Prognostic significance of long non-coding RNA MALAT-1 in various human carcinomas: a meta-analysis

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ABSTRACT. The long non-coding RNA MALAT-1 plays an important role in cancer prognosis. The present research aimed to elucidate its precise predictive value in various human carcinomas. A quantitative meta-analysis was performed by searching PubMed, Embase, Web of Science, and Cochrane Library (most recently, January 2015) databases, and extracting data from studies that investigated the association between MALAT-1 expression and survival outcomes in patients of various cancers. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated as a measure of generalized effect. This meta-analysis included 1317 cases from 12 datasets. Our investigation revealed that poor overall survival (OS; HR = 2.14, 95% CI = 1.74-2.64) and shortened disease-free, recurrence-free, disease-specific, or progression-free survival (HR = 2.13, 95% CI = 1.22-3.72) can be predicted by high MALAT-1 expression for various cancers. Moreover, elevated MALAT-1 levels significantly correlated with

decreased OS in a renal cell carcinoma (RCC) subgroup (HR = 3.43, 95% CI = 1.80-6.53). These results imply that MALAT-1 can be used to predict unfavorable prognoses for several cancers, particularly RCC.

Key words: Long non-coding RNA; MALAT-1; Cancer; Prognosis; Survival

INTRODUCTION

Cancer is a multi-factorial disease and has become a major cause of morbidity and mortality in most countries (Bray et al., 2013). The five-year survival rate remains low for many cancers, and elaborate efforts have been made in the generation of reliable and persuasive evidence to identify prognostic biomarkers for carcinoma patients (Gonzalez and Agudo, 2012). However, efficient prognostic markers associated with high cancer mortality are lacking because of complex interactions between molecular abnormalities and cancer pathogenesis.

The discovery of long non-coding RNAs (lncRNAs) raised the prospect of their use in tumor diagnosis and therapy. The human genome sequencing project found that 70% of the human genome is transcribed, but only up to 2% comprises protein-coding sequences (Bertone et al., 2004; Kapranov et al., 2007). lncRNAs are endogenous transcripts greater than 200 nucleotides long and lack significant lengths of open reading frame (Chen and Carmichael, 2010). More importantly, influences on diverse biological processes, including cell development and pathogenesis, as well as prognosis, have been attributed to lncRNAs.

In recent years, several lncRNAs have been shown to participate in carcinogenesis and cancer progression (Gutschner and Diederichs, 2012). Metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1) was initially recognized owing to its high expression in lung cancer tissue, and was identified as a prognostic factor for the survival of stage I non-small cell lung cancer (NSCLC) patients (Ji et al., 2003). Studies have revealed that MALAT-1 can promote cancer cell proliferation and metastasis by activating the ERK/MAPK pathway and interacting with hnRNP in cell cycle regulation (Yang et al., 2013; Wu et al., 2014). Moreover, research has demonstrated that high MALAT-1 expression can serve as an important prognostic element in other cancers such as pancreatic and colorectal malignancies and gliomas (Liu et al., 2014; Zheng et al., 2014; Ma et al., 2015).

However, most studies that have investigated the implications of MALAT-1 expression have been limited by small sample sizes and single tumor types. Therefore, we conducted a systematic review and quantitative meta-analysis to clarify the prognostic role of MALAT-1 expression in human cancers.

MATERIAL AND METHODS

Search strategy

This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology group (Stroup et al., 2000). We searched international databases (PubMed, Embase, Web of Science, and Cochrane) for relevant articles (most recently, January 19, 2015), using a strategy involving both Medical Subject Heading terms and free-text words to increase search sensitivity. The following key or text words were used: "long non-coding RNA", "lncRNA", "MALAT-1", "Metastasis-Associated-in-Lung-Adenocarcinoma-Transcript-1", "neoplasm", "cancer", "tumor", and "prognosis". Bibliographies of relevant reviews and included studies were also checked for other eligible investigations.

Study selection

The following inclusion criteria were used: studies had to 1) involve patients with any type of carcinoma; 2) determine MALAT-1 expression levels in human tissues by quantitative real-time polymerase chain reaction (qRT-PCR) or microarray expression analysis or other methods; 3) investigate the relationship between MALAT-1 expression and survival outcome; 4) include a hazard ratio (HR) or survival curve for overall survival (OS) or time of recurrence, and an available or calculable 95% confidence interval (CI; if data were published in more than one article, only the most recent article was included); and 5) consist of full-text articles in English. The following were excluded: 1) reviews, letters, or laboratory studies lacking original data; 2) studies with overlapping or duplicate data; 3) investigations of non-dichotomous MALAT-1 expression levels and those lacking survival outcome; and 4) articles published in languages other than English.

Data extraction

Data from all eligible studies were independently extracted by two investigators (J.W. and A.M.X.) and comprised the first author's name, year of publication, study population, nationality, median or mean age of patients, ethnicity, type of disease and sample used, detection method, cut-off definition, follow-up time, and HRs associated with high MALAT-1 expression for OS, recurrence-free survival (RFS), disease-free survival (DFS), disease-specific survival (DSS), or progression-free survival (PFS), along with their 95% CIs and P values. If only Kaplan-Meier curves were available, we reconstructed HR estimates by extracting several survival rates at specified times from the survival curves, using previously reported methods (Williamson et al., 2002; Tierney et al., 2007). To reduce observer variation, data from Kaplan-Meier survival curves were independently evaluated by three researchers (J.W., A.M.X., and J.Y.Z.) using Engauge Digitizer version 4.1. All the above-mentioned data are presented in detail in Tables 1 and 2.

Statistical analysis

Statistical heterogeneity was assessed by visual inspection of forest plots, the chi-square test (and assessment of associated P values) and Higgins's I^2. When P values were less than 0.05 and/or I^2 exceeded 50%, indicating the presence of heterogeneity, a random-effect model (the DerSimonian-Laird method) was used. Otherwise, a fixed-effect model (the Mantel-Haenszel method) was employed. Moreover, we minimized the influence of heterogeneity by classifying the studies included into subgroups based on similar characteristics. Sensitivity analysis was performed, and Galbraith plots were generated to identify the source of heterogeneity. Publication bias was estimated by visually assessing the asymmetry of an inverted funnel plot. Additionally, Begg's funnel plot test and Egger's linear regression test were performed to provide quantitative evidence of publication bias. P values < 0.05 were considered statistically significant. All analyses were performed using Stata version 12.0 (StataCorp, College Station, TX, USA).

RESULTS

Characteristics of eligible studies

As shown in Figure 1, ninety-six records relating to MALAT-1 expression and human cancer were identified in PubMed, Embase, Web of Science, and Cochrane databases. After

reviewing the abstracts, 76 studies were excluded because they were irrelevant to the current analysis, were letters, reviews, or duplicate studies, or were not published in English. Furthermore, eight potentially suitable works were excluded as they lacked sufficient survival data (HRs and survival curves) for analysis. Therefore, 12 eligible articles were included in this meta-analysis (Ji et al., 2003; Schmidt et al., 2011; Lai et al., 2012; Cho et al., 2014; Liu et al., 2014; Okugawa et al., 2014; Zheng et al., 2014; Hirata et al., 2015; Ma et al., 2015; Pang et al., 2015; Shen et al., 2015; Zhang et al., 2015).
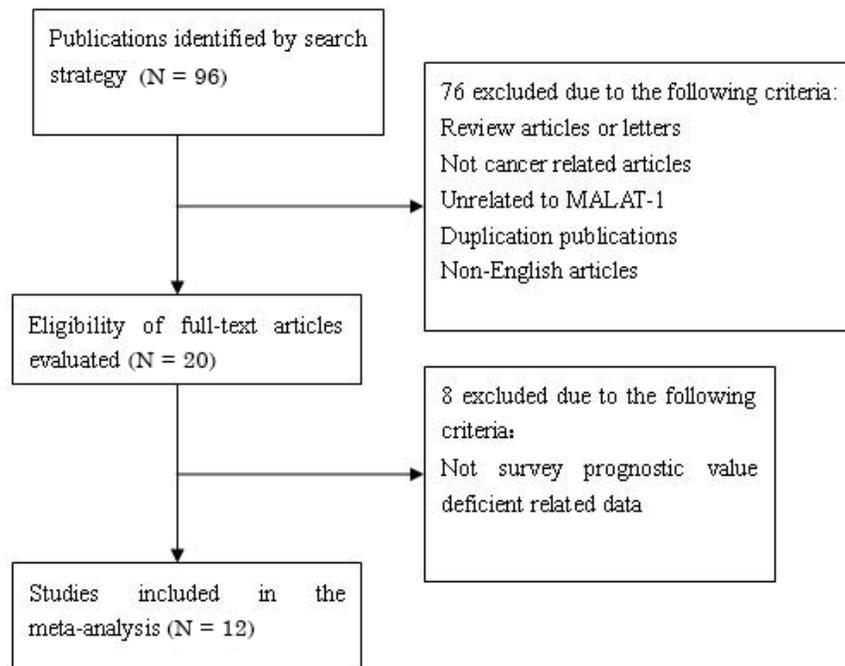
Figure 1. Flow diagram of the study selection process.

The main features and results of the eligible articles are summarized in Tables 1 and 2. These studies investigated a total of 1337 cases from China, Japan, and Germany. The patients were classified as either Asian or Caucasian according to their ethnic background, with 10 articles involving the former and two the latter. Ten studies used only one measure of survival. Of these, seven focused on OS, while DFS, DSS, and RFS were used separately in three investigations. One report tested both OS and PFS, while another calculated OS and DFS. All selected studies were published within the last five years with one exception, which was published more than 10 years ago. Regarding the method used to detect MALAT-1 expression, nine studies utilized qRT-PCR, one performed *in situ* hybridization, one conducted microarray analysis, and one employed subtractive hybridization. The cancers under investigation in these studies included renal cell carcinoma (RCC), gastric cancer, multiple myeloma, pancreatic cancer, NSCLC, glioma, colorectal cancer, hepatocellular carcinoma (HCC), and pancreatic ductal adenocarcinoma. MALAT-1 expression levels were measured in tumor tissues in all articles except one. The mean or median length of follow-up among these studies ranged from 40 to 416.67 months.

Table 1. Main characteristics of the studies included in the meta-analysis.

First author and publication year	Participants' nationality	Main ethnicity	Cancer type	Median or mean age	Sample type	Survival analysis	Source of HR	Max. follow-up (months)
Hirata et al., 2015	Japanese	Asian	RCC	60.24^{median}	Tissue	OS	SC	100
Okugawa et al., 2014	Japanese	Asian	Gastric cancer	69^{median}	Tissue	OS	Reported	60
Cho et al., 2014	Chinese	Asian	Multiple myeloma	61.3^{mean}	Bone marrow	PFS/OS	SC	50
Zhang et al., 2015	Chinese	Asian	RCC	65^{median}	Tissue	OS	Reported	60
Pang et al., 2015	Chinese	Asian	Pancreatic cancer	60^{median}	Tissue	OS	Reported	60
Shen et al., 2015	Chinese	Asian	NSCLC	NM	Tissue	DFS	SC	80
Zheng et al., 2014	Chinese	Asian	CRC	65^{median}	Tissue	OS/DFS	Reported	84
Liu et al., 2014	Chinese	Asian	PDAC	58^{median}	Tissue	DSS	Reported	40
Ma et al., 2015	Chinese	Asian	Glioma	45^{median}	Tissue	OS	Reported	60
Schmidt et al., 2011	German	Caucasian	NSCLC	65^{median}	Tissue	OS	Reported	416.67
Lai et al., 2012	Chinese	Asian	HCC	50^{median}	Tissue	RFS	Reported	50
Ji et al., 2003	German	Caucasian	NSCLC	NM	Tissue	OS	SC	100

RCC = renal cell carcinoma, NSCLC = non-small cell lung cancer, CRC = colorectal cancer, PDAC = pancreatic ductal adenocarcinoma, HCC = hepatocellular carcinoma, OS = overall survival, PFS = progression-free survival, DFS = disease-free survival, DSS = disease-specific survival, RFS = recurrence-free survival, HR = hazard ratio, SC = survival curve, NM = not mentioned, Max. = maximum.

Table 2. Hazard ratios and 95% confidence intervals relating to the relationship between various patient survival measures and MALAT-1 expression in the included studies.

First author and publication year	Detection method	Cut-off value	Number of cases		OS		RFS/DFS/DSS/PFS	
			High expression	Low expression	HR (95% CI)	P	HR (95% CI)	P
Hirata et al., 2015	qRT-PCR	Median	25	25	9.14 (1.14-73.16)#	0.037	NM	NM
Okugawa et al., 2014	ISH	Mean	88	62	1.54 (0.92-2.58)M	0.105	NM	NM
Cho et al., 2014	qRT-PCR	Normalized to GAPDH: 1.50	20	16	2.45 (0.95-6.32)#	0.064	0.74 (0.35-1.55)#	0.74
Zhang et al., 2015	qRT-PCR	NM	46	60	3.09 (1.81-7.02)M	< 0.001	NM	NM
Pang et al., 2015	qRT-PCR	Two-fold compared to normal tissue	63	63	1.76 (1.10-2.82)#	0.02	NM	NM
Shen et al., 2015	qRT-PCR	NM	24	54	NM	NM	2.53 (1.31-4.88)#	0.006
Zheng et al., 2014	qRT-PCR	NM	73	53	2.863 (1.66- 4.94)M	< 0.001	3.46 (2.01-5.96)M	0.002
Liu et al., 2014	qRT-PCR	Two-fold compared to normal tissue	26	19	NM	NM	1.80 (1.18-7.75)M	0.007
Ma et al., 2015	qRT-PCR	Two-fold compared to normal tissue	59	59	2.287 (1.37-3.81)M	0.002	NM	NM
Schmidt et al., 2011	Microarray	NM	123	229	1.78 (1.08-2.92)M	0.026	NM	NM
Lai et al., 2011	qRT-PCR	Two-fold compared to normal tissue	27	33	NM	NM	3.28 (1.52-7.10)M	0.003
Ji et al., 2003	Subtractive hybridization	NM	32	38	5.23 (1.17-23.39)#	0.031	NM	NM

qRT-PCR = quantitative real-time polymerase chain reaction, ISH = in situ hybridization, NM = not mentioned, OS = overall survival, CI = confidence interval, PFS = progression-free survival, DFS = disease-free survival, DSS = disease-specific survival, RFS = recurrence-free survival, HR = hazard ratio. #HR and 95% CI calculated using survival curve, MReported HR and 95% CI as derived from multivariate analysis.

Correlation between MALAT-1 expression and OS

Among the nine articles evaluating OS, no statistically significant heterogeneity was evident (I^2 = 4.3%, P = 0.399). Therefore, a fixed-effect model was used to calculate the pooled HR and 95% CI. The results showed that MALAT-1 expression was significantly associated with poor OS outcome in various carcinomas, with a pooled HR of 2.14 (95% CI = 1.74-2.64; Figure 2). The effect of MALAT-1 expression was further evaluated via subgroup analysis based on the cancer types investigated in those studies having measured OS. Upregulation of MALAT-1 was significantly associated with worse OS in RCC (HR = 3.43, 95% CI = 1.80-6.53). By contrast, no significant relationship was observed in the NSCLC subgroup (HR = 2.40, 95% CI = 0.93-6.17; Figure 3).
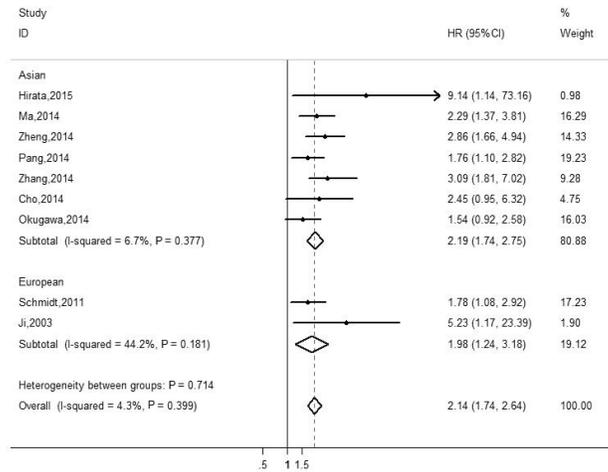
Figure 2. Forest plot summarizing the association between MALAT-1 expression and overall survival in patients with various cancers. HR = hazard ratio, CI = confidence interval.
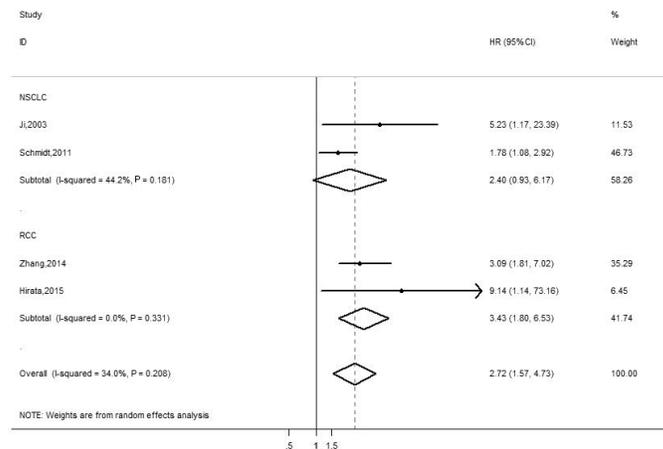
Figure 3. Forest plots representing subgroup analyses of the relationship between overall survival and MALAT-1 expression in different cancer types. HR = hazard ratio, CI = confidence interval, NSCLC = non-small cell lung cancer, RCC = renal cell carcinoma.

Correlation between MALAT-1 expression and other survival measures

As statistically significant heterogeneity was apparent among the five studies included in the DFS/RFS/DSS/PFS analysis (I^2 = 67.3%, P = 0.016), we used a random-effects model to pool HRs. MALAT-1 overexpression was found to be significantly associated with poor DFS/RFS/DSS/PFS in various cancers, with a pooled HR of 2.13 (95% CI = 1.22-3.72). However, these results also identified one study (Cho et al., 2014) as a possible source of the observed heterogeneity (Figure 4).
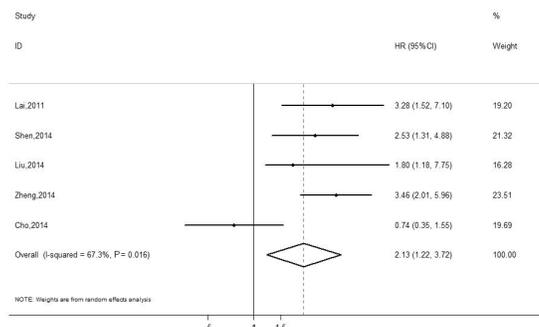
Figure 4. Forest plot of studies having assessed the association between expression of MALAT-1 and disease-, recurrence-, progression-free, and disease-specific survival of patients with various cancers. HR = hazard ratio, CI = confidence interval.

Heterogeneity analysis

Sensitivity analysis was performed by sequential omission of individual studies using the fixed-effect model. This test suggested that the Cho et al. (2014) study had influenced the overall result of the DFS/RFS/DSS/PFS analysis (Figures 5A and 5B). When the Galbraith plot was assessed, the same investigation (Cho et al., 2014) was also identified as an outlier causing heterogeneity in the analysis of survival measures other than OS (Figures 5C and 5D). By excluding this study, a similar and significant pooled HR was obtained (HR = 2.88, 95% CI = 2.05-4.06). In addition, heterogeneity was found to be absent (P = 0.647, I^2 = 0.0%; Figure 6).
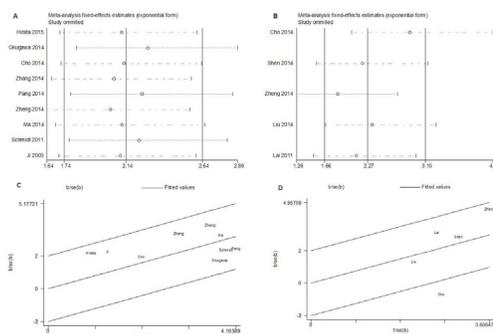
Figure 5. Sensitivity analyses and Galbraith radial plots for each analysis conducted. SE = standard error. **A.** Sensitivity analysis of studies having measured overall survival (OS). **B.** Sensitivity analysis of studies having measured disease-, recurrence-, progression-free, or disease-specific survival (DFS, RFS, PFS, and DSS, respectively). **C.** Galbraith radial plot of studies having measured OS. **D.** Galbraith radial plot of studies having measured DFS, RFS, PFS, or DSS.
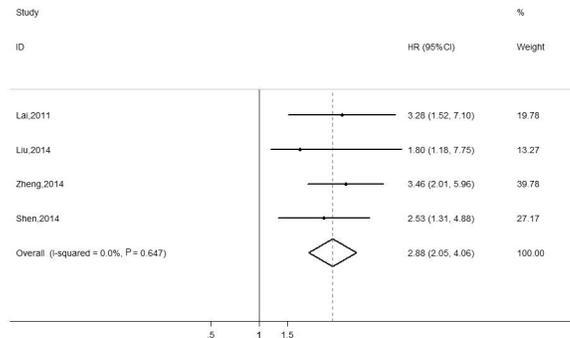
Figure 6. Forest plot of studies having evaluated the association between expression of MALAT-1 and disease-, recurrence-, progression-free, or disease-specific survival of patients with various cancers, following exclusion of data from Cho et al. (2014). HR = hazard ratio, CI = confidence interval.

Publication bias

Begg's funnel plots and the Egger test were used to evaluate publication bias (Figures 7A and 7B). For the pooled analyses of OS and DFS/RFS/DSS/PFS, the Egger test returned P values of 0.23 and 0.418, respectively, and no obvious asymmetry was discerned in the corresponding funnel plots. Hence, this meta-analysis was free of any apparent publication bias.
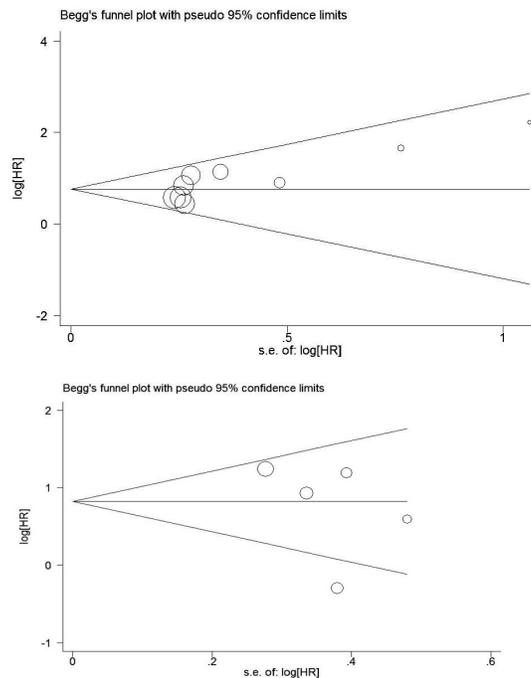
Figure 7. Funnel plots used to assess publication bias. HR = hazard ratio, SE = standard error. **A.** Begg's funnel plot relating to analysis of overall survival. **B.** Begg's funnel plot relating to analysis of disease-, recurrence-, progression-free, and disease-specific survival.

DISCUSSION

In recent years, an increasing number of studies have focused on the role of lncRNAs in tumorigenesis and cancer outcomes. Some lncRNAs, such as HOX antisense intergenic RNA, prostate-specific transcript 1, cancer upregulated drug resistant, and lncRNA associated with microvascular invasion in HCC have been shown to participate in typical cancer processes, including progression and metastasis (Gutschner and Diederichs, 2012; Yuan et al., 2012). Importantly, lncRNAs have been considered potential biomarkers of cancer prognosis, given their unique expression profiles in the tissues or sera of cancer patients.

MALAT-1, also known as *HCN*, *NEAT2*, and *PRO2853*, is located on chromosome 11q13.1 and encodes a polyadenylated ncRNA of approximately 8 kb (Hutchinson et al., 2007). First established as a prognostic marker of lung cancer metastasis, it has also been linked to several other human tumors (Gutschner et al., 2013). In previous studies, MALAT-1 was found to be abnormally expressed in a variety of different human cancers, and highly conserved across several species, underscoring its functional importance (Yamada et al., 2006; Tano et al., 2010; Xu et al., 2011; Lai et al., 2012). Moreover, it has been shown to be upregulated in metastatic bladder cancer tissues and to contribute to bladder cancer cell migration (Ying et al., 2012). More importantly, MALAT-1 is an independent prognostic factor for HCC recurrence after liver transplant, and can interact with microRNAs to promote aggressive RCC (Lai et al., 2012; Hirata et al., 2015). However, the results of these studies are inconsistent, which may be attributed to differences in cancer types, patient ethnicities, and sample sources. To our knowledge, few studies have systematically evaluated the role of MALAT-1 expression in predicting clinical outcomes. Therefore, we conducted this meta-analysis to explore the prognostic value of MALAT-1 in survival and disease recurrence.

In this meta-analysis, we investigated the prognostic role of MALAT-1 in multiple human cancers, and included studies from Asian and Western countries to enhance its universal applicability to some extent. In addition, subgroup analyses using fixed- or random-effect models and sensitivity analysis were performed to optimize its statistical power to detect the role played by MALAT-1 in various cancers.

Upregulation of MALAT-1 correlated with poor survival rates (both OS and DFS/RFS/DSS/PFS) in patients suffering from a range of cancers in this comprehensive investigation of 1337 cases from 12 datasets. Our OS analysis revealed a pooled HR of 2.14 (95% CI = 1.74-2.64), implying that increased MALAT-1 expression is associated with poor prognosis. Subsequently, the pooled result of the free survival analysis also indicated that increased MALAT-1 expression is predictive of worse outcome, with an HR of 2.13 (95% CI = 1.22-3.72). These significant findings suggest that MALAT-1 may serve as a novel independent predictive factor for poor prognosis in several cancers. Consequently, the current study provides new and strong evidence for the important role of MALAT-1 in the development and progression of various human tumors.

In addition, subgroup analyses based on cancer type revealed a statistically significant relationship with OS in the RCC subgroup, with a pooled HR of 3.43 (95% CI = 1.80-6.53). However, within the NSCLC subgroup, no such association was observed (pooled HR = 2.40, 95% CI = 0.93-6.17). This finding was intriguing, as when considered independently, the included NSCLC studies both demonstrated that elevated MALAT-1 expression can indicate poor prognosis, but a pooled analysis of the combined data returned no statistically significant result. This finding may be attributed to differences in tumor stage and classification, publication year, and statistical methods used. Overall, these results suggest that the detection of MALAT-1 expression in RCC patients may be valuable in the determination of prognoses.

Following sensitivity analysis, one study (Cho et al., 2014) was identified as an outlier in the DFS/RFS/DSS/PFS assessment. When we excluded these data, heterogeneity was no longer evident (I^2 = 0.0%, P = 0.647). After careful consideration, we concluded that potential sources of heterogeneity in this article may derive from the following factors. 1) Different diagnosis method. In this study, diagnoses of multiple myeloma were confirmed by bone marrow analyses showing monoclonal plasma cell counts over 10% and related laboratory tests. 2) Different sample storage conditions. In this research, isolated bone marrow samples were stored at -80°C until RNA extraction. 3) Different RNA source. In this investigation, RNA was extracted from bone marrow samples. 4) The included studies differed in the qRT-PCR parameters and systems used, possibly affecting the results. 5) The cut-off value used to determine categories of MALAT-1 expression may also account for some inter-study heterogeneity.

Although the predictive value of MALAT-1 was statistically supported by this meta-analysis, our conclusions should be carefully interpreted for the following reasons. 1) The cut-off values deciding high and low MALAT-1 expression varied between studies. A unanimous value would be relatively difficult to achieve. 2) Post-operative treatment protocols differed among the diverse studies included, and these differences may have significantly influenced patient survival, resulting in some heterogeneity. 3) The statistical power of the association between MALAT-1 and DFS/RFS/DSS/PFS was reduced as a result of the relatively small sample size of 365 patients included in the five studies used in this particular meta-analysis. Thus, larger studies of improved design should be conducted to verify our results. 4) Some HRs could not be directly obtained from the primary studies, requiring us to extract HR estimates from survival curves. 5) We only included papers written in the English language. 6) Most of the included studies reported positive results, as those with negative findings are generally less likely to be published. Therefore, our results may overestimate the predictive significance of MALAT-1 in cancer prognosis to some extent.

In conclusion, this meta-analysis summarized current research on the relationship between aberrant MALAT-1 expression and cancer patient prognosis. Furthermore, it clarified that upregulation of MALAT-1 is significantly associated with poor survival in patients with various carcinomas, particularly RCC. MALAT-1 expression may serve as a novel predictive factor for poor prognosis in different cancer types. However, further investigation of the relationship between MALAT-1 levels and cancer prognosis is required to enable future clinical applications concerning this gene.

Conflicts of interest

The authors declare no conflict of interest.

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