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Original Article

Long non-coding RNA H19 as a prognostic marker in human cancer: a meta-analysis

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Abstract: Long non-coding RNA (lncRNA) H19 is found to be overexpressed and associated with clinicopathological features in patients with cancer. To evaluate the clinical value of lncRNA H19 as a prognostic marker in human cancers, this meta-analysis collected all relevant articles and explored the association of H19 expression levels with prognosis in patients with carcinoma. Literature collections were conducted by searching electronic databases PubMed, Medline, EMBASE, Web of Science, Ovid and Cochrane library (up to July 10, 2015). Pooled hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated to estimate the strength of the link between H19 and clinical prognosis by STATA 12.0 software. 9 eligible studies with a total of 2105 patients conducted in 5 countries were matched to our inclusion criteria. The result showed that overexpression of H19 could predict poor overall survival (OS) and disease-free survival (DFS) incancer patients, with HR of 1.08 (95% CI 1.05-1.12), HR of 1.08 (95% CI 1.02-1.14), respectively. Cancer type (digestive and respiratory system carcinoma), paper quality (>85%, <85%), different methods of analysis (univariate and multivariate analysis) did not alter the predictive value of lncRNA H19 on poor prognosis in investigated cancers. This meta-analysis demonstrated that lncRNA H19 may potentially be used as a prognostic marker for predictingsurvival of cancer patients.

Keywords: Meta-analysis, lncRNA, H19, prognosis, cancer

Introduction

With the development of deep sequencing and DNA tiling array technology, an increasing number of investigators are focusing on non-coding RNAs (ncRNAs). Non-coding RNAs are RNAs that do not encode proteins, usually including long non-coding RNA (lncRNA), microRNA (miRNA, miR), small interfering RNA (short interfering RNA, silencing RNA, siRNA) and PIWI-interacting RNA (piRNA) [1, 2]. Recent studies have indicated that at least 70% of the human genome is transcribed into RNAs, which are mostly lncRNAs, longer than 200 nucleotides [3]. Emerging evidence suggests that lncRNAs have many biological actions, such as transcriptional and posttranscriptional regulation by interfering with the promoter of gene, the reorganization of chromatin, the induction of histone modification, the regulation of subcellular localization and/or function of proteins and the production of endogenous siRNA [4, 5]. Increasing evidences have indicated that lncRNAs play a key role in cell proliferation, invasion and metastasis and may be used as biomarkers for the diagnosis, treatment and prognosis of cancer [6-11].

Oncofetal lncRNA H19, paternally imprinted and maternally expressed, resides close to the telomeric region of chromosome 11p15.5 and is highly expressed from the early stages of embryogenesis to fetal life in many organs, but nearly unexpressed after birth [12]. Emerging evidences have shown that overexpressed H19 is significantly correlated with many types of human cancer: downregulated lncRNA H19 can represses prostate cancer metastasis [13]. Elevated lncRNA H19 promotes glioma cell invasion [14]. Upregulated lncRNA H19 may be associated with the proliferation and metastasis of bladder cancer [15, 16]. Overexpressed H19 enhances tumorigenesis and metastasis of breast cancer cells [17]. These all suggesting that H19 may serve as an authentic prognostic biomarker for patients with cancer.

In view of the fact that there is an association between H19 expression and the clinicopathological features of human cancers, most studies reported so far are limited in their sample size and discrete outcomes.Therefore, we analyze all previously published data based on the robust evidence of the expression and impact of H19 in tumorigenesis, and conduct a systematic review and quantitative meta-analysis to evaluatethe clinical value of H19 as a prognostic marker in human cancer.

Material and methods

Search strategy

A systematic literature search of PubMed, Medline, EMBASE, Web of Science, Ovid and Cochrane library. The literature covered was restricted to publications in English. The following key words were used for the search: "H19", "long non-coding RNA or lncRNA", "cancer or carcinoma or tumor or neoplasma or neoplasm or malignancy or sarcoma", "prognostic or prognosis", "outcome", "mortality", "survival" and "recurrence". The literature search was stopped at July 10, 2015.

Selection criteria and quality assessment

Inclusion criteria were as follows: (1) information of study population and regions; (2) information of any type of human cancer; (3) description of study design; (4) investigation of the correlation between H19 expression level and survival outcome; (5) description of H19 measurement, such as quantitative PCR or in situ hybridization in human tissue; (6) description of the relationship between H19 and overall survival (OS) or disease-free survival (DFS) or progression-free survival (PFS) or other indicators related to survival outcome; (7) description of the cut-off value of H19; (8) period of follow-up. The exclusion criteria were as follows: (1) meta-analysis paper; (2) review paper; (3) non-English paper; (4) conference abstract; (5) non-human data; (6) paper lacking all hazard ratio (HR), 95% confidence interval (CI) and *p* value and raw data.

For quality control of a paper, the assessment was performed by two authors, who reached an agreement on all items assessed. The categories of score assessment included the scientific design (five items: study objective definition, study design, outcome definition, statistical consideration, statistical method and test description), laboratory methodology (seven items: blinding in the biological assays performance, tested factor description, tissue sample conservation, description of the relevant test procedure of the biological factor, description of the negative and positive control procedures, test reproducibility control, definition of the level of positivity of the test), generalisability (six items: patient selection criteria, patients' characteristics, initial investigation, treatment description, source of samples, number of unassessable samples with exclusion causes) and results analysis (four items: follow-up description, survival analysis according to the biological marker, univariate analysis of the prognostic factors for survival, multivariate analysis of the prognostic factors for survival). Each item was scored as follows: 2 points if it was clearly defined in the article, 1 point if its description was incomplete or unclear and 0 point if it was not defined or was inadequate. The maximum theoretical score was 44 points. The final quality score was presented as percentage, which was calculated using the formula (the sum of the total points divided by 44 and multiplied by 100). An optimal threshold was yet to be defined, which the cut-off point of 85% of the quality scores represented half of the investigated studies. Higher percentages reflected better reporting quality of the paper.

Data extraction

The extracted data included author name, year of publication, country in which study participants were enrolled, the number of patients, study design, the expression level of H19, the clinical stage of the tumor, follow-up, treatment data, cut-off values, HRs of elevated H19 for overall OS, DFS, and PFS, as well as their 95% CIs and *P* values. There were four methods used to obtain the HRs. In method 1, the HRs were obtained directly from publications. In method 2, according to the primary survival date, calculated the HRs and 95% CIs by univariate analysis with STATA 12.0 software. In method 3, the HRs were extracted from Kaplan-Meier curves, the HR estimate was reconstructed by extracting several survival rates at specified times from the survival curves using the Engauge Digitizer software [18-21]. In method 4, the HRs were calculated from the total num-

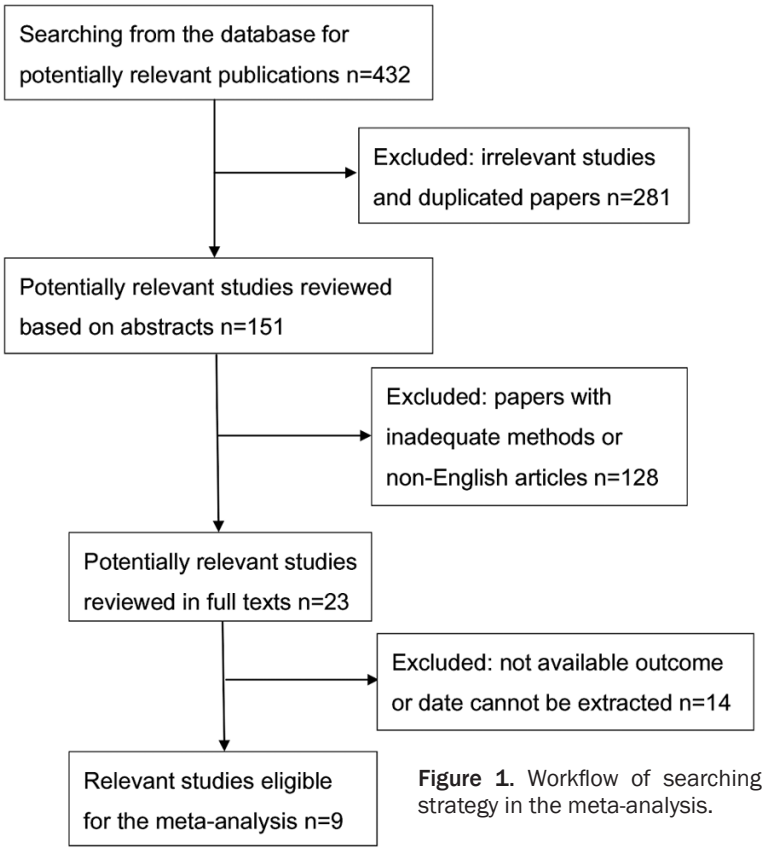

Figure 1. Workflow of searching strategy in the meta-analysis.

ber of events and its *P* value with the formula: $HR=[P_0/(1-P_0)]/[P_1/(1P_1)]$, where P_0 represents a 5-year survival rate in the group with low expression of H19 and P_1 represents a 5-year survival rate in the group with high expression of H19. The formula of 95% CI was exp (lnHR± 1.96×SE), where exp=exponential, lnHR=the natural logarithm HR and SE of HR [20, 21]. In this meta-analysis, only method 1, 2, 3 were used to calculate the HRs.

Statistical analysis

The data were analyzed using Stata 12.0 software. The HRs with the corresponding 95% CIs were used to estimate the strength of the link between H19 and clinical prognosis. The HRs with their 95% CIs and *P* values were collected from the original articles. However, if not available, we calculated the HRs and their 95% CIs using previously reported methods, as indicated above. A random-effect model was applied if heterogeneity was observed, whereas a fixed-effect model was usedin the absence of between-study heterogeneity. The factors contributing to heterogeneity were analysed by subgroup analysis, meta-regression or sensitivity analysis by a sequential omission of each individual study. The test for heterogeneity of combined HRs was carried out using a χ^2-based Cochran Q test and Higgins I^2 statistic. A *P* value of <0.05 or an I^2 value of >50% was considered statistically significant. Publication bias was evaluated using a funnel plot with Begg's bias indicator test [22].

Results

Data selection and characteristics of eligible studies

Based on the study design, our search with key terms disclosed 432 articles by July 10, 2015. The titles and abstracts were reviewed, and 281 irrelevant studies and duplicates were excluded. 128 studies were eliminated from the remaining 151 because different statistics methods had been used or the articles were not in English. After data extraction, 9 studieswith a total of 2105 patients [23-31], were matched to our inclusion criteria and were eligible for the meta-analysis (**Figure 1**).

Table 1 shows the main characteristics of all of the studies. The cut-off values of the high and low expression of H19 in these studies were found to be inconsistent owing to different detection methods, such as quantitative PCR and in situ hybridization.

Association of H19 expression with prognosis in human cancer

We obtained the HRs directly from four studies and indirectly from five studies by calculation using methods 2 and 3 as described. First, we investigated whether H19 was predictive for the survival (OS, DFS) of patients with cancer. The elevated expression of H19 was found to be significantly associated with poor OS (HR 1.08, 95% CI 1.05-1.12) and poor DFS (HR 1.08, 95% CI 1.02-1.14). There was no evi-

Table 1. Characteristics of studies included in the meta-analysis

Study	Year	Region	Tumor type	No.	Stage	PT	SO	Cut-off value	Me	Survival analysis	Follow up	Quality score
Zhang et al [23]	2014	China	Grastric cancer	80	I-IV	NO	OS	Mean	1	U+M	60 months	81.8%
Zhang et al [24]	2015	China	Non-small-cell lung cancer	70	I-IV	NA	OS	Median	1	U+M	60 months	93.2%
Li et al [25]	2014	China	Grastric cancer	74	I-IV	NA	OS	6-fold upregulation	3	U	53 months	81.8%
Zhang et al [26]	2013	China	Hepatocellular carcinoma	113	I-IV	NA	DFS	Median	1	M	24 months	86.4%
Chen et al [27]	2013	America	Lung cancer	1404#	NA	NA	OS	NA	3	U	200 months	72.7%
Esteves et al [28]	2005	Brazil	Head and neck carcinomas	35	I-IV	NO	OS	NA	2	U	86 months	72.7%
Iizuka et al [29]	2004	Japan	Hepatocellular carcinoma	59	I-III	NO	RFS*	Mean	3	U	80 months	86.4%
Yang et al [30]	2015	Korea	Hepatocellular carcinoma	240	I-IV	NO	OS DFS	Median	1	U U+M	120 months	93.2%
Jiang et al [31]	2015	China	Glioblastoma	30	NA	NO	PFS	Mean	3	U	30 months	81.8%

PT preoperative treatment, NA not available, Memethod (1=HRs obtained directly from publications, 2=HRs calculated from the primary survival data, 3=HRs extracted from Kaplan-Meier curves), U univariate, M multivariate, SO survival outcome, OS overall survival, DFS disease-free survival, PFS progression-free survival, RFS recurrence-free survival. #In the study of Chen 2013, the survival data of the 1404 samples was obtained from a clinical microarray database of lung cancer. *In the study of Iizuka 2004, RFS was defined as the survival of no disease, so, RFS was considered as DFS in the following meta-analysis.

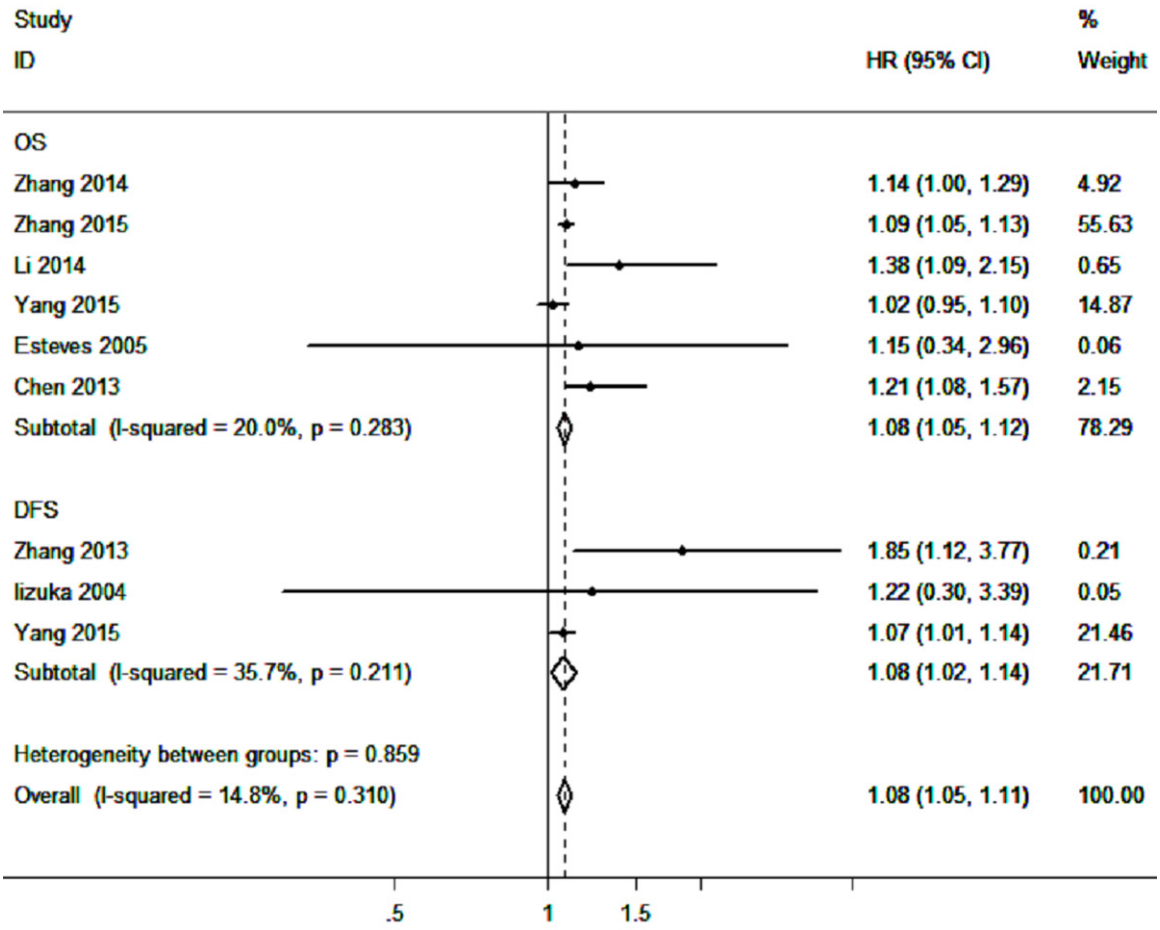

Figure 2. Forest plot for the correlation between H19 expression and poor prognosis (OS, DFS) of patients with cancers.

dence of statistically significant heterogeneity within the subgroups of patients with OS (P=0.283), DFS (P=0.211) (**Figure 2**).

Subsequent analyses of subgroups were performed based on different cancer, the elevated expression of H19 was found to be significantly associated with poor prognosis in patients with digestive system carcinoma (HR 1.07, 95% CI 1.02-1.12), respiratory system carcinoma (HR 1.09, 95% CI 1.05-1.13). There was no evidence of statistically significant heterogeneity within the subgroups of patients with digestive system malignancy (P=0.177), respiratory system carcinoma (P=0.270) (**Figure 3**).

We then examined the quality of the published paper in the studies and found that the scores (more or less than 85%) did not change the result of the estimated HR (HR 1.19, 95% CI 1.08-1.31 and HR 1.08, 95% CI 1.04-1.11, respectively) and that there was no evidence of statistically significant heterogeneity across the studies within the subgroups with scores of more or less than 85% (P=0.621 and P=0.160, respectively) (**Figure 4**).

Using different methods of analysis, we obtained similar results for the association of H19 expression with prognosis with multivariate analysis (HR 1.08, 95% CI 1.05-1.11) and univariate analysis (HR 1.28, 95% CI 1.10-1.48). No evidence of statistically significant heterogeneity was found across the studies (P=0.119 by multivariate analysis and P=0.867 by univariate analyses) (**Figure 5**).

Publication bias

Next, the potential publication bias was assessed using Begg's funnel plot. The funnel plot showed that there was no significant asym-

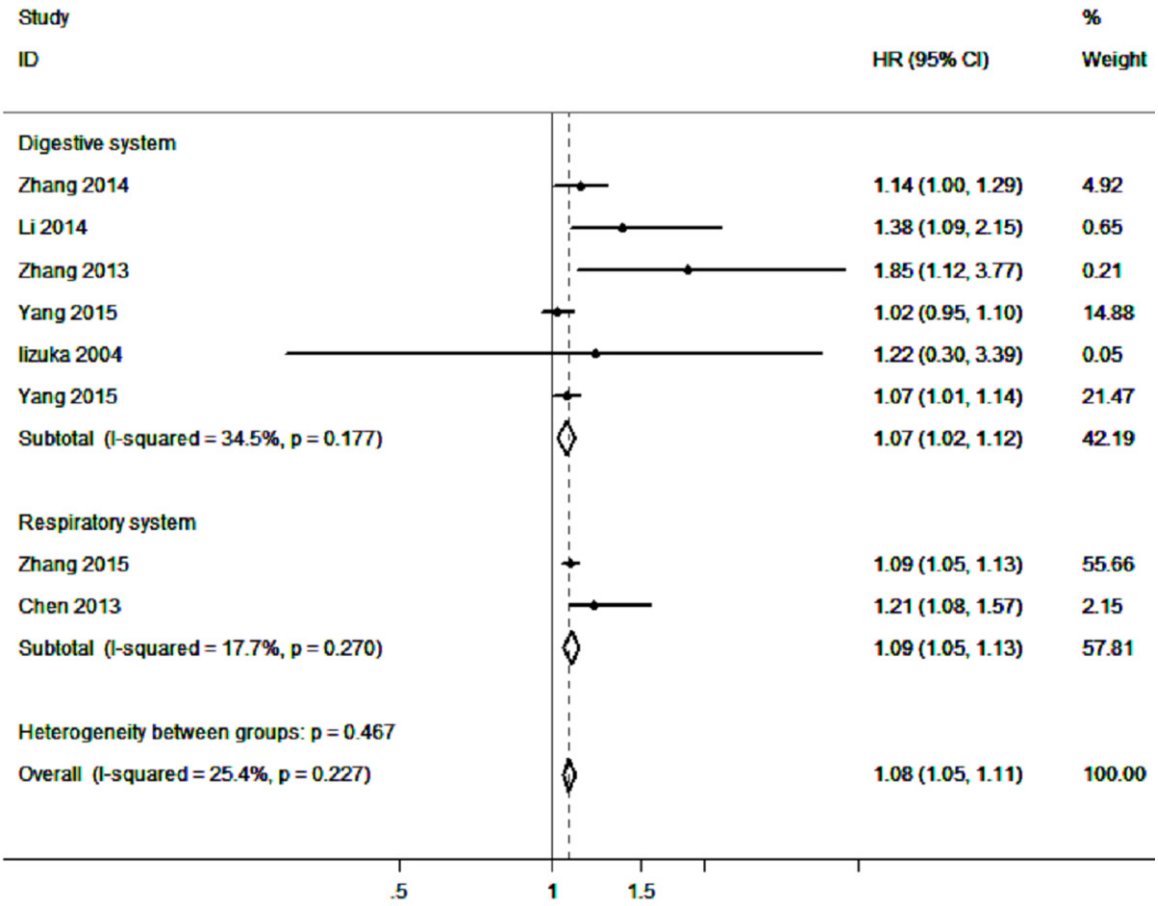

Figure 3. Forest plot of subgroup analysis showed the correlation of H19 expression with poor prognosis in different cancers.

metry, *P* value of Begg's test was 0.452. Therefore, no significant publication bias was detected in this meta-analysis (**Figure 6**).

Sensitivity analysis

Moreover, the sensitivity analysis showed that the pooled HR of OS was reliable (**Figure 7**). The exclusion of any individual study did not change the pooled HR significantly.

Discussion

This study disclosed the prognostic value of H19, an important lncRNA involved in cancer progression. This meta-analysis of published clinical studies, using a detailed search strategy and selection criteria, provided convincing evidence that H19 expression is predictive of poor tumor survival.

It has been shown that lncRNAs play important roles in pathophysiological processes. An increasing number of studies showing the involvement of lncRNAs in the development and the progression of various tumours have drawn attention towards these RNA species. H19, one of the lncRNAs, has been shown to be aberrantly expressed in different types of cancer, our meta-analysis summarised the tumour prognostic role of H19 and provided evidence for the association between H19 expression and clinicopathological characteristics of human cancers, suggesting that H19 may be used as a negative, unfavourable prognostic marker for most cancers.

We examined 9 independent studies comprising data from 2105 patients, elevated expression of H19 was found to be significantly associated with poor OS and DFS. Subgroup analysis including cancer type (digestive system carcinoma, respiratory system carcinoma), paper quality (with a score of more or less than 85%), methods of analysis (multivariate analysis and univariate analysis) showed that these factors

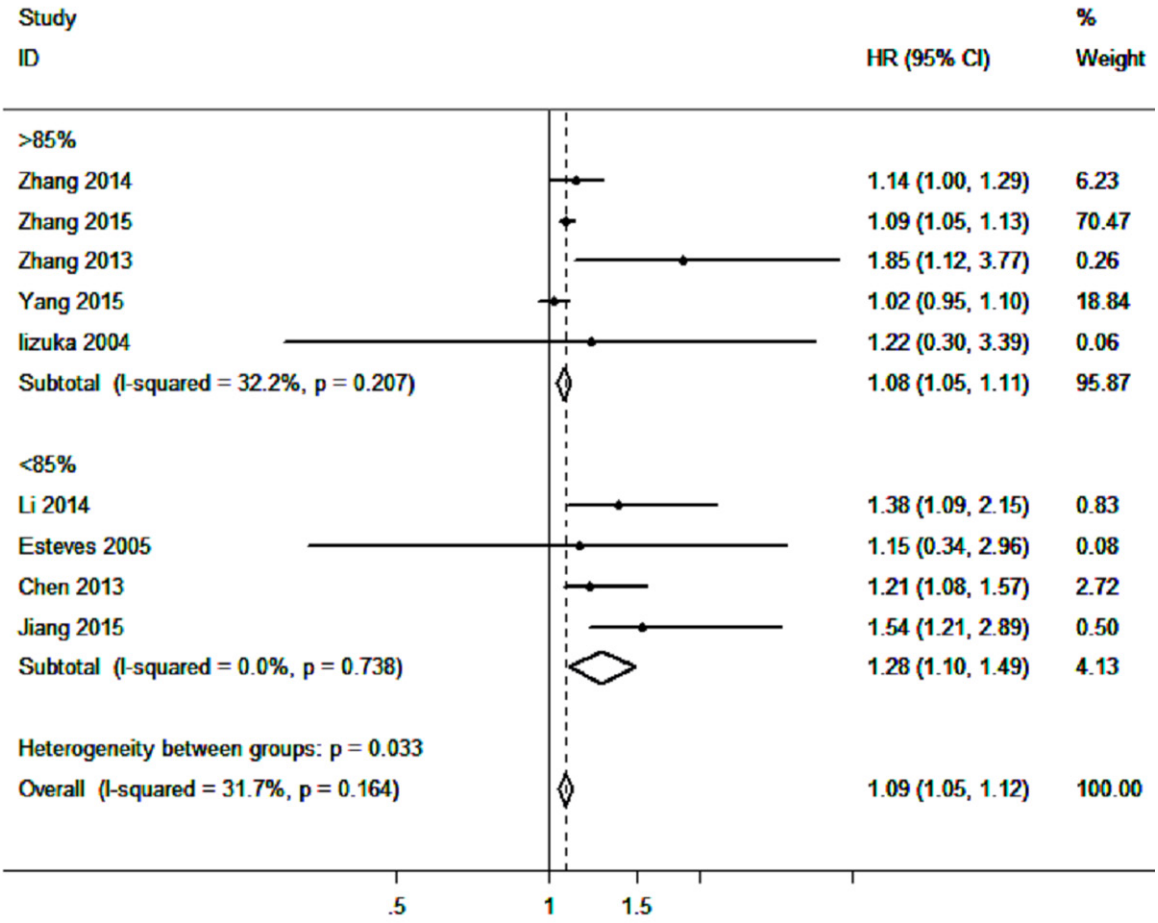

Figure 4. Forest plot of subgroup analysis showed the correlation of H19 expression with poor prognosis in studies with different quality scores.

did not alter the predictive value of H19 on poor prognosis among the investigated cancers and no evidence of statistically significant heterogeneity existed across the studies. Furthermore, Begg's test showed no significant publication bias concerning the prognostic role of H19 in the different types of cancer. Therefore, this meta-analysis supports the outcomes of many studies which found that H19 is a molecular predictor of poor prognosis.

Recently, the function and role of H19 in tumorigenesis has been extensively investigated. H19 has been shown to promote malignancy as its knockdown attenuates cell proliferation, decreases cell-matrix attachment in vitro and in vivo in pluripotent human embryonic carcinoma and embryonic stem cells. Mice transplanted with H19 down-regulated embryonic carcinoma cells exhibit slower kinetics of tumor formation, resulting in an increased animal survival [32]. The mechanism underlying the relationship between elevated H19 expression and poor prognosis in patients with cancer is uncertain. Many possible mechanisms have been proposed. LncRNA H19 increases cancer metastasis by associating with EZH2 and inhibiting E-cadherin expression [33]. LncRNA H19 regulates miR-675 positively, and overexpression of miR-675 induces a G1 arrest and inhibits cell apoptosis by its negative regulatory role for p53 expression [34]. H19 promotes cancer metastasis by derepressing let-7's suppression on its target HMGA2-mediated EMT [35]. Based on these studies and owing to its functions, H19 may be a consequential biomarker, and also be one of the causal factors for tumorigenesis in general.

As with any meta-analysis, our analysis has a few limitations due to the discrete data across these clinical studies. For example, the criteria

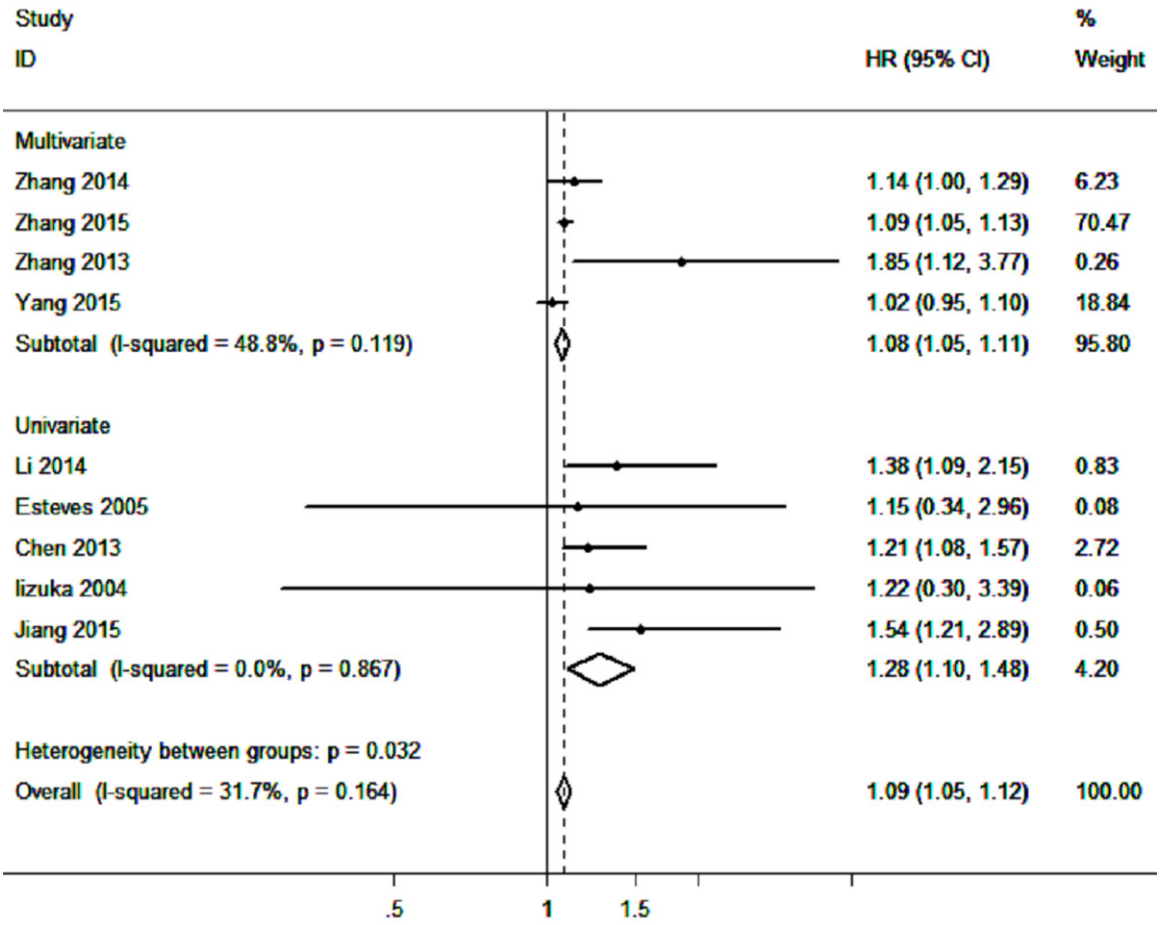

Figure 5. Forest plot of subgroup analysis showed the correlation of H19 expression with poor prognosis in studies with different methods of analysis.

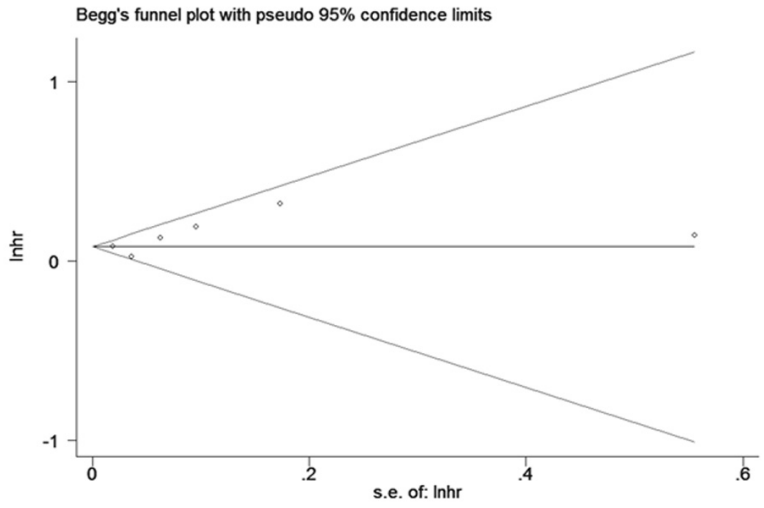

Figure 6. Funnel plot for the publication bias test of the included studies for H19 expression and overall survival.

for calculating the cut-off value were not the same in different studies. The inclusion of a relatively small number of studies in different regions might have decreased the applicability of our results across different ethnicities. In this meta-analysis, only summarised data rather than individual patient data were used. Furthermore, some of the HRs were calculated by reconstructing survival curves rather than directly obtained from the primary studies. The data collection may be incomplete because data from non-English language papers were not included. Therefore, it is possible that our results might overestimate the predictive significance of H19 in the prognosis of patients with cancer. We believe that more clinical studies should be conducted

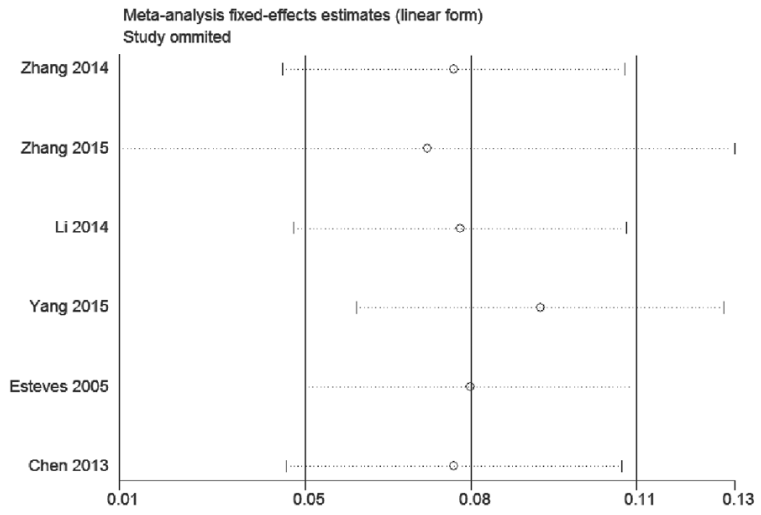

Figure 7. Sensitivity analysis of the pooled HR of H19 expression for overall survival for the included studies.

to evaluate the prognostic potential of H19 in other types of cancer that have not been included.

In summary, this meta-analysis shows that elevated H19 expression is common to cancer and that it is significantly associated with the poor prognosis. Furthermore, the functional role of H19 in the regulation of cell proliferation, apoptosis and metastasis suggests that H19 may play a key role in tumour progression. Thus, H19 may potentially be used as a new marker to predict the prognosis. More clinical studies on the different types of human cancer that have not yet been investigated need to be conducted.

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Disclosure of conflict of interest

None.

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