zhang et al., 2015). Details regarding the participants of these studies are summarized in Table 1. Figure 2 provides an overall picture of the methodological quality of the selected investigations, as evaluated by the quality assessment tool for diagnostic accuracy studies (QUADAS; Whiting et al., 2011).

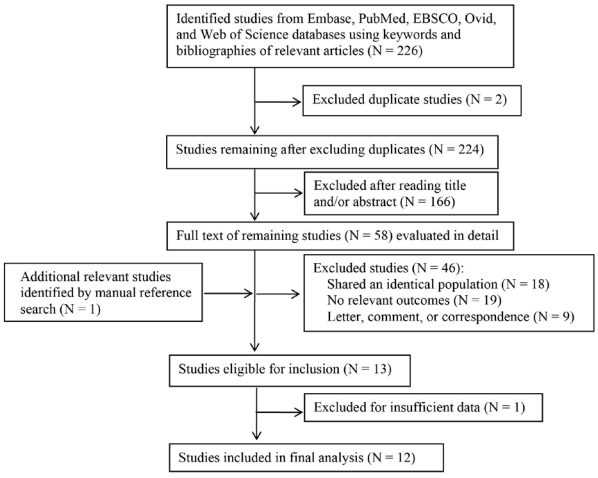

Figure 1. Flow chart of study identification and inclusion.

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

First author	Year	Country	Cancer type	Number		Gender (M/F)		Age (years)	Type of intervention	Included period	Follow-up period (months)
				High *MALAT1* expression	Low *MALAT1* expression	High *MALAT1* expression	Low *MALAT1* expression				
Zhang et al.	2015	China	ccRCC	46	60	26/20	32/28	NR	Underwent radical surgical resection without preoperative chemotherapy or radiotherapy	2006-2008	NR
Pang et al.	2015	China	Pancreatic cancer	63	63	37/26	32/31	28-71	Underwent radical surgical resection without preoperative chemotherapy or radiotherapy	NR	5-60
Ma et al.	2015	China	Glioma	59	59	28/31	35/24	NR	Underwent radical surgical resectio without preoperative chemotherapy or radiotherapy	NR	NR
Li et al.	2015	China	Pituitary adenoma	32	20	14/18	11/9	51 (26-71)	Underwent surgical resection without preoperative chemotherapy or radiotherapy	2010-2012	NR
Dong et al.	2015	China	Osteosarcoma	14	5	9/5	3/2	NR	Underwent radical surgical resection	2009-2011	NR
Zheng et al.	2014	China	CRC	73	73	53/20	36/37	NR	Underwent radical surgical resection without preoperative chemotherapy or radiotherapy	2007-2009	56.2
Okugawa et al.	2014	USA	Gastric cancer	88	62	68/20	51/11	NR	Underwent radical surgical resection without preoperative chemotherapy or radiotherapy	2000-2009	NR
Liu et al.	2014	China	Pancreatic cancer	26	19	15/11	11/8	NR	Underwent radical surgical resection	2010-2011	NR
Lai et al.	2012	China	Hepatocellular carcinoma	33	27	30/3	25/2	NR	NR	2003-2005	18.6
Hirata et al.	2015	USA	ccRCC	25	25	34/16		60.2 (37-77)	NR	NR	NR
Cho et al.	2014	China	Multiple myeloma	20	16	21/15		61.3 ± 8.3	Underwent radical surgical resection	2007-2012	12-48
Ji et al.	2003	Germany	NSCLC	22	28	NR	NR	NR	Underwent radical surgical resection	NR	≥ 60

M = male; F = female; CRC = colorectal cancer; ccRCC = clear cell renal cell carcinoma; NSCLC = non-small cell lung cancer; NR = not reported.

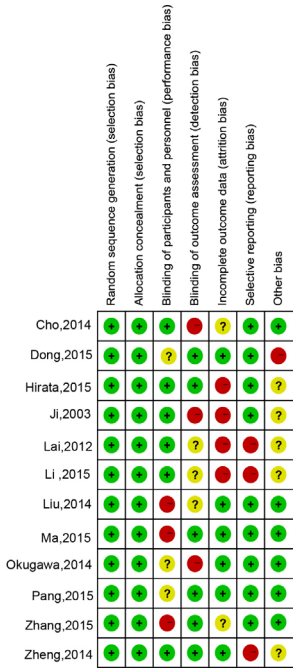

Figure 2. An overall picture of the methodological quality of the included studies, as evaluated by the quality assessment tool for diagnostic accuracy studies.

Meta-analysis of the association between *MALAT1* expression and human cancers

Heterogeneity was observed in some of the data used in our meta-analysis, thus both random- and fixed-effects models were employed. We found that expression of *MALAT1* was connected with tumor prognosis (HR = 3.11, 95%CI = 1.98-4.23, P = 0.000), implying that it may be useful in predicting cancer outcome (Figure 3A). With respect to clinical pathological features, patients overexpressing *MALAT1* had larger tumors than those showing low expression (OR = 0.40, 95%CI = 0.21-0.74, P = 0.003; Figure 3B), but no connection was found between *MALAT1* level and tumor differentiation, T-stage, lymph node (LN) metastasis, or distant metastasis (all P > 0.05; Figures 3C to 3F).

Subgroup analysis of the association between *MALAT1* expression and human cancers

Subgroup analysis was performed based on sample size. We observed a clear correlation between increased *MALAT1* expression and poor cancer prognosis in both the large (HR = 2.75, 95%CI = 1.92-3.57, P = 0.000; Figure 4A), and small sample-size subgroup (HR = 4.22, 95%CI = 0.04-8.40, P = 0.048). Concerning clinical features, increased expression was found to be related to tumor size in patients from studies with larger sample sizes (OR = 0.30, 95%CI = 0.13-0.71, P = 0.006; Figure 4B), but no such connection was discerned using the small sample-size dataset (P = 0.246). In addition, elevated *MALAT1* expression was associated with T-stage in the small sample-size subset (OR = 0.14, 95%CI = 0.04-0.55, P = 0.005; Figure 4D). Elevated *MALAT1* expression

was also associated with distant metastasis in the small sample-size subset (OR = 0.13, 95%CI = 0.03-0.70, P = 0.017; Figure 4F). However, no link between *MALAT1* levels and tumor differentiation, LN metastasis was apparent in either subgroup (all P > 0.05; Figures 4C, 4E).

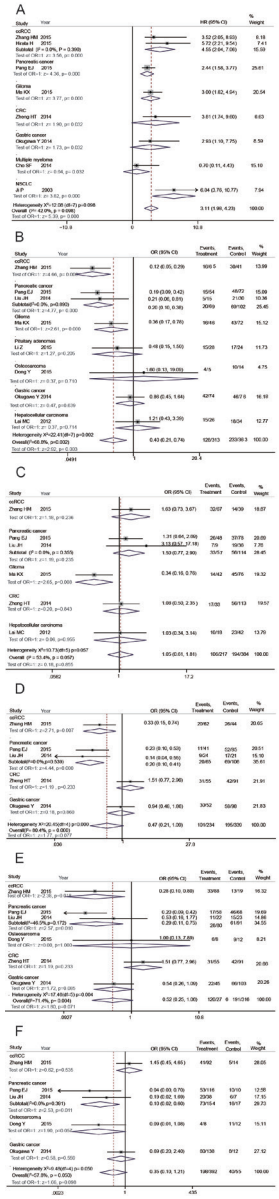

Figure 3. Forest plots of the relationship between *MALAT1* expression and clinical pathological features and prognosis of cancers. Individual and pooled hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) regarding the association between *MALAT1* expression and (A) prognosis, (B) tumor size, (C) histological grade, (D) T-stage, (E) lymph node metastasis, and (F) distant metastasis are shown. ccRCC = clear cell renal cell carcinoma; CRC = colorectal cancer; NSCLC = non-small cell lung cancer; df = degrees of freedom.

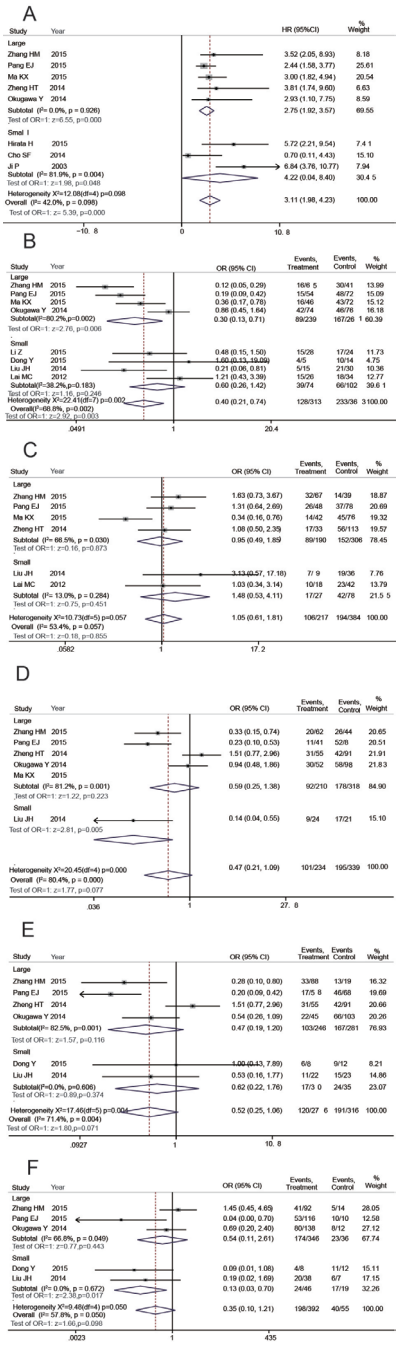

Figure 4. Sample-size subgroup analysis of the relationship between *MALAT1* expression and clinical pathological features and prognosis of cancers. Individual and pooled hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) regarding the association between *MALAT1* expression and (A) prognosis, (B) tumor size, (C) histological grade, (D) T-stage, (E) lymph node metastasis, and (F) distant metastasis are shown. df = degrees of freedom.

Publication bias

No obvious asymmetry was distinguished in the funnel plots, and in accordance with these results, Egger's regression test revealed no publication bias in all six analyses (all P > 0.05; Figure 5).

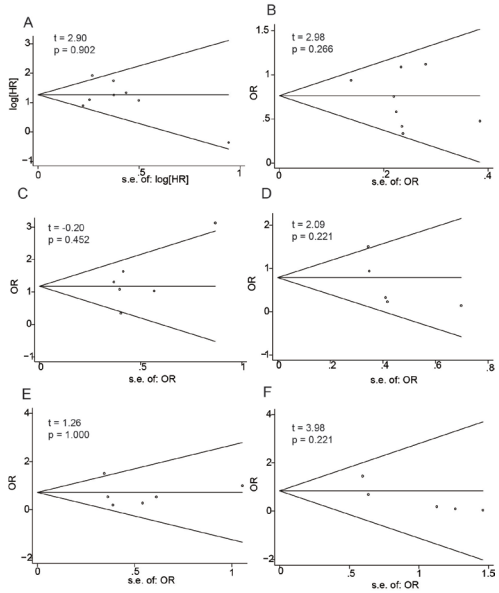

Figure 5. Funnel plots assessing publication bias in our meta-analysis of the association between *MALAT1* expression and (A) cancer prognosis, (B) tumor size, (C) histological grade, (D) T-stage, (E) lymph node metastasis, and (F) distant metastasis. HR = hazard ratio; OR = odds ratio; SE = standard error.

DISCUSSION

In the current meta-analysis, we systematically investigated the link between *MALAT1* expression and the clinical pathological characteristics and prognosis of various malignancies. Our results suggest that the expression of *MALAT1* is correlated with tumor prognosis, implying that it might constitute an important indicator of cancer out come. However, the mechanism behind this association has not yet been elucidated. Therefore, we suggest here some of the processes that may be responsible. Previous studies have indicated that *MALAT1* may enhance cell proliferation and plays a key role in tumorigenesis, and when its expression is knocked down in cancer cells, ontogenesis is significantly impaired (Tano et al., 2010; Zheng et al., 2014). Furthermore, elevated expression of this lncRNA appears to accelerate the migration and epithelial to mesenchymal transition of tumor cells by activating the Wnt pathway (Ying et al., 2012). Considering this, it is possible to conclude that *MALAT1* expression exerts an important influence on cancer outcome. Consistent with our results, Pang et al. (2015) also suggested that overexpression of *MALAT1* might be a reliable biomarker of unfavorable prognosis in cancer patients.

The results of our investigation into the relationship between *MALAT1* and clinical pathological features revealed that patients over expressing this gene had larger tumors than those demonstrating low expression, but no connection was established with histological grade, T-stage, LN metastasis, or distant metastasis. This may be partially explained by the fact that *MALAT1*

regulates the levels of active serine/argentine splicing factors, and thus modulates the splicing of pre-mRNAs, thereby performing significant part in cancer formation and invasion (Dong et al., 2015). It has been shown that *MALAT1* participates in the regulation of cell cycle progression and the genesis and growth of tumors by interfering with E2F1 activity (Tripathi et al., 2013; Zheng et al., 2014). Another possible explanation was provided by a previous study in which knockdown of *MALAT1* appeared to strongly reduce PI3Kp85α and phosphorylatedAkt expression (Dong et al., 2015). It is widely accepted that the PI3K/Akt pathway is a vital signal transduction mechanism, and by activating the PI3K/Akt signaling cascade, *MALAT1* may promote rapid tumor growth and invasion (Liu et al., 2008; Dong et al., 2015).

In order to further understand the role of *MALAT1* expression in cancer, subgroup analysis was conducted based on sample size. We observed a close correlation between *MALAT1* expression and poor prognosis in the large and small sample-size subgroups. With regard to clinical features, we found that the level of this lncRNA was related to tumor size in patients from studies with larger sample sizes, and with patient T-stage and distant metastasis in small sample-size investigations. In addition, no significant association with histological grade, LN metastasis was established in either subgroup. In conclusion, the overall results of our meta-analysis were in accordance with the principal findings of previous studies, suggesting that measurement of *MALAT1* expression may be useful in evaluating the prognosis and clinical pathological characteristics of cancer patients.

Some limitations need to be taken into account when interpreting our results. First, the cut-off values used to define categories of *MALAT1* expression differed between studies, potentially introducing bias. All factors that may influence the pooled results should therefore be carefully considered. Second, although no publication bias was evident in this analysis; most studies tend to report positive, rather than negative, results. In addition, as we restricted the publication languages to English and Chinese, relevant articles that may have met our inclusion criteria could have been overlooked, representing a potential source of selection bias. Third, the majorities of studies included (12) were performed in Asia, which may have led to selection bias, and influences the broader applicability of our results. Finally, although various clinical pathological measurements were included, only tumor size was confirmed to be positively correlated with *MALAT1* expression. Moreover, the statistical analysis for several clinical parameters incorporated only one or two studies, possibly affecting the reliability of the final results. The heterogeneity of study designs may be responsible for this issue.

Taken together, our findings clarify the significance of *MALAT1* as an important clinical biomarker of poor prognosis and adverse pathological features in cancer patients. These results could have significant value in pathological examination and outcome prediction, as well as providing a new insight for the selection of therapeutic approaches in clinical application. However, the present results should be interpreted cautiously due to the above limitations, and the implementation of further large sample-size, multicenter studies would assist in clarifying this matter.

Conflicts of interest

The authors declare no conflict of interest.

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