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Original Article

Prognosis and clinicopathology of long non-coding RNA HOTTIP in tumors

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Abstract: Objective: We performed this study to clarify the correlation between the HOXA transcript at the distal tip (HOTTIP) and the prognosis and related clinicopathology of tumor patients. Methods: We searched PubMed, Cochran, EMBASE, and CNKI databases for articles published before June 13, 2017. Pooled hazard ratios (HR) with 95% confidence interval (95% CI) were calculated to summarize the effect. Results: Eight studies were eligible which included 752 patients. The pooled HR for overall survival (OS) was 2.40 (95% CI: 1.89-3.06; P < 0.001) in 7 studies while in digestive system tumors, it was 2.257 (95% CI: 1.75-2.9; P < 0.001). Additionally, high expression of HOTTIP was associated with clinical stage (III+IV: OR 3.29, 95% CI: 2.31-4.67; P < 0.001), local invasion (T3+T4: OR 1.83, 95% CI: 1.29-2.60; P = 0.001), tumor differentiation (poor: OR 1.55, 95% CI: 1.03-2.32; P = 0.04), lymph node invasion (present: OR 2.40, 95% CI: 1.70-3.37; P < 0.001), distal metastasis (present: OR 3.30, 95% CI: 1.78-6.12; P < 0.001), and tumor size (large: OR 3.02, 95% CI: 1.87-4.86; P < 0.001). Conclusions: HOTTIP could be a promising predictive factor for the prognosis and correlative clinicopathology of these deadly diseases.

Keywords: Long non-coding RNA HOTTIP, tumor, prognosis, clinicopathology

Introduction

Cancer is one of the leading causes of death worldwide [1, 2]. Despite improvements of various types of therapy, cancer still causes public health and economic issues around the world [3]. In order to reform treatment methods and reduce cancer-related mortality, it is essential to know more about the mechanism of carcinogenesis.

With advances of sequencing technologies, vital roles of long non-coding RNA (lncRNA) in the generation and development of tumors are being revealed. lncRNAs, which used to be considered transcript noise, are termed as a group of RNAs longer than 200 nucleotides with a limited protein-coding function or no protein-coding function [4]. Multiple studies have reported the critical role of lncRNAs in the progression of various cancers [5-7].

lncRNA HOXA transcript at the distal tip (HOTTIP) is one of them, which was originally identified in anatomically distal human fibroblasts, such as those from the hand, foot, or foreskin, and the HOTTIP gene was located at the homeobox A (HOXA) locus (chromosomal locus 7p15.2), which encodes the 3764 bp transcript [8]. It has been revealed that HOTTIP participates in the biological progress of tumors according to the regulation of HOX genes [9].

A number of studies confirmed that expression of HOTTIP is elevated in a variety of malignancies [9]. Furthermore, the expression level was found to be associated with tumor clinicopathological features and patient prognosis. Therefore, we collected relevant publications, and a meta-analysis was performed to clarify the association between HOTTIP expression and clinical outcome in tumors.

Materials and methods

Literature search

We searched the PubMed, Cochran, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) databases for relevant articles pub-

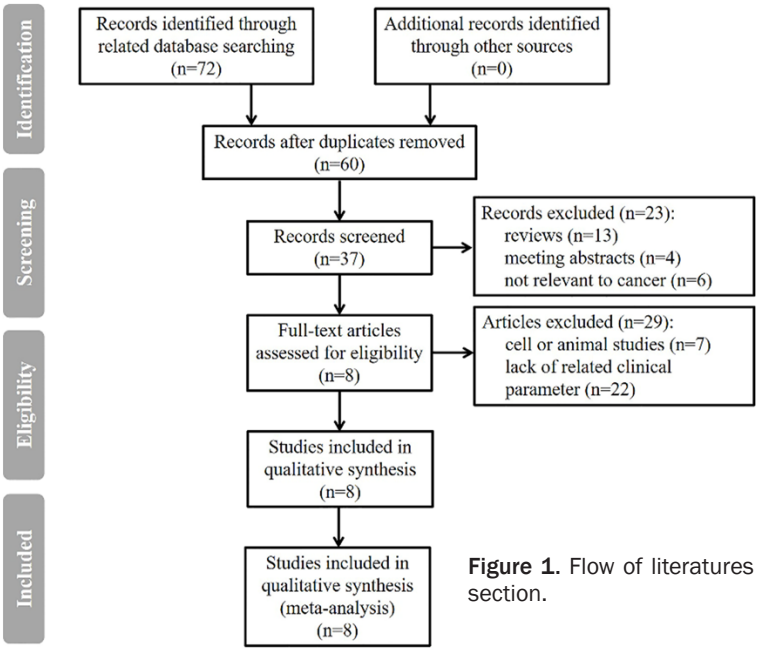

Figure 1. Flow of literatures section.

lished before June 13, 2017. The search term used was "long non-coding RNA HOTTIP". Furthermore, relevant articles were also reviewed to identify from the reference lists.

Inclusion and exclusion criteria

Studies with the following characteristics were included: (I) Cohort design; (II) Investigated the association between HOTTIP and cancer prognosis (OS) or clinicopathology; (III) Sufficient original data for calculating a hazard ratio (HR) with its 95% confidence interval (CI). Studies with the following characteristics were excluded: (I) Reviews, letters to editors, animal experiments, or cell lines experiments; (II) Not enough information for HR estimation analysis. If there was more than one study using the same patient cases, the one with the most comprehensive population was included. All the opinions among the authors were in consensus with each other, including the third investigator (Shan Zhu). Different opinions were solved through discussion.

Data extraction and quality assessment

The data was independently extracted and reviewed by two investigators. The extracted data was as follows: the first author's name, the publication year, patient ages, genders, duration of follow-up, sample size, histology, stage, cut-off value, methods, OS, and co-variants. Since all included studies were cohort studies, we introduced the Newcastle-Ottawa Scale (NOS) to evaluate the methodological quality [19].

Statistical analysis

We evaluated the prognostic role of HOTTIP expression by computing the hazard ratios (HRs) and its corresponding 95% confidence intervals (CIs) of OS from the primary studies. Already reported HR and their 95% CI directly came from the literature. For the literature in which the HR and 95% CI were not directly given, Tierney et al. [20] and Parmar et al. [21] have introduced a method to estimate them. OS was defined as the time between diagnosis and death.

The classical Q statistic was used to assess heterogeneity and heterogeneity was considered statistically significant when $p < 0.10$ and/or $I^2>50$ %. Random effects model was chosen if the heterogeneity was significant. Otherwise, a fixed-effects model was used. Potential publication bias was assessed with a funnel plot, Begg's test, and Egger's test. Statistical significance indicated that the *p* value is less than 0.05.

STATA 12.0 software (Stata Corporation, College Station, TX, USA) was used to carry out all the statistical analyses.

Results

Study characteristics

The search process of the literature is shown in detail in **Figure 1**. After excluding duplicate articles, we selected 60 potentially eligible studies. A detailed evaluation was then performed, and 8 studies were finally selected for the meta-analysis, which included 752 cancer patients (**Table 1**). Of the 8 studies, 2 concerned colorectal cancer, and the rest of the studies concerned hepatocellular carcinoma, pancreatic cancer, tongue squamous cell carcinoma, osteosarcoma, breast cancer, and gastric cancer, while 7 studies investigated the

Table 1. Characteristics of the included studies

First author	Year	Cancer type	Total number	Tumor stage	Follow-up (months)	Criterion of high expression	Detection method	Outcome measures	Multivariate analysis	NOS
Ying-Kun Ren	2015	CRC	156	97/59 (I-II/III-IV)	33-65	Median expression	qRT-PCR	OS	Yes	9
Luca Quagliata	2014	HCC	52	37/15 (I-II/III-IV)	11-35	Median expression	qRT-PCR	OS	No	8
Ying-Xue Wang	2015	PAC	144	NA	14-45	The cut-off value	qRT-PCR	OS	Yes	8
Hua Zhang	2015	TSCC	86	38/48 (I-II/III-IV)	23-60	Median expression	qRT-PCR	OS	Yes	8
Fan Li	2015	OSS	68	30/38 (IIA/IIB-III)	Over 60	Median expression	qRT-PCR	OS	Yes	8
Heng Ye	2016	GC	98	33/65 (I-II/III)	Over 60	Median expression	qRT-PCR	OS	No	9
Yin-long Yang	2017	BC	100	42/58 (I-II/III-IV)	Over 100	Median expression	qRT-PCR	OS/DFS	Yes	9
Yi-Fan Lian	2015	CRC	48	19/29 (I-II/III-IV)	NA	NA	NA	/	/	/

Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; PAC, pancreatic cancer; TSCC, tongue squamous cell carcinoma; OSS, osteosarcoma; GC, gastric cancer; BC, breast cancer; OS overall survival; qRT-PCR, quantitative real-time-polymerase chain reaction; NA, not available.

association between HOTTIP and overall survival (OS).

Association between the expression of HOTTIP and OS of tumor patients

A cumulative meta-analysis was performed to assess the function of HOTTIP for OS in patients with cancer. The association between the expression of HOTTIP and OS was investigated in 7 studies (**Figure 2**). We found a statistically significant negative association between levels of HOTTIP and OS (HR = 2.40; 95% CI: 1.89-3.06; P < 0.001). Additionally, in subgroup analysis, we also observed a significant association between HOTTIP and OS in digestive system (HR = 2.257; 95% CI: 1.75-2.9; P < 0.001) and non-digestive system (HR = 3.91; 95% CI: 1.90-8.07; P < 0.001) tumor patients. Publication bias was not obvious for OS evaluated by Begg's and Egger's test as well as funnel plot in this meta-analysis (P = 0.266 in Begg's test and 0.058 in Egger's test, **Figure 2B**).

This results demonstrate that high expression level of HOTTIP correlated with a worse survival.

Increased expression of HOTTIP and related clinicopathological parameters

From the pooled results (**Table 2**), we found that increased HOTTIP was significantly associated with the clinical stage (III+IV: OR 3.29, 95% CI: 2.31-4.67; P < 0.001), local invasion (T3+T4: OR 1.83, 95% CI: 1.29-2.60; P < 0.001), tumor differentiation (poor: OR 1.55, 95% CI: 1.03-2.32; P = 0.04), lymph node invasion (present: OR 2.40, 95% CI: 1.70-3.37; P < 0.001), distal metastasis (present: OR 3.30, 95% CI: 1.78-6.12; P < 0.001), and tumor size (large: OR 3.02, 95% CI: 1.87-4.86; P = 0.000) (**Figure 3A-F**). Additional, subgroup analysis showed a significant association between HOTTIP and clinical stage in digestive system (III+IV: OR 2.81, 95% CI: 1.87-4.23; P = 0.000) and non-digestive system (III+IV: OR 5.12, 95% CI: 2.56-10.23; P = 0.000). However, there was no significant correlation between increased HOTTIP expression and age or gender (**Figure 3G**, **3H**).

These results indicated that high HOTTIP expression was positively correlated with the advanced clinical stage, no matter in digestive system or non-digestive system tumor patients. Furthermore, the local invasion depth and tumor size were increased in high HOTTIP expression group. Additionally, those patients with upregulated HOTTIP may develop an elevated risk of lymph node metastasis and distal metastasis.

Publication bias

As mentioned above, publication bias was evaluated through Begg's test and Egger's test, and no obvious publication bias was observed (P = 0.2666 for Begg's test and 0.058 for Egger's test) for OS (**Figure 2B**). We then used a funnel plot to reveal that there were no publication biases in studies with pathological indicators. There was no obvious evidence of asymmetry showing in the shape of the funnel plots (**Figure 4A-H**). In the present meta-analysis, the stability of the results was assured by sensitivity analysis, which identified that the data extracted from all the studies for investigating the prognostic value of HOTTIP expression were stable and convincing with OS.

Discussion

The HOTTIP gene is located at the chromosomal locus 7p15.2 and encodes a 4665-bp tran-

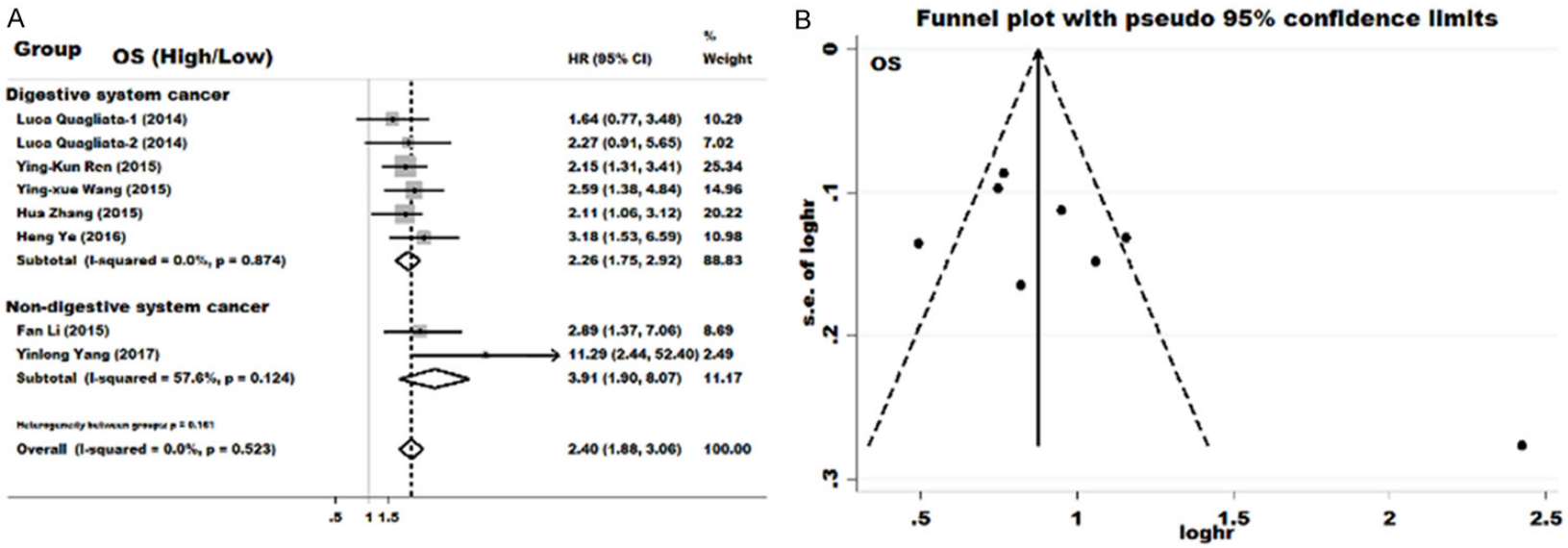

Figure 2. Negative association between expression levels of HOTTIP and OS. A. Forest plot showing the subgroup analysis for the association between the expression level of HOTTIP and overall survival of different cancers; B. Funnel plot analysis of potential publication bias in OS group (Begg's and Egger's test).

Table 2. Meta-analysis results of the association between over-expressed HOTTIP and clinicopathological parameters

Clinicopathological parameter	Studies (n)	Number of Patients	OR (95% CI)	*P*-value	Heterogeneity		
					I^2 (%)	P_h	Model
Age (Old vs. young)	8	752	0.93 (0.69-1.27)	0.91	0	0.77	Fixed effects
Gender (Female vs. male)	7	652	1.06 (0.75-1.49)	0.75	0	0.85	Fixed effects
Tumor size (Large vs. small)	4	314	3.02 (1.87-4.86)	0.000	0	0.56	Fixed effects
Lymph node metastasis (Present vs. absent)	6	632	2.40 (1.70-3.37)	0.000	0	0.96	Fixed effects
Distant metastasis (Present vs. absent)	3	310	3.30 (1.78-6.12)	0.000	0	0.48	Fixed effects
Tumor differentiation (Poor vs. well/moderate)	5	532	1.55 (1.03-2.32)	0.04	0	0.67	Fixed effects
Clinical stage (III/IV vs. I/II)	7	608	3.29 (2.31-4.67)	0.000	0	0.83	Fixed effects
Local invasion (T3/T4 vs. T1/T2)	5	584	1.83 (1.29-2.60)	0.001	34.9	0.19	Fixed effects

script, lncRNA HOTTIP, which was recently revealed [8]. As a tumor promotor, HOTTIP is upregulated in a number of tumors [10-17].

As for the precise mechanism of the regulation of HOTTIP in carcinogenesis, it is being explored in a growing number of studies. In summary, the lncRNA HOTTIP can be an up-regulator of multiple 5' HOXA genes by way of its interaction with the WDR5/MLL complex, which enhances histone H3 lysine 4 trimethylation of the target genes [8]. Furthermore, the activation of HOX genes may then silence related tumor suppressor genes such as p21 [10].

Accumulated evidence showed that there is a close relationship between HOTTIP and HOXA13 [11, 18]. There are several instances of research that have been conducted to clarify the association between them. Quagliata et al. [11] and Li et al. [18] found that high expression level of HOTTIP and HOXA13 is associated with metastasis and dismal prognosis in hepatocellular carcinoma (HCC) and pancreatic cancer (PC), respectively. As for the detailed mechanism, further exploration is needed. Therefore, we searched for and reviewed related literature with the search terms "HOTTIP" and "HOXA13" to identify more potentially eligible literature.

Our study explored this meta-analysis to evaluate the relationship between HOTTIP expression levels and cancer prognosis and related clinicopathology. First, we revealed that high expression level of HOTTIP is a negative prognosis predictor for cancer patients. We found a statistically significant negative association between levels of HOTTIP and OS (HR = 2.40; 95% CI: 1.89-3.06; P < 0.001). Additionally, in subgroup analysis, we also observed a significant association between HOTTIP and OS in digestive system (HR = 2.257; 95% CI: 1.75-2.9; P < 0.001) and non-digestive system (HR = 3.91; 95% CI: 1.90-8.07; P < 0.001) tumor patients.

Second, the related clinicopathological significance of elevated HOTTIP expression levels was also demonstrated in this meta-analysis. We conclude that over-expressed HOTTIP is positively correlated with the advanced clinical stage (III+IV: OR 3.29, 95% CI: 2.31-4.67; P < 0.001; digestive system III+IV: OR 2.81, 95% CI: 1.87-4.23; P < 0.001; non-digestive system III+IV: OR 5.12, 95% CI: 2.56-10.23; P < 0.001), tumor size (large: OR 3.02, 95% CI: 1.87-4.86; P < 0.001) and local invasion depth (present: OR 2.40, 95% CI: 1.70-3.37; P < 0.001). Additionally, those patients with upregulated HOTTIP may develop an elevated risk of lymph node metastasis (present: OR 2.40, 95% CI: 1.70-3.37; P < 0.001) and distal metastasis (present: OR 3.30, 95% CI: 1.78-6.12; P < 0.001).

However, there are several limitations in this present meta-analysis. There are relatively few studies included in our meta-analysis. Also, most of the studies were performed with Chinese sample populations, and not all of the studies reported the cutoff values of HOTTIP. Therefore, larger, multi-center, and higher quality studies with a unified criterion for determining HOTTIP expression level are urged to confirm the conclusions of this meta-analysis.

Acknowledgements

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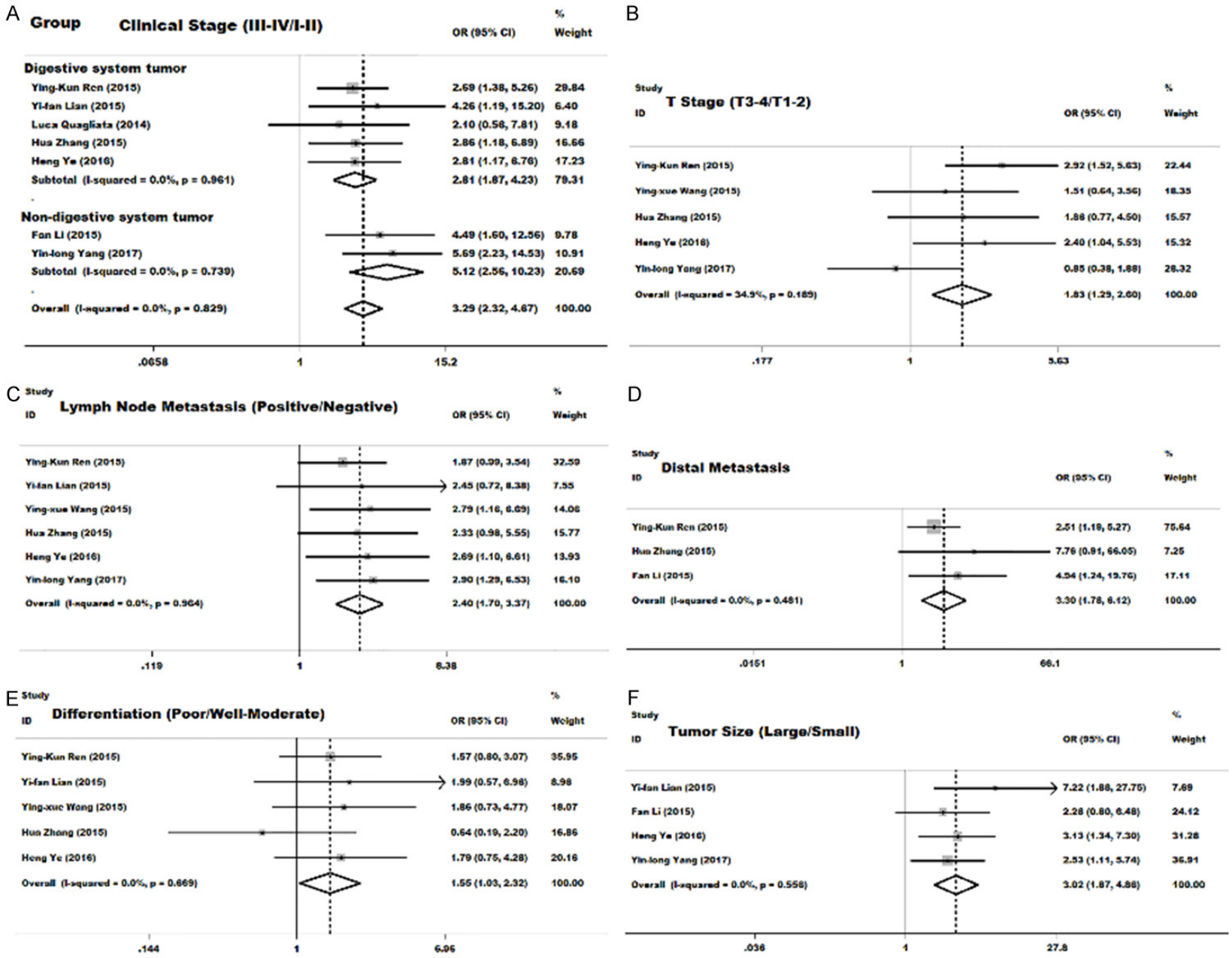
Disclosure of conflict of interest

None.


A
Group
Clinical Stage (III-IV/I-II)
OR (95% CI)
%
Weight
Digestive system tumor
Ying-Kun Ren (2015) 2.69 (1.38, 5.26) 29.84
Yi-fan Lian (2015) 4.26 (1.19, 15.20) 6.40
Luca Quagliata (2014) 2.10 (0.56, 7.81) 9.18
Hua Zhang (2015) 2.86 (1.18, 6.89) 16.66
Heng Ye (2016) 2.81 (1.17, 6.76) 17.23
Subtotal (I-squared = 0.0%, p = 0.961) 2.81 (1.87, 4.23) 79.31
Non-digestive system tumor
Fan Li (2015) 4.49 (1.60, 12.56) 9.78
Yin-long Yang (2017) 5.69 (2.23, 14.53) 10.91
Subtotal (I-squared = 0.0%, p = 0.739) 5.12 (2.56, 10.23) 20.69
Overall (I-squared = 0.0%, p = 0.829) 3.29 (2.32, 4.67) 100.00
.0658
1
15.2
B
Study
ID
T Stage (T3-4/T1-2)
OR (95% CI)
%
Weight
Ying-Kun Ren (2015) 2.92 (1.52, 5.63) 22.44
Ying-xue Wang (2015) 1.51 (0.64, 3.56) 18.35
Hua Zhang (2015) 1.88 (0.77, 4.60) 15.57
Heng Ye (2016) 2.40 (1.04, 5.53) 15.32
Yin-long Yang (2017) 0.85 (0.38, 1.88) 28.32
Overall (I-squared = 34.9%, p = 0.189) 1.83 (1.29, 2.60) 100.00
.177
1
5.63
C
Study
ID
Lymph Node Metastasis (Positive/Negative)
OR (95% CI)
%
Weight
Ying-Kun Ren (2015) 1.87 (0.99, 3.54) 32.59
Yi-fan Lian (2015) 2.45 (0.72, 8.38) 7.55
Ying-xue Wang (2015) 2.79 (1.16, 6.69) 14.06
Hua Zhang (2015) 2.33 (0.98, 5.55) 15.77
Heng Ye (2016) 2.69 (1.10, 6.61) 13.93
Yin-long Yang (2017) 2.90 (1.29, 6.53) 16.10
Overall (I-squared = 0.0%, p = 0.964) 2.40 (1.70, 3.37) 100.00
.119
1
8.38
D
Study
ID
Distal Metastasis
OR (95% CI)
%
Weight
Ying-Kun Ren (2015) 2.51 (1.19, 5.27) 75.64
Hua Zhang (2015) 7.76 (0.91, 66.05) 7.25
Fan Li (2015) 4.54 (1.24, 15.76) 17.11
Overall (I-squared = 0.0%, p = 0.481) 3.30 (1.78, 6.12) 100.00
.0151
1
66.1
E
Study
ID
Differentiation (Poor/Well-Moderate)
OR (95% CI)
%
Weight
Ying-Kun Ren (2015) 1.57 (0.80, 3.07) 35.95
Yi-fan Lian (2015) 1.99 (0.57, 6.98) 8.98
Ying-xue Wang (2015) 1.86 (0.73, 4.77) 18.07
Hua Zhang (2015) 0.64 (0.19, 2.20) 16.86
Heng Ye (2016) 1.79 (0.75, 4.28) 20.16
Overall (I-squared = 0.0%, p = 0.669) 1.55 (1.03, 2.32) 100.00
.144
1
6.96
F
Study
ID
Tumor Size (Large/Small)
OR (95% CI)
%
Weight
Yi-fan Lian (2015) 7.22 (1.88, 27.75) 7.69
Fan Li (2015) 2.28 (0.80, 6.48) 24.12
Heng Ye (2016) 3.13 (1.34, 7.30) 31.28
Yin-long Yang (2017) 2.53 (1.11, 5.74) 36.91
Overall (I-squared = 0.0%, p = 0.558) 3.02 (1.87, 4.88) 100.00
.036
1
27.8

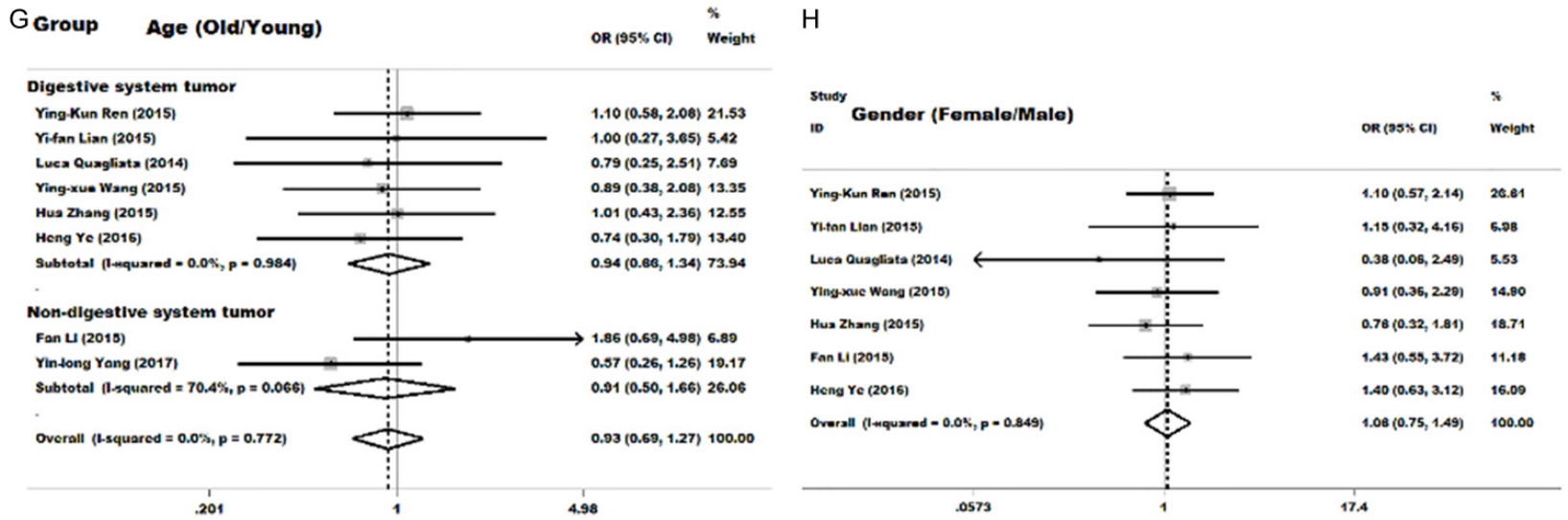


Figure 3. Forest plot for the association between HOTTIP and related clinicopathological parameters (A-H). The relationship between high expression of HOTTIP and clinical stage (A), local invasion (B), differentiation (C), lymph node metastasis (D), distal metastasis (E), tumor size (F), age (G) and gender (H).

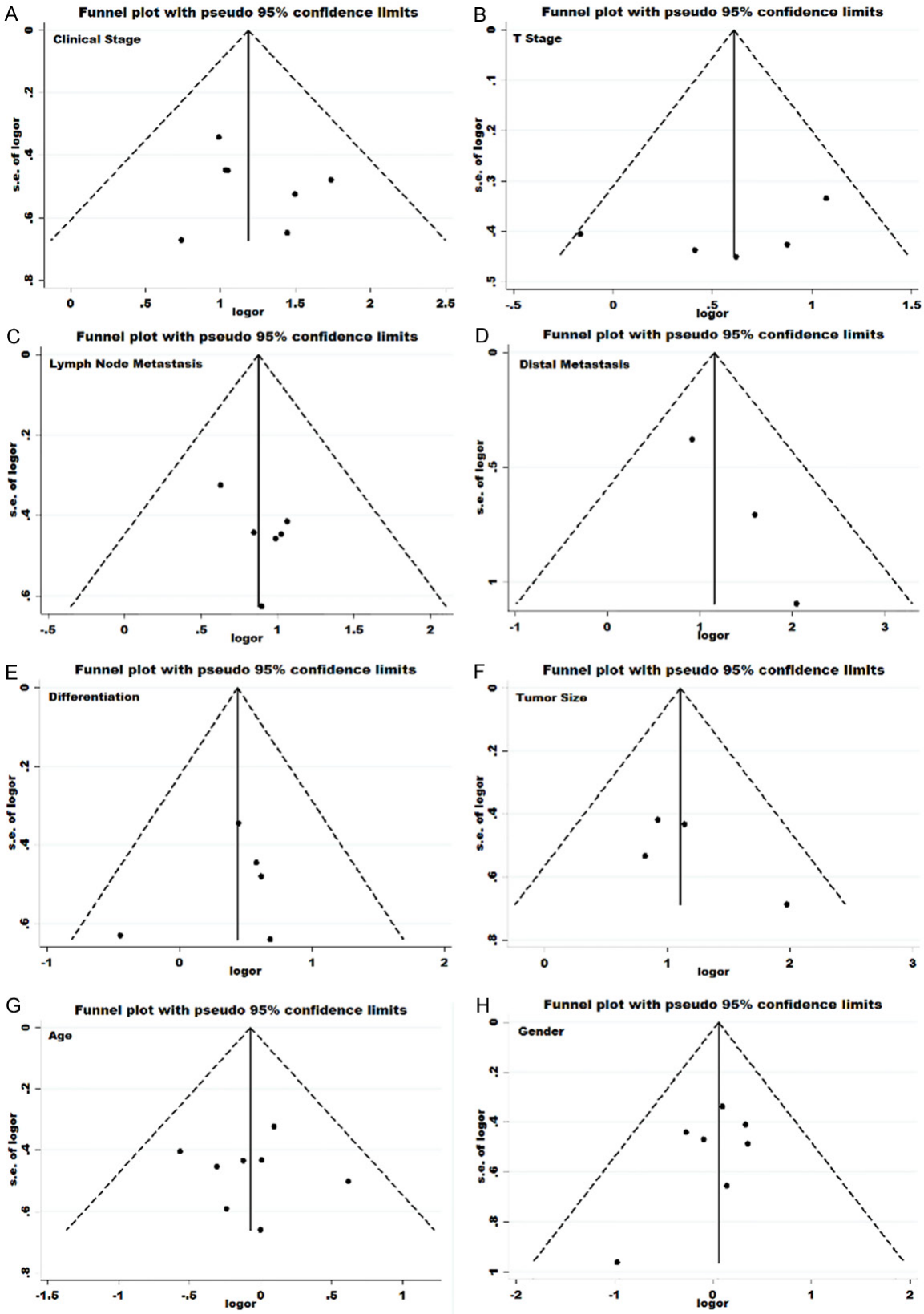


Figure 4. Funnel plot was performed to evaluate the potential publication bias. The shape of these studies' Funnel plot did not reveal obvious asymmetric, which suggested that publication bias was not obvious in related clinicopathological parameters (A-H). The relationship between high expression of HOTTIP and clinical stage (A), local invasion (B), differentiation (C), lymph node metastasis (D), distal metastasis (E), tumor size (F), age (G) and gender (H).

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