

Review Article

Long noncoding RNA HOTTIP predicts a poor prognosis for human cancers: a systematic review and meta-analysis

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Abstract: Long noncoding RNA HOTTIP (lncRNA HOTTIP) has been demonstrated to be expressed in human cancers and to correlate with cancer metastasis and prognosis. We investigated the prognostic value of lncRNA HOTTIP expression in patients with different tumors. We searched the electronic databases PubMed and Web of Science to collect all relevant researches to identify the association of lncRNA HOTTIP expression with lymph node metastasis (LNM), distant metastasis (DM) and overall survival (OS) until August 15, 2016. We demonstrated that high levels of lncRNA HOTTIP expression could predict LNM (pooled OR: 2.17, 95% CI: 1.39-3.39, P=0.001), DM (pooled OR: 3.13, 95% CI: 1.89-5.18, P=0.000) and poor OS (pooled HR: 2.34, 95% CI: 1.79-3.07, P=0.000) in multiple cancers by using a fixed-effects model. The present meta-analysis provides evidence suggests that high expression of lncRNA HOTTIP might potentially serve as a reliable biomarker for prognosis in different cancers.

Keywords: Long non-coding RNA, HOTTIP, metastasis, prognosis, meta-analysis

Introduction

The long non-coding RNAs (lncRNAs) are a kind of non-coding transcripts, which more than 200 nucleotides in length and can not to code proteins. A lot of studies have shown that the lncRNAs play important roles in a lot of diseases including cancer [1-4]. Thence, many researchers focus on investigating the relationship between lncRNAs and prognosis of cancers [5-7].

The HOXA transcript at the distal tip (HOTTIP) lncRNA, situated at the 5'tip of the HOXA locus, which was characterized recently [8]. HOTTIP is also deemed as a negative prognostic factor in various types of cancer, including hepatocellular carcinoma [9].

Therefore, HOTTIP might be feasible as a potential prognostic biomarker for human cancers. We conducted this quantitative meta-analysis to evaluate the correlation of HOTTIP with metastasis and prognosis.

Materials

Publication search

We searched the electronic databases, included PubMed and Web of Science until August 15, 2016. The following search terms were adopted: "long non-coding RNA HOTTIP", "HOTTIP", "cancer", "carcinoma", "metastasis", "survival", "prognosis". This meta-analysis collected all relevant researches and explored the association of lncRNA HOTTIP with LNM, DM and OS. Studies were included if they met the following criteria: 1) articles investigating the relationship between HOTTIP and patients with cancer; 2) the expression levels of HOTTIP in tumor tissues were measured; 3) the clinical and pathological characteristics were described; 4) patients were divided into high and low groups according to expression levels; 5) the article was in English. Studies were excluded if they met the following criteria: 1) editorials, letters, expert opinions, case reports and reviews;

Lnc HOTTIP can predict a poor prognosis

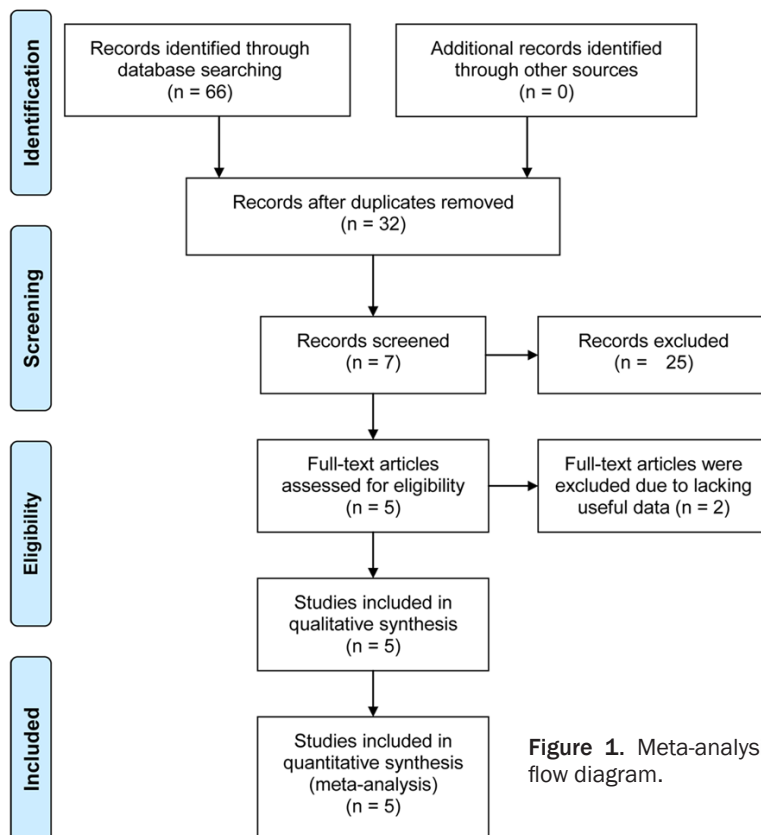


Figure 1. Meta-analysis flow diagram.

2) studies without usable data; 3) duplicate publications.

Data extraction

Two investigators extracted data independently from the eligible studies, and disagreements were decided by discussing with the third investigator. The following information was recorded: reference, year of publication, country, tumor type, patients number, number of high HOTTIP expression group with LNM, number of high HOTTIP expression group without LNM, number of high HOTTIP expression group with DM, number of high HOTTIP expression group without DM, detection method of HOTTIP, survival analysis method, the sources of relative risk, 95% confidence interval. In one study, we extracted the relevant numerical value to calculate HRs with their 95% CIs from the Kaplan-Meier survival curve by making use of Engauge Digitizer version 4.1 [10] and the other HRs could be extracted directly from data in the article.

Statistical analysis

Statistical analyses of the ORs for LNM and DM, and HRs for OS were calculated using

Stata 12.0 (Stata Corporation, College Station, TX, USA). The I^2 statistic and P value was used to assess statistical heterogeneity. The random-effects model was used if there was significant heterogeneity ($I^2 > 50\%$ or $P < 0.05$). If not, fixed-effects model was adopted [11-12]. The stability of the results was evaluated by sensitivity analysis. The presence of publication bias was estimated by using Begg's test and Egger's test ($P < 0.05$ represents significant) [13].

Results

Studies characteristics

A total of 66 articles were obtained by searching PubMed and Web of Science databases. Due to duplicate publications and irrelevant contents, 59 articles were excluded. After full-text reading

the remaining 7 articles, another 2 articles lacking available HRs and ORs or adequate data were excluded. Finally, 5 articles consisting of 552 patients were included in this meta-analysis [14-18]. These 5 studies all come from China. Five different types of cancer were adopted in this systematic review and meta-analysis, which including 1 gastric cancer (GC), 1 osteosarcoma (OS), 1 tongue squamous cell carcinoma (TSCC), 1 colorectal cancer (CRC) and 1 pancreatic cancer (PC). **Figure 1** showed the flow diagram of the literature research process. The main characteristics were generalized in **Table 1** and **Table 2**. All of the LNM and DM were diagnosed by pathology examination.

Association of HOTTIP expression with lymph node metastasis

To assess the associations between HOTTIP expression and LNM, 3 studies consisting of 340 patients were included. The fixed-effects model was adopted because the heterogeneity is not significant ($I^2 < 0.0\%$, $P = 0.797$). A pooled odds ratio (OR) of 2.17 with 95% CI 1.39-3.39 ($p = 0.001$, **Figure 2**) was calculated. Compared with low expression of HOTTIP, tumors with high

Lnc HOTTIP can predict a poor prognosis

Table 1. Characteristics of included studies involving LNM and DM

Reference	Year	Country	Tumor type	Patients number	Expression level of HOTTIP								Detection method	
					High with LNM	High without LNM	Low with LNM	Low without LNM	High with DM	High without DM	Low with DM	Low without DM		
Ye Heng [20]	2016	China	GC	98	39	10	29	20						qRT-PCR
Zhang Hua [18]	2015	China	TSCC	86	28	16	18	24	7	37	1	41		qRT-PCR
Ren Ying-Kun [16]	2015	China	CRC	156	47	30	36	43	27	50	14	65		qRT-PCR
Li Fan [19]	2015	China	OS	68					11	23	3	31		qRT-PCR
Wang Ying-xue [17]	2015	China	PC	144					75	43	10	16		qRT-PCR

GC: gastric cancer; TSCC: tongue squamous cell carcinoma; OS: osteosarcoma; CRC: colorectal cancer; PC: pancreatic cancer; LNM: lymph node metastasis; DM: distant metastasis.

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Table 2. Characteristics of included studies involving OS

Reference	Year	Country	Tumor type	HR	95% CI	Survival analysis	HR estimated
Ye Heng [20]	2016	China	GC	2.54	1.26-5.13	Multivariate	Survival curve
Zhang Hua [18]	2015	China	TSCC	2.151	1.306-3.415	Multivariate	Reported
Ren Ying-Kun [16]	2015	China	CRC	2.887	1.367-7.06	Multivariate	Reported
Li Fan [19]	2015	China	OS	2.589	1.385-4.839	Multivariate	Reported
Wang Ying-xue [17]	2015	China	PC	2.113	1.062-3.115	Multivariate	Reported

GC: gastric cancer; TSCC: tongue squamous cell carcinoma; OS: osteosarcoma; CRC: colorectal cancer; PC: pancreatic cancer; OS: overall survival; HR: hazard ratio; 95% CI: confidence interval.

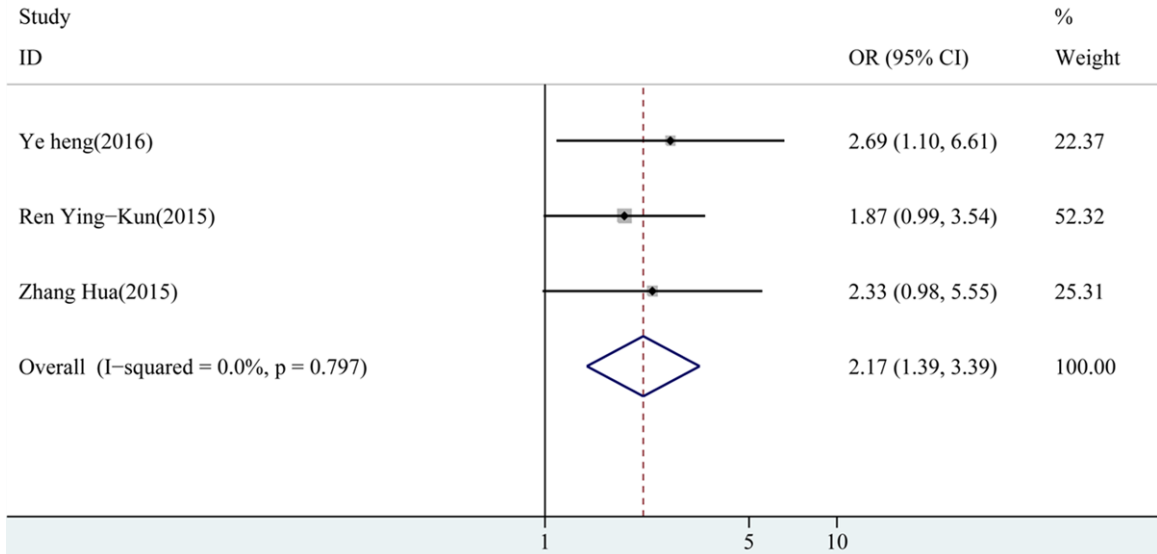


Figure 2. Forest plot of association between HOTTIP expression in tumor tissues and LNM.

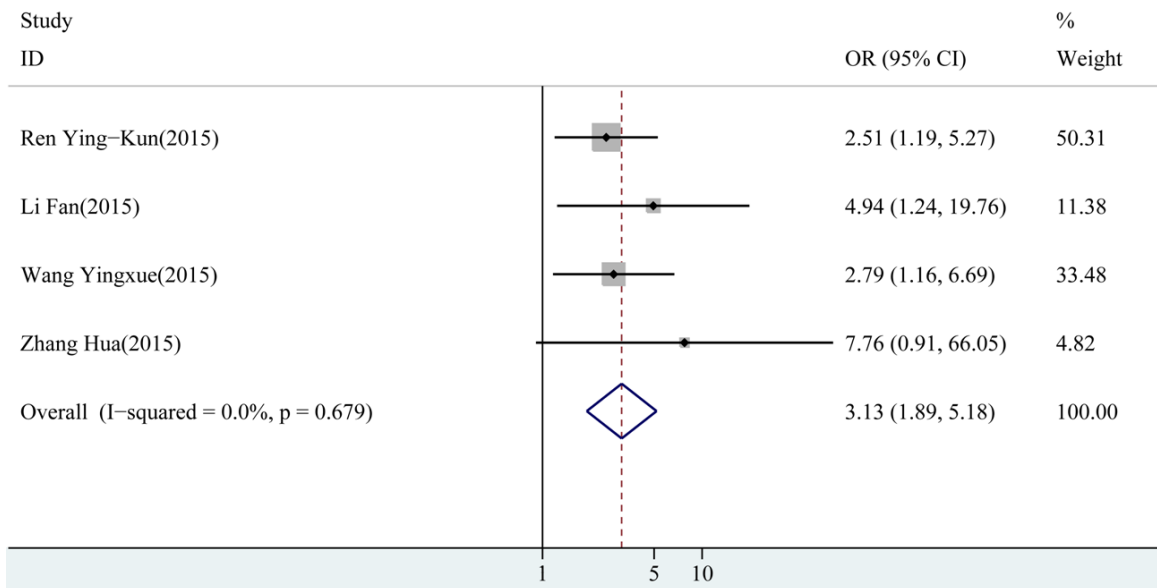


Figure 3. Forest plot of association between HOTTIP expression in tumor tissues and DM.

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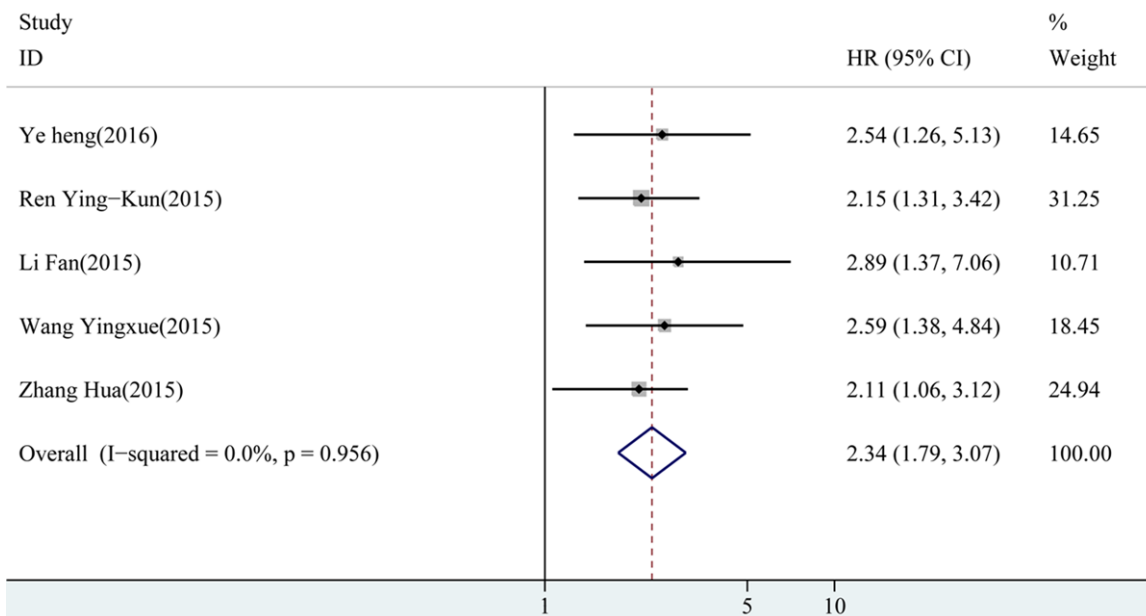


Figure 4. Forest plot of association between HOTTIP expression in tumor tissues and OS.

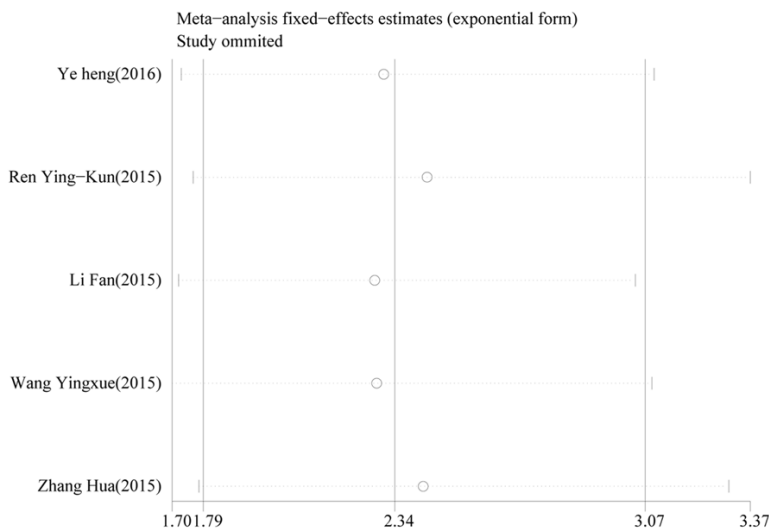


Figure 5. Sensitivity analysis of the pooled HRs of HOTTIP expression and OS for the included studies.

expression show more susceptibility to develop LNM.

Association of HOTTIP expression with distant metastasis

Four studies reported the number of patients with distant metastasis based on different HOTTIP expression levels in a total of 454 individuals. The fixed-effects model was used with-

out significant heterogeneity ($I^2=0\%$, $P=0.679$). Analysis showed a pooled OR of 3.13 with 95% CI: 1.89-5.18 ($P=0.000$, **Figure 3**). Compared with low expression of HOTTIP, tumors with high expression show more possibility to develop DM.

Association of HOTTIP expression with overall survival

We analyzed pooled hazard ratio (HRs) derived from five studies with 552 patients included in this meta-analysis of OS. Due to the heterogeneity was not significant ($I^2=0\%$, $P=0.956$), a fixed-effects model was used.

Analysis showed a pooled HR of 2.34 with 95% CI: 1.79-3.07 ($P=0.000$, **Figure 4**). Compared with patients low expression of HOTTIP, those with high expression of HOTTIP had a poorer OS.

Sensitivity analysis and publication bias

The relationship between HOTTIP expression and OS was not significantly influenced by the

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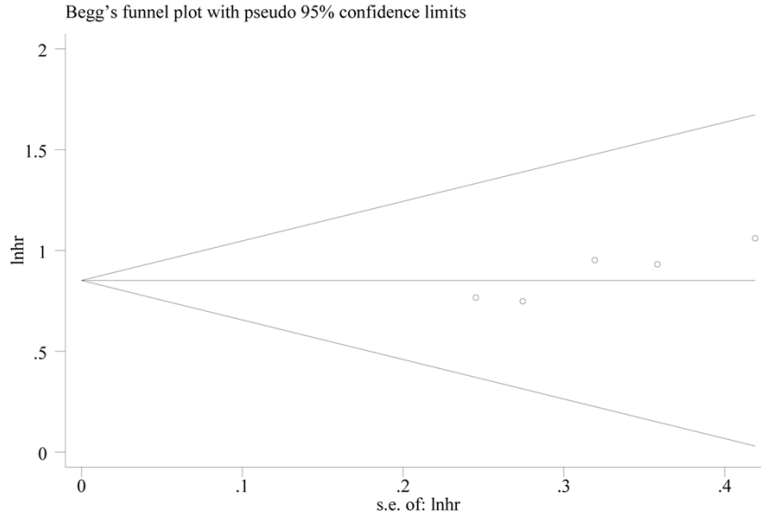


Figure 6. Begg's funnel plot to explore publication bias between HOTTIP expression and OS in these included studies.

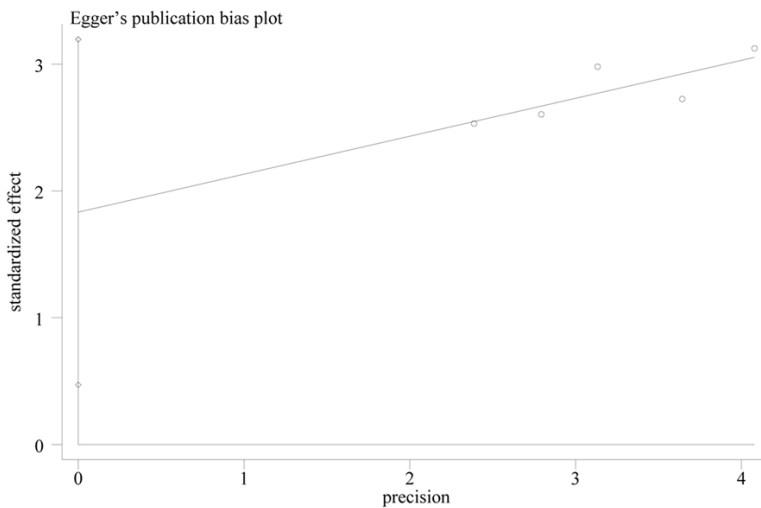


Figure 7. Egger's funnel plot to explore publication bias between HOTTIP expression and OS in these included studies.

sensitivity analysis (**Figure 5**). Visual inspection of the Begg's (**Figure 6**) and Egger's funnel plot (**Figure 7**) indicated funnel plots were symmetric. Egger's test and Begg's test suggested the publication bias was not significant ($P=0.221$ for Egger's test and Begg's test).

Discussion

Recently, a lot of studies have identified that lncRNAs were aberrantly expressed in different types of cancers. It was demonstrated that lncRNAs play important roles in metastasis and carcinogenesis [19]. Some well-studied

research has been analyzed to investigate the roles of lncRNAs in cancer prognosis [20-23]. However, little is known about the clinical significance of HOTTIP expression and all human cancer prognosis.

The lncRNAs HOTTIP is associated with the WDR5/MLL1 and PRC2 chromatin modifying complexes and directly binds WDR5 [24], and recent studies showed a close association between HOTTIP and HOXA13 in hepatocellular carcinoma [25] and pancreatic cancer [26]. These findings indicated that HOTTIP might have the similar oncogenic functions as the lncRNA HOTAIR, but each lncRNA has different target genes and function in human cancers. Given the different cancers in this study, several clinical features, including tumor differentiation and depth of invasion, were not adopted due to their variability. However, lymph node metastases or distant organ metastases are the important prognostic indicators in many tumors [27-28].

In our meta-analysis, high HOTTIP expression of tumor tissues was significantly correlated with DM, LNM and poor OS. There were five studies indicating that HOTTIP expression correlated with OS significantly in colorectal cancer ($p=0.017$) [14], pancreatic cancer ($p<0.001$) [15], tongue squamous cell carcinoma ($p=0.023$) [16], osteosarcoma ($P=0.007$) [17], and gastric cancer ($P=0.015$) [18]. After meta-analysis, HOTTIP showed significant association with prognosis, suggesting that high HOTTIP expression in tumor tissues is an unfavorable prognostic factor. However, it needed more research to confirm the association between HOTTIP expression and prognosis.

Lnc HOTTIP can predict a poor prognosis

Similar to other meta-analyses, our study also had limitations. The first, the different types of cancer increased the heterogeneity included in this study. The second, we calculated HRs according to survival curve in one study, which might increase the possibility of inaccurate results. The third, all these studies were from China could increase area heterogeneity. Last but not least, we only adopted English papers, which might increase the language heterogeneity.

The results demonstrated high HOTTIP expression was correlated with LNM, DM and poor OS significantly. Our meta-analysis suggests that lncRNAs HOTTIP may act as a potential tumor marker. However, more trials are needed to confirm the prognostic function of lncRNAs HOTTIP.

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Disclosure of conflict of interest

None.

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Lnc HOTTIP can predict a poor prognosis

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