

Emerging role of long non-coding RNA MALAT1 in predicting clinical outcomes of patients with digestive system malignancies: A meta-analysis

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Abstract. Digestive system malignancies are the most common cancer types worldwide and exhibit an extremely low overall 5-year survival rate. Therefore, clinically applicable biomarkers for predicting clinical outcome are urgently required. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is abnormally expressed in several cancer types. However, to the best of our knowledge, the association between MALAT1 expression and the prognosis of digestive system malignancies remains unknown. Therefore, the current study performed a meta-analysis to comprehensively summarize the association between MALAT1 expression and digestive system malignancies. A total of 1,157 Asian patients from 12 eligible studies [eight studies that investigated overall survival (OS), two studies that investigated disease-free survival and two studies that investigated both indicators] were analyzed. The present results identified a significant association between MALAT1 abundance and poor OS in patients with digestive system malignancies, with a pooled hazard ratio (HR) of 1.62 [95% confidence interval (CI), 1.35-1.88; $P < 0.001$]. The tumor type, region, sample size and analysis type did not alter the predictive value of MALAT1 as an independent factor for survival. Furthermore, MALAT1 overexpression was an unfavorable prognostic factor for the overall survival of patients with esophageal carcinoma, pancreatic cancer, hepatocellular carcinoma and gastric cancer, with HRs of 1.89 (95% CI, 1.29-2.49), 1.76 (95% CI, 0.89-2.63), 1.46 (95% CI, 0.76-2.17) and 1.41

(95% CI, 1.04-1.78), respectively. In particular, increased MALAT1 expression levels were significantly associated with decreased OS in patients with colorectal cancer (HR, 3.04; 95% CI, 1.77-4.31). In conclusion, lncRNA MALAT1 may be a potential prognostic factor for digestive system malignancies in Asian populations.

Introduction

It is understood that digestive system malignant tumors, which threaten human health in developing and developed countries, are the most common cancer types worldwide (1). The 5-year survival rate is low for digestive system cancer types and the prognosis of patients with cancer of the digestive system remains unfavorable (2). Numerous studies have attempted to generate reliable and persuasive results that may improve the prognosis for patients with digestive system cancer (3-5). However, no specific molecular biomarkers have been routinely applied for these types of tumors. Therefore, novel biomarkers to improve prognosis prediction and novel therapeutic targets are urgently required.

Investigations regarding potential biomarkers of tumorigenesis have typically focused on protein-coding genes (6). With advancements in sequencing technology, it has been estimated that 98% of the human genome is non-protein coding (7). Long non-coding RNAs (lncRNA) are transcribed RNA molecules with a length >200 nucleotides and are located in nuclear or cytosolic fractions with no protein-coding capacity (8). Previous studies have identified that lncRNAs serve important roles in numerous biological processes, including malignant roles in digestive system malignancies by promoting carcinogenesis, metastasis, migration and invasion (9,10). Furthermore, a number of studies have demonstrated that aberrantly expressed lncRNAs are correlated with cell apoptosis, the cell cycle, cell proliferation, cell differentiation, and mRNA transcription and splicing (11,12). Therefore, lncRNAs may be associated with cancer treatment and prognosis, and may serve a role as novel therapeutic targets.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), also termed nuclear-enriched abundant

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transcript 2 or LINC00047, has been the focus of a number of studies due to its association with various cancer types (13). MALAT1 has been revealed to be upregulated in numerous human cancer types, including lung cancer, hepatocellular carcinoma, colorectal cancer (CRC), pancreatic cancer, gastric cancer (GC) and esophageal carcinoma (14-19). Furthermore, a number of epidemiologic studies have reported that MALAT1 is associated with poor survival outcome among patients with advanced lung adenocarcinoma, osteosarcoma, nasopharyngeal carcinoma and breast cancer (20-22). Wang *et al* (20) identified that the rs3200401 CC genotype of MALAT1 was associated with poor survival for patients with advanced lung adenocarcinoma. Furthermore, Wang *et al* (22) suggested that MALAT1 serves as an oncogene in osteosarcoma by inhibiting osteosarcoma cell metastasis and proliferation, and inducing cell cycle arrest. A multivariable analysis conducted in the USA confirmed that MALAT1 exhibits independent prognostic significance in a subset of patients with triple-negative breast cancer (21). In addition, previous studies have suggested that the expression of MALAT1 is associated with the development and prognosis of digestive system carcinomas, while *in vitro* studies have revealed that MALAT1 is involved in the regulation of cancer cell apoptosis and proliferation, and the induction of cell cycle arrest, tumorigenicity and epithelial-mesenchymal transition (EMT) (14,23,24). A previous study demonstrated that MALAT1 mediates certain cellular events underlying metastatic transformation in various cancer cell types (15). Subsequent studies have reported that MALAT1 expression exhibits a role in cell metastasis and the EMT process, which is associated with invasion and metastasis in GC and CRC (25,26). These investigations suggest that MALAT1 should be exploited as a potential prognostic factor for digestive system malignancies.

Previous studies have been limited due to the investigation of single tumor types and small sample sizes. To the best of our knowledge, no meta-analysis has been performed for digestive system malignant tumors. Therefore, the current study performed a meta-analysis to evaluate the association between MALAT1 expression and the prognosis of patients with digestive system malignancies. Furthermore, a comprehensive review concerning the mechanisms of MALAT1 during digestive system malignancies is presented. The present study demonstrated that MALAT1 is associated with the progression of digestive malignant tumors, which suggests it may serve as a prognostic factor for digestive system malignancies.

Materials and methods

Publication search. To obtain relevant articles for the present meta-analysis, previous studies were searched for in PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>), Embase (<https://www.embase.com/>) and Web of Science (<http://apps.webofknowledge.com/>), and studies published in the Chinese language were identified from the China National Knowledge Infrastructure (<http://www.cnki.net/>) and WanFang databases (<http://www.wanfangdata.com.cn/index.html>) up to August 2017. The search strategy involved free-text words and medical subject heading terms. The following key terms

were searched: 'long non-coding RNA', 'lncRNA', 'MALAT1', 'Metastasis associated lung adenocarcinoma transcript 1', 'neoplasm', 'cancer', 'tumor', 'colorectal cancer', 'esophageal carcinoma', 'pancreatic cancer', 'hepatocellular carcinoma', 'gastric cancer', 'prognosis', 'survival', 'mortality', 'follow-up', 'outcome' and 'predictor'. The bibliographies of the retrieved articles and relevant reviews, as well as conference reports, were also checked for other eligible studies.

Inclusion and exclusion criteria. Eligible studies had to meet the following criteria: i) Diagnosis with digestive system cancer must be histopathologically confirmed; ii) the expression level of MALAT1 was examined in malignant tissues; iii) the association between the expression level of MALAT1 and patient survival time was comparatively analyzed; iv) a description of MALAT1 expression level measurement, including quantitative polymerase chain reaction, in human tissues; v) a description of the cut-off value of MALAT1; vi) the hazard ratios (HRs) and 95% confidence intervals (CIs) for survival rate was reported or could be calculated from the published data; and vii) the more comprehensive or recent study was selected when there were duplicate studies. The exclusion criteria were as follows: i) studies without usable data; ii) animal studies, case reports, letters, reviews and conference abstracts; iii) meta-analysis studies; iv) studies that included patients with benign tumors in the digestive system; and v) studies that did not contain HRs, 95% CIs, P-values or raw data.

Data extraction and quality assessment. The extraction of relevant data from the eligible studies was independently performed by two individuals. The extracted data included the first author, year of publication, country, cancer type, sample size, Tumor-Node-Metastasis stage (27), follow-up months, adjuvant therapy prior to surgery (yes or no), cut-off value, method of MALAT1 expression level measurement, survival rates [overall survival (OS) and disease-free survival (DFS)], HRs and 95% CIs. If they were not present, HR estimates were reconstructed by extracting several survival rates at specific times from Kaplan-Meier curves, as described previously (28,29), using Engauge Digitizer software version 4.1 (<http://digitizer.sourceforge.net/>). The quality of eligible studies was assessed using the Newcastle-Ottawa quality assessment scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), as presented in Table I. NOS criteria scores range from 0 (lowest) to 9 (highest). Typically, an NOS score ≥ 6 is considered to indicate a high-quality study. Disagreements were discussed with other independent investigators.

Statistical analysis. HRs and 95% CIs were extracted to indicate the association of MALAT1 expression with the survival of patients with digestive system malignancies. A HR value not equal to 1 was considered statistically significant, while a HR >1 indicated a worse survival outcome for the group with an increased MALAT1 expression level. Statistical heterogeneity among these studies was tested using Q-test, and the I^2 statistic was performed to quantify the heterogeneity across studies. An I^2 statistic $>50\%$ and a Q-test result with $P < 0.05$ indicated strong heterogeneity

Table I. Assessment of study quality by NOS.

NOS item	Cao <i>et al</i> (19)	Zheng <i>et al</i> (16)	Li <i>et al</i> (37)	Lai <i>et al</i> (15)	Liu <i>et al</i> (17)	Okugawa <i>et al</i> (36)	Pang <i>et al</i> (35)	Yao <i>et al</i> (38)	Wang <i>et al</i> (39)	Li <i>et al</i> (18)	Luo <i>et al</i> (33)	Li <i>et al</i> (34)
Is the case definition adequate?	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a
Representativeness of the cases	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a
Selection of controls	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a
Definition of controls	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a
Study controls for the most important factor	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a
Study controls for the second important factor	Y ^b	Y ^b	Y ^b	Y ^b	Y ^b	Y ^b	Y ^b	Y ^b	Y ^b	Y ^b	Y ^b	Y ^b
Was the measurement method of exposure described?	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a
Were the methods of measurements similar for cases and controls?	Y ^b	Y ^a	Y ^b	Y ^b	Y ^b	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^b	Y ^a
Non-response rate	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^b	Y ^a	Y ^a	Y ^a	Y ^a	Y ^a	Y ^b
Total Score	6	7	6	6	6	8	7	7	7	7	6	8

^a Awarded when the respective information was available. ^b Awarded if the respective information was unavailable. NOS, Newcastle-Ottawa scale; Y, yes.

across studies (30). The random-effects model was used to estimate the pooled HR, and if it was more appropriate, a fixed-effect model was used. Furthermore, the influence of heterogeneity was minimized by classifying studies into subgroups according to the following characteristics: Tumor type, histology type, country, sample size and analysis type. Furthermore, a sensitivity analysis was performed, and Galbraith plots were generated to identify the source of heterogeneity. Potential publication bias was tested using Begg's and Egger's tests (31). These were used to detect publication bias when the publications were tendentially deleted (32). All meta-analyses were performed using Stata 12.0 software (StataCorp LP, College Station, TX, USA). $P < 0.05$ was considered to indicate a statistically significant result.

Results

Literature search and study characteristics. According to the criteria, a total of 138 references were retrieved in the initial search following meticulously screening. Finally, 12 publications were categorized as eligible for the present meta-analysis to investigate the prognostic value of MALAT1 in digestive system cancer types. The detailed selection steps are summarized in the flow chart presented in Fig. 1. Among the 12 studies, three studies investigated hepatocellular carcinoma (15,33,34), two studies investigated pancreatic cancer (17,35), two studies investigated GC (18,36), two studies investigated CRC (16,37) and three studies investigated esophageal carcinoma (19,38,39). A total of 1,157 patients with survival data were included in the present meta-analysis, with a mean sample size of 96.42 (range, 32-150). The 12 studies all took place in Asia, 11 studies were performed in China and one study was performed in Japan, and study design details were available from all. The overall time period of all 12 studies was from 2012 to 2017. The main characteristics of the studies are summarized in Table II. The participants in all studies were categorized into two groups, a high MALAT1 expression group and a low MALAT1 expression group. The method used to determine the MALAT1 cut-off value varied, as presented in Table II. A total of ten studies reported the OS rate and four studies reported the DFS rate. HR and 95% CI values were extracted directly from seven studies, while HRs for five studies were extrapolated by graphical representations of the survival curve. The quality assessment of eligible studies was scored using the Newcastle-Ottawa quality assessment scale (Table I).

The prognostic value of MALAT1 in digestive system malignancies. A total of ten studies reported the OS of 1,052 patients, according to MALAT1 expression levels. Heterogeneity analysis revealed no heterogeneity among these studies, therefore, the fixed-effects model (I^2 , 0.0%; $P=0.528$) was assessed in the meta-analysis. Overall, the pooled results confirmed a significant association between high MALAT1 expression and poor OS in digestive system malignancies, with a HR value of 1.62 (95% CI, 1.35-1.88; $P < 0.001$; Fig. 2). Although there was no significant heterogeneity among the studies, a subgroup meta-analysis was conducted on tumor

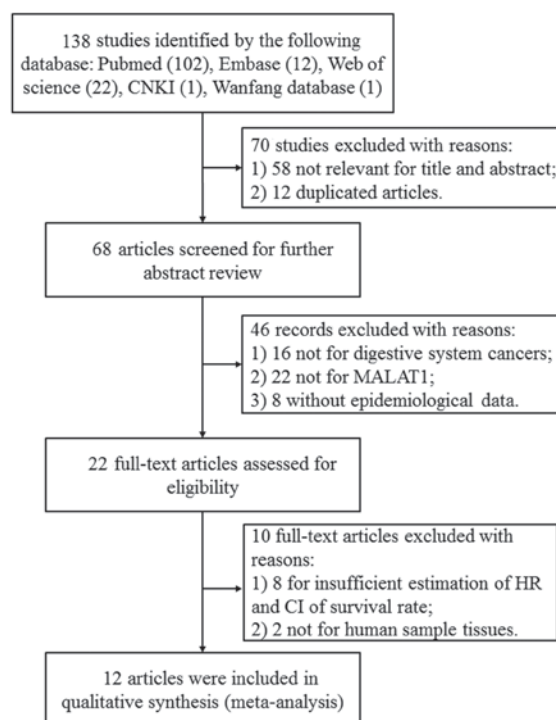


Figure 1. Search strategy and study selection. HR, hazard ratio; CI, confidence intervals; CNKI, China National Knowledge Infrastructure.

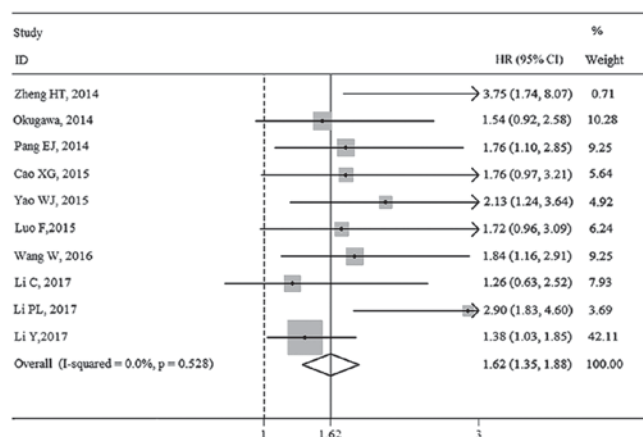


Figure 2. Forest plot of studies that evaluated the pooled HRs of the expression level of MALAT1 and overall survival in digestive system malignancies. The point estimate was bounded by a 95% CI. Each square represents the HR point estimate and its size is proportional to the weight of the study. The solid line represents the overall survival summary estimate, in which 95% CI is given through its width. The dotted vertical line demonstrates the null value (hazard ratio=1), which represents no increased risk for the outcome. HR, hazard ratio; CI, confidence interval.

type, country, sample size and analysis type (Table III). A significant association was identified between the expression of MALAT1 and the OS of patients with digestive system malignant tumors in China (HR, 1.63; 95% CI, 1.34-1.91). The association between MALAT1 and OS was significant in studies with a sample size ≥ 100 (HR, 1.57; 95% CI, 1.27-1.88; $P < 0.001$) and < 100 (HR, 1.76; 95% CI, 1.21-2.31; $P < 0.001$). Furthermore, MALAT1 was also identified to be significantly associated with OS of patients in studies with multivariate analysis (HR, 1.51; 95% CI, 1.19-1.84; $P < 0.001$)

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

First author, year	Country	Cancer type	Sample Size	TNM stage	Follow-up time, months	AT (yes/no)	Cut-off value	Multivariate analysis	HR (95% CI)	NOS score	(Refs.)
Lai, 2012	China	HCC	60	I-IV	18.6 ^a	NA	Median expression	Yes	DFS: 3.28 (1.52-7.09)	6	(15)
Zheng, 2014	China	CRC	146	I-III	56.2 ^a	113/15	Median expression	Yes	OS: 3.75 (1.74-8.07)		(16)
Okugawa, 2014	Japan	GC	150	I-IV	26 ^a	NA	Median expression	Yes	DFS: 2.86 (1.66-4.94)	7	
Liu, 2014	China	PC	45	I-IV	>40	NA	Median expression	Yes	OS: 1.54 (0.92-2.58)	8	(36)
Pang, 2014	China	PC	126	I-IV	>60	NA	Median expression	Yes	DFS: 1.80 (1.18-2.75)	6	(17)
Cao, 2015	China	EC	77	I-III	37 ^a	45/32	Median expression	Yes	OS: 1.76 (1.10-2.85)	7	(35)
Yao, 2015	China	EC	137	I-IV	>30	NA	Median expression	No	OS: 1.76 (0.97-3.21)	6	(19)
Luo, 2015	China	HCC	32	I-IV	>20	0/32	Median expression	No	DFS: 1.81 (0.97-3.41)	7	(38)
Wang, 2016	China	EC	106	I-IV	>30	0/106	Median expression	No	OS: 2.13 (1.24-3.64)	6	(33)
Li, 2017	China	HCC	60	I-IV	>60	0/60	Median expression	No	OS: 1.72 (0.96-3.09)	7	(39)
Li, 2017	China	CRC	68	I-IV	>40	68/0	Median expression	No	OS: 1.84 (1.16-2.91)	7	(34)
Li, 2017	China	GC	150	I-IV	>30	NA	Median expression	Yes	OS: 1.26 (0.63-2.52)	7	
									DFS: 1.88 (0.91 -3.89)	6	(37)
									OS: 2.90 (1.83-4.60)	8	(18)

^aData are presented as the median. CRC, colorectal cancer; EC, esophageal carcinoma; PC, pancreatic cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; AT, adjuvant therapy prior to surgery; NOS, Newcastle-Ottawa quality assessment scale; NA, not available.

Stratified analysis	Studies, n	Patients, n	Pooled HR (95% CI)	P-value	Heterogeneity		
					I ² , %	P-value	Model
Tumor type	10	1,052					
Colorectal cancer	2	214	3.04 (1.77-4.31)	<0.001	0.0	0.630	Fixed effects
Pancreatic cancer	1	126	1.76 (0.89-2.63)	<0.001	-	-	Fixed effects
Hepatocellular carcinoma	2	92	1.46 (0.76-2.17)	<0.001	0.0	0.527	Fixed effects
Gastric cancer	2	300	1.41 (1.04-1.78)	<0.001	0.0	0.735	Fixed effects
Esophageal cancer	3	320	1.89 (1.29-2.49)	<0.001	0.0	0.897	Fixed effects
Country							
China	9	902	1.63 (1.34-1.91)	<0.001	0.3	0.431	Fixed effects
Japan	1	150	1.54 (0.71-2.37)	<0.001	-	-	Fixed effects
Sample size							
≥100	6	815	1.57 (1.27-1.88)	<0.001	0.0	0.544	Fixed effects
<100	4	237	1.76 (1.21-2.31)	<0.001	18.6	0.298	Fixed effects
Analysis type							
Multivariate	5	649	1.51 (1.19-1.84)	<0.001	0.0	0.588	Fixed effects
Other	5	403	1.84 (1.37-2.31)	<0.001	0.0	0.410	Fixed effects
HR, hazard ratio; CI, confidence interval.							

HR, hazard ratio; CI, confidence interval.

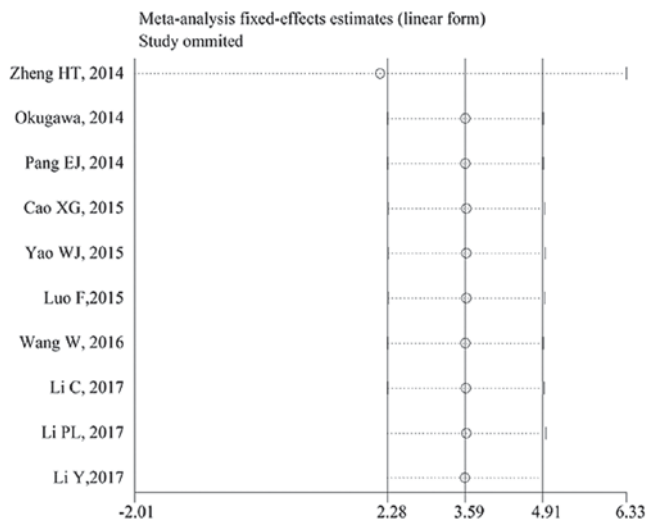


Figure 3. Sensitivity analysis of the meta-analysis. The solid line represents the meta-analysis fixed-effects estimates, in which the 95% confidence interval is given through the width of the dotted horizontal line. The circle represents each study.

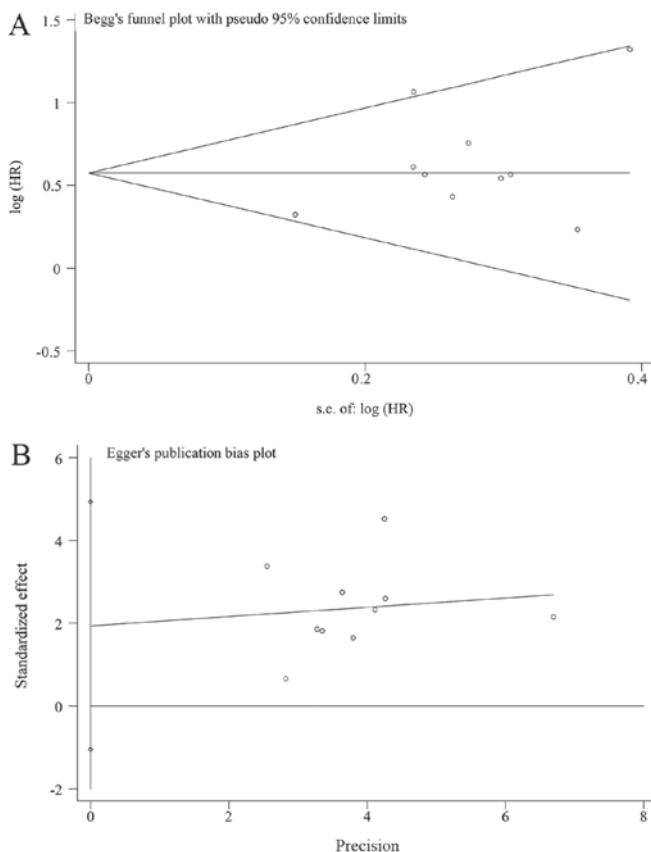


Figure 4. Funnel plot for identifying publication bias. (A) Begg's funnel plot analysis for publication bias. (B) Egger's funnel plot analysis for publication bias. Each point represents a separate study. HR, hazard ratio; s.e., standard error.

and non-multivariate analysis (HR, 1.84; 95% CI, 1.37-2.31; $P < 0.001$). Furthermore, sensitivity analysis indicated the robustness of the meta-analysis results (Fig. 3).

Publication bias was assessed using Begg's funnel plot (Fig. 4A) and Egger's test (Fig. 4B). The shapes of

the funnel plot were symmetrical. Therefore, publication bias was not identified by Begg's test ($z = 0.18$, $P = 0.858$) or Egger's test ($t = 1.49$, $P = 0.174$). In studies with DFS data, a high expression level of MALAT1 was observed to be associated with poor DFS (HR, 2.01; 95% CI, 1.41-2.61) and no significant heterogeneity was identified ($I^2 = 0\%$; $P = 0.53$) (Fig. 5A). Furthermore, subgroup analysis for DFS was not performed due to a limited number of studies but sensitivity analysis was performed (Fig. 5B) and publication bias was assessed (Fig. 5C-D).

Independent prognostic value of MALAT1 for OS in different cancer types. The analysis of subgroups suggested that no significant heterogeneity existed among the studies for the five main types of digestive system cancers ($I^2 = 0.0\%$; $P > 0.05$; Fig. 6). Therefore, the fixed-effects model was utilized to combine HRs with the corresponding 95% CI. Notably, it was identified that MALAT1 was a significant prognostic indicator for the OS of patients with CRC (HR, 3.04; 95% CI, 1.77-4.31; $P < 0.001$), pancreatic cancer (HR, 1.76; 95% CI, 0.89-2.63; $P < 0.001$), hepatocellular carcinoma (HR, 1.46; 95% CI, 0.76-2.63; $P < 0.001$), GC (HR, 1.41; 95% CI, 1.04-1.78; $P < 0.001$) and esophageal cancer (HR, 1.89; 95% CI, 1.29-2.49; $P < 0.001$). Furthermore, the subgroup analysis revealed that the aforementioned factors were not associated with the predictive value of MALAT1. Furthermore, the pooled meta-analysis results confirmed that high MALAT1 expression level in digestive cancer tissue was a significant independent predictor of poor OS in numerous types of digestive system malignancies.

Systematic review of the molecular mechanism. The mechanism of action for MALAT1 on the development of digestive system malignancies has been investigated in numerous *in vivo* and *in vitro* studies. The most recent studies have demonstrated that the expression of MALAT1 is associated with the development and prognosis of digestive system cancer, while *in vivo* and *in vitro* studies have indicated that MALAT1 is involved in the regulation of cancer cell apoptosis and proliferation, and the induction of cell cycle arrest, tumorigenicity, migration, invasion and metastasis (Fig. 7). MALAT1 acts as a molecular sponge of miR-146b-5p and downregulates its expression in hepatocellular carcinoma. miR-146b-5p targets TRAF6-mediated Akt phosphorylation and may suppress the expression of Bcl-2 and Bcl-xL, therefore decreased expression of miR-146b-5p is associated with increased cancer cell proliferation and lower rates of cell apoptosis (34). In addition, MALAT1 significantly induces the proliferation and metastasis of cancer cells *in vitro* and *in vivo* through the activation of the Wnt, extracellular-signal-related kinase/mitogen activated protein kinase, Erb-B2 receptor tyrosine kinase 3 and c-Myc signaling pathways (18). A number of studies have indicated that p53 is the main downstream mediator for MALAT1 activity and MALAT1 may be regulated by SP1 nuclear transcription factor/latent transforming growth factor β -binding protein 3 and transforming growth factor- β , which disrupts the replication of the S-phase, as well as the cell population of G1 and G2/M cells (40). Furthermore, MALAT1 promotes tumorigenicity in GC cells by recruiting splicing factor 2 (SF2)/alternative splicing factor (ASF),

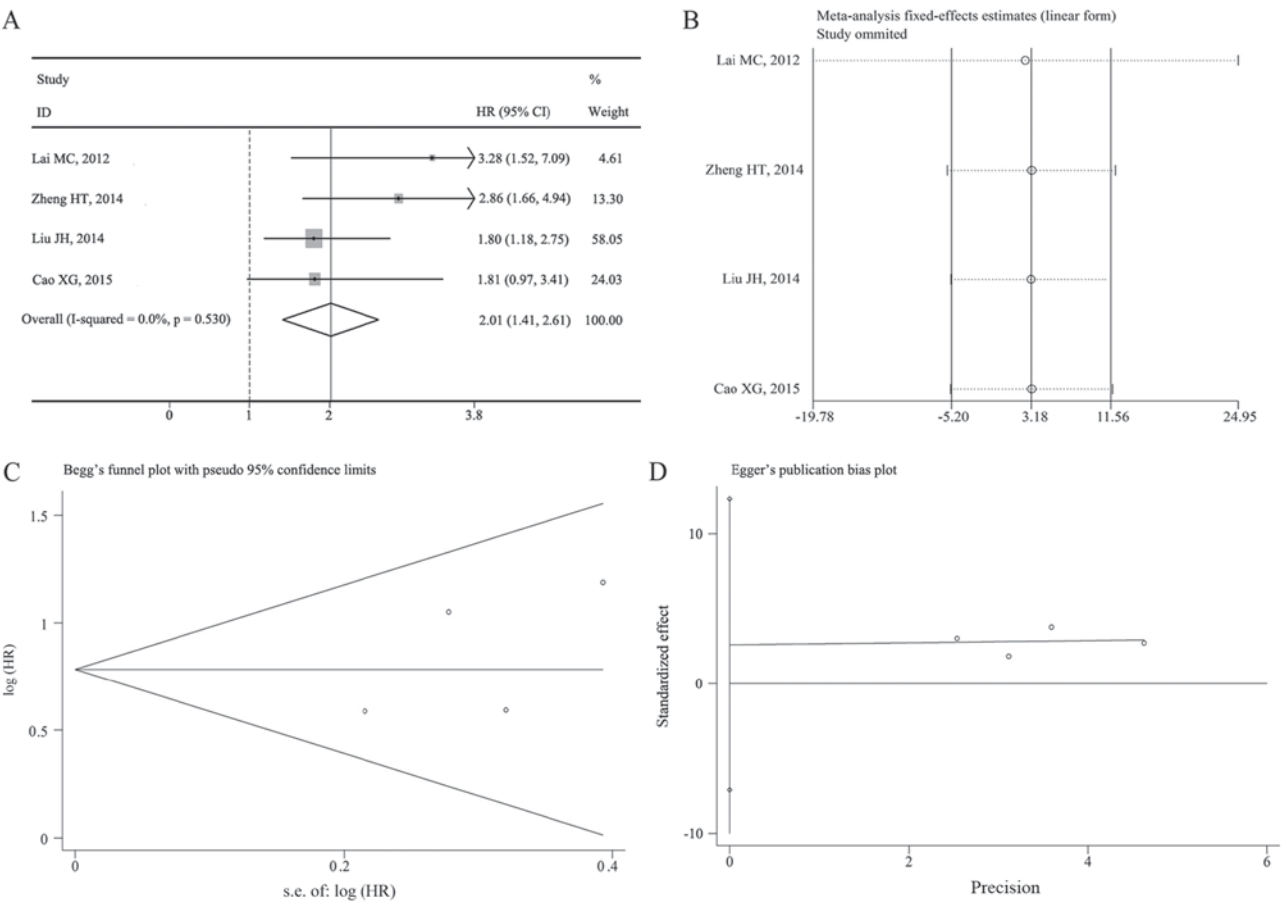


Figure 5. Meta-analysis of pooled HRs to analyze the association between high expression level of MALAT1 and DFS. (A) Forest plot of the studies with DFS data. The solid line represents the overall summary estimate, in which the 95% CI is given through its width. The dotted vertical line demonstrates the null value (hazard ratio=1), which represents no increased risk for the outcome. (B) Sensitivity analysis. The solid line represents the meta-analysis fixed-effects estimates, in which the 95% confidence interval is given through the width of the dotted horizontal line. The circle represents each study. (C) Begg's funnel plot analysis. (D) Egger's funnel plot analysis. HR, hazard ratio; CI, confidence interval; DFS, disease-free survival; s.e., standard error.

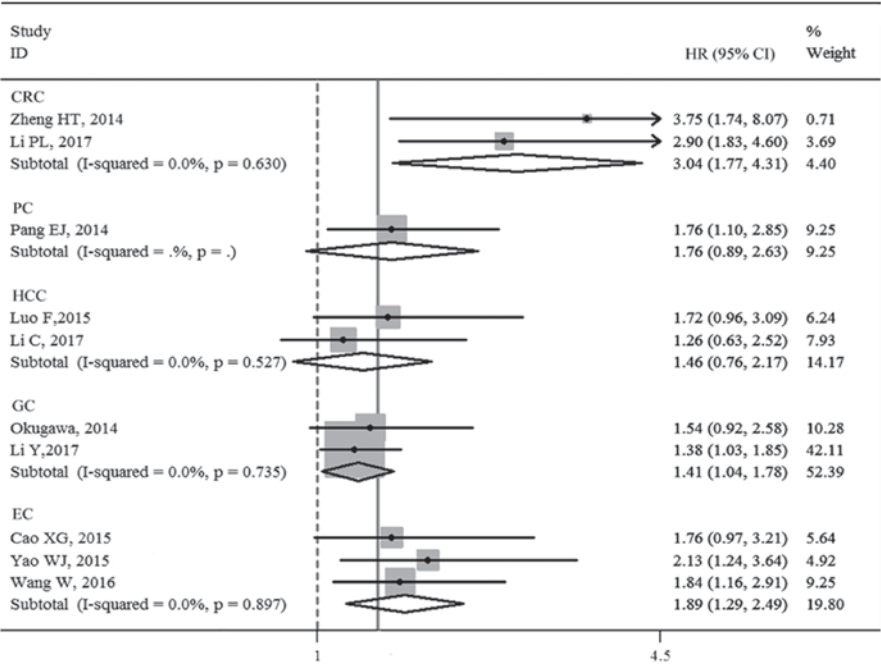


Figure 6. Forest plots for the analysis of the association between MALAT1 expression level and overall survival in different cancer types. Each square represents the HR point estimate and its size is proportional to the weight of the study. The dotted vertical line demonstrates the null value (hazard ratio=1), which represents no increased risk for the outcome. HR, hazard ratio; CI, confidence interval; CRC, colorectal cancer; PC, pancreatic cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; EC, esophageal cancer.

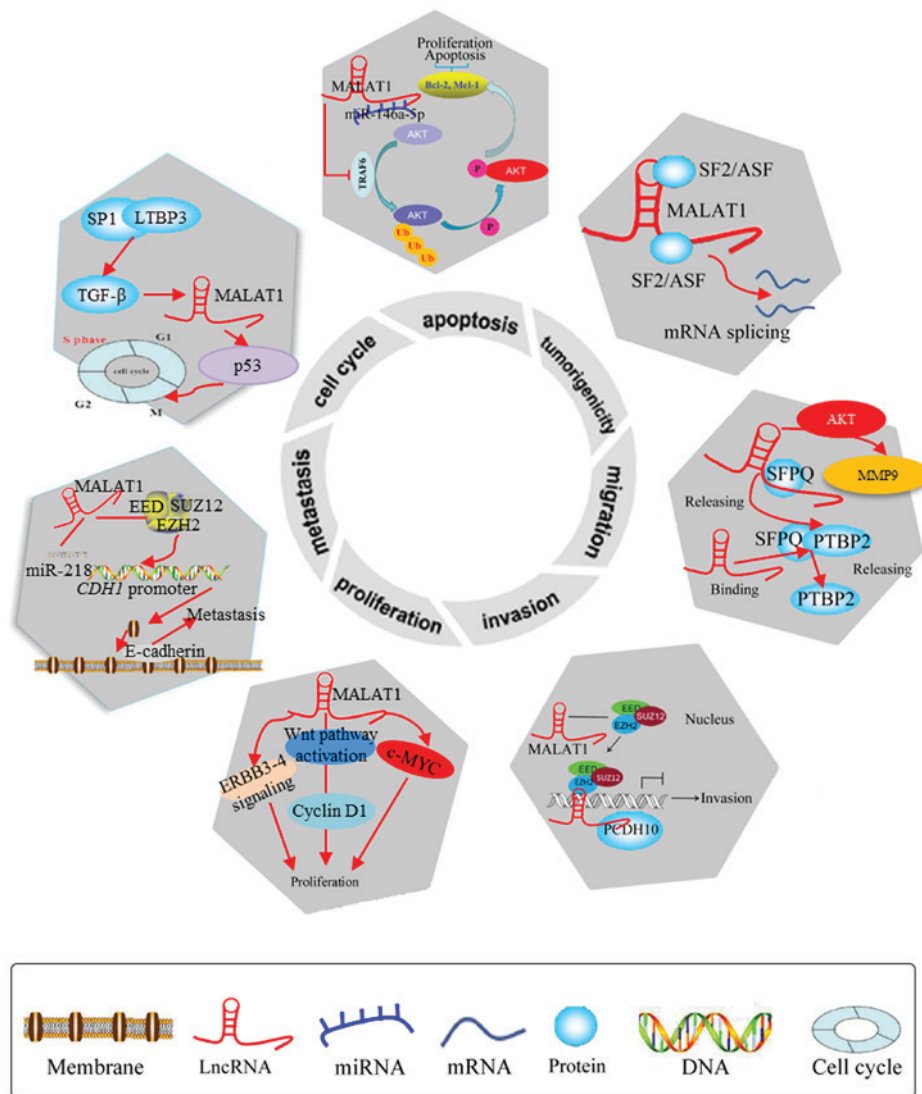


Figure 7. Association of MALAT1 expression levels and the development of digestive system malignancies via the regulation of cell apoptosis, cell cycle, cell invasion, migration, metastasis and tumorigenicity. TRAF6, tumor necrosis factor receptor associated factor 6; SF2, splicing factor 2; ASF, alternative splicing factor; SFPQ, splicing factor proline/glutamine rich; PTBP2, polypyrimidine tract binding protein 2; EED, embryonic ectoderm development; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; SUZ12, SUZ12 polycomb repressive complex 2 subunit; PCDH10, protocadherin 10; ERBB2, erb-b2 receptor tyrosine kinase 2; SP1, SP1 nuclear transcription factor; LTBP3, latent transforming growth factor β -binding protein 3; lncRNA, long non-coding RNA; TGF- β , transforming growth factor- β ; MMP9, matrix metalloproteinase 9.

which indirectly influences mRNA splicing (41). In cancer migration studies, MALAT1 has been identified as one of the several important splicing factor proline/glutamine-rich (SFPQ)-binding RNAs. MALAT1 may competitively bind to SFPQ to release SFPQ from SFPQ/polypyrimidine tract binding protein 2 (PTBP2), which affects the AKT/matrix metalloproteinase 9 signaling pathway. This is critical for the regulation of cell migration (42). In cancer invasion studies, it has been revealed that enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) is tethered by MALAT1 to the protocadherin 10 (PCDH10) locus, which promotes cancer metastasis and invasion by suppressing PCDH10 (25). Additionally, MALAT1 tethers EZH2 to the cadherin 1 promoter and suppresses miR-218, which promotes CRC cell EMT, metastasis and chemoresistance (37). Overall, MALAT1 mediates cancer cell proliferation, migration, invasion and metastasis, and may therefore be a potential prognostic factor for digestive system malignancies.

Discussion

Previously, a number of studies have demonstrated that lncRNAs participate in tumorigenesis and cancer prognosis. Certain lncRNAs, including HOX transcript antisense intergenic RNA, colon cancer-associated transcript 2, PVT1 oncogene, maternally expressed gene 3 and MALAT1 have been demonstrated to serve a role in cancer progression and metastasis in digestive system malignancies (43,44). With advancements in high-throughput sequencing, lncRNAs have become a key interest for RNA biology studies. MALAT1 is abnormally expressed in human malignancies (16,19,37,42). However, to the best of our knowledge, the independent prognostic role of MALAT1 in digestive system malignancies remains unclear. Therefore, the current study performed a meta-analysis to evaluate the clinical implication and prognostic value of MALAT1 in five principal digestive system malignancies. According to present knowledge, this is a

meaningful meta-analysis to explore the association between MALAT1 expression and OS in human digestive system cancer types.

A previous study has provided certain information regarding the prognostic value of MALAT1 (45), however the current study provides a more recent update and performs subgroup analysis. The present meta-analysis included 12 studies that focused on digestive system cancer types. The prognostic value of MALAT1 in digestive system cancer was assessed. The present study demonstrated that high expression levels of MALAT1 were associated with poor OS in patients (HR, 1.62; 95% CI, 1.35-1.88). Furthermore, subgroup analysis revealed a significant association between high expression of MALAT1 and disease prognosis, while country, type of cancer, sample size and analysis method did not significantly affect these pooled results. The heterogeneity Q statistic ($P > 0.05$) and I^2 value was 0.00%, indicating no statistical evidence for heterogeneity among the selected studies. Both Begg's test and Egger's test revealed no publication bias, and sensitivity analysis supported the statistical power of the current study to investigate the independent prognostic role of MALAT1 for the OS of digestive system cancer. Particularly, elevated MALAT1 levels were significantly associated with decreased OS in the CRC subgroup (HR, 3.04; 95% CI, 1.77-4.31). A number of studies have demonstrated that MALAT1 serves an important role in CRC (37,46-49).

MALAT1, regarded as one of the most common oncogenic lncRNAs, has also been identified to be highly expressed in other various cancer types, including hepatocellular carcinoma (50), non-small cell lung cancer (42), GC (36), pancreatic cancer (17,35), CRC (16), clear cell renal cell carcinoma (51), esophageal cancer (52,53), gallbladder cancer (54), bladder cancer (55), osteosarcoma (56) and breast cancer (57,58). A larger number of these studies were predominantly performed in Asian populations, with few taking place in European countries; the most common countries were China, Japan and Germany. These studies identified that MALAT1 regulates tumor cell viability, invasiveness, migration and EMT (59,60). In addition, a number of studies have revealed that overexpression of MALAT1 is significantly associated with high-risk grade, metastasis and patients' survival in numerous cancer types in Asian populations (37,39,61). Notably, a Chinese study identified a positive association between single nucleotide polymorphisms in MALAT1 and cancer risk, therefore, genetic variants in MALAT1 may serve crucial roles in the development of cancer in Chinese populations (62). The small variation in regions in which previous studies have been performed may be a limitation that decreases the applicability of the current results across different ethnicities.

lncRNAs regulate gene expression by a number of mechanisms, including transcription, posttranscriptional processing, chromatin modification, and protein function regulation (9). To provide further insights, the mechanism of action for MALAT1 in digestive system malignancies was summarized based on a systematic review. This revealed that MALAT1 is involved in the regulation of cancer cell apoptosis and proliferation, in addition to the induction of cell cycle arrest, tumorigenicity, migration, invasion and metastasis. This can be summarized as two modes of action for MALAT1. On one hand, an increasing number of studies have indicated

that MALAT1 promotes cancer progression by regulating the expression of genes, including apoptosis-associated genes (Akt, Bax, Bcl2, and Mcl1) (34), cell cycle-associated genes (P53 and Mybl2) (40), EMT and metastasis-associated genes (ZEB1, ZEB2, Slug and E-cadherin) (25), cancer invasion-associated genes (EZH2 and PCDH10). On the other hand, MALAT1 has been identified to serve a role in alternative mRNA splicing. For example, MALAT1 promotes tumorigenicity by recruiting SF2/ASF, which subsequently indirectly influences mRNA splicing (41). In addition, MALAT1 affects cancer migration-associated splicing factors, including SFPQ and PTBP2 (42). In summary, there is an urgent requirement to determine the exact molecular mechanisms of MALAT1 in the progression of digestive system cancer types.

A number of limitations are unavoidable when performing a meta-analysis. Firstly, potential bias may exist due to the more frequent publication of positive results. Secondly, studies with small sample sizes may not adequately investigate potential associations. Thirdly, adjuvant therapeutic strategies are different in different types of digestive system malignancy, which may affect the postoperative survival of patients. In addition, potential bias may exist in the selection of studies, partly due to the language in which they are published. Finally, all studies included in the present meta-analysis were conducted in Asian populations, particularly, Chinese and Japanese populations. Furthermore, the current study attempted to conduct a multivariable analysis, which requests original data of the selected studies and helps determine the prognostic significance of MALAT1. However, due to various difficulties, multivariable analysis was not conducted. Therefore, the present conclusions regarding the prognostic significance of MALAT1 in different types of digestive system malignancy should be interpreted with caution.

In summary, the present meta-analysis demonstrated that the overexpression of MALAT1 is associated with poor prognosis in various types of digestive system malignancy, particularly CRC. This aids understanding on the potential prognostic significance of MALAT1 in clinical practice.

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Availability of data and materials

The datasets analyzed for the present study are available from the corresponding author upon reasonable request.

Authors' contributions

CW and JY conceived and designed the study. CW, QZ, and YH. searched and selected publications. CW, QZ, YH and

JZ analyzed the data. CW and QZ prepared the figures. CW contributed materials/analysis tools. CW, and JY wrote and revised the paper. All authors critically reviewed the manuscript and approved the final draft.

Ethics approval and consent to participate

Not applicable. All the data/samples were collected from the articles in online databases and used anonymously.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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