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Long non-coding RNA MALAT1 as a valuable biomarker for prognosis in osteosarcoma: A systematic review and meta-analysis

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ABSTRACT

Background: Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (lncRNA, MALAT1) has been found to be aberrantly expressed in osteosarcoma, while high MALAT1 expression is correlated with both metastasis and prognosis. This meta-analysis set out to investigate the prognostic value of lncRNA MALAT1 in patients living with osteosarcoma.

Methods: We conducted a systematical search of available databases from inception to May 2019. Odds ratios (OR) of clinical parameters, as well as hazard ratio (HR) of overall survival (OS), were calculated in order to evaluate the relationship between MALAT1 expression and the prognosis of patients living with osteosarcoma.

Results: Nine eligible studies which included a total of 599 osteosarcoma patients were enrolled in the present study. Pooled results found that high MALAT1 expression was associated with clinical stage and distant metastasis, but not age, gender, tumor anatomical location or tumor size. When compared to patients with low MALAT1 expression, patients with high MALAT1 expression were markedly correlated with a worse OS. Moreover, MALAT1 may be an independent predictive factor for OS in patients living with osteosarcoma.

Conclusions: This meta-analysis suggests that high MALAT1 expression is associated with advanced clinicopathological features as well as unfavorable prognosis. LncRNA MALAT1 has the potential to serve as a moderate prognostic biomarker for osteosarcoma.

1. Introduction

LncRNAs are defined as RNA molecules which are more than 200 nucleotides in length and have little or no protein-coding ability [1]. By virtue of their primary sequence and spatial structure, lncRNAs can interact with DNA, RNA and proteins as well as playing regulatory roles in various biological processes and diseases [2]. It has been well established that lncRNAs participate in the progression of multiple cancers and metastasis, including osteosarcoma [3,4].

Osteosarcoma is a primary malignant bone tumor which can affect children and young adults and has a worldwide incidence of 3.4 per million people per year [5]. Recent studies have shown that while sequential therapies of neoadjuvant and adjuvant chemotherapy or surgical resection improve the survival rates, osteosarcoma still leads to unfavorable clinical outcomes and high rates of disability in adolescents [6]. In order to ameliorate the prognosis of osteosarcoma, new biomarkers and novel therapeutic strategies based on molecular mechanisms need to be developed for early diagnosis and treatment. It has been found that lncRNAs are aberrantly expressed in osteosarcoma tissues and are correlated with clinical outcomes and disease status [4]. Recent findings indicate that altered lncRNAs may serve as prognostic biomarkers for patients with osteosarcoma [7].

Elevated MALAT1 has been found in osteosarcoma tissues and multiple cell lines [8]. It has been demonstrated that MALAT1 was able to facilitate cell viability and metastasis [9–11]. Targeting MALAT1 may suppress tumor cell growth and ultimately inhibit osteosarcoma's progression [12]. Furthermore, MALAT1 appeared to be a prognostic biomarker and therapeutic target for osteosarcoma [13]. In this study, we conducted a meta-analysis in order to evaluate the role of MALAT1 expression in the prognosis of patients living with osteosarcoma.

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2. Material and methods

2.1. Literature search

This systematic review was reported according to the guidelines including Preferred Reporting Item for Systematic Review and Meta-Analysis checklist (PRISMA) and Assessing the methodological quality of systematic reviews (AMSTAR). All analyses were based on published studies and no ethical approval was required. This systematic review and meta-analysis has been registered in PROSPERO: CRD42019135916. We comprehensively searched PubMed, Embase, Web of Science, Cochrane Library, Wanfang database and the Chinese National Knowledge Infrastructure database (CNKI) from their dates of inception up to May 2019. Keywords for the literature search were: metastasis-associated lung adenocarcinoma transcript 1 or MALAT1 and osteosarcoma. In addition, we conducted a manual search of reference lists from all original articles and identified reviews. This systematic search was carried by two independent reviewers (Miao Liu and Peng Yang).

2.2. Selection criteria

Studies which met the flowing criteria were eligible: (i) studies exploring the correlation between MALAT1 expression and the prognosis of patients with osteosarcoma; (ii) studies in which patients were divided into two groups according to their expression level of MALAT1; (iii) studies in which clinical parameters such as tumor size, clinical stage and distant metastasis were described; (iiii) studies which provided available HRs and 95% CIs of OS or survival curves for calculating. The following studies were excluded: (i) reviews, case reports, letters, conference papers and abstracts; (ii) studies which only focused on the molecular mechanism and function of MALAT1, such as cell and animal-related studies; (iii) studies without any of the aforementioned outcomes.

2.3. Data extraction and quality assessment

All data were extracted from article texts, tables, and figures by two independent reviewers (Miao Liu and Peng Yang). The following data were extracted: surname of the first author, publication date, country, participants' age and gender, sample size, tumor size, anatomic location, clinical stage, distant metastasis and OS. If the HRs with 95% CIs of OS were not available, we collected Kaplan-Meier survival curves for further computation, using the GetData Graph Digitizer software according to the method described by Tierney [14]. All eligible studies were non-randomized controlled studies. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) and a NOS score of ≥ 6 was considered high quality. Any discrepancies were discussed by the two reviewers. Where necessary, a third investigator was consulted (Hong Sun).

2.4. Statistical methods

All statistical analyses were carried out using Stata12 (Stata Corp, College Station, Texas). HRs and ORs were used to compare OS and clinicopathologic parameters respectively. Heterogeneity among studies was assessed using Chi-square Q test and I^2 statistic. The P value of Q test (P_Q) < 0.05 and $I^2 > 50\%$ indicated statistical heterogeneity among studies. The random-effect model was used to calculate pooled results. Otherwise, the fixed effect model was employed. Potential publication bias was measured using Begg's funnel plots and Harbord's modified test. $P < 0.05$ was considered statistically significant.

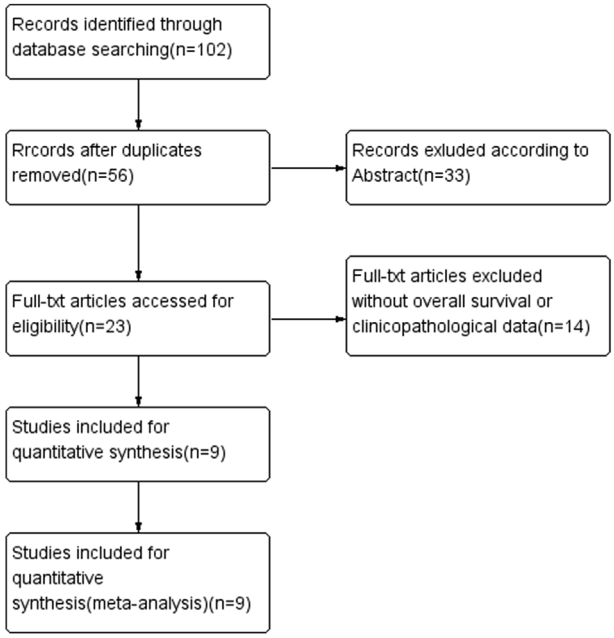


Fig. 1. Flow diagram of study selection procedure.

3. Results

3.1. Study selection

Fig. 1 shows a flow chart of included and excluded studies. A total of 102 studies were retrieved as potentially relevant. After duplicates were removed, 56 studies were carefully screened by titles and abstracts. Some 33 studies were eliminated as they were reviews, letters, reports or meta-analyses. Following further evaluation of full articles, we eliminated 14 records which did not include OS or clinicopathological features. Ultimately, nine studies were eligible for data extraction and meta-analysis.

3.2. Characteristics of eligible studies

The major characteristics of the eligible studies can be seen in Table 1. All nine studies were from China and had been published between 2016 and 2019. Expression of MALAT1 was measured using qRT-PCR and normalized to GAPDH or β-actin. According to the lncRNAs expression, enrolled patients were dived into high expression and low expression groups. Among studies for the meta-analysis of OS, only two [13,15] directly provided the HR and 95% CI for OS and five were calculated from the Kaplan-Meier survival curves, while the remaining two [8,16] didn't report the HR. All studies scored ≥ 6 according to NOS score criteria and were therefore considered high quality.

3.3. Meta-analyses of clinical parameters

As shown in Fig. 2 and Table 2, four studies were included in the meta-analysis of clinical parameters [8,13,16,17]. The clinical stage was available in three studies [13,16,17]. Pooled results indicated that high MALAT1 expression predicted advanced clinical stage (IIB/III vs I + IIA: OR = 0.227, 95 %CI: 0.129 to 0.400, $P < 0.001$), with no significant heterogeneity ($I^2 = 0.0\%$, $P_Q = 0.956$). Four of the studies were included for meta-analysis of distant metastasis [8,13,16,17]. Pooled results demonstrated that high MALAT1 expression was significantly associated with distant metastasis (Present vs Absence: OR = 4.019, 95 %CI: 2.230 to 7.244, $P < 0.001$), with no significant heterogeneity ($I^2 = 0.0\%$, $P_Q = 0.788$). However, pooled results suggested that high MALAT1 expression was not correlated with age (adult

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

Study	Year	Country	Sample size(F/M)	Detection method	High expression (n/%)	HR	Tumor size (large, cm)	Outcomes	NOS
Dong YQ	2014	China	19(7/12)	qRT-PCR	14/73.68%	NA	NA(T3 + 4)	CPF	6
Gao KT	2016	China	162(89/73)	qRT-PCR	80/49.38%	Reported	≥8	OS, CP	6
Wang JT	2017	China	70(NA)	qRT-PCR	29/41.43%	Calculated	NA	OS	6
Li QB	2017	China	64(25/39)	qRT-PCR	43/67.19%	Reported	≥6	OS, CP	7
Huo YQ	2017	China	68(29/39)	qRT-PCR	45/66.18%	Calculated	≥6	OS, CP	6
Sun YX	2018	China	42(22/20)	qRT-PCR	26/61.90%	Calculated	≥5	OS, CP	6
Chen Y	2018	China	68(NA)	qRT-PCR	NA	Reported	≥8	OS	6
Duan GC	2018	China	30(13/17)	qRT-PCR	16/53.33%	NA	≥8	CP	6
Sun ZY	2019	China	76(53/23)	qRT-PCR	23/30.26%	Calculated	NA	OS	6

F/M, Female/male; HR, hazard ratio; NOS, Newcastle–Ottawa–Scale; CP, clinical parameters; OS, overall survival.

vs juvenile: OR = 1.373, 95 %CI: 0.791 to 2.384, $P = 0.260$), gender (female vs male: OR = 0.791, 95 %CI: 0.478 to 1.308, $P = 0.360$), anatomic location (tibia/femur vs elsewhere: OR = 0.793, 95 %CI: 0.440 to 1.431, $P = 0.441$) or tumor size (large vs small: OR = 2.012, 95 %CI: 0.530 to 7.643, $P = 0.304$). Begg's funnel plot and Harbord's modified test were performed to access publication bias among studies. Diagrams of the funnel plot revealed symmetry among clinicopathological outcomes (Fig. 3). Moreover, Harbord's modified test indicated no publication bias for age ($P = 0.400$), gender ($P = 0.451$), tumor size ($P = 0.160$), clinical stage or distant metastasis ($P = 0.961$).

3.4. Meta-analyses of OS

Seven eligible studies reported the number of patients with OS, based on different MALAT-1 expression levels [13,15,17–21]. Due to the lack of heterogeneity between studies ($I^2 = 0.0\%$, $P_Q = 0.517$), the fixed-effect model was used to calculate pooled HR. As shown in Fig. 4A, elevated MALAT-1 expression predicted unfavorable OS in patients living with osteosarcoma (HR = 2.125, 95 %CI: 1.672 to 2.701, $P < 0.001$). Begg's funnel plots and Harbord's modified test were used to assess publication bias for OS. The shape of the funnel plot showed no evidence of asymmetry (Fig. 4B). Furthermore, results of Harbord's modified test demonstrated no obvious publication bias for OS ($P = 0.169$). Sensitivity analysis was performed in order to assess the stability of pooled HR. Results were not significantly influenced when any study was omitted, which confirms the robustness of our conclusion that elevated MALAT1 expression is associated with an unfavorable survival outcome in patients living with osteosarcoma (Fig. 6).

3.5. Independent prognostic value of MALAT1 in osteosarcoma

The independent prognostic value of MALAT-1 in osteosarcoma was measured based on the multivariate analysis in two studies with a total of 228 patients [13,18]. As shown in Fig. 5A, pooled results suggested that MALAT-1 had the potential to be an independent prognostic factor for OS in patients with osteosarcoma (HR = 3.31, 95% CI = 1.98 to 5.53, $P < 0.001$), with no significant heterogeneity ($I^2 = 0.0\%$, $P_{Q=}$ 0.865). The shape of the funnel plot was symmetrical (Fig. 5B).

4. Discussion

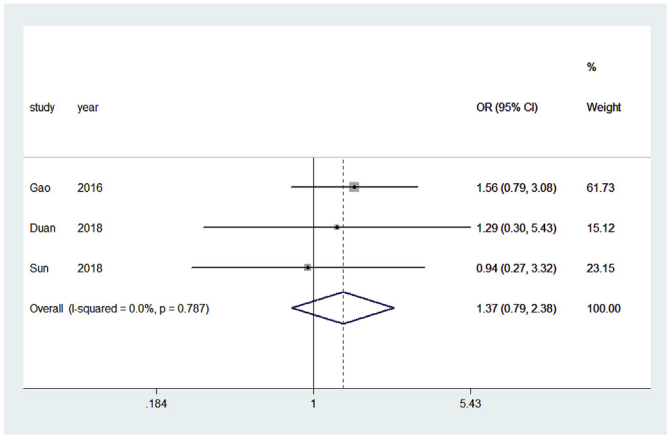
Osteosarcoma is the most common malignant bone tumor and is characterized by highly aggressive and rapid metastasis [22]. The five-year survival rate is approximately 77.3% for patients without metastasis, which declines to 33.9% for patients with metastasis [23]. It is therefore crucial to explore the underlying molecular mechanisms of OS and to identify novel reliable diagnostic biomarkers and effective therapeutic targets. Recently, accumulating evidence has indicated that lncRNAs have emerged as important regulators in the pathogenesis, diagnosis and prognosis of osteosarcoma [24]. Therefore, lncRNAs may hold a great promise for the early diagnosis of osteosarcoma and serve as prospective antitumor targets. Here, we focused on lncRNAs MALAT1, which has been shown to be involved in the development of osteosarcoma.

MALAT1, one of the first reported cancer-associated lncRNAs, is overexpressed in human osteosarcoma cells and is significantly associated with osteosarcoma's progression [9]. It has been suggested that up-regulated MALAT1 accelerated proliferation and metastasis by acting as ceRNA of miR-144–3p as well as miR-140–5p in osteosarcoma cells [17,25]. Silencing MALAT1 slowed the pro-angiogenic effects of osteosarcoma and thus inhibited tumor growth [12]. Several studies have also indicated that PI3K/Akt and Rac1/JNK pathways play critical roles in mediating osteosarcoma progression and metastasis [8,15,26]. Therefore, MALAT1 appears to function as a prospective therapeutic target for people living with osteosarcoma [27,28].

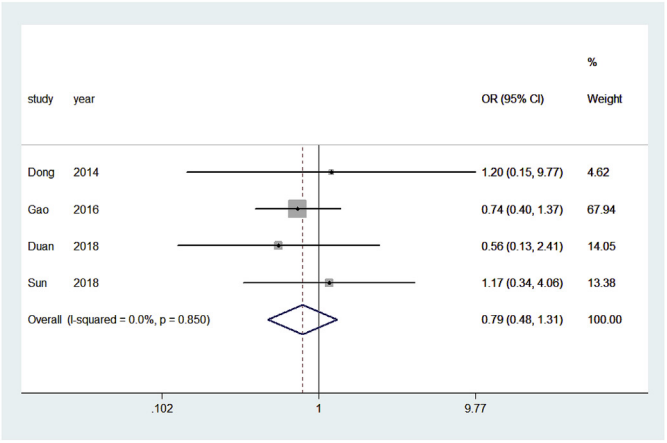
Interestingly, the ectopic expression of MALAT1 in osteosarcoma tissues and cells can predict overall survival and also act as a prognostic biomarker in this disease. High levels of MALAT1 with a shorter survival time suggest that MALAT1 may be considered as a prognostic biomarker for osteosarcoma [13]. The study by Huo and colleagues found that MALAT1 was a potential diagnostic and prognostic factor in patients with osteosarcoma [19]. While some studies with small sample sizes have investigated the correlation between MALAT1 expression and clinicopathological features of osteosarcoma, the significance of MALAT1 for predicting prognosis and metastasis of osteosarcoma remains unknown and controversial.

To the best of our knowledge, this is the first meta-analysis which evaluated the association between the MALAT1 level and clinical prognosis in osteosarcoma. This meta-analysis has been conducted comprehensively in order to explore the prognostic value of MALAT1 expression in osteosarcoma. An advanced tumor clinical stage and distant metastasis were found in patients with high MALTA expression compared to those with a low MALTA expression. Combined results also demonstrated that patients with an elevated MALAT1 expression were associated with worse OS. Moreover, data based on the multivariate analysis in two of the studies indicated that a high MALAT1 expression can act as an independent prognostic factor for OS in patients living with osteosarcoma. Therefore, our study suggests that MALAT1 could be used to forecast the prognosis of patients living with osteosarcoma.

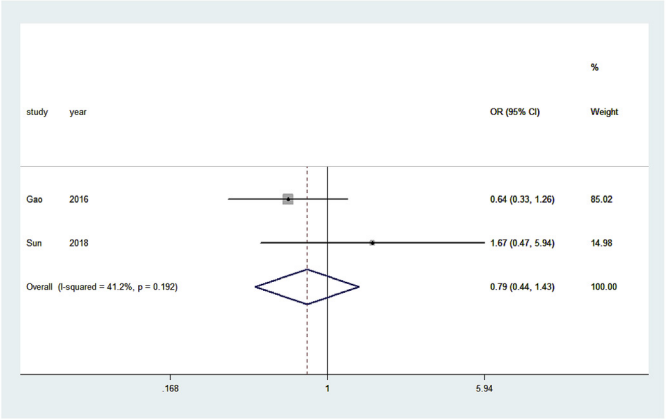
However, there are several limitations to the present meta-analysis. Firstly, only nine studies were included, and all studies were undertaken in China. The small sample size of the eligible literature may weaken the validity of the pooled results. Results may also be more relevant to the Chinese population, meaning that caution should be used when applying these findings to other ethnic populations. Secondly, six of the studies failed to provide HRs with their corresponding 95% CIs of OS. We calculated these indirectly by reconstructing Kaplan-Meier survival curves. Thirdly, the value of lncRNA expression and tumor size were different in each study, which again may influence the strength of pooled results. Fourthly, many confounding factors such as different clinical stages, treatment timing,



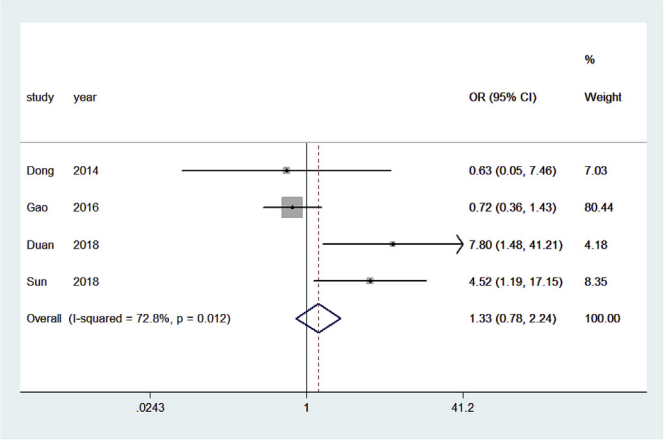
A, age



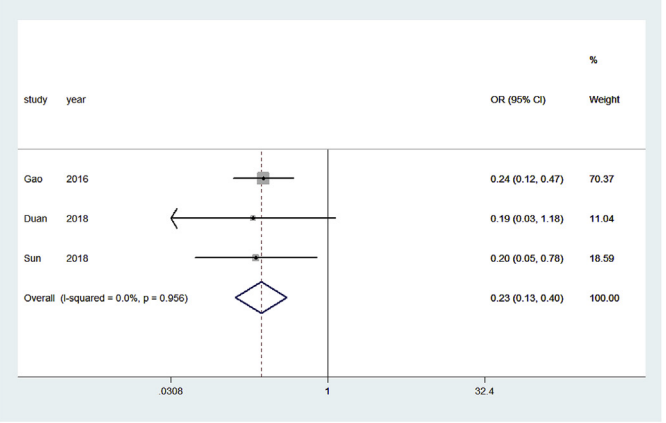
B, gender



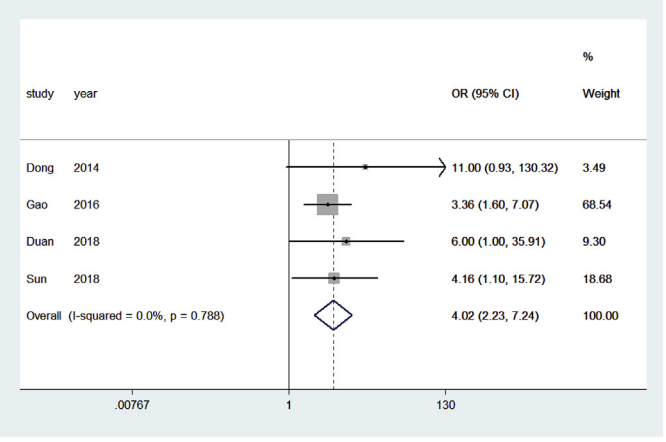
C, Tumor anatomical location



D, Tumor size



E, clinical stage

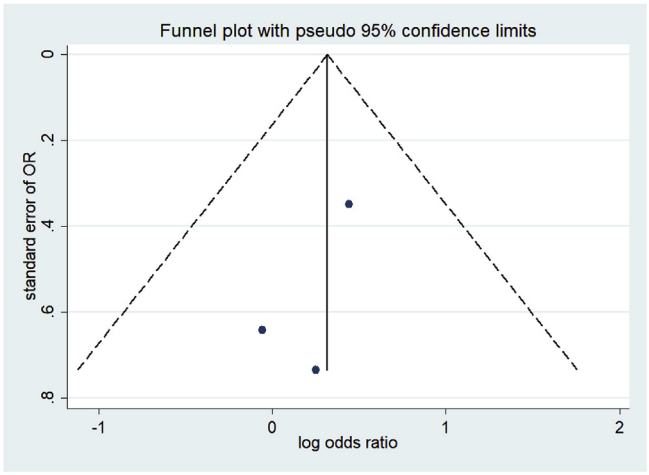


F, distant metastasis

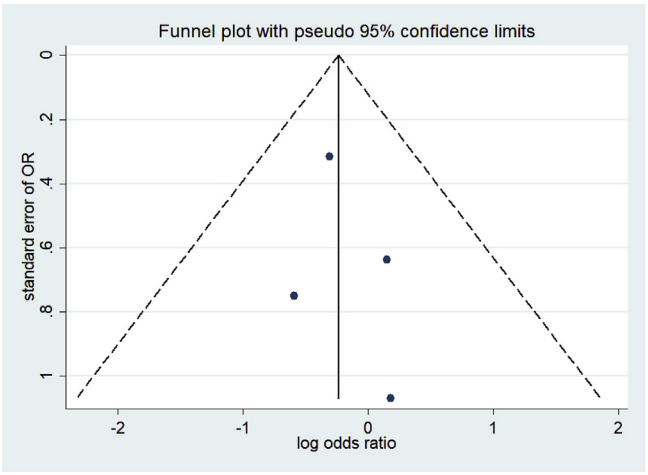
Fig. 2. Forest plot for the meta-analysis of clinical parameters. A, age; B, gender; C, anatomical location; D, tumor size; E, clinical stage; F, distant metastasis.

Table 2
The meta-analyses of clinical parameters.

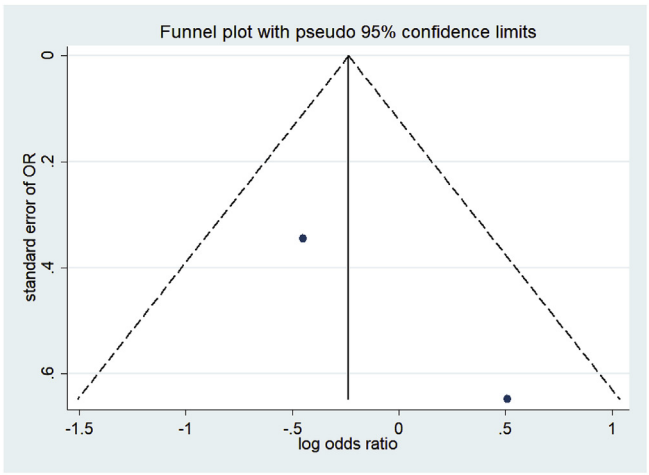
Variables	No. of studies	Patients(n)	OR 95% CI	*P*	I^2	P_Q	Model
Age	3	234	1.373[0.791,2.384]	0.260	0.0%	0.787	fixed
Gender	4	253	0.791[0.478,1.308]	0.360	0.0%	0.850	fixed
Anatomic location	2	204	0.793[0.440,1.431]	0.441	41.2%	0.192	fixed
Tumor size	4	253	2.012[0.530,7.643]	0.304	72.8%	0.012	random
Clinical stage	3	234	0.227[0.129,0.400]	0.000	0.0%	0.956	fixed
Distant metastasis	4	253	4.019[2.230,7.244]	0.000	0.0%	0.788	fixed



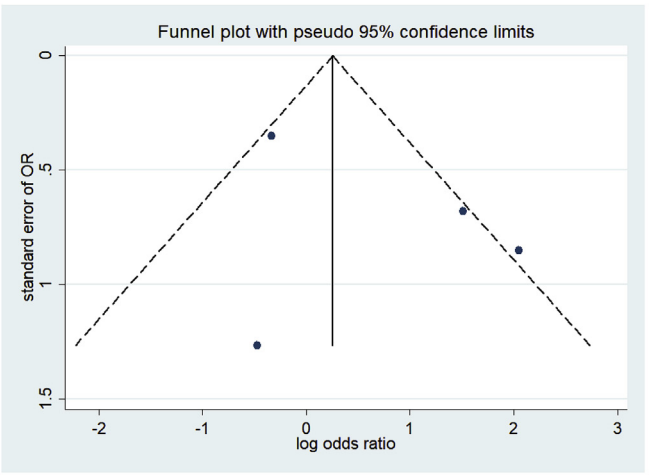
A, age



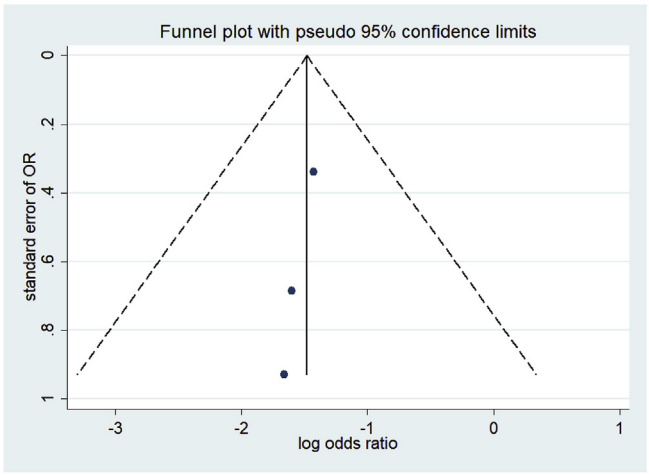
B, gender



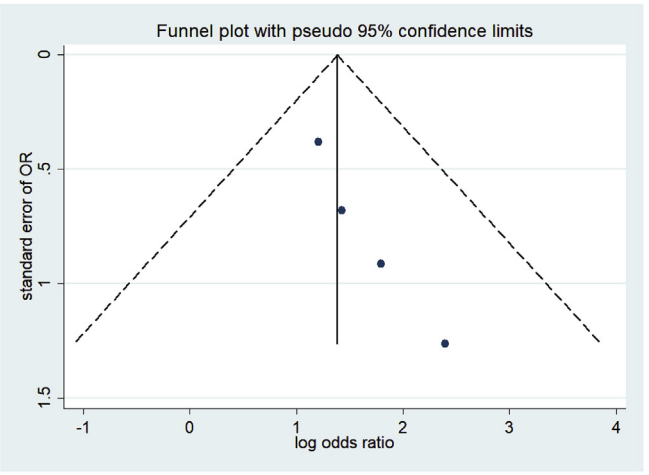
C, anatomical location



D, tumor size



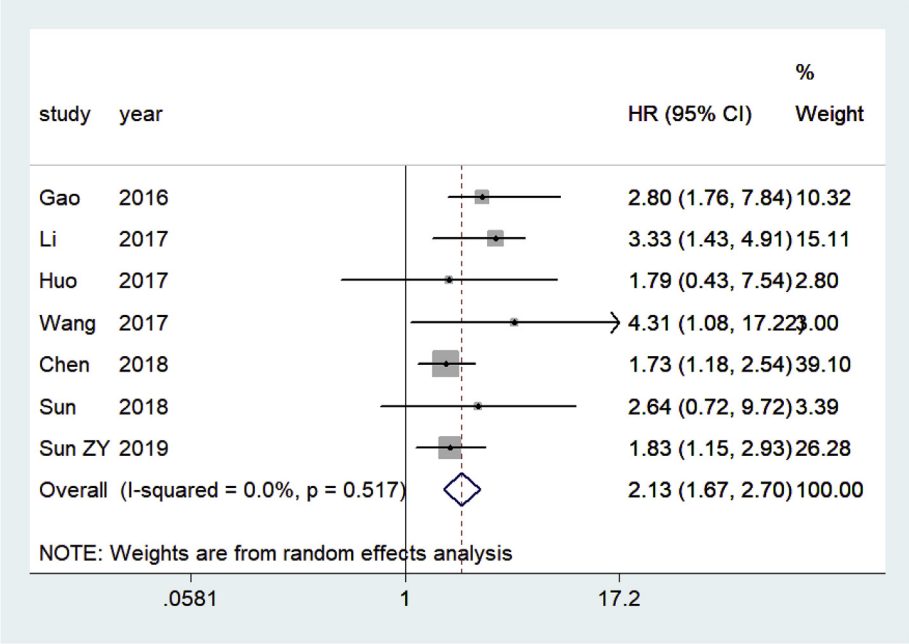
E, clinical stage



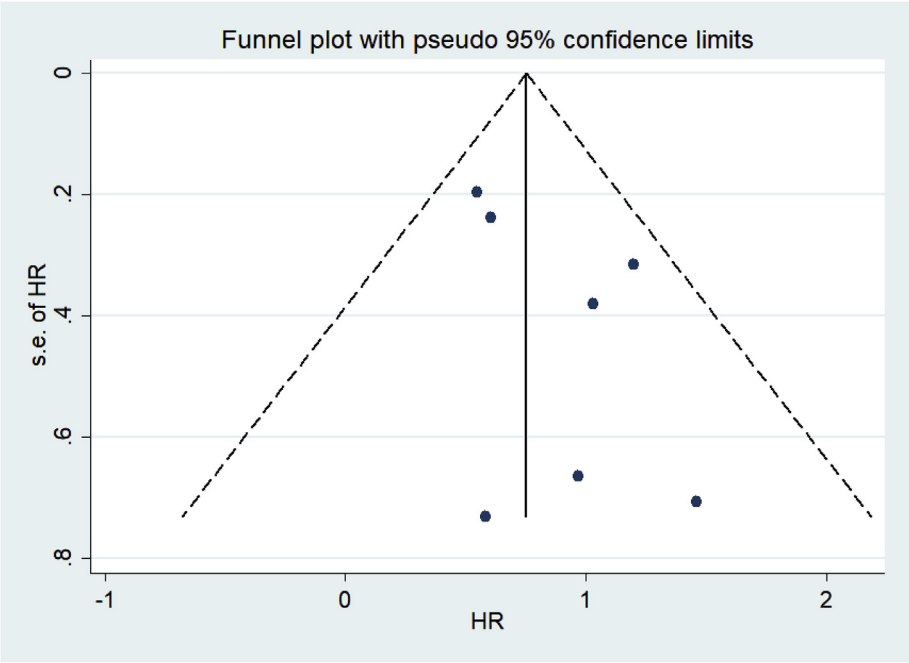
F, distant metastasis

Fig. 3. Begg's funnel plots for clinical parameters related studies. A, age; B, gender; C, anatomical location; D, tumor size; E, clinical stage; F, distant metastasis.

therapies and concomitant diseases may affect the prognosis of osteosarcoma patients. Fifthly, due to the limited research, results failed to detect prognostic value in several important clinicopathological features, including any association between MALAT1 and tumor size. In addition, it should be mentioned that the clinical parameters listed in the study by Sun et al. [17] could not draw the conclusion described in their results section, which claimed that higher MALAT1 was strongly correlated with advanced staging (IIB/III), bigger tumor size and distant metastasis. After careful calculation, we believe that these authors have mistaken lines of high expression and low expression in the clinical parameters table, which meant that patients with low expression were in fact patients with high expression. Unfortunately, the authors



A, forest plot for the meta-analysis of OS



B, Begg's funnel plot of OS related studies

Fig. 4. Forest plots and Begg's funnel plot of studies to evaluate the relation between MALAT1 expression and overall survival (OS). A, forest plot for the meta-analysis of OS; B, Begg's funnel plot of OS related studies.

did not respond to our queries. In this study, we extracted patients of low expression for the meta-analysis of the association between high MALAT1 expression and clinical parameters.

5. Conclusion

Our results suggested that highly expressed MALAT1 in osteosarcoma is associated with advanced clinicopathological features and unfavorable OS. MALAT1 has the potential to serve as a moderate prognostic biomarker for patients living with osteosarcoma. However, large-scale and high-quality studies are needed to validate the efficacy of MALAT1 for the prognosis of osteosarcoma.

Ethical approval

All analyses were based on published studies and no ethical approval were required.

Sources of funding

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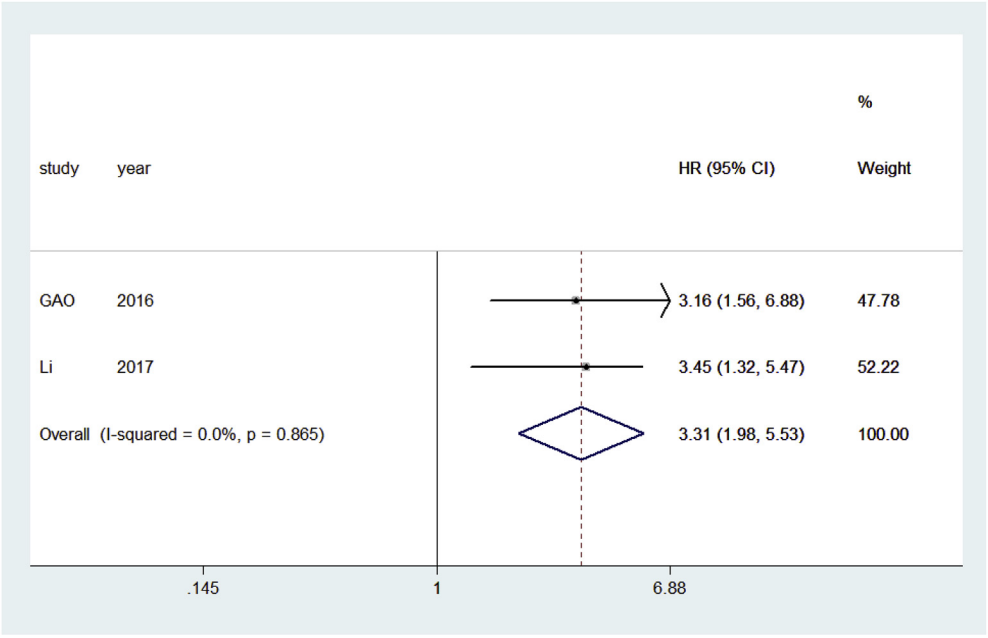
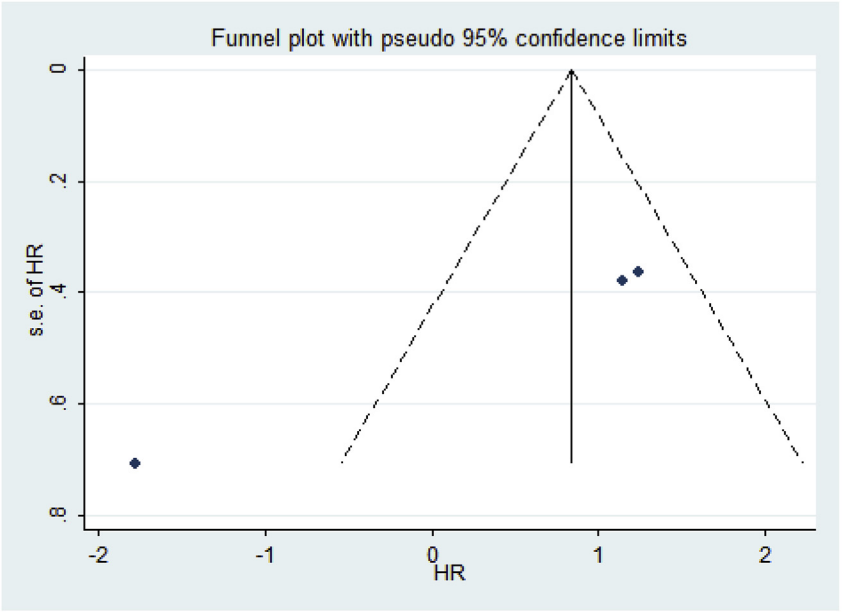


A, forest plot for the meta-analysis of independent predictive factor



B, Begg's funnel plot of independent predictive factor related studies

Fig. 5. Forest plots and Begg's funnel plot of independent predictive factor related studies. A, forest plot for the meta-analysis of independent predictive factor; B, Begg's funnel plot of independent predictive factor related studies.

Author contribution

Conceptualization: Hong Sun, Jin Deng, Hua Yang.
Data curation: Miao Liu, Peng Yang, Guping Mao.
Formal analysis: Guping Mao, Guoxuan Peng.
Funding acquisition: Jin Deng.
Methodology: Ning Xu, Hua Yang.
Writing-original draft: Miao Liu, Guping Mao, Hong Sun.
Writing-review & editing: Xu Ning, Hua Yang, Hong Sun.

Trial registry number

This study has been registered in PROSPERO and the registration number is CRD42019135916.
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=135916.

Guarantor

Miao Liu and Hong Sun.

Provenance and peer review

Not commissioned, externally peer-reviewed.

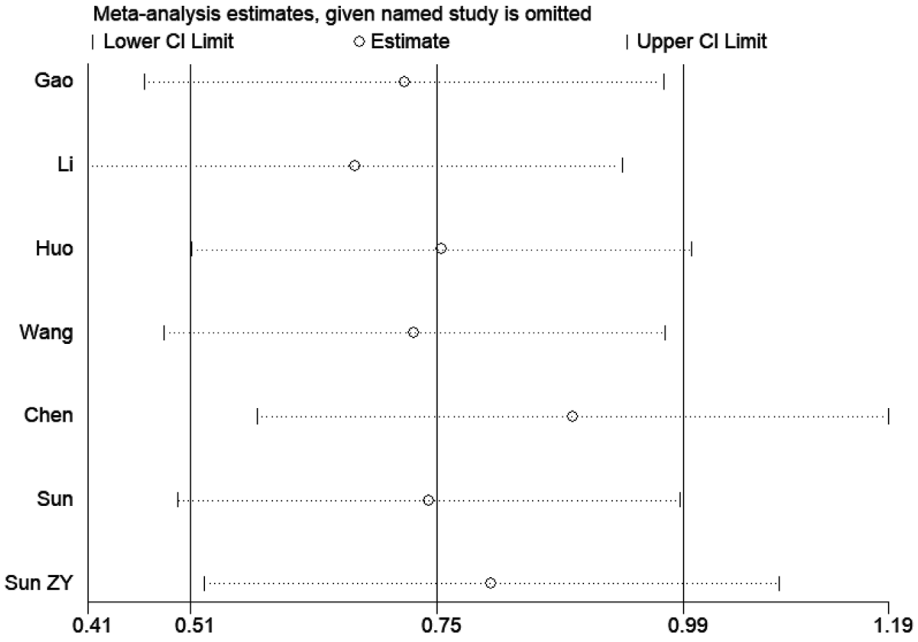


Fig. 6. Sensitivity analysis for overall survival (OS).

Data statement

The data used to support the findings of this study are included within the article. The primary data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

All authors declare that there is no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.11.004.

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