The value of IncRNAs as prognostic biomarkers on clinical outcomes in osteosarcoma: a meta-analysis

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Abstract

Background: In recent years, emerging studies have demonstrated critical functions and potential clinical applications of long non-coding RNA (lncRNA) in osteosarcoma. To further validate the prognostic value of multiple IncRNAs, we have conducted this updated meta-analysis.

Methods: Literature retrieval was conducted by searching PubMed, Web of Science and the Cochrane Library (last update by October 2, 2019). A meta-analysis was performed to explore association between IncRNAs expression and overall survival (OS) of osteosarcoma patients. Relationships between IncRNAs expression and other clinicopathological features were also analyzed respectively.

Results: Overall, 4351 patients from 62 studies were included in this meta-analysis and 25 lncRNAs were identified. Pooled analyses showed that high expression of 14 lncRNAs connoted worse OS, while two lncRNAs were associated with positive outcome. Further, analysis toward osteosarcoma clinicopathologic features demonstrated that overexpression of TUG1 and XIST indicated poor clinical parameters of patients.

Conclusions: This meta-analysis has elucidated the prognostic potential of 16 lncRNAs in human osteosarcoma. Evidently, desperate expression and functional targets of these lncRNAs offer new approaches for prognosis and therapy of osteosarcoma.

Keywords: LncRNAs, Osteosarcoma, Meta-analysis, Prognosis

Background

Osteosarcoma is the most common primary bone malignancy with an annual incidence of 3.1 per million [1]. Despite various treatments, such as chemotherapy, radiotherapy, surgery and targeted therapy, have been used for osteosarcoma, the prognosis remains poor [2, 3]. Of note, the 5-year survival rate for children and adults with non-metastatic osteosarcoma is 71.8%, while for patients with metastatic osteosarcoma dramatically decrease to 30.4% [4, 5]. Therefore, identification of new prognostic or therapeutic hallmarks are in urgent need to improve current situation. In fact, numerous studies have been conducted upon this issue in recent years, and some have shed light on the roles of multiple molecules, including RNAs, regulatory proteins, etc. [6–8]

With advancement of next-generation sequencing technologies, several kinds of non-coding RNAs (ncRNAs) have been discovered, such as the miRNA, siRNA, snoRNA, piRNA and lncRNA. LncRNAs, a cluster of non-coding RNA with more than 200 nucleotides, show no potential of protein coding but exert crucial functions in maintenance of the cellular homeostasis [9]. Mechanisms of lncRNAs in biological processes contain chromatin modifications, transcriptional modifications.
and post-transcriptional modifications that regulate the expression and features of other genes [10]. They have been elucidated to play critical roles in the development of various diseases, especially tumors [11]. Gouri et al. have reviewed the roles of LncRNAs in pancreatic ductal adenocarcinoma in which they demonstrated that LncRNAs closely associated with the tumorigenesis, partially through dysregulating the KRAS pathway. And it was noticed that the expression level of multiple LncRNAs were altered in tissue, plasma or serum specimens of pancreatic cancer patients, which support the idea that LncRNAs may serve as therapeutic biomarker for pancreatic ductal adenocarcinoma [12]. Moreover, researchers have demonstrated functional mechanisms of LncRNAs in regulating multiple physiological and pathophysiological processes by interacting with other intrinsic molecules [13]. Notably, roles of LncRNAs in progression, prognosis and metastasis of osteosarcoma have been broadly identified [14]. And circulating LncRNAs showed significant potential in osteosarcoma prognosis [15]. To further demonstrate the roles and prognostic potential of LncRNAs in osteosarcoma, we have conducted this meta-analysis.

Methods

Literature search strategy

Two independent researchers retrieved the published literature from database of Pubmed, Web of Science and Cochrane Library at the same time. Search terms used were the following: (osteosarcoma OR “osteogenic sarcoma”) AND (“long non-coding RNA” OR LncRNA OR “LINC RNA” OR “Long ncRNAs”). The last research time was October 2, 2019.

Selection criteria

A total of 550 articles were initially identified after removal of duplication. Two independent researchers (Wenchao Zhang and Xiaolei Ren) reviewed the title, abstract and full-text of all included articles. Articles that met the following criteria were included: (1) Research topic related to the LncRNAs expression and osteosarcoma prognosis; (2) the survival outcome was available in OS form and shown in table, Kaplan-Meier curve or HR value; (3) patients were divided into two groups based on the expression of LncRNAs (high versus low). The exclusive criteria were: (1) the review, case report, conference abstract, letters, sequencing data, bioinformatics analysis, retreated articles and meta-analysis; (2) survival data was obtained from online database such as the TCGA; (3) when more than one study reported on the same patient cohort, only the most recent one was included. Disagreements between the two reviewers were discussed to reach an consensus.

Data extraction and quality assessment

All articles were reviewed by two independent well-trained investigators to retrieve available data. The following information was listed for all articles: Name of first author, publication year, country where study conducted, detection method, sample number, LncRNA type, tumor stage, follow-up time, cut-off value, survival data (multivariate analysis was prioritized if both the univariate and multivariate analysis were provided), outcome measure, Hazard ratio (HR) of LncRNAs expression for OS and the corresponding 95% CI. If HR and 95% CI were not directly provided while a Kaplan-Meier curve was available, we retrieved the HR and 95% CI by using Engauge Digitizer version 4.1 and Tierney’s method as previously described [16]. Then, the quality of the included studies was assessed by two independent reviewers (Wenchao Zhang and Xiaolei Ren) following the Newcastle-Ottawa Scale (NOS) [17].

Statistical analysis

Stata 12.0 (Stata Corporation, TX, USA) and Review Manager 5.3 (The Cochrane Collaboration, 2014.) were used in this meta-analysis to pool the HR and its 95% CI. Q-test was applied to evaluate the heterogeneity among the studies [18]. If the heterogeneity was substantial (I^2 > 50%, P < 0.05), the random effect model would be adopted, otherwise the fixed effect model would be used. A pooled HR > 1 connoted a poor prognosis in patients with LncRNAs overexpression, while a pooled HR < 1 supported a better prognosis. P < 0.05 was considered statistically significant. LncRNAs that have been studied in more than two articles were included to further analyze the clinical parameters, aiming to figure out the association between clinical parameters and LncRNAs expression. Publication bias was measured by Begg’s and Egger's tests [19].

Results

Characteristics of included studies

Overall, 62 articles comprising 4351 patients were recruited in our study after selection by following the criteria. The study filtrating process was shown in Fig. 1. Among the included 62 articles, 25 LncRNAs were identified and only four have been studied in more than three articles. The most extensively studied LncRNA was Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), which was shown in eight articles, followed by Taurine up-regulated gene 1 (TUG1), X-inactive specific transcript (XIST) and Nuclear enriched abundant transcript 1 (NEAT1). Almost all of the studies were conducted in China while only one study originated from Brazil. All the articles...
were published between 2015 and 2019, mostly in 2018 and 2019. The sample number in the selected studies ranged from 30 to 204. All studies used quantitative real-time polymerase chain reaction (qRT-PCR) to measure the expression of lncRNAs, and tissue was the most widely used sample. The cut-off values of lncRNAs expression varied among studies, mainly including median, optimal or mean value. The specific information was shown in Table 1. The quality evaluation showed that NOS scores of all the included studies were greater than 5 (Additional Figures S1 and S2).

**Overexpression of lncRNAs indicate different prognosis of osteosarcoma**

In this meta-analysis, 25 lncRNAs were analyzed individually. The result showed that overexpression of 14 lncRNAs were associated with poor prognosis while two indicated a positive outcome. The overexpression of the rest nine lncRNAs were independent of osteosarcoma prognosis (Table 2).

More attention was paid to the four most studied lncRNAs among all included studies, the MALAT1, TUG1, XIST and NEAT1. For MALAT1, eight articles included 605 patients were pooled. Overexpression of
### Table 1: The main characteristics of the included studies in the meta-analysis

| ID | Study | country | LncRNA name | Sample number | Tumor stage | Distant metastasis | Follow-up (months) | Detected sample | Detection method | Cut-off value | Survival analysis | Outcome measure | HR (95% CI) |
|----|-------|---------|-------------|---------------|-------------|-------------------|-------------------|-----------------|-----------------|--------------|----------------|----------------|-------------|
| 1  | Ju L (2016) [20] | China | BCAR4 | 168 | IIA-IIB/III | 48 | 70 | tissue | qRT-PCR | median | Multivariate analysis | OS | 3.22 (0.89, 7.88) |
| 2  | Chen F (2016) [21] | China | BCAR4 | 60 | I-II | 13 | 60 | tissue | qRT-PCR | median | N/A | OS/RFS | 1.83 (0.68, 4.96) |
| 3  | Ruan R (2018) [22] | China | CCAT2 | 50 | IA-III | 16 | 70 | tissue | qRT-PCR | median | N/A | OS | 1.30 (0.29, 5.79) |
| 4  | Yan L (2018) [23] | China | CCAT2 | 40 | N/A | N/A | 60 | tissue | qRT-PCR | N/A | N/A | OS/RFS | 3.57 (0.89, 14.18) |
| 5  | Jiang N (2017) [24] | China | DANCR | 34 | N/A | 18 | 60 | tissue | qRT-PCR | median | N/A | Multivariate analysis | OS/DFS | 1.08 (1.23, 5.79) |
| 6  | Wang Y (2018) [25] | China | DANCR | 95 | I-III | 58 | 60 | tissue | qRT-PCR | optimal | N/A | OS | 2.4 (0.85, 3.25) |
| 7  | Fei D (2018) [26] | China | FER1L4 | 48 | I-IV | 10 | 60 | tissue | qRT-PCR | median | N/A | OS/PFS | 0.45 (0.17, 0.97) |
| 8  | Chen Z (2018) [27] | China | FER1L4 | 73 | I-IV | 25 | 60 | tissue | qRT-PCR | median | N/A | OS/PFS | 0.43 (0.05, 0.86) |
| 9  | Ren Z (2019) [28] | China | FOXD2-AS1 | 35 | I-II | N/A | 60 | tissue | qRT-PCR | median | N/A | OS | 1.55 (0.31, 7.82) |
| 10 | Zhang H (2019) [29] | China | FOXD2-AS1 | 40 | N/A | N/A | 60 | tissue | qRT-PCR | median | N/A | OS | 1.66 (0.45, 5.82) |
| 11 | Cai L (2017) [30] | China | HNF1A-AS1 | 72 | IIA-III | 42 | <60 | tissue | qRT-PCR | median | Multivariate analysis | OS | 2.63 (1.53, 5.65) |
| 12 | Zhao H (2016) [31] | China | HNF1A-AS1 | 43 | I-II | 11 | 60 | tissue | qRT-PCR | median | N/A | OS | 2.64 (1.39, 5.42) |
| 13 | Cao K (2019) [32] | China | HOXA11-AS1 | 61 | I-II | 17 | 60 | tissue | qRT-PCR | median | N/A | OS | 1.5 (0.43, 5.26) |
| 14 | Cui M (2017) [33] | China | HOXA11-AS1 | 51 | I-II | 13 | 60 | tissue | qRT-PCR | median | N/A | OS | 3.22 (0.31, 33.42) |
| 15 | Gu W (2018) [34] | China | HOXD-AS1 | 43 | I-III | N/A | 60 | tissue | qRT-PCR | median | N/A | OS | 1.63 (1.19, 2.96) |
| 16 | Qu Y (2018) [35] | China | HOXD-AS1 | 46 | I-II | 11 | 60 | tissue | qRT-PCR | median | N/A | OS | 1.9 (1.53, 5.68) |
| 17 | Maciel Uzan (2016) [36] | Brazil | HULC | 33 | I-II | 10 | 100 | tissue | qRT-PCR | optimal | Multivariate analysis | OS/EFS | 22.01 (2.26, 16.13) |
| 18 | Sun X (2015) [37] | China | HULC | 78 | IIA-III | 21 | 60 | tissue | qRT-PCR | median | N/A | OS | 2.28 (1.48, 5.43) |
| 19 | He W (2019) [38] | China | LSINCT5 | 124 | I-II | 22 | 72 | tissue | qRT-PCR | median | Multivariate analysis | OS | 1.68 (1.02, 2.76) |
| 20 | Kong D (2018) [39] | China | LSINCT5 | 42 | I-II | 18 | 60 | tissue | qRT-PCR | N/A | N/A | OS/DFS | 1.39 (1.13, 5.68) |
| 21 | Chen Y (2018) [40] | China | MALAT1 | 68 | N/A | N/A | 60 | tissue | qRT-PCR | median | Multivariate analysis | OS | 2.22 (0.31, 16.49) |
| 22 | Gao K (2016) [41] | China | MALAT1 | 162 | I-III | 44 | 70 | tissue | qRT-PCR | median | N/A | OS | 2.81 (1.48, 5.43) |
| 23 | Huo Y (2017) [42] | China | MALAT1 | 68 | I-II | 33 | 60 | tissue | qRT-PCR | median | N/A | OS | 2.24 (0.72, 7.99) |
| 24 | Li Q (2017) [43] | China | MALAT1 | 64 | I-II | 33 | 60 | tissue | qRT-PCR | optimal | Multivariate analysis | OS | 2.13 (0.43, 9.61) |
| 25 | Sun Z (2018) [44] | China | MALAT1 | 42 | I-II | 20 | 60 | tissue | qRT-PCR | median | N/A | OS | 2.22 (1.13, 5.68) |
| 26 | Sun Z (2019) [45] | China | MALAT1 | 76 | I-II | 46 | 120 | tissue | qRT-PCR | median | N/A | OS | 2.51 (1.16, 5.38) |
| 27 | Wang J (2017) [46] | China | MALAT1 | 70 | N/A | N/A | <60 | tissue | qRT-PCR | median | N/A | OS | 2.34 (0.56, 11.31) |
| 28 | Wang Y (2017b) [47] | China | MALAT1 | 55 | I-II | 31 | 60 | tissue | qRT-PCR | median | N/A | OS | 2.09 (0.56, 8.21) |
| 29 | Shen B (2019) [48] | China | MEG3 | 204 | I-II | 80 | 50 | tissue | qRT-PCR | median | Multivariate analysis | OS | 1.88 (0.47, 7.49) |
| 30 | Tian Z (2015) [49] | China | MEG3 | 64 | I-II | 90 | 60 | tissue | qRT-PCR | median | N/A | OS | 1.9 (1.53, 5.68) |
| 31 | J S (2019) [50] | China | NEAT1 | 72 | I-II | 76 | 120 | tissue | qRT-PCR | median | N/A | OS | 2.34 (0.56, 11.31) |
| 32 | LI (2018) [51] | China | NEAT1 | 76 | I-II | 38 | 60 | tissue | qRT-PCR | median | N/A | OS | 1.88 (0.47, 7.49) |
| ID  | Study            | country | LncRNA name | Sample number | Tumor stage | Distant metastasis | Follow-up (months) | Detected sample | Detection method | Cut-off value | Survival analysis | Outcome measure | HR (95% CI)       |
|-----|------------------|---------|-------------|---------------|-------------|------------------|-------------------|-----------------|-----------------|---------------|------------------|-----------------|------------------|
| 33  | Tan H (2019)     | China   | NEAT1       | 47            | I-III       | 11               | 50                | tissue          | qRT-PCR         | median         | N/A              | OS              | 1.84 (0.61, 5.57) |
| 34  | Zhu K (2019)     | China   | OIP5-AS1    | 80            | N/A         | 60               | tissue            | qRT-PCR         | N/A             | N/A            | OS              | 1.48 (0.42, 5.15) |
| 35  | Dai J (2018)     | China   | OIP5-AS1    | 48            | I-III       | 60               | tissue            | qRT-PCR         | median          | N/A            | OS              | 1.77 (1.17, 2.94) |
| 36  | Zhang C (2016)   | China   | ODRUL       | 60            | N/A         | 12               | 80                | tissue          | qRT-PCR         | median          | N/A            | OS              | 1.21 (0.36, 4.06) |
| 37  | Zhu K (2017)     | China   | ODRUL       | 80            | N/A         | 48               | 100               | tissue          | qRT-PCR         | N/A            | N/A            | OS              | 2.35 (1.08, 5.15) |
| 38  | Huang J (2018)   | China   | PCAT1       | 62            | I-III       | 35               | 60                | tissue          | qRT-PCR         | median          | N/A            | Multivariate analysis | OS/PFS | 1.53 (1.37, 2.92) |
| 39  | Zhang X (2018)   | China   | PCAT1       | 30            | I-III       | 17               | 60                | tissue          | qRT-PCR         | mean           | N/A            | OS              | 4.01 (1.56, 4.57) |
| 40  | Song J (2017)    | China   | PVT1        | 46            | I-III       | 70               | tissue            | qRT-PCR         | mean           | N/A            | OS              | 1.63 (0.05, 3.59) |
| 41  | Zhou Q (2016)    | China   | PVT1        | 53            | N/A         | 13               | 60                | tissue          | qRT-PCR         | median          | N/A            | OS              | 1.70 (0.66, 4.37) |
| 42  | Zhou B (2018)    | China   | SNHG12      | 64            | N/A         | 80               | tissue            | qRT-PCR         | N/A             | N/A            | OS              | 2.10 (0.66, 6.64) |
| 43  | Zhou S (2018)    | China   | SNHG12      | 31            | I-III       | 21               | 60                | tissue          | qRT-PCR         | mean           | N/A            | OS              | 1.52 (1.00, 1.84) |
| 44  | Liao S (2019)    | China   | SNHG16      | 96            | I-III       | 51               | 60                | tissue          | qRT-PCR         | median          | N/A            | Multivariate analysis | OS      | 1.58 (0.65, 3.86) |
| 45  | Wang X (2019)    | China   | SNHG16      | 65            | I-III       | 28               | 60                | tissue          | qRT-PCR         | median          | N/A            | OS              | 2.62 (0.82, 8.36) |
| 46  | Wang W (2018)    | China   | SNHG20      | 32            | I-III       | 60               | tissue            | qRT-PCR         | median          | N/A            | OS              | 1.94 (1.19, 3.17) |
| 47  | Zhang J (2018)   | China   | SNHG20      | 140           | I-III       | 24               | 72                | tissue          | qRT-PCR         | N/A            | Multivariate analysis | OS      | 2.05 (0.53, 7.92) |
| 48  | Chen X (2019)    | China   | TP73-AS1    | 132           | I-III       | 22               | 72                | tissue          | qRT-PCR         | N/A            | Multivariate analysis | OS      | 1.89 (1.15, 3.13) |
| 49  | Yang G (2018)    | China   | TP73-AS1    | 46            | I-III       | 11               | 50                | tissue          | qRT-PCR         | mean           | N/A            | OS              | 1.98 (0.61, 6.28) |
| 50  | Ma B (2016)      | China   | TUG1        | 76            | I-III       | 36               | 60                | tissue          | qRT-PCR         | optimal         | Multivariate analysis | OS/PFS | 2.77 (1.29, 5.98) |
| 51  | Sheng K (2019)   | China   | TUG1        | 40            | N/A         | 26               | 60                | plasma          | qRT-PCR         | median          | N/A            | OS              | 1.59 (1.36, 1.97) |
| 52  | Wang Q (2018)    | China   | TUG1        | 94            | IIA - III    | 26               | 70                | tissue          | qRT-PCR         | median          | Multivariate analysis | OS      | 1.10 (0.96, 1.53) |
| 53  | Wang Y (2017a)   | China   | TUG1        | 44            | I-III       | 28               | 120               | tissue          | qRT-PCR         | median          | N/A            | OS              | 2.12 (1.44, 3.67) |
| 54  | Yu X (2019)      | China   | TUG1        | 40            | I-III       | 11               | 60                | tissue          | qRT-PCR         | N/A            | N/A            | OS              | 1.59 (1.15, 2.54) |
| 55  | Li W (2016)      | China   | UCA1        | 135           | I-III       | 34               | 60                | tissue          | qRT-PCR         | median          | Multivariate analysis | OS      | 2.19 (0.87, 5.55) |
| 56  | Wen J (2017)     | China   | UCA1        | 151           | IIA - III    | 79               | 60                | tissue          | qRT-PCR         | optimal         | Multivariate analysis | OS      | 2.52 (1.34, 4.83) |
| 57  | Li G (2017)      | China   | XIST        | 145           | I-IV        | 44               | 60                | tissue          | qRT-PCR         | N/A            | N/A            | OS              | 1.75 (1.00, 3.06) |
| 58  | Wang W (2019)    | China   | XIST        | 64            | IA - III    | 15               | 70                | tissue          | qRT-PCR         | median          | N/A            | OS              | 1.92 (1.25, 3.29) |
| 59  | Yang C (2018)    | China   | XIST        | 40            | I-III       | 60               | tissue            | qRT-PCR         | N/A             | N/A            | OS              | 3.07 (1.84, 11.15) |
| 60  | Zhang R (2017)   | China   | XIST        | 50            | N/A         | 26               | 60                | tissue          | qRT-PCR         | median          | N/A            | OS              | 1.59 (1.38, 2.88) |
| 61  | Li N (2017)      | China   | ZFAS1       | 53            | I-III       | 16               | 60                | tissue          | qRT-PCR         | median          | Multivariate analysis | OS/PFS | 1.14 (0.23, 5.61) |
| 62  | Liu G (2017)     | China   | ZFAS1       | 50            | N/A         | 30               | tissue            | qRT-PCR         | median          | N/A            | OS              | 1.59 (0.64, 3.95) |

DFS disease-free survival, PFS progression-free survival, RFS recurrence-free survival, OS overall survival, N/A not available
MALAT1 was a risk factor of osteosarcoma (HR = 2.15, 95%CI: 1.67–2.76, P < 0.001, Fig. 2a). We noticed that in one of these eight studies, the detected sample was serum rather than tissue. So, we analyzed the remaining seven studies after eliminating this one, and the predicted tendency of MALAT1 in osteosarcoma was not altered (HR = 2.20, 95%CI: 1.70–2.85, P < 0.001). Since no heterogeneity among studies was noted, we did not perform subgroup analysis (I² = 0.0%, P = 0.676). Then, five studies focused on TUG1 containing 294 patients were analyzed, which showed that overexpression of TUG1 was associated with unfavorable clinical outcome of osteosarcoma patients (HR = 2.41, 95%CI: 1.42–4.07, P = 0.001, Fig. 2b). There was also a study that used plasma instead of tissue as the detected sample. Thus, we did another analysis without this study. The result showed the negative prediction role of TUG1 as well. (HR = 1.68, 95%CI: 1.43–1.99, P = 0.001). A negative association between XIST expression and OS of osteosarcoma patients was noticed (HR = 1.79, 95%CI: 1.40–2.30, P < 0.001, Fig. 2c) based on the analysis of four researches containing 299 patients. Finally, three studies incorporating 199 patients were analyzed to explore the association between NEAT1 expression and OS. It proved that the high expression of NEAT1 forebode poor prognosis. (HR = 1.96, 95%CI: 1.05–3.68, P = 0.035, Fig. 2d).

**LncRNAs expression and osteosarcoma clinicopathologic features**

Furthermore, the clinicopathologic features, including age, gender, clinical stage, tumor size and distant metastasis, were analyzed. We mainly focused on the MALAT1, TUG1 and XIST. lncRNAs that owned available data we needed in more than three articles. There were no significant differences in MALAT1 expression detected in different age (HR = 0.73, 95%CI: 0.43–1.24, P = 0.240), gender (HR = 0.73, 95%CI: 0.44–1.20, P = 0.210), clinical stage (HR = 1.48, 95%CI: 0.27–7.94, P = 0.650), tumor size (HR = 0.95, 95%CI: 0.50–1.81, P = 0.890) and distant metastasis (HR = 1.98, 95%CI: 0.32–12.05, P = 0.40). However, the distinction of TUG1 expression was observed in different clinical stage (HR = 4.66, 95%CI: 2.47–8.79, P < 0.001), tumor size (HR = 4.07, 95%CI: 2.33–7.12, P < 0.001) and distant metastasis (HR = 3.53, 95%CI: 1.20–10.41, P = 0.020). Osteosarcoma tissue derived from patients with higher clinical stage, larger tumor size and distant metastasis expressed high TUG1. Differences also have been found in XIST expression upon the clinical stage and metastasis. High clinical stage (HR = 3.92, 95%CI: 2.31–6.66, P < 0.001) and metastasis (HR = 3.15, 95%CI: 1.64–6.05, P < 0.001) were associated with high expression of XIST in tumor tissue. More detailed information was shown in Table 3.

**Sensitivity analysis**

We did sensitivity analysis to the four lncRNAs which had studied in more than three articles respectively even though there was no heterogeneity detected (I² = 0.0%, P > 0.05). The results showed that this meta-analysis was reliable (Fig. 3).

**Publication Bias**

Publication bias was measured by using the Begg’s and Egger’s test. We only analyzed the publication bias of lncRNAs that have been studied in more than three articles, including MALAT1, TUG1, XIST and NEAT1. No significant publication bias was found in any of the lncRNAs. Begg’s funnel plot was shown in Fig. 4. However, publication bias between different lncRNAs was persistent since the number of published articles lacked consensus for them.

**Discussion**

Osteosarcoma remains intractable in clinical practice, and new approaches for prognostic evaluation and treatment of osteosarcoma are continuously requisite. Recently, targeted therapy and molecular biomarker diagnosis have emerged as the focus in cancers [82, 83]. LncRNAs, as indispensable regulators in a majority of biological processes [84], possess great potential for prognostic hallmarks. Further, advancement of technologies for structural and functional study enable us to unveil more evident features of lncRNAs serving as idea clinical biomarkers [85]. Considering the vast lncRNAs studied in osteosarcoma [14], we conducted the meta-analysis, with the aim to provide stronger evidences in this regard.

In this meta-analysis, a total of 4351 cases were included, and 25 lncRNAs were analyzed in which high expression of 14 lncRNAs connotes worse OS while two were associated with positive outcomes. Mechanisms involved in these lncRNAs are multifaced. BCAR4 promoted proliferation and migration by GLI2 target genes including RPS3, IL6, MUC5AC and TGF-β [20, 21]. HNF1A-AS1 targeted Wnt/β-catenin pathway to enhance proliferation and G1/S transition, migration and invasion by reducing the EMT [31]. Meanwhile, MALAT1 positively regulated RET to activate the PI3K-Akt signaling pathway by competitively binding with miR-129-5p, and thus enhancing stem cell-like properties [40]. Furthermore, MALAT1/miR-144-3p/ ROCK1 axis promoted the proliferation and metastasis of osteosarcoma [40]. Moreover, MALAT1 promoted proliferation and metastasis via miR-205/SMAD4 axis [43] and miR-140-5p/HDAC4 axis [44]. NEAT1 could up-regulate HOXA13 by decoying of miR-34a-5p, while NEAT1/miR-186-5p/HIF-1α axis enhanced proliferation and reduced apoptosis [50–52]. Rho-associated protein kinase
(ROCK1), a serine/threonine kinase, is critical regulator of development and progression in various human malignant tumors. Importantly, TUG1 served as a ceRNA of miR-335-5p to affect ROCK1-mediated migration and invasion [72]. Besides, other important hallmarks of osteosarcoma demonstrate close association with TUG1. The effects of TUG1 overexpression on runt-related transcription factor 2 (RUNX2) expression were elucidated. It was noticed that overexpression of lncRNA TUG1 significantly down-regulated RUNX2 level [70]. Likewise, TUG1 could impede osteosarcoma cells proliferation, migration, and invasion by miR-140-5p/PFN2 axis [86]. XIST is another potential biomarker of osteosarcoma which has been reported to modulate osteosarcoma proliferation and invasion through miR-320b/RAP2B [87], miR-193a-3p/RSF1 [88], miR-21-5p/PDCD4 [79], and miR-195-5p/YAP axis [78]. In addition, SNHG16/miR-1301/BCL9 axis [64], MEG3/miR-361-5p/FoxM1 axis [48], SNHG20/miR-139/RUNX2 axis [65], TP73-AS1/miR-142/Rac1 axis [68] and SNHG12/miR-195-5p/Notch2 [62] axis worked as critical roles of enhancing proliferation, migration and invasion. Additionally, OIP5-AS1 and SNHG12 were involved in osteosarcoma doxorubicin resistance via miR-200b-3p/FN1 and miR-320a/MCL1 pathways, respectively [53, 61]. Further, enhancer of zeste homolog 2 (EZH2) was involved in DNA methylation and its mutations have been identified in various malignancies. HOXD-AS1 suppressed p57 expression by binding with EZH2 [34]. LSINCT5 binding with EZH2 inhibited APC transcription that could down-regulate the Wnt/β-catenin pathway and activate the PI3K-Akt signaling pathway [39]. The detailed mechanisms are shown in Fig. 5.

Previously, meta-analysis by Wang Y et al. in 2017 [47] and Chen D et al. in 2018 [89] have illustrated the relationship between osteosarcoma and IncRNAs. How ever, numbered IncRNAs (TUG1, UCA1, BCAR4, Table 2

| LncRNA name | No. of patients | No. of studies | HR(95%CI)-model | P value | heterogeneity |
|-------------|----------------|---------------|----------------|---------|---------------|
| BCAR4       | 228            | 2             | 2.36 (1.13, 4.93)-fixed | 0.022   | 0.0%          | 0.453 |
| CCAT2       | 90             | 2             | 2.18 (0.81, 5.86)-random | 0.123   | 71.2%         | 0.062 |
| DANC1       | 129            | 2             | 1.65 (0.76, 3.60)-random | 0.209   | 57.1%         | 0.127 |
| FER1L4      | 121            | 2             | 0.44 (0.16, 0.72)-fixed | 0.032   | 0.0%          | 0.945 |
| FOXD2-AS1   | 75             | 2             | 1.62 (0.60, 4.38)-fixed | 0.344   | 0.0%          | 0.948 |
| HNF1A-AS1   | 115            | 2             | 2.63 (1.58, 4.39)-fixed | 0.000   | 0.0%          | 0.994 |
| HOXA11-AS1  | 112            | 2             | 1.78 (0.59, 3.36)-fixed | 0.307   | 0.0%          | 0.573 |
| HOXD-AS1    | 89             | 2             | 1.61 (1.04, 2.50)-fixed | 0.033   | 0.0%          | 0.852 |
| HULC        | 111            | 2             | 5.38 (0.62, 46.50)-random | 0.126   | 71.5%         | 0.061 |
| LSINCT5     | 166            | 2             | 1.59 (1.04, 2.44)-fixed | 0.031   | 0.0%          | 0.695 |
| MALAT1      | 605            | 8             | 2.15 (1.67, 2.76)-fixed | 0.000   | 0.0%          | 0.876 |
| MEG3        | 268            | 2             | 0.55 (0.36, 0.84)-fixed | 0.005   | 0.0%          | 0.770 |
| NEAT1       | 195            | 3             | 1.96 (1.05, 3.68)-fixed | 0.035   | 0.0%          | 0.983 |
| ODRUL       | 140            | 2             | 1.73 (1.12, 2.67)-fixed | 0.013   | 0.0%          | 0.793 |
| OIP5-AS1    | 128            | 2             | 1.93 (1.00, 3.73)-fixed | 0.049   | 0.0%          | 0.367 |
| PCAT1       | 92             | 2             | 2.43 (1.95, 6.24)-random | 0.065   | 87.9%         | 0.004 |
| PVT1        | 99             | 2             | 1.69 (0.70, 4.06)-fixed | 0.241   | 0.0%          | 0.974 |
| SNHG12      | 95             | 2             | 1.85 (0.75, 4.58)-fixed | 0.181   | 0.0%          | 0.733 |
| SNHG16      | 161            | 2             | 1.91 (0.94, 3.86)-fixed | 0.074   | 0.0%          | 0.498 |
| SNHG20      | 172            | 2             | 1.95 (1.23, 3.09)-fixed | 0.004   | 0.0%          | 0.309 |
| TP73        | 178            | 2             | 1.90 (1.20, 3.02)-fixed | 0.006   | 0.0%          | 0.943 |
| TUG1        | 294            | 5             | 1.64 (1.42, 1.92)-fixed | 0.000   | 0.0%          | 0.435 |
| UCA1        | 286            | 2             | 2.41 (1.42, 4.07)-fixed | 0.001   | 0.0%          | 0.809 |
| XIST        | 299            | 4             | 1.79 (1.40, 2.30)-fixed | 0.000   | 0.0%          | 0.601 |
| ZFAS1       | 103            | 2             | 1.47 (0.66, 3.23)-fixed | 0.343   | 0.0%          | 0.723 |

CI confidence interval, HR hazard ratio

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Fig. 2 Forest plot of overall survival for four most studied lncRNAs: a MALAT1, b TUG1, c XIST, d NEAT1

Table 3 Analysis of clinical features

| Outcome                  | No. of Studies | No. of Participants | OR (95% CI)   | P value | Model | Heterogeneity |
|--------------------------|----------------|---------------------|---------------|---------|-------|---------------|
|                          |                |                     |               |         |       | Chi², P-value, I² |
| MALAT1                   |                |                     |               |         |       |               |
| Age                      | 3              | 259                 | 0.73 (0.43, 1.24) | 0.24     | Fixed | 0.36, 0.84, 0% |
| Gender                   | 3              | 259                 | 0.73 (0.44, 1.20) | 0.21     | Fixed | 0.16, 0.92, 0% |
| Clinical stage           | 3              | 259                 | 1.48 (0.27, 7.94) | 0.65     | Random | 15.91, 0.0004, 87% |
| Tumor size               | 3              | 259                 | 0.95 (0.50, 1.81) | 0.89     | Random | 10.77, 0.005, 81% |
| Distant metastasis       | 3              | 259                 | 1.98 (1.02, 3.80) | 0.46     | Random | 16.26, 0.003, 88% |
| TUG1                     |                |                     |               |         |       |               |
| Age                      | 5              | 294                 | 1.2 (0.48, 3.02) | 0.28     | Fixed | 1.97, 0.74, 0% |
| Gender                   | 5              | 294                 | 1.02 (0.62, 1.65) | 0.95     | Fixed | 2.97, 0.56, 0% |
| Clinical stage           | 4              | 254                 | 4.66 (2.47, 8.79) | <0.0001  | Fixed | 0.45, 0.93, 0% |
| Tumor size               | 4              | 254                 | 4.07 (2.33, 7.12) | <0.0001  | Fixed | 2.96, 0.4, 0% |
| Distant metastasis       | 5              | 294                 | 3.53 (1.20, 10.41) | 0.02    | Random | 13.52, 0.009, 70% |
| XIST                     |                |                     |               |         |       |               |
| Age                      | 2              | 209                 | 1.18 (0.44, 3.15) | 0.74     | Random | 2.55, 0.11, 61% |
| Gender                   | 3              | 249                 | 0.91 (0.56, 1.50) | 0.72     | Fixed | 1.56, 0.46, 0% |
| Clinical stage           | 3              | 249                 | 3.92 (2.31, 6.66) | <0.0001  | Fixed | 0.92, 0.63, 0% |
| Tumor size               | 3              | 249                 | 1.15 (0.41, 3.23) | 0.80     | Random | 6.74, 0.03, 70% |
| Distant metastasis       | 2              | 209                 | 3.10 (1.61, 5.95) | 0.0007   | Fixed | 0.58, 0.45, 0% |

CI confidence interval, OR odds ratio
HULC, etc.) were analyzed, which led to significant limitation for their research. Among the 25 enrolled lncRNAs, four (MALAT1, TUG1, XIST and NEAT1) reported in more than three studies respectively have been the focus of our meta-analysis because efficacy confirmed in multiple datasets tend to be more convicive. Their high expression predicted poor prognosis of osteosarcoma (MALAT1 (HR = 2.15, 95%CI: 1.67–2.76, \( P < 0.001 \)), TUG1 ((HR = 2.41, 95%CI: 1.42–4.07, \( P = 0.001 \)), XIST (HR = 1.79, 95%CI: 1.40–2.30, \( P < 0.001 \)), NEAT1 (HR = 1.96, 95%CI: 1.05–3.68, \( P = 0.035 \))). Specifically, we observed that, for lncRNA MALAT1 and TUG1,
each contained one study that did not employ neoplastic tissue as the test item. Therefore, we did another analysis after eliminated them respectively in order to minimize the potential bias. Results showed no obvious difference compared to the previous analysis.

Besides, we have evaluated the relationship between IncRNAs expression and clinicopathological features of osteosarcoma. MALAT1 expression level was not associated with the age, gender, clinical stage, tumor size and metastasis. However, patients with elder age, larger tumor size and distant metastasis were accompanied by overexpression of TUG1 and XIST, which further demonstrated the negative role of IncRNA TUG1 and XIST in osteosarcoma progression. Furthermore, a series of IncRNAs have been elucidated to serve as important prognostic hallmarks in numerous tumors, for instance, MALAT1 in breast cancer and digestive system cancer [90, 91], XIST in various solid tumors [92], BCAR4 and SNHG16 in diverse human neoplasms [93–95].

To date, functional implications that support the prognostic roles of IncRNAs in human cancers have been expounded. Importantly, IncRNAs are capable of altering gene expression of cancer stem cells via interplaying with chromatin modification, transcriptional and post-transcriptional factors [96]. Cancer stem cells are critical initiators of tumors which are able to differentiate into heterogeneous lineages of cancer cells, thereby it is of great significance for neoplastic progress. Moreover, epithelial-mesenchymal transition, a prevalent process in tumors, is largely regulated by multiple IncRNAs transcriptionally or post-transcriptionally [84]. Besides, involvement of IncRNAs in regulating some key oncogenic factors such as p53 and MYC has provided evidence for their cancer-relevant functions [10]. And currently, the use of antisense oligonucleotides, small molecules for the targeting of IncRNAs, and tools based on CRISPR–Cas systems may provide new approaches for IncRNA-based targeted therapy [10].
However, adopting IncRNAs as the prognostic or therapeutic markers remains experimentally proposed since the lack of large sample trial to confirm their efficacy and safety. Our meta-analysis that pool and analyze the published dataset thus provide stronger evidence and somewhat promote the progress in this regard.

Ultimately, this meta-analysis yielded valuable results, but there were limitations: (1) Using different methods to extract data can lead to bias, and some HR values are obtained through the tool software indirectly, which makes the bias even greater. (2) Almost all of the included studies are from China, leading to bias caused by geographical differences. (3) Some enrolled studies have different follow-up time and cut-off value.

Conclusions
In conclusion, our study confirmed that IncRNAs are of significant potential in serving as molecular markers for prognosis of osteosarcoma. High expression of a set of IncRNAs predict positive prognosis while some indicate poor outcomes. This meta-analysis has laid a theoretical foundation for experimental exploration and clinical application of IncRNAs in the future.

Supplementary Information
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Additional file 1 Study quality and bias in the retrospective cohort studies judged by the Newcastle-Ottawa Scale (NOS) checklist. Figure A.1 Quality assessment of all included studies. "Risk of bias summary" of all included studies. Figure A.2 Quality assessment of all included studies. "Risk of bias graph" of all included studies.

Additional file 2. PRISMA Checklist.

Abbreviations
LncRNA: Long non-coding RNA; OS: overall survival; HR: hazard ratio; NOS: Newcastle-Ottawa Scale; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; TUG1: Taurine up-regulated gene 1; XIST: X-inactive specific transcript; NEAT1: nuclear enriched abundant transcript 1; ROCK1: Rho-associated protein kinase 1; EZH2: Enhancer of zeste homolog 2

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Authors’ contributions
WCZ and XLR conceived and designed the work. Material preparation, data collection and analysis were performed by WCZ, XLR, LQ and CHZ. The first draft of the manuscript was written by WCZ and XLR and all authors commented on previous versions of the manuscript. CT revised the manuscript. ZHL contributed to article drafting, critical revision and final approval of the version to be published. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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