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**Research Paper** 

## Abnormally expressed long non-coding RNAs in prognosis of Osteosarcoma: A systematic review and meta-analysis



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#### ARTICLE INFO

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### ABSTRACT

heterogeneity.

*Background:* Numerous studies have reported the relationship between Long non-coding RNAs (LncRNAs) expression and prognosis of osteosarcoma, but less consensus has been reached. Our meta-analysis was conducted to quantitatively assess the relationship between the expression of LncRNAs, prognosis and clinical pathology in osteosarcoma development.

*Methods*: PubMed,Embase,Web of Science,The Cochrane Library,SionMed,CNKI and WanFang databases were carefully searched to identify eligible studies. The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to evaluate the prognostic significance of LnCRNAs expression in osteosarcoma. Moreover, meta-regression analysis and subgroup analysis were carried out to explore the potential sources of heterogeneity. *Results*: A total of 20 studies comprising 1749 patients were included in present meta-analysis. The results showed that the over-expression of LnCRNA had a significant correlation with overall survival (OS) (HR = 2.16, 95% CI:1.68–2.79), and was not related to disease free survival (DFS) (HR = 0.71, 95% CI:0.05–9.53). Subgroup analysis further indicated that LnCRNA transcription level was significantly associated with alkaline phosphatase (HR = 2.13, 95% CI:1.58–2.88), tumor size (< 8/ ≥ 8:HR = 1.97, 95% CI: 1.55–2.62), metastasis (yes/no: HR = 2.14,95% CI:1.15–3.97), distant metastasis(presence/absence: HR = 4.02, 95% CI:3.05–5.23) and Enneking stage(IIA / IIB-III:HR = 3.2, 95% CI:2.48–4.14), but not associated with age ( $\leq 25/ > 25$ :HR = 1.01, 95% CI:0.78–1.3), gender(female/male: HR = 1.15, 95% CI: 0.96–1.37), tumor site (femur,tibia/ elsewhere:HR = 1.15, 95% CI:0.94–1.4) and chemotherapy (yes/no: HR = 1.45, 95% CI:0.46–4.63). *Conclusions:* This study demonstrated that abnormal LncRNA sexpression might be potential prognostic markers to predict worse overall survival in osteosarcoma patients. However, the cut-off values may be the source of

#### 1. Introduction

Osteosarcoma (OS) is a highly malignant tumor of bone in children and adolescents [1], which accounts for about 2.4% of malignant tumors in children, and the incidence of OS is about 1–5 cases per million people per year [2,3]. Most patients are diagnosed as OS under the age of 25 years, and there are more men than women among the OS patients [4,5]. Both the metastasis and mortality rates of OS are high in clinic practice. About 20% OS patients were diagnosed with lung metastases at the time of the first diagnosis, and 80% OS metastases occur in the lung [6]. At present, the treatment of OS is mainly based on the combination of surgical resection and multiple chemotherapeutic drugs [7]. The average treatment rate of OS was 65% [8]. The average five-year survival rate of OS patients without metastasis was about 80% [9,10]. 90% OS patients died of recurrence or metastasis due to the presence of tumor resistance, drug side effects and other causes, and the five-year survival rate of OS patients was only 20–30% [11–13]. So far, the molecular mechanism of OS remains unclear. Therefore, finding

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Received 17 June 2018; Received in revised form 19 September 2018; Accepted 20 September 2018 Available online 22 September 2018 2212-1374/ © 2018 The Authors. Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

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Fig. 1. Flow diagram of study selection process.

Table 1									
Comparison of	p values	of relationships	between	lncRNAs	and	clinicopathological	features i	n osteosarco	oma.

Jiang Name2017DANCRChina34NAup-regulate up-regulateNANANA<0.05	Author	Year	LncRNAs	Country	Case number	Cut-off	Expression	Gender	Age	Tumor site	Tumor size	Tumor stage	Metastasis	ALP	Chemotherapy
Wen 2017 UCA1 China 151 NA up-regulated 0.572 0.199 0.804 0.907 0.001 0.007 NA NA   Cai 2017 HNF1A-AS1 China 72 median up-regulated 0.030 NA <	Jiang	2017	DANCR	China	34	NA	up-regulated	NA	NA	NA	< 0.05	NA	< 0.05	NA	NA
Cai2017HNF1A-MSChina72medianup-regulate0.2150.5340.1430.3110.0190.0090.1280.031O'Lav2017PARTICLEGermany40NAup-regulated0.03NANANANANA0.01NANAHuo2017MALAT1China46medianup-regulated0.7590.473NA0.0080.0010.0090.74NAWang2017SOX2-OTChina155NAup-regulated0.7230.1150.1910.0360.0080.001NANANAPeng2016CALChina46medianup-regulated0.5550.2000.5020.1340.0170.006NANAJu2016BANCRChina16medianup-regulated0.5550.2000.5020.1340.0020.0010.190.841Ju2016BANCRChina168medianup-regulated0.5550.4360.7540.0370.0410.028NANAJu2016BCAR4China160medianup-regulated0.8550.7640.0370.0410.0280.2030.202Gao2016TUG1China76fold-changeup-regulated0.8550.7430.6740.0370.0410.028NANAGao2016TUSC7China76fold-change </td <td>Wen</td> <td>2017</td> <td>UCA1</td> <td>China</td> <td>151</td> <td>NA</td> <td>up-regulated</td> <td>0.572</td> <td>0.199</td> <td>0.804</td> <td>0.907</td> <td>0.001</td> <td>0.007</td> <td>NA</td> <td>NA</td>	Wen	2017	UCA1	China	151	NA	up-regulated	0.572	0.199	0.804	0.907	0.001	0.007	NA	NA
OLear PLUE2017PARTICLEGermany40NAup-regulated up-regulated up-regulated 	Cai	2017	HNF1A-AS1	China	72	median	up-regulated	0.215	0.534	0.143	0.311	0.019	0.009	0.128	0.031
Huo2017MALAT1China46medianup-regulated0.7590.473NA0.0080.0080.000NANALi2017XISTChina145NAup-regulated0.8270.1020.8860.0090.0010.0090.704NAWang2017SOX2-OTChina138medianup-regulated0.7230.1150.1910.0360.0080.001NANAZhou2016CAALChina46medianup-regulated0.5550.2000.5140.0040.0020.306NANAPeng2016BCAR4China168medianup-regulated0.5050.8140.0030.0010.1910.841Ju2016BCAR4China168medianup-regulated0.7950.4360.7540.0370.0410.028NANAMa2016TGG1China76fold-changeup-regulated0.8350.7010.0930.0110.0020.8020.2350.202Gao2016MALAT1China162medianup-regulated0.3810.4940.9200.3140.001NANANAMa2016TGG1China162medianup-regulated0.7550.4360.7540.0370.0410.028NANAMa2016TGG1China160medianup-regulated0.785 <td>O'Leary</td> <td>2017</td> <td>PARTICLE</td> <td>Germany</td> <td>40</td> <td>NA</td> <td>up-regulated</td> <td>0.030</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>NA</td> <td>0.01</td> <td>NA</td> <td>NA</td>	O'Leary	2017	PARTICLE	Germany	40	NA	up-regulated	0.030	NA	NA	NA	NA	0.01	NA	NA
Li2017XISTChina145NAup-regulated0.8270.1020.8860.0090.0010.0090.704NAWang2017SOX2-OTChina138medianup-regulated0.7230.1150.1910.0360.0080.001NANAZhou2016CALChina46medianup-regulated0.5550.200.5020.1340.0170.006NANAPeng2016BCAR4China168medianup-regulated0.5050.8140.0820.8100.0020.0110.841Ju2016BCAR4China168medianup-regulated0.3810.4940.9820.8100.0020.8020.3250.203Ghen2016BCAR4China168medianup-regulated0.3810.4940.9820.8100.0020.001NANAMa2016BCAR4China168medianup-regulated0.3850.7010.0930.0110.0020.8020.2350.202Gao2016MALAT1China162medianup-regulated0.3850.7010.9360.4140.0000.001NANAGao2016MALAT1China162medianup-regulated0.4350.4730.5470.677NA0.999NANAGao2016MALAT1China33ROCup-regula	Huo	2017	MALAT1	China	46	median	up-regulated	0.759	0.473	NA	0.008	0.058	0.000	NA	NA
Wang 2017 SOX2-OT China 138 median up-regulated 0.723 0.115 0.191 0.036 0.008 0.001 NA NA   Zhou 2016 CCAL China 46 median up-regulated 0.555 0.200 0.502 0.134 0.017 0.006 NA NA   Peng 2016 BANCR China 84 median up-regulated 0.505 0.814 0.008 0.004 0.020 0.366 NA   Ju 2016 BCAR4 China 168 median up-regulated 0.381 0.494 0.982 0.810 0.002 0.001 0.191 0.841   Chen 2016 BCAR4 China 60 median up-regulated 0.385 0.701 0.093 0.011 0.002 0.802 0.235 0.202   Gao 2016 MALAT1 China 82 fold-change up-regulated 0.473 0.627 NA	Li	2017	XIST	China	145	NA	up-regulated	0.827	0.102	0.886	0.009	0.001	0.009	0.704	NA
Zhou 2016 CCAL China 46 median up-regulated 0.555 0.200 0.502 0.134 0.017 0.006 NA NA   Peng 2016 BANCR China 84 median up-regulated 0.505 0.814 0.008 0.004 0.020 0.366 NA   Ju 2016 BCAR4 China 168 median up-regulated 0.381 0.494 0.982 0.810 0.002 0.001 0.191 0.841   Chen 2016 BCAR4 China 60 median up-regulated 0.795 0.43 0.747 0.041 0.028 NA NA   Ma 2016 TUG1 China 162 median up-regulated 0.335 0.202 0.193 0.344 0.000 0.001 NA NA   Gao 2016 MALAT1 China 162 median up-regulated 0.473 0.627 NA 0.294 0.087<	Wang	2017	SOX2-OT	China	138	median	up-regulated	0.723	0.115	0.191	0.036	0.008	0.001	NA	NA
Peng 2016 BANCR China 84 median up-regulated 0.505 0.814 0.008 0.004 0.020 0.366 NA   Ju 2016 BCAR4 China 168 median up-regulated 0.381 0.494 0.982 0.810 0.002 0.001 0.191 0.841   Chen 2016 BCAR4 China 60 median up-regulated 0.795 0.436 0.754 0.001 0.011 0.028 NA NA   Ma 2016 TUG1 China 67 fold-change up-regulated 0.335 0.202 0.193 0.011 0.002 0.802 0.235 0.202   Gao 2016 MALAT1 China 162 median up-regulated 0.335 0.202 0.193 0.344 0.002 0.087 NA NA   Cong 2016 HULC Brazil 33 ROC up-regulated 0.497 0.274 0.67	Zhou	2016	CCAL	China	46	median	up-regulated	0.555	0.200	0.502	0.134	0.017	0.006	NA	NA
Ju 2016 BCAR4 China 168 median up-regulated 0.381 0.494 0.982 0.810 0.002 0.001 0.191 0.841   Chen 2016 BCAR4 China 60 median up-regulated 0.795 0.436 0.754 0.037 0.041 0.028 NA NA   Ma 2016 TUG1 China 76 fold-chang up-regulated 0.835 0.701 0.037 0.041 0.028 NA NA   Gao 2016 MALAT1 China 162 median up-regulated 0.335 0.202 0.193 0.344 0.000 0.001 NA NA   Cong 2016 MLLC Brazil 33 ROC up-regulated 0.997 0.165 0.274 0.67 NA 0.999 NA NA   Xia 2016 HULC Brazil 33 ROC up-regulated 0.497 0.297 0.114 <0.001	Peng	2016	BANCR	China	84	median	up-regulated	0.509	0.505	0.814	0.008	0.004	0.020	0.366	NA
Chen 2016 BCAR4 China 60 median up-regulated 0.795 0.436 0.754 0.037 0.041 0.028 NA NA   Ma 2016 TUG1 China 76 fold-change up-regulated 0.835 0.701 0.093 0.011 0.002 0.802 0.235 0.020   Gao 2016 MALAT1 China 162 median up-regulated 0.335 0.202 0.193 0.344 0.000 0.001 NA NA   Gao 2016 TUSC7 China 82 fold-change up-regulated 0.355 0.627 NA 0.294 0.087 NA NA   Uzan 2016 HULC Brazil 33 ROC up-regulated 0.997 0.165 0.274 0.677 NA 0.999 NA NA   Xia 2016 HULC Brazil 33 Median up-regulated 0.497 0.927 0.114 <0.00	Ju	2016	BCAR4	China	168	median	up-regulated	0.381	0.494	0.982	0.810	0.002	0.001	0.191	0.841
Ma 2016 TUG1 China 76 fold-change up-regulated 0.835 0.701 0.093 0.011 0.002 0.802 0.235 0.020   Gao 2016 MALAT1 China 162 median up-regulated 0.335 0.202 0.193 0.344 0.000 0.001 NA NA   Cong 2016 TUSC7 China 82 fold-change dowm- 0.65 0.473 0.627 NA 0.294 0.087 NA NA   Uzan 2016 HULC Brazil 33 ROC up-regulated 0.997 0.657 0.67 NA 0.999 NA NA   Xia 2016 HULC Brazil 33 ROC up-regulated 0.997 0.114 <0.001 0.015 0.936 NA 0.023   Li 2015 GG3 China 135 median up-regulated 0.573 0.39 0.512 0.005 <0.001	Chen	2016	BCAR4	China	60	median	up-regulated	0.795	0.436	0.754	0.037	0.041	0.028	NA	NA
Gao 2016 MALAT1 China 162 median up-regulated 0.335 0.202 0.193 0.344 0.000 0.001 NA NA   Cong 2016 TUSC7 China 82 fold-change dowm- regulated 0.65 0.473 0.627 NA 0.294 0.087 NA NA   Uzan 2016 HULC Brazil 33 ROC up-regulated 0.999 0.065 0.274 0.677 NA 0.999 NA NA   Xia 2016 HULC Brazil 33 ROC up-regulated 0.997 0.114 <0.001 0.015 0.999 NA NA   Xia 2016 HULC Brazil 33 ROC up-regulated 0.997 0.114 <0.001 0.015 0.998 NA 0.023   Li 2015 MEG3 China 68 median up-regulated 0.573 0.312 0.161 0.1000 0.003	Ma	2016	TUG1	China	76	fold-change	up-regulated	0.835	0.701	0.093	0.011	0.002	0.802	0.235	0.020
Cong 2016 TUSC7 China 82 fold-change dowm- regulated 0.65 0.473 0.627 NA 0.294 0.087 NA NA   Uzan 2016 HULC Brazil 33 ROC up-regulated 0.999 0.065 0.274 0.67 NA 0.999 NA NA   Xia 2016 91H China 67 median up-regulated 0.497 0.927 0.114 <0.001	Gao	2016	MALAT1	China	162	median	up-regulated	0.335	0.202	0.193	0.344	0.000	0.001	NA	NA
Uzan 2016 HULC Brazil 33 ROC up-regulated 0.999 0.065 0.274 0.67 NA 0.999 NA NA   Xia 2016 91H China 67 median up-regulated 0.997 0.114 <0.001	Cong	2016	TUSC7	China	82	fold-change	dowm-	0.65	0.473	0.627	NA	0.294	0.087	NA	NA
Uzan 2016 HULC Brazil 33 ROC up-regulated 0.999 0.065 0.274 0.67 NA 0.999 NA NA   Xia 2016 91H China 67 median up-regulated 0.497 0.927 0.114 <0.001							regulated								
Xia 2016 91H China 67 median up-regulated 0.497 0.927 0.114 <0.001 0.015 0.936 NA 0.023   Li 2016 UCA1 China 135 median up-regulated 0.573 0.339 0.512 0.005 <0.001	Uzan	2016	HULC	Brazil	33	ROC	up-regulated	0.999	0.065	0.274	0.67	NA	0.999	NA	NA
Li 2016 UCA1 China 135 median up-regulated 0.573 0.339 0.512 0.005 <0.001 0.002 NA NA Tian 2015 MEG3 China 64 median dowm- 0.614 0.302 0.281 0.076 0.006 0.011 NA NA regulated Li 2015 HOTTIP China 68 median up-regulated 0.465 0.215 0.161 0.120 0.003 0.016 NA NA Sun 2015 HULC China 78 median up-regulated 0.492 0.352 0.624 0.496 0.003 0.005 NA NA	Xia	2016	91H	China	67	median	up-regulated	0.497	0.927	0.114	< 0.001	0.015	0.936	NA	0.023
Tian 2015 MEG3 China 64 median dowm- regulated 0.614 0.302 0.281 0.076 0.006 0.011 NA NA   Li 2015 HOTTIP China 68 median up-regulated 0.455 0.215 0.161 0.120 0.003 0.016 NA NA   Sun 2015 HULC China 78 median up-regulated 0.492 0.352 0.624 0.496 0.003 0.005 NA NA	Li	2016	UCA1	China	135	median	up-regulated	0.573	0.339	0.512	0.005	< 0.001	0.002	NA	NA
regulated Li 2015 HOTTIP China 68 median up-regulated 0.465 0.215 0.161 0.120 0.003 0.016 NA NA Sun 2015 HULC China 78 median up-regulated 0.492 0.352 0.624 0.496 0.003 0.005 NA NA	Tian	2015	MEG3	China	64	median	dowm-	0.614	0.302	0.281	0.076	0.006	0.011	NA	NA
Li 2015 HOTTIP China 68 median up-regulated 0.465 0.215 0.161 0.120 0.003 0.016 NA NA Sun 2015 HULC China 78 median up-regulated 0.492 0.352 0.624 0.496 0.003 0.005 NA NA							regulated								
Sun 2015 HULC China 78 median up-regulated 0.492 0.352 0.624 0.496 0.003 0.005 NA NA	Li	2015	HOTTIP	China	68	median	up-regulated	0.465	0.215	0.161	0.120	0.003	0.016	NA	NA
	Sun	2015	HULC	China	78	median	up-regulated	0.492	0.352	0.624	0.496	0.003	0.005	NA	NA

Notes: LncRNA, long non-coding RNA;ALP, alkaline phosphatase;NA, not available.

new molecular markers for early diagnosis and prognosis and therapeutic targets of OS is very important for improving the survival rate of OS patients. Encouragingly, some LncRNAs have recently been reported to play a key role in OS pathogenesis.

LncRNA is a class of non-coding RNAs that are longer than 200 nucleotides in length, with little or no protein coding capacity [14].

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