

Long non-coding RNA HOTTIP is able to predict poor prognosis in various neoplasms: A meta-analysis

NING JIN^{1*}, LING-YUN YANG^{2*} and ZI-PENG XU³

¹Department of Pathology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210011;

²Department of Pediatrics, Wuxi Children's Hospital, Wuxi, Jiangsu 214002; ³Department of General Surgery, Xishan People's Hospital, Wuxi, Jiangsu 214011, P.R. China

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Abstract. HOXA distal transcript antisense RNA (HOTTIP), a critical oncogenic long non-coding RNA, has been reported to be aberrantly regulated in various cancer types. The present meta-analysis aimed to investigate HOTTIP as a potential clinical applicable prognostic biomarker in malignant neoplasms. Literature collections were performed by searching the electronic databases, PubMed and Web of Science (up to July 20, 2016). All the relevant searches were conducted to identify the association of HOTTIP with the overall survival (OS) rate. A total of six articles consisting of 508 patients were included in the present meta-analysis. The results suggested that the overexpression of HOTTIP is closely correlated with poor OS (hazard ratio=2.28; 95% confidence interval=1.71-3.04; P=0.000). In conclusion, the present meta-analysis has demonstrated that an increased expression level of HOTTIP is correlated with poor OS in different types of cancer, suggesting that HOTTIP potentially serves as a reliable prognostic biomarker in different types of cancer.

Introduction

Long non-coding RNAs (lncRNAs) are a class of transcripts >200 nucleotides in length with limited protein-coding potential (1). Recently, several studies have revealed that lncRNAs are dysregulated in numerous types of human cancers, including gastric, colorectal, gastric, ovarian, lung and breast cancer (2-7). Certain lncRNAs have multiple functions in a wide range of biological processes, including proliferation, apoptosis, or cell migration (2,3,6).

HOXA distal transcript antisense RNA is an antisense non-coding transcript located at the 5'-end of the Homeobox A (HOXA) cluster (8). An increased expression level of HOTTIP has been observed in various types of tumor (9-14). Furthermore, the overexpression of HOTTIP has been previously shown to be significantly correlated with poor prognosis (9-14). Therefore, HOTTIP may be a candidate to serve as a feasible prognostic factor. Therefore, the aim of the present study was to perform a quantitative meta-analysis to further determine the correlation of HOTTIP with tumor prognosis.

Data collection methods

Search strategy. Electronic databases were searched, including PubMed and Web of Science (up to July 20, 2016). The following keywords were used for the search: 'long non-coding RNA HOTTIP', 'lncRNA HOTTIP', 'cancer', 'prognosis', and 'survival'.

Selection criteria. Inclusion criteria were as follows: i) patients were divided into high and low groups, according to the expression levels of HOTTIP; ii) the correlation between HOTTIP expression quantity and overall survival (OS) was investigated. Exclusion criteria were as follows: i) editorials, expert opinions, letters, case reports and reviews were excluded, as were ii) studies lacking helpful data on OS and iii) duplicate publications.

Data extraction. Two investigators (LY.Y. and N.J.) independently extracted data from the eligible studies, and disagreements were resolved by discussion with a third investigator (Z-P.X.). The extracted data included the first author, year of publication, the country in which the study participants were enrolled, number of patients, tumor type, detection method of HOTTIP, cut-off values, survival analysis method, the sources of hazard ratios (HRs) [95% CIs (confidence intervals)], and the numbers in the high and low HOTTIP expression groups. The HRs were obtained using two methods. First, the HRs were obtained directly from publications; secondly, the HRs were extrapolated using Engauge Digitizer version 4.1 software from the Kaplan-Meier survival curve (15). The strength of the link between HOTTIP and survival outcome were evaluated by the HRs with corresponding 95% CIs. The I^2 statistic was used to

Correspondence to: Dr Zi-Peng Xu, Department of General Surgery, Xishan People's Hospital, 588 Guangrui Road, Wuxi, Jiangsu 214011, P.R. China
E-mail: xuzipeng1989@126.com

*Contributed equally

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Table I. Characteristics of HOTTIP studies included in the meta-analysis.

Authors	Year	Country	Cancer type	Total no.	HOTTIPP detection method	Cut-off	Outcome	Survival analysis	HR estimate	(Refs.)
Quagliata <i>et al</i>	2014	Switzerland	HCC	52	RT-qPCR	Median	OS	Univariate	Survival curve	(12)
Ge <i>et al</i>	2015	China	HCC	48	RT-qPCR	Median	OS	Univariate	Survival curve	(14)
Zhang <i>et al</i>	2015	China	TSCC	86	RT-qPCR	Median	OS	Multivariate, univariate	Reported	(9)
Ren <i>et al</i>	2015	China	CRC	156	RT-qPCR	Median	OS	Multivariate, univariate	Reported	(11)
Li <i>et al</i>	2015	China	OSA	68	RT-qPCR	Mean	OS	Multivariate, univariate	Reported	(13)
Ye <i>et al</i>	2016	China	GC	98	RT-qPCR	Median	OS	Univariate	Survival curve	(10)

HOTTIP, HOXA distal transcript antisense RNA; HR, hazard ratio; OS, overall survival; HCC, hepatocellular carcinoma; TSCC, tongue squamous cell carcinoma; CRC, colorectal cancer; OSA, osteosarcoma; GC, gastric cancer; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

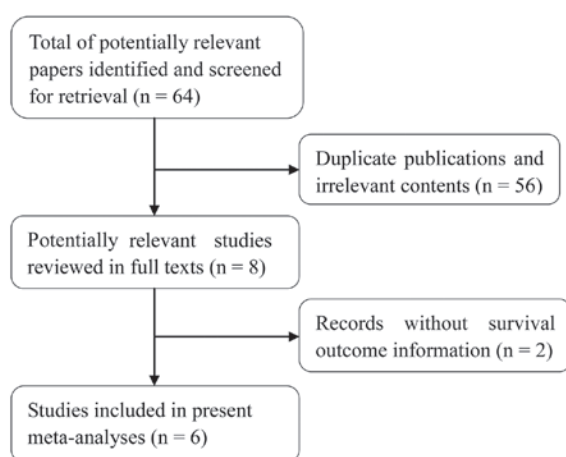


Figure 1. Flow diagram of publication selection.

evaluate the heterogeneity of the data (16). The random-effects model was used if there was significant heterogeneity between studies ($I^2 > 50\%$ or $P < 0.05$), whereas the fixed-effects model was applied for the present meta-analysis. The meta-analysis results were displayed using Forest plots. The stability of the results was evaluated using sensitivity analysis. Begg's funnel plots were used to evaluate publication bias (17). All the statistical analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX, USA).

Results

As shown in Fig. 1, the searches with key terms disclosed that 64 articles that had been published up to July 20, 2016. After screening the title and abstract carefully, 56 references were excluded due to duplicate publications and irrelevant content.

Upon further review of the full articles, 2 were excluded since they were records lacking information concerning the survival outcomes. Finally, 6 articles consisting of 508 patients were included in the present meta-analysis. Among these 6 studies, 5 came from China and 1 was from Switzerland. Five different types of cancer were evaluated, with 2 cases of hepatocellular carcinoma, 1 case of tongue squamous cell carcinoma, 1 of colorectal cancer, 1 of osteosarcoma, and 1 of gastric cancer. All these characteristics are summarized in Table I.

Association between HOTTIP and OS. To investigate the association between HOTTIP expression and OS, 6 studies consisting of 508 patients were included. Heterogeneity analysis revealed that no evidence of statistically significant heterogeneity across these 6 studies was identified ($P = 0.983$ for heterogeneity test; $I^2 = 0\%$). Subsequently, a fixed-effect model was used to calculate the HR with corresponding 95% CI. According to the meta-analysis results ($HR = 2.28$; 95% CI = 1.71–3.04; $P < 0.0001$, Fig. 2), it may be concluded that patients for whom a high expression of HOTTIP in cancerous tissues was detected were more prone to a poor outcome.

Sensitivity analysis and publication bias. Sensitivity analysis indicated that the exclusion of any individual study did not change the significance of HR (Fig. 3). This demonstrated that the HR of the OS was reliable. A Begg's funnel plot and Egger's linear regression test were performed to evaluate publication bias. The Egger's and Begg's tests suggested the publication bias was not significant ($P = 0.151$ for Egger's test; $P = 0.06$ for Begg's test) (Fig. 4).

Discussion

HOTTIP is an lncRNA transcribed from the 5'-end of the HOXA. It is able to bind to and target WD repeat-containing

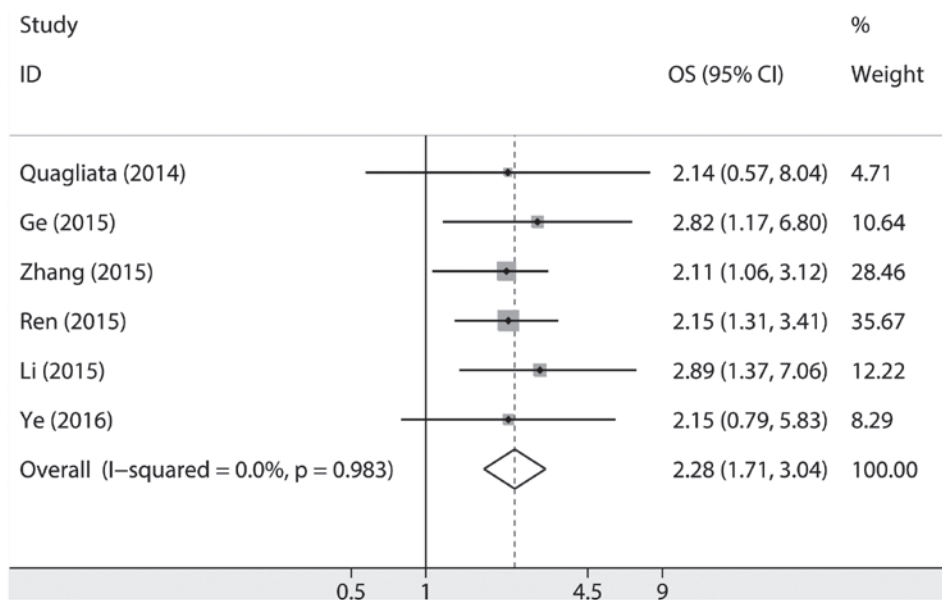


Figure 2. Forest plots showing the association between HOTTIP expression and the OS. OS, overall survival; HR, hazard ratio.

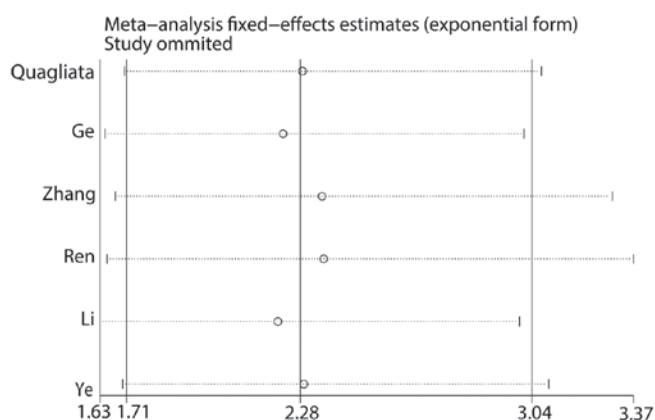


Figure 3. Sensitivity analysis of the HRs of HOTTIP expression and OS for the included studies.

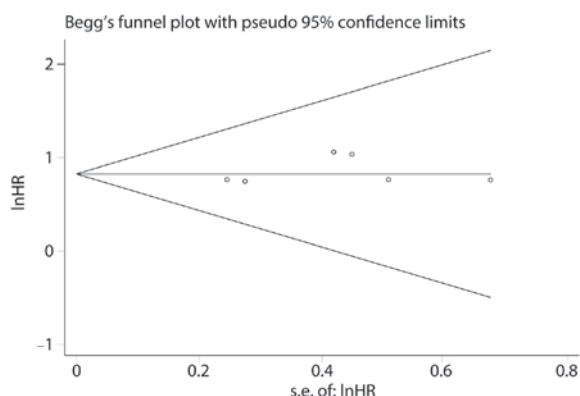


Figure 4. Begg's funnel plot to explore publication bias of the included studies between HOTTIP and OS. lnHR, logarithm of hazard ratio; s.e., standard error.

and gene transcription (8). The most recently published studies have identified that HOTTIP is a critical oncogenic lncRNA that is highly expressed in numerous types of cancers, including hepatocellular carcinoma and colorectal, gastric, and lung cancer. At the same time, these studies have demonstrated that the HOTTIP/HOXA13 axis is associated with cell growth and the cell cycle, which serves an important role in the genesis and progression of cancer (18,19). Although it has already been demonstrated that HOTTIP is closely associated with multiple tumors, the prognostic role of HOTTIP expression in different types of cancer has yet to be fully elucidated. Therefore, a meta-analysis was performed to explore the connection between a high expression level of HOTTIP and the OS rate for cancer patients. The present meta-analysis has highlighted the tumor prognostic role of HOTTIP, and provided sufficient evidence to establish an association between HOTTIP expression and the prognosis of different human cancer types, suggesting that over-expression of HOTTIP is significantly corrected with poor OS. However, it should be emphasized that there were several limitations in the present study. First, the cut-off definition of HOTTIP expression varied in each study. Secondly, only 6 studies with 508 patients were included in the present meta-analysis, which may influence the reliability of our results. Thirdly, three HRs in our study were calculated according to the survival curve, which may have affected the accuracy of the research results. Fourthly, only English language papers were included in the present study.

Taken together, the present meta-analysis has demonstrated that elevated levels of HOTTIP expression are significantly associated with a poor OS (HR=2.28; 95% CI=1.71-3.04; $P<0.0001$). Therefore, HOTTIP may be used as a negative, unfavorable prognostic marker for most types of cancer.

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