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REVIEW

Prognostic significance of the long noncoding RNAs in nasopharyngeal carcinoma: a systematic review and meta-analysis

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Background and objective: Nasopharyngeal carcinoma (NPC) is a common head and neck malignancy. Despite recent advances in treatment, the prognosis, particularly for those at the advanced stages, remains poor. Moreover, the underlying genetic and molecular events have remained obscure so far. Recently, increasing evidence has demonstrated that long noncoding RNAs (lncRNAs) could act as either oncogenes or tumor suppressor genes in various cancers depending on their targets. And some lncRNAs have been shown to be aberrantly expressed in NPC. In this meta-analysis, we try to elucidate the possible role of lncRNAs and their expression on prognosis in NPC.

Methods: We searched the databases of PubMed, Embase, and Web of Science for relevant articles ranging from January 2000 to December 2017. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were used to evaluate the prognostic value of lncRNAs in NPC. Odds ratios (ORs) were used to assess the association between lncRNAs and clinicopathological characteristics.

Results: A total of 14 eligible publications including 14 on prognosis and eight on clinicopathological characteristics were identified. Our results demonstrated that the high expression of lncRNAs was related to poor overall survival (OS; HR =1.55; 95% CI =1.01, 2.40; *P*=0.05) and disease-free survival (DFS; HR =1.83; 95% CI =1.07, 3.13; *P*=0.03) of NPC. Moreover, the expression of lncRNAs was correlated with male gender (OR =1.42; 95% CI =1.05, 1.91; *P*=0.02), lymph node status (OR =2.20; 95% CI =1.29, 3.73; *P*=0.004), and tumor node metastasis (TNM) clinical stage (OR =2.55; 95% CI =1.12, 5.78; *P*=0.03).

Conclusion: This meta-analysis shows that the level of expression of lncRNAs may be a potential prognostic indicator in NPC.

Keywords: long noncoding RNAs, nasopharyngeal carcinoma, prognosis, overall survival, meta-analysis

Introduction

Nasopharyngeal carcinoma (NPC) is a distinctive type of head and neck cancer and originates from nasopharyngeal epithelial cells. Although rarely occurring worldwide, the incidence and mortality rates of this tumor are remarkably high among Southeast Asia and Southern China.[1,2] The distinct geographical distribution highlights the significance of several etiologic factors in NPC tumorigenesis, including Epstein–Barr virus (EBV) infection, genetic predisposition, and intake of preserved food. The World Health Organization (WHO) recognizes the following three histological patterns: type I, keratinizing squamous-cell carcinoma; type II, differentiated nonkeratinizing carcinoma; and type III, undifferentiated carcinoma; the nonkeratinizing subtypes constitute

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most cases.[3] However, the understanding of the development of NPC is still unclear. Local recurrence and metastasis to cervical lymph nodes are the main cause of mortality in NPC. During the last decades, the outcome of the treatment has improved considerably. Concurrent chemoradiotherapy has become the choice of treatment for advanced NPC.[4]

Patients with NPC often do not show specific symptoms in the early stage, and when first diagnosed, most of them have stepped into advanced stage. So far, the clinical tumor node metastasis (TNM) staging system is the most commonly used predictor of prognosis for NPC patients; what is troubling, the prognosis often varies even at the same stage. Therefore, more specific and sensitive prognostic indicators need to be discovered and applied for the early diagnosis and individualized treatment for NPC patients.

Previous studies have found that long noncoding RNAs (lncRNAs) are extensively transcribed from genomes. They have been shown to play a role in carcinogenesis and cancer progression by modulating the expression of many oncogenes or tumor suppressor genes.[5–7] However, there are limited studies on lncRNAs in human NPC and the expression and function of lncRNAs in NPC remain uncovered. lncRNAs, >200 nucleotides (nts), with limited capacity of protein coding,[8,9] were considered transcriptional "noise" or "junk". Now, increasing evidence has demonstrated that these lncRNAs are junk no more, and in contrast, these lncRNAs have important biological functions in transcriptional regulation, epigenetic gene regulation, and disease.[8–12] Due to their essential role at every level of gene expression, lncRNAs have attracted major attention as molecules with structural and functional roles in various physiological processes, including development, differentiation, and metabolism.[13,14] Nevertheless, functional roles of the majority of these molecules remain to be identified.

To date, several studies have shown that a number of lncRNAs are involved in the development and progression of NPC, including HOTAIR, MALAT1, NEAT1, HNF1A-AS, AFAP1-AS1, and LINC00312.[15–20] He et al[21] summarized the different types of associated lncRNAs and their functional mechanisms in the development of NPC, and lncRNA was considered as a novel biomarker for the clinical diagnosis and treatment of NPC. Many studies had already evaluated the role of lncRNAs in NPC for prognosis; however, the small number of studies, limited number of lncRNAs, and paucity of multivariate analyses are the limitations; hence, this meta-analysis aims to comprehensively assess the value of lncRNAs both in the prognosis and clinical outcomes for patients with NPC.

Methods

Publication search strategy

PubMed, Embase, and Web of Science were searched for relevant literature published from January 2000 to December 2017. We mainly focused on "lncRNA", "nasopharyngeal", and "carcinoma", and the specific search strategy was as follows: "long non-coding RNA", "lncRNA", "lincRNA", "long intergenic non-coding RNA", "long untranslated RNA" and "NPC", "nasopharyngeal carcinoma", "nasopharyngeal neoplasm", "nasopharyngeal cancer". Studies explored the expression level of lncRNAs in different data set were considered to be different studies.

Inclusion and exclusion criteria

In this meta-analysis, the inclusion criteria for the eligible studies were as follows: 1) diagnosed with NPC; 2) analyzed the association between lncRNAs and NPC; 3) prognostic values such as overall survival (OS), disease-free survival (DFS), and recurrence-free survival (RFS) were investigated; 4) usable and sufficient published data were provided to calculate hazard ratios (HRs) and 95% confidence intervals (CIs); and 5) more complete and updated studies and data are preferred. Exclusion criteria were as follows: 1) no usable or insufficient data; 2) case reports, reviews, letters, and conference abstracts; and 3) animal experiments and Chinese literature.

Data extraction

Three of us (HuanHuan Guo, Shuo Huang, and Shuang Li) extracted the provided data including author, publication year, lncRNAs and their biotypes, methods, case number, outcomes, cut-off value, and follow-up months. The HRs and 95% CIs for survival analysis were obtained from the articles if available, and for studies that did not provide OS, DFS, or RFS directly, we also digitized and extracted the data from the given Kaplan–Meier survival curves using the Engauge Digitizer version 4.1.[22]

Statistical analysis

The relation between lncRNAs and prognosis in NPC was evaluated by the calculated HRs and 95% CIs. HR >1 implied a worse survival for the group with increased lncRNAs expression. Conversely, HR <1 implied a better survival for the group with increased lncRNAs expression. Meanwhile, the association between lncRNAs and clinicopathological characteristics (including gender, histological classification, tumor classification, lymph node status, metastasis, and

TNM clinical stage) were assessed by odds ratios (ORs) and 95% CIs. RevMan 5.2 software (RevMan; Cochrane Collaboration, Copenhagen, Denmark) was used to perform this meta-analysis, and the heterogeneity within studies was evaluated by Cochrane's Q and I^2 tests.[23] When heterogeneity was observed ($I^2 \leq 50\%$ and $P > 0.1$), the fixed-effect model was applied, otherwise, only the random-effect model was applied to calculate the pooled HRs or ORs. We evaluated the sensitivity and publication bias of the included articles by the Stata12.0 Software (StataCorp LP, College Station, TX, USA), and publication bias was evaluated by Begg's rank correlation method and Egger's weighted regression method. $P<0.05$ was considered statistically significant.

Results

Study characteristics

We searched 219 publications in the databases including 70 in PubMed, 61 in Embase, and 88 in Web of Science, and the flowchart of the literature review is shown in Figure 1. A total of 104 duplicated publications were removed, then 41 articles

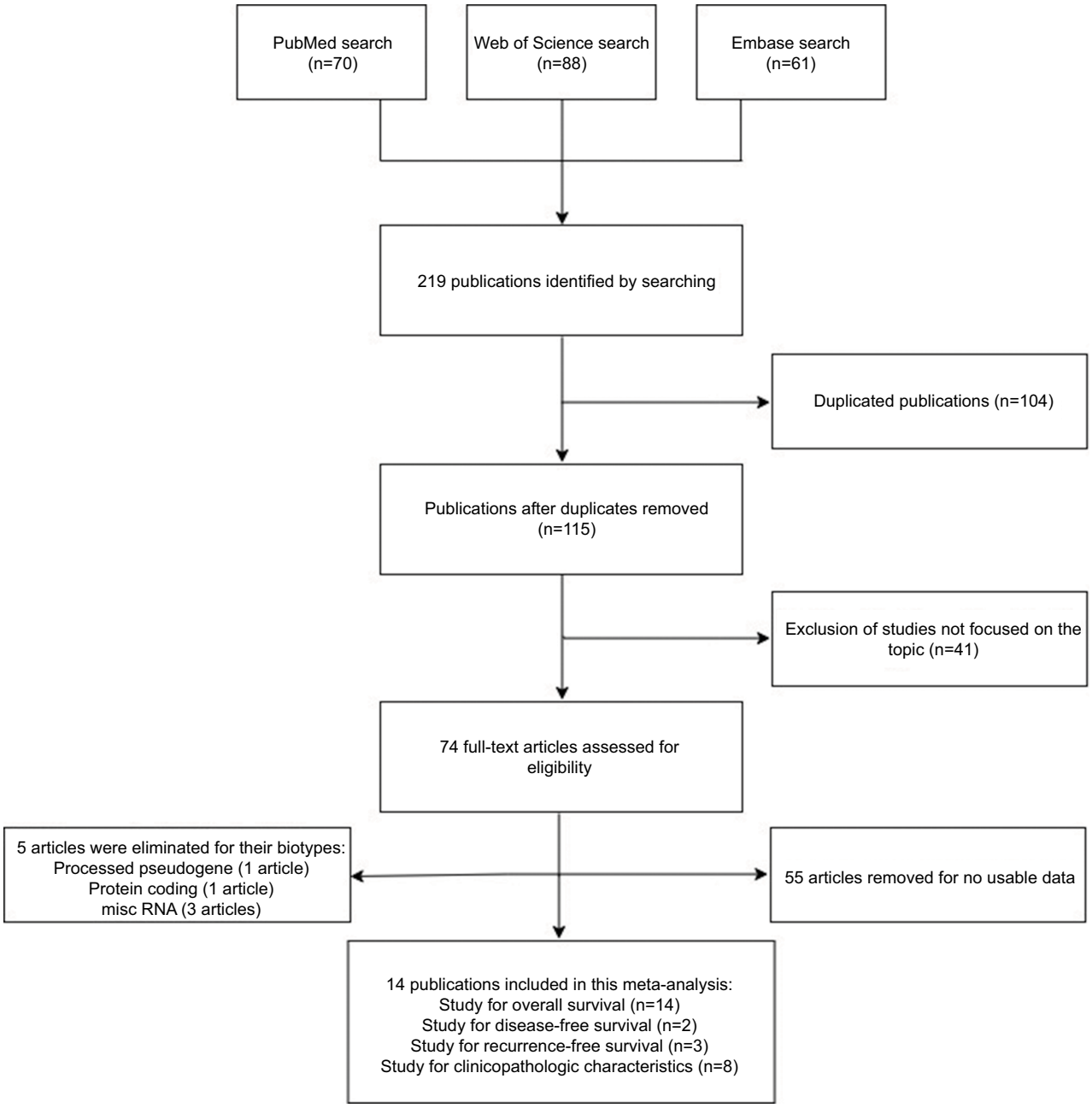

Figure 1 Flowchart of the search and selection of studies for the meta-analysis.

were excluded after screening the titles and abstracts, and 55 articles were removed for no usable data. After reviewing the studies, five articles were eliminated for their biotypes (Table S1). As a result, 14 articles were included in this systematic review and meta-analysis.[16–19,24–33]

The main characteristics of the included 14 studies are summarized in Table 1, and the biotypes of different lncRNAs according to the Ensembl are shown later. Eight studies analyzed the association between the expression of lncRNAs and gender,[16–19,24,25,28,29] two studies indicated that lncRNAs were related to histological classification,[17,24] eight studies were on tumor classification,[16–19,24,25,28,29] seven studies were about lymph node status,[16–19,24,28,29] eight studies referred to the metastasis,[16–19,24,25,28,29] and eight studies reported that lncRNAs were significantly correlated with TNM clinical stage (Table 2).[16–19,24,25,28,29]

Prognosis

Among the included studies, 14 studies performed the correlation between lncRNAs and OS.[16–19,24–33] HRs and 95% CIs were extracted or calculated by the provided data in these studies. The expression of lncRNAs was related to OS in NPC (HR =1.55; 95% CI =1.01, 2.40; *P*=0.05, random-effect) (Figure 2A). From the forest plot, we found that the high level of AFAP1-AS1, HULC, MALAT1, LINC00460, PCAT7, HOTAIR, EWSAT1, XIST, CASC9, and ANRIL was correlated with poor prognosis, whereas the low level of NEAT1 and LET was correlated with poor prognosis in NPC.

Only two studies explored that the level of lncRNAs was associated with DFS in patients with NPC.[17,28] The elevated level of HOTAIR and ANRIL indicated a relatively poor prognosis. And the enrolled studies showed the correlation between the increased expression of lncRNAs and DFS in

Table 1 Characteristics of studies included in this meta-analysis

Author	Year	lncRNAs	Biotype (Ensembl)/ length (bp)	Method	Case number (high/low)	Outcome	Cut-off	Follow-up months
Nie et al[17]	2013	HOTAIR	Antisense RNA/2421	qRT-PCR and ISH	91/69	OS, DFS, and RFS	SI =6	Median of 69
Bo et al[24]	2015	AFAP1-AS1	Antisense RNA/6795	qRT-PCR and ISH	23/55	OS and RFS	1.5-Fold	120
Sun et al[25]	2015	LET	Sense intronic/2283	qRT-PCR	34/34	OS and RFS	Median	100
Jin et al[18]	2016	MALAT1	lincRNA/8708	qRT-PCR and ISH	66/65	OS	SI =6	60
Lu et al[19]	2016	NEAT1	lincRNA/22743	qRT-PCR and ISH	66/65	OS	SI =6	60
Song et al[26]	2016	XIST	lincRNA/19275	qRT-PCR	76/32	OS	2.31-Fold	140
Song and Yin[27]	2016	EWSAT1	lincRNA/2498	qRT-PCR	76/32	OS	2.36-Fold	140
Zou et al[28]	2016	ANRIL	Antisense RNA/3835	qRT-PCR	44/44	OS and DFS	Median	100
Jiang and Liu[29]	2017	HULC	lincRNA/556	qRT-PCR	78/42	OS	2.5-Fold	50
Liu et al[31]	2017	PCAT7	Retained intron/1164	qRT-PCR	38/12	OS	NA	140
Su et al[30]	2017	CASC9	lincRNA/1164	qRT-PCR	45/45	OS	2.5-Fold	60
Tang et al[16]	2017	AFAP1-AS1	Antisense RNA/6795	qRT-PCR and ISH	68/28	OS	NA	120
Wang et al[32]	2017	NEAT1	lincRNA/22743	qRT-PCR and AM	39/31	OS	2-Fold	50
Kong et al[33]	2018	LINC00460	lincRNA/739	qRT-PCR	25/25	OS	Median	140

Abbreviations: AM, affymetrix microarray; DFS, disease-free survival; ISH, in situ hybridization; lincRNA, long intergenic noncoding RNA; lncRNAs, long noncoding RNAs; NA, not available; NPC, nasopharyngeal carcinoma; OS, overall survival; qRT-PCR, quantitative real time polymerase chain reaction; RFS, recurrence-free survival; SI, staining index.

Table 2 Correlation between high expression of lncRNAs and clinicopathological characteristics of patients with NPC

Characteristics	Studies	Case number	Pooled OR (95% CI)	*P*	Heterogeneity	
					I^2 (%)	*P*
Gender (male/female)	8	470	1.42 (1.05, 1.91)	0.02	0	0.54
Histological classification (WHO type II/III)	2	106	0.91 (0.39, 2.13)	0.82	NA	NA
T classification (T1–T2/T3–T4)	8	455	1.33 (0.69, 2.56)	0.39	80	<0.00001
N classification (N0–N1/N2–N3)	7	447	2.20 (1.29, 3.73)	0.004	67	0.005
Metastasis (no/yes)	8	499	1.41 (0.69, 2.87)	0.34	74	0.0004
TNM clinical stage (I–II/III–IV)	8	497	2.55 (1.12, 5.78)	0.03	85	<0.00001

Abbreviations: CI, confidence interval; lncRNAs, long noncoding RNAs; NA, not applicable; NPC, nasopharyngeal carcinoma; OR, odds ratio; TNM, tumor node metastasis; WHO, World Health Organization.

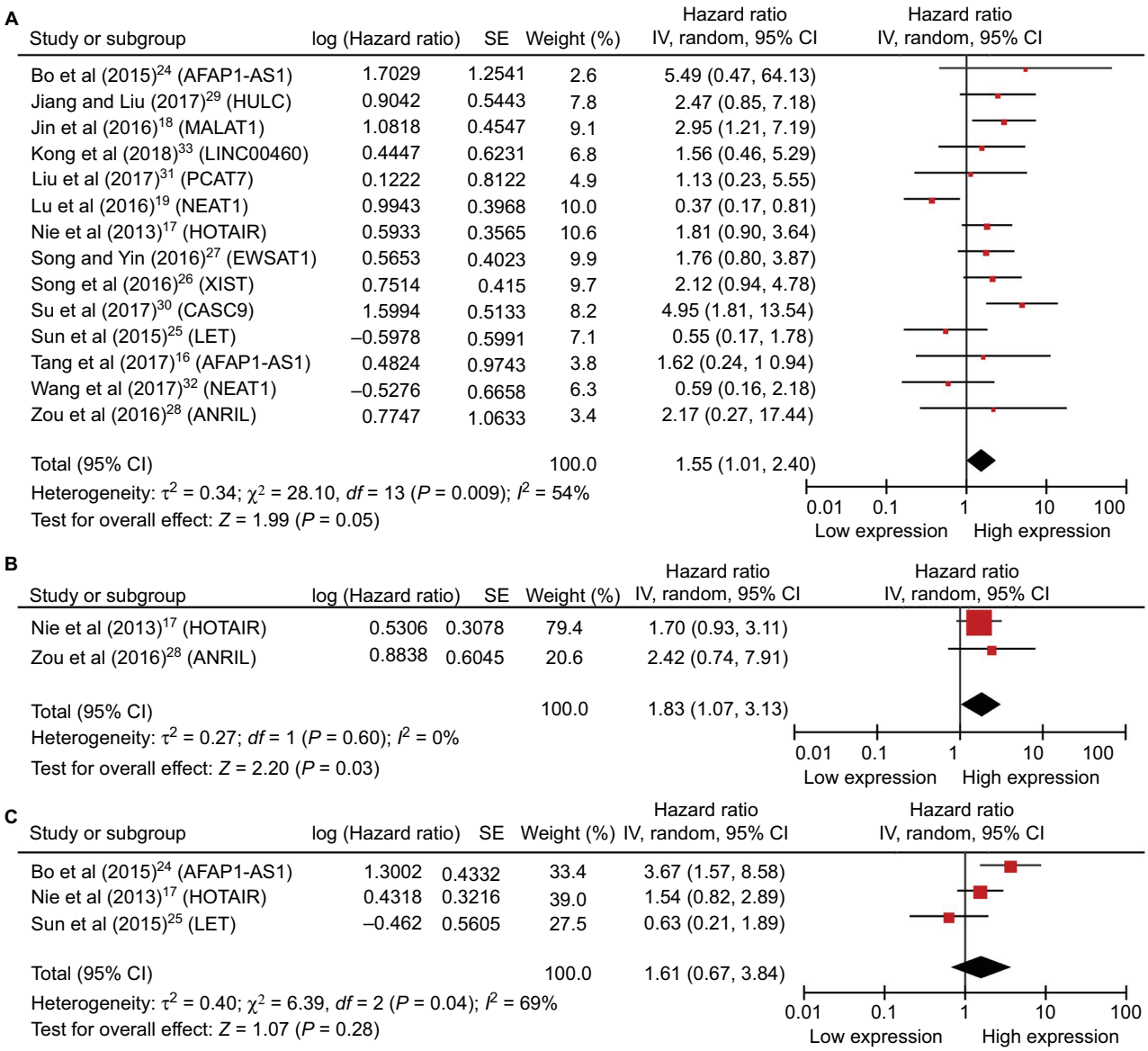

Figure 2 (**A**) Forest plot of studies evaluating HRs of lncRNAs' expression and the overall survival in NPC. (**B**) Forest plot of studies evaluating HRs of lncRNAs' expression and the disease-free survival in NPC. (**C**) Forest plot of studies evaluating HRs of lncRNAs' expression and the recurrence-free survival in NPC. The point estimate is bounded by a 95% CI, and the perpendicular line represents no increased risk for the outcome.

Abbreviations: CI, confidence interval; HRs, hazard ratios; lncRNAs, long noncoding RNAs; NPC, nasopharyngeal carcinoma.

NPC (HR =1.83; 95% CI =1.07, 3.13; *P*=0.03, fixed-effect) (Figure 2B).

And three studies showed that lncRNAs' expression was associated with the RFS in NPC (HR =1.61; 95% CI =0.67, 3.84; *P*=0.28, random-effect) (Figure 2C).[17,24,25]The high expression of AFAP1-AS1 and HOTAIR predicted a shorter RFS time, while the high expression of LET demonstrated a better outcome.

With only one or two studies included in this meta-analysis, with maybe the exception of NEAT1 (Figure 3), the analysis may be considered inadequate and this may be of limited practicability and should be elaborated prudently; furthermore, comprehensive and larger sample size studies are required to be validated.

Due to the expression of lncRNAs that varies in NPC and the high expression as shown earlier, some may be associated with improved survival whereas others may definitely be correlated with reduced survival; thus, we performed the subgroup analyses (Figure 4). The upregulated lncRNAs were divided into two groups according to helpful

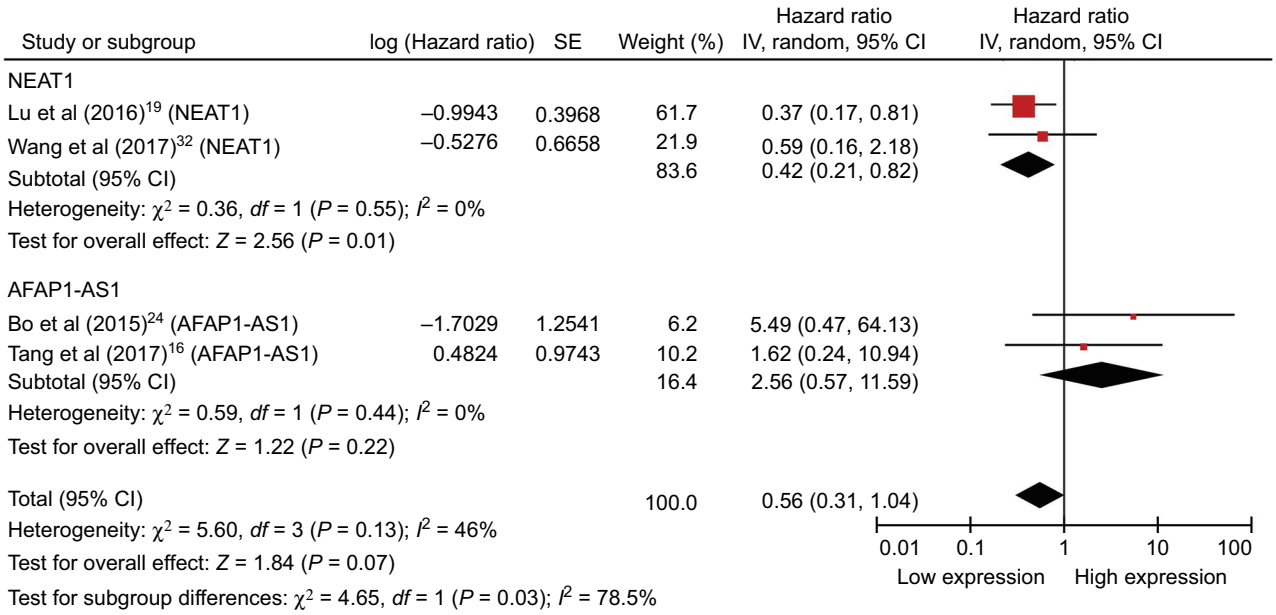

Figure 3 Forest plot showing the combined HR from studies for the association between high NEAT1 and AFAP1-AS1 levels and overall survival.
Abbreviations: CI, confidence interval; HR, hazard ratio.

for prognosis and harmful to prognosis (Figure 4A). And we also divided the included studies into three subgroups based on the biotypes of lncRNAs in the Ensembl database (Figure 4B). As shown in the forest plots, the heterogeneity has been reduced to some extent in several subgroups, but the total heterogeneity still cannot be ignored. Due to the small sample sizes of the included studies, we did not perform meta-regression.

Correlation between the expression of lncRNAs and clinicopathological characteristics in NPC

Table 2 summarizes the association between the expression levels of lncRNAs and clinicopathological characteristics of NPC patients. ORs >1 implied that elevated expression of lncRNAs might be more susceptible to the characteristic. And the analysis indicated that the increased expression of lncRNAs was correlated with gender (OR =1.42; 95% CI =1.05, 1.91; P=0.02, fixed-effect), lymph node status (OR =2.20; 95% CI =1.29, 3.73; P=0.004, random-effect), and TNM clinical stage (OR =2.55; 95% CI =1.12, 5.78; P=0.03, random-effect) (Figure S1). Unfortunately, there was no correlation with histological classification (OR =0.91; 95% CI =0.39, 2.13; P=0.82, fixed-effect), tumor classification (OR =1.33; 95% CI =0.69, 2.56; P=0.39, random-effect), and metastasis (OR =1.41; 95% CI =0.69, 2.87; P=0.34, random-effect) (Figure S2). As shown earlier, a significant heterogeneity was observed among tumor classification (I^2=80%), lymph node status (I^2=67%), metastasis (I^2=74%), and TNM clinical stage (I^2=85%). We suspected that the main causes of the significant heterogeneity in this analysis were the different cut-off definitions of the expression and the different roles of the lncRNAs in different studies. And we did not perform subgroup analysis due to the limited number of the enrolled studies, and further studies should be conducted to verify this conclusion.

Publication bias and sensitivity analysis

Begg's funnel plot and Egger's test were performed to assess the potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (Figure 5) and all the values of P>0.05. Egger's test also showed that there was no statistical significance for the evaluation of publication bias (Figure S3; OS: P=0.732, RFS: P=0.900; gender: P=0.294, tumor classification: P=0.679, lymph node status: P=0.878, metastasis: P=0.811, and TNM stage: P=0.826).

Sensitivity analysis, after removing one study at a time, was performed to evaluate the stability of the result. We found little change in the estimated results (Figure 6), indicating that our results were statistically robust.

Discussion

In the patients with NPC, many factors including stage of disease, nodal involvement, distant metastasis, histopathologic type, tumor volume, age, and parapharyngeal extension have been evaluated as potential prognostic indicators.[3,34] In recent years, the searches for novel prognostic factors that more

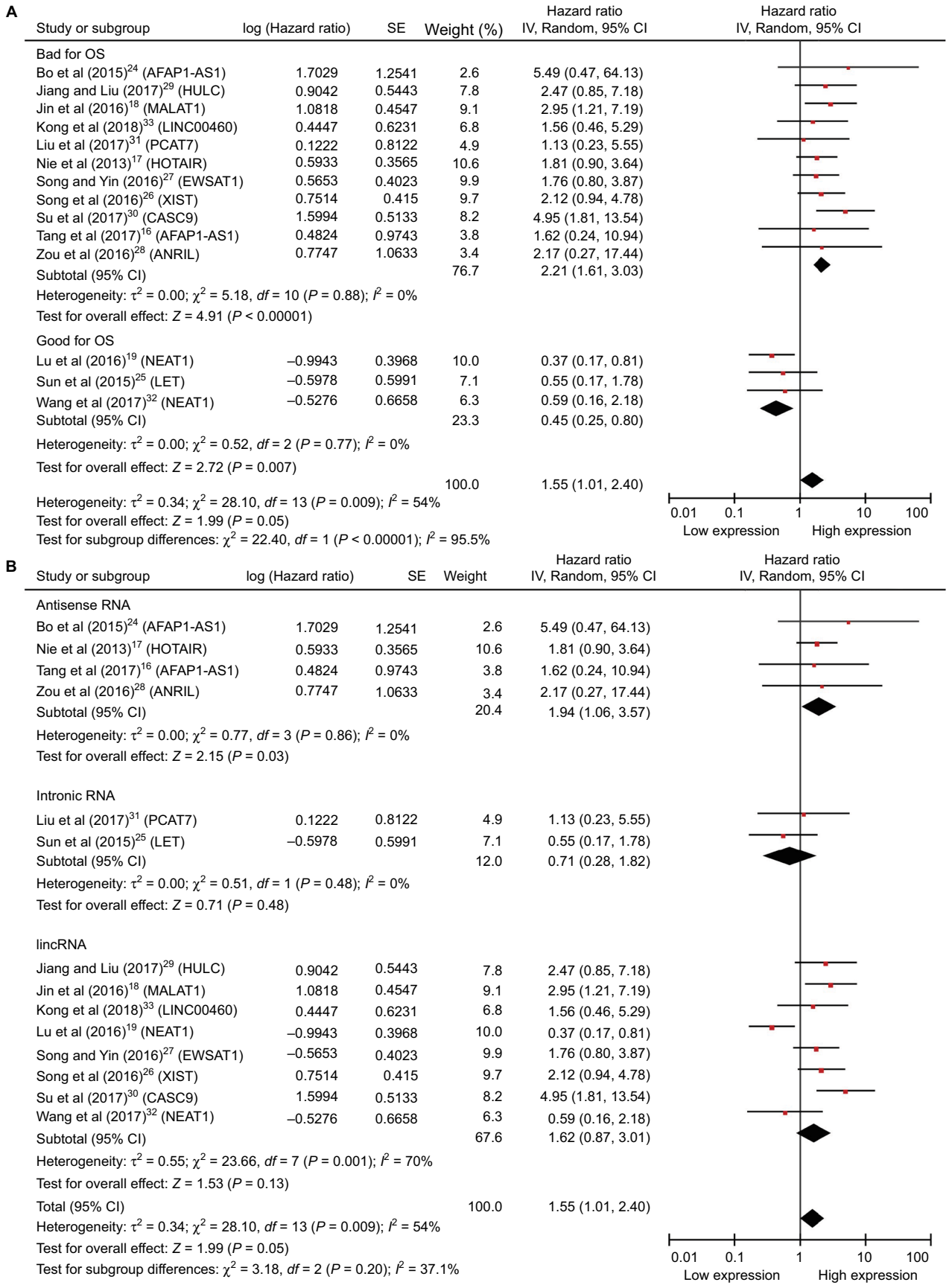

Figure 4 Forest plots of studies evaluating HRs of upregulated lncRNAs and the OS of NPC patients.
Notes: (**A**) Subgroup outcome and (**B**) subgroup biotype.
Abbreviations: CI, confidence interval; HRs, hazard ratios; lincRNA, long intergenic noncoding RNA; lncRNAs, long noncoding RNAs; OS, overall survival; NPC, nasopharyngeal carcinoma.

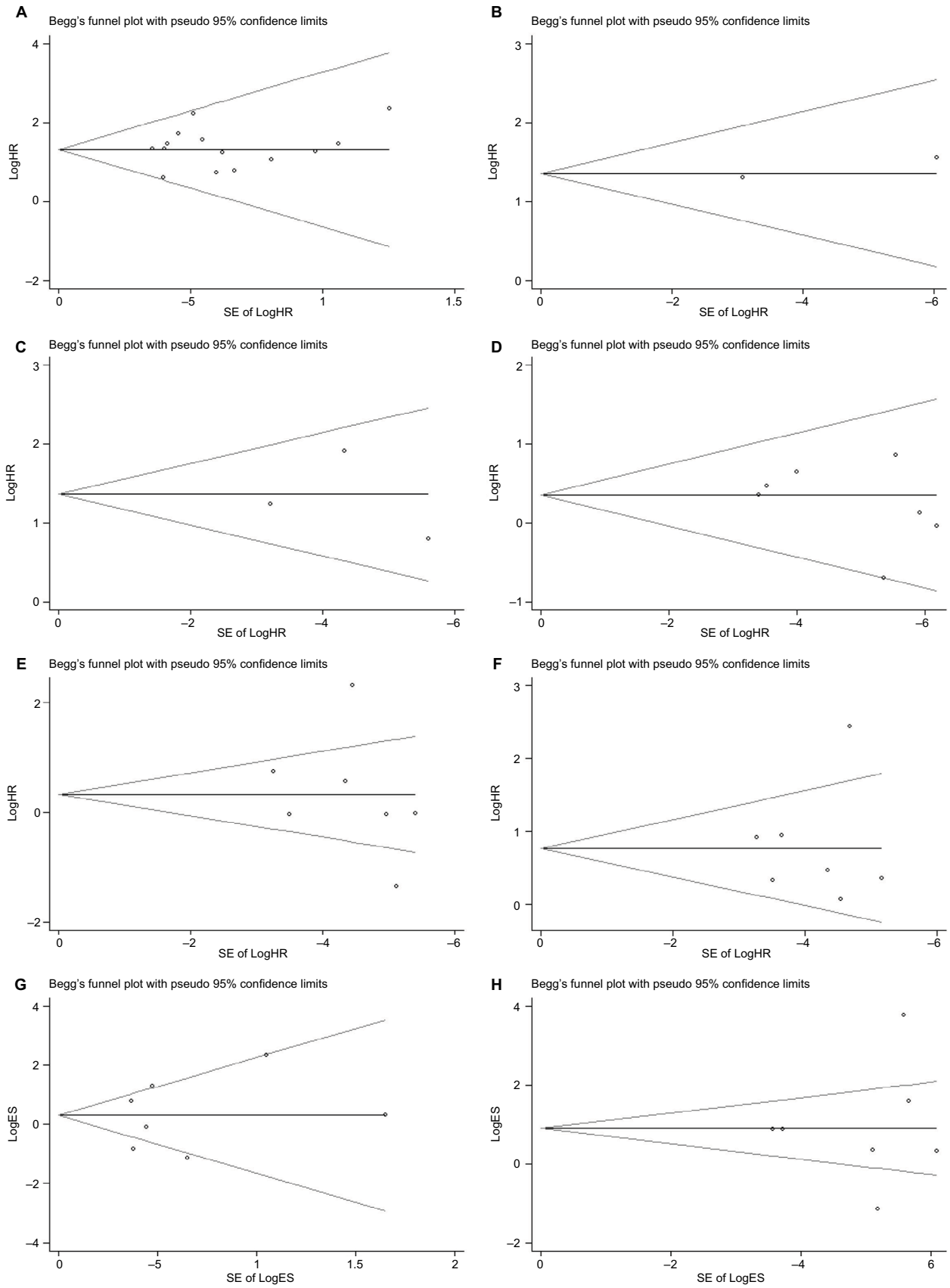

Figure 5 Begg's test for publication bias.

Notes: (**A**) Overall survival, (**B**) disease-free survival, (**C**) recurrence-free survival, (**D**) gender, (**E**) tumor classification, (**F**) lymph node status, (**G**) metastasis, and (**H**) TNM stage.

Abbreviations: HR, hazard ratio; TNM, tumor node metastasis; ES, effect size; SE, standard error.

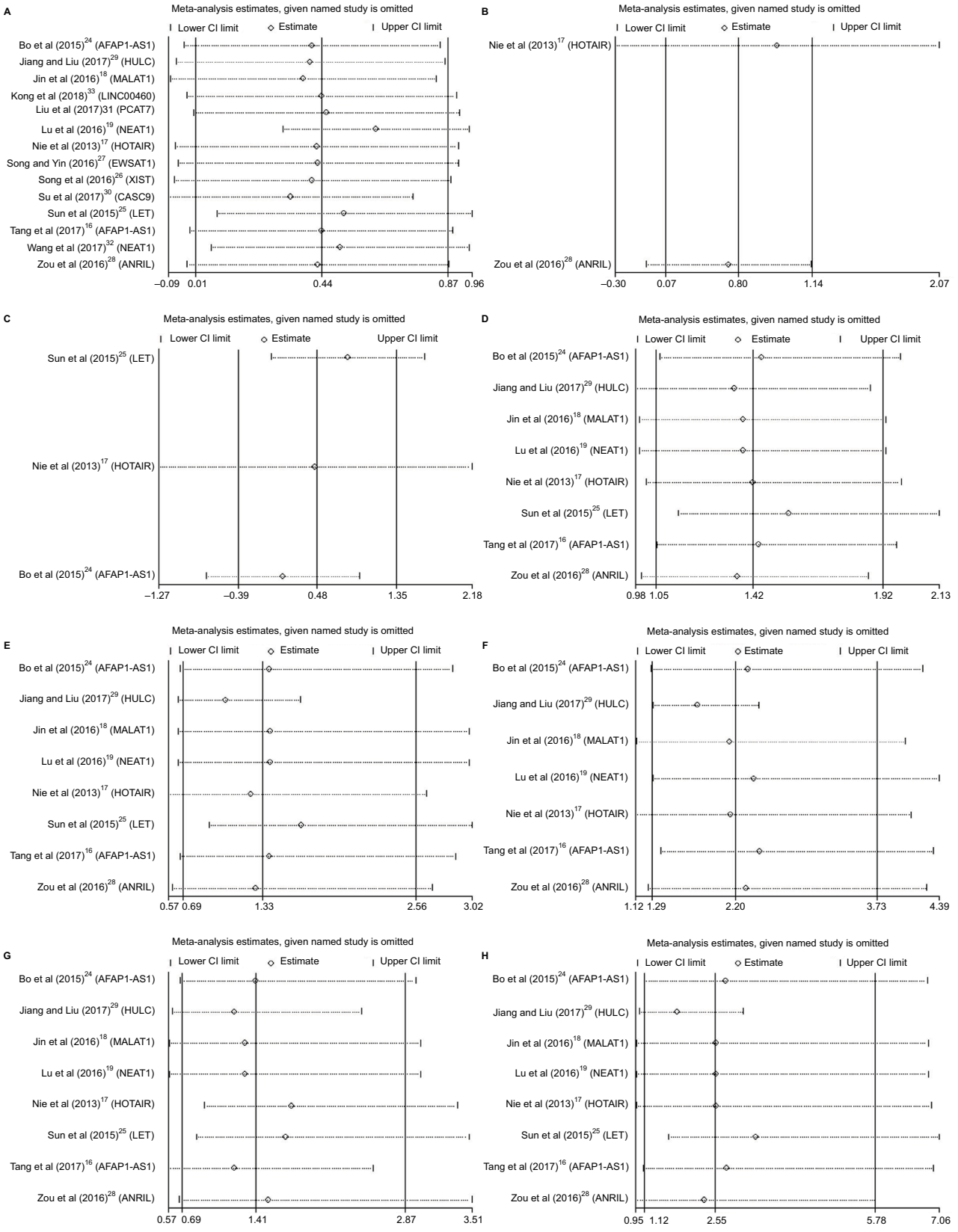

Figure 6 Sensitivity analyses of the studies.

Notes: (**A**) Overall survival, (**B**) disease-free survival, (**C**) recurrence-free survival, (**D**) gender, (**E**) tumor classification, (**F**) lymph node status, (**G**) metastasis, and (**H**) TNM stage.

Abbreviations: CI, confidence interval; TNM, tumor node metastasis.

reliably predict the biological behavior of the tumors have focused on the role of various molecular biomarkers at the genetic levels,[35] including lncRNAs.[36] In this meta-analysis, we comprehensively assessed the associations of aberrantly expressed lncRNAs with the prognosis and clinicopathological parameters in NPC and we demonstrated that the higher expression of lncRNAs was significantly associated with the worse OS and DFS.

Recently, increasing evidence suggests that the dysregulation of lncRNAs was involved in cancer, and alterations in lncRNA expression and their mutations promote tumorigenesis and metastasis.[5,6,37,38] Many cancer-associated lncRNAs have been identified and characterized, and these lncRNAs help further understand the molecular mechanism of cancer.[13,39] In addition, most of these cancer-associated lncRNAs could be effective prognostic biomarkers and even therapeutic targets.[39–41] HOTAIR is transcribed from the antisense strand of homeobox C (*HOXC*) gene locus in chromosome 12, and it coordinates with chromatin-modifying enzymes and regulates gene silencing. It is a scaffolding lncRNA, silences genes via interaction with PRC2 and LSD1, and aids protein degradation via interaction with E3 ubiquitin ligases; the knockdown of HOTAIR reduces tumor invasiveness and disrupts epithelial mesenchymal transition. And it is one of the well-studied lncRNAs that is overexpressed in various cancers including breast, pancreatic, colorectal, hepatocellular, gastrointestinal, and non-small-cell lung carcinomas.[42–44] Furthermore, the aberrantly upregulated expression in NPC correlates with clinical stage progression and contributes to the malignant character of NPC cells through involvement in diverse cellular processes, including migration, invasion, and proliferation, and also indicates a poorer prognosis for DFS and OS. AFAP1-AS1 promoted cancer cell metastasis via regulation of actin filament integrity. And its knockdown significantly inhibited the NPC cell migration and invasive capability. The study indicated that the AFAP1-AS1 expression was upregulated in NPC and associated with NPC metastasis and poor prognosis.[24] H19 affected the expression of enhancer of zeste homolog 2 (*EZH2*) to promote cell invasion by suppressing the activity of miR-630. Furthermore, H19 inhibited E-cadherin expression and promoted the cell invasion of NPC cells via the miR-630/EZH2 pathway.[45] MALAT1 was originally found to be overexpressed in primary non-small-cell lung cancers,[46,47] and it undergoes posttranscriptional processing to produce a short RNA (cytoplasmic MALAT1-associated small cytoplasmic RNA [mascRNA]) and a long MALAT1 transcript that are localized to nuclear speckles and influence the level of phosphorylated splicing-associated serine arginine (SR) proteins. And it is also overexpressed in other cancers including bladder carcinoma, breast cancer, prostate cancer, and ovarian cancer and is a potential biomarker and therapeutic target. HULC, an oncogenic lncRNA, which was first identified in hepatocellular carcinoma (HCC), acts as a miRNA sponge and sequesters miR-372, and its knockdown inhibits cell proliferation and increases chemosensitivity. HULC promoter possesses a binding site for transcription factor cAMP response element binding (CREB), and its expression is potentially regulated by CREB phosphorylation. It is highly expressed in NPC patients and correlated with a poor prognosis in cancer patients. Overexpressed HULC promotes NPC cell growth, while downregulated HULC activated p53 and induced the increased expression of p21, which finally caused cell cycle arrest and cell apoptosis.[29] Prostate cancer-associated transcript 7 (PCAT7), a novel lncRNA, was found to be overexpressed and associated with good prognosis in NPC, which might contribute to the tumor progression by functioning as a competitive endogenous RNA (ceRNA) to sponge miR-134-5p and regulating miR-134-5p/ELF2 signal pathway.[31] FOXCUT, which is located upstream of *forkhead box C1* (*FOXC1*), was upregulated in clinical NPC tissues and cultured NPC cell lines, and the high levels of FOXCUT expression were correlated with lymph node metastasis and distant metastasis.[48]

There are also some reports suggesting that some lncRNAs may serve as antitumor factors in NPC and could predict a good prognosis, such as MEG3,[49] LINC0086,[50] LINC00312,[20] LOC401317,[51] LncRNA-LET,[25] and NEAT1.[19,32] LINC00312, also called NPC-associated gene 7 (NAG7), could inhibit proliferation and induce apoptosis in NPC cells but also stimulate NPC cell invasion. And positive expression of LINC00312 was associated with good prognosis in NPC patients with no lymph node metastasis and was associated with poor prognosis in NPC patients with lymph node metastasis.[20] Further studies indicated that LOC401317 is directly regulated by p53 through a p53-binding site adjacent to its potential promoter and that LOC401317's overexpression inhibits HNE2 cell proliferation in vitro and in vivo by inducing cell cycle arrest and apoptosis. And these results suggest that LOC401317 exerts antitumor effects in HNE2 NPC cells.[51] LncRNA-LET was transcriptionally repressed by EZH2-mediated H3K27 histone methylation on the LET promoter and significantly downregulated in NPC, and its decreased level is significantly related to advanced clinical stage, larger tumor size, increased lymph node tumor burden, and poor survival in NPC patients.[25]

Resistance to radiotherapy and chemotherapy is the primary cause of NPC patients' death. In the current studies, some lncRNAs played a critical functional role in chemoresistance or radioresistance. LincRNA-ROR was highly associated with the proliferation, metastasis, and apoptosis of NPC.[52] And the enrichment of lincRNA-ROR was associated with chemoresistance.[53] Further investigation found that NEAT1 upregulated ZEB1 expression by negatively regulating miR-204 expression and regulated radioresistance by modulating epithelial mesenchymal transition phenotype in NPC.[19] Furthermore, MALAT1 regulated cancer stem cell activity and radioresistance by modulating miR-1/slug axis.[18] Moreover, knockdown of ANRIL represses tumorigenicity and enhances cisplatin (DDP)-induced cytotoxicity via regulating microRNA let-7a in NPC cells.[54] Upregulated CCAT1 results in significantly enhancing paclitaxel resistance in nasopharyngeal cancer cells. And lncRNA CCAT1 regulates the sensitivity of paclitaxel in NPC cells via miR-181a/CPEB2 axis.[55] Together, the current study provide a molecular basis for a comprehensive understanding of, and exploring new therapies for, NPC.[35]

At present, a number of studies have shown that the expression of lncRNAs was correlated with clinicopathological characteristics in NPC: histological type, tumor size, TNM clinical stage, and some others. In this meta-analysis, we also found that the lncRNAs were related to the male, lymph node status, and TNM clinical stage. There are some limitations in this meta-analysis. First, our results were based on unadjusted estimates, while the lack of information (such as age and family history) for the date analysis may cause serious confounding bias. Second, because of incomplete raw data or publication limitations (the enrolled studies are only English and all from China), some relevant studies could not be included in our analysis. Third, the number of published studies was not sufficiently large for a comprehensive analysis and some studies with small size may not have enough statistical power to explore the real association.

Taking these observations into consideration, the novel molecular mechanisms by which the lncRNAs regulate carcinogenesis and metastasis are expected to be elucidated. And they will developed to be new clinical prognostic biomarker as well as new therapeutic target for NPC. Nevertheless, discovering novel lncRNAs, identifying their function and association with various cancer subtypes, and developing novel lncRNA-based strategies for diagnosis and targeted therapies appear very promising, bring a new paradigm in cancer research, and may emerge as a major therapeutic strategy for the treatment of cancer in the near future.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All the authors approved the final paper.

Disclosure

The authors report no conflicts of interest in this work.

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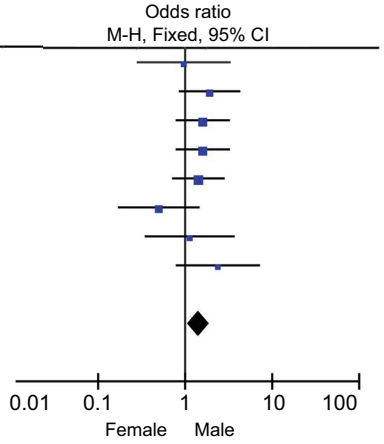
Supplementary materials

A

Study or subgroup	Male Events	Male Total	Female Events	Female Total	Weight (%)	Odds ratio M-H, Fixed, 95% CI
Bo et al (2015)[24] (AFAP1-AS1)	19	93	4	19	7.2	0.96 (0.29, 3.24)
Jiang and Liu (2017)[29] (HULC)	56	80	22	40	12.0	1.91 (0.87, 4.19)
Jin et al (2016)[18] (MALAT1)	34	60	32	71	17.3	1.59 (0.80, 3.18)
Lu et al (2016)[19] (NEAT1)	34	60	32	71	17.3	1.59 (0.80, 3.18)
Nie et al (2013)[17] (HOTAIR)	65	100	26	51	19.5	1.42 (0.73, 2.77)
Sun et al (2015)[25] (LET)	21	47	13	21	13.6	0.50 (0.17, 1.42)
Tang et al (2017)[16] (AFAP1-AS1)	57	80	11	16	7.2	1.13 (0.35, 3.60)
Zou et al (2016)[28] (ANRIL)	38	70	6	18	5.9	2.38 (0.80, 7.04)
Total (95% CI)		599		307	100.0	1.42 (1.05, 1.91)
Total events	324		146			

Heterogeneity: $\chi^2 = 5.99$; $df = 7$ ($P = 0.54$); $I^2 = 0\%$

Test for overall effect: $Z = 2.30$ ($P = 0.02$)

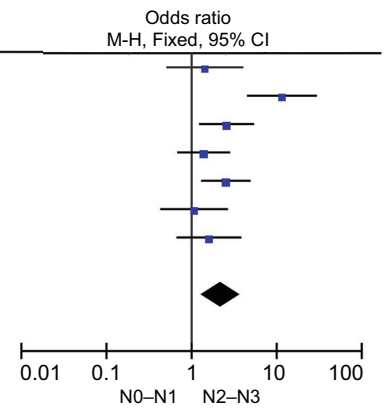


B

Study or subgroup	N2–N3 Events	N2–N3 Total	N0–N1 Events	N0–N1 Total	Weight (%)	Odds ratio M-H, Fixed, 95% CI
Bo et al (2015)[24] (AFAP1-AS1)	13	61	7	44	12.0	1.43 (0.52, 3.95)
Jiang and Liu (2017)[29] (HULC)	57	65	21	55	13.1	11.54 (4.60, 28.90)
Jin et al (2016)[18] (MALAT1)	49	70	29	61	15.5	2.57 (1.26, 5.27)
Lu et al (2016)[19] (NEAT1)	39	70	29	61	15.8	1.39 (0.70, 2.77)
Nie et al (2013)[17] (HOTAIR)	55	81	36	79	16.4	2.53 (1.33, 4.81)
Tang et al (2017)[16] (AFAP1-AS1)	40	56	28	40	13.4	1.07 (0.44, 2.61)
Zou et al (2016)[28] (ANRIL)	28	51	16	37	13.8	1.60 (0.38, 3.75)
Total (95% CI)		454		377	100.0	2.20 (1.29, 3.73)
Total events	281		166			

Heterogeneity: $\tau^2 = 0.34$; $\chi^2 = 18.34$, $df = 6$ ($P = 0.005$); $I^2 = 67\%$

Test for overall effect: $Z = 2.91$ ($P = 0.004$)



C

Study or subgroup	III–IV Events	III–IV Total	I–II Events	I–II Total	Weight (%)	Odds ratio M-H, Fixed, 95% CI
Bo et al (2015)[24] (AFAP1-AS1)	18	83	4	24	11.4	1.38 (0.42, 4.57)
Jiang and Liu (2017)[29] (HULC)	71	79	7	44	11.0	43.11 (14.44, 128.68)
Jin et al (2016)[18] (MALAT1)	44	61	36	70	13.4	2.44 (1.18, 5.07)
Lu et al (2016)[19] (NEAT1)	44	61	36	70	13.4	2.44 (1.18, 5.07)
Nie et al (2013)[17] (HOTAIR)	79	114	19	46	13.6	2.44 (1.21, 4.90)
Sun et al (2015)[25] (LET)	16	41	18	27	12.2	0.32 (0.12, 0.88)
Tang et al (2017)[16] (AFAP1-AS1)	53	73	15	23	12.8	1.41 (0.52, 3.84)
Zou et al (2016)[28] (ANRIL)	39	66	5	22	11.8	4.91 (1.62, 14.92)
Total (95% CI)		578		323	100.0	2.55 (1.12, 5.78)
Total events	357		140			

Heterogeneity: $\tau^2 = 1.16$; $\chi^2 = 45.40$, $df = 7$ ($P = 0.00001$); $I^2 = 85\%$

Test for overall effect: $Z = 2.24$ ($P = 0.03$)

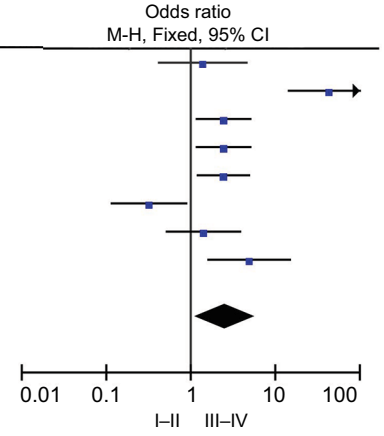


Figure S1 Forest plot of studies evaluating ORs of lncRNAs' expression and the clinicopathological characteristics of NPC patients. (**A**) Gender; (**B**) lymph node status; and (**C**) TNM clinical stages.

Abbreviation: CI, confidence interval.

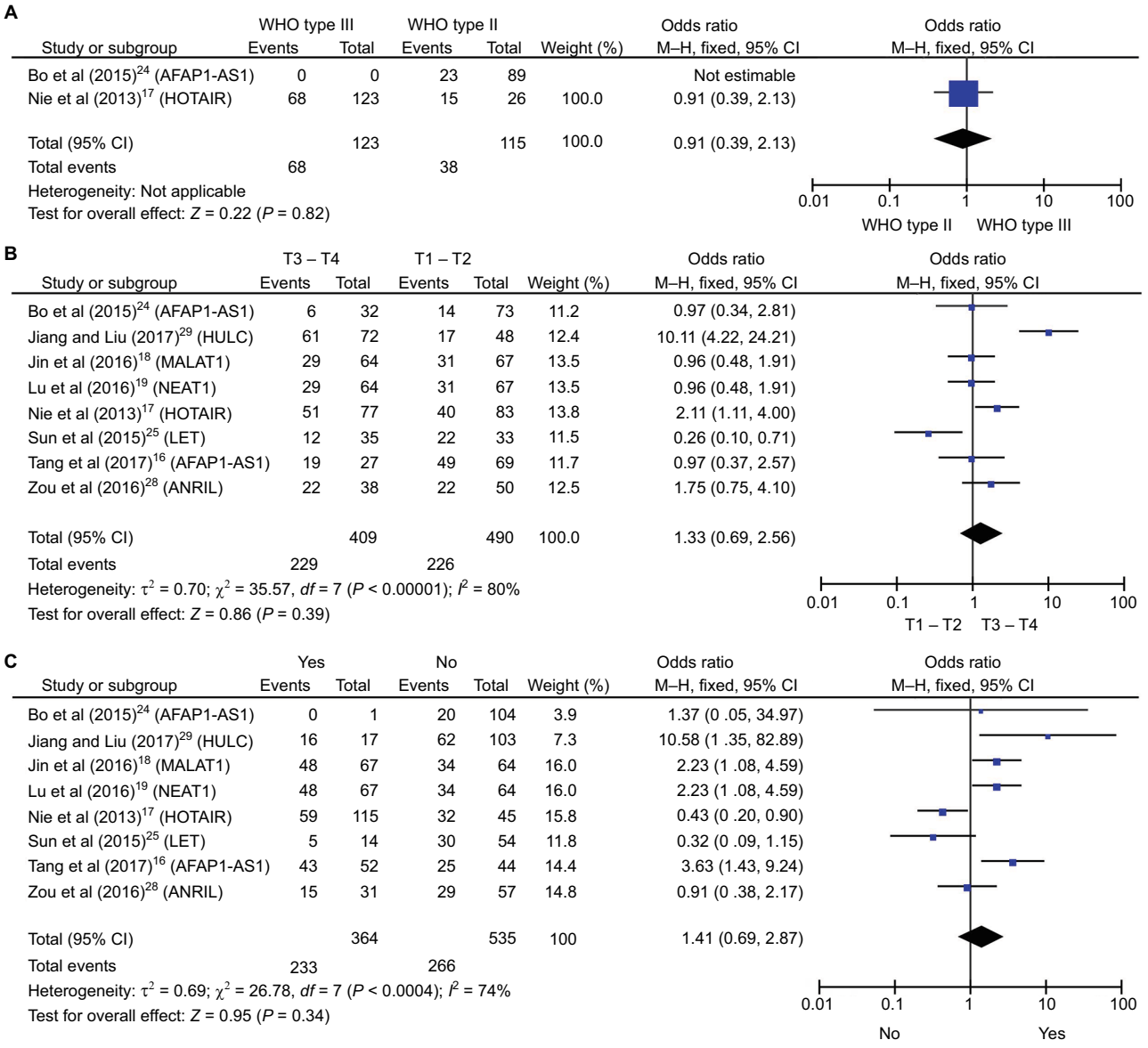


Figure S2 Forest plot of studies evaluating ORs of lncRNAs' expression and the clinicopathological characteristics of NPC patients. (**A**) histological classification; (**B**) tumor classification; and (**C**) metastasis.

Abbreviations: CI, confidence interval; WHO, World Health Organization; M-H, Mantel Haenszel test.

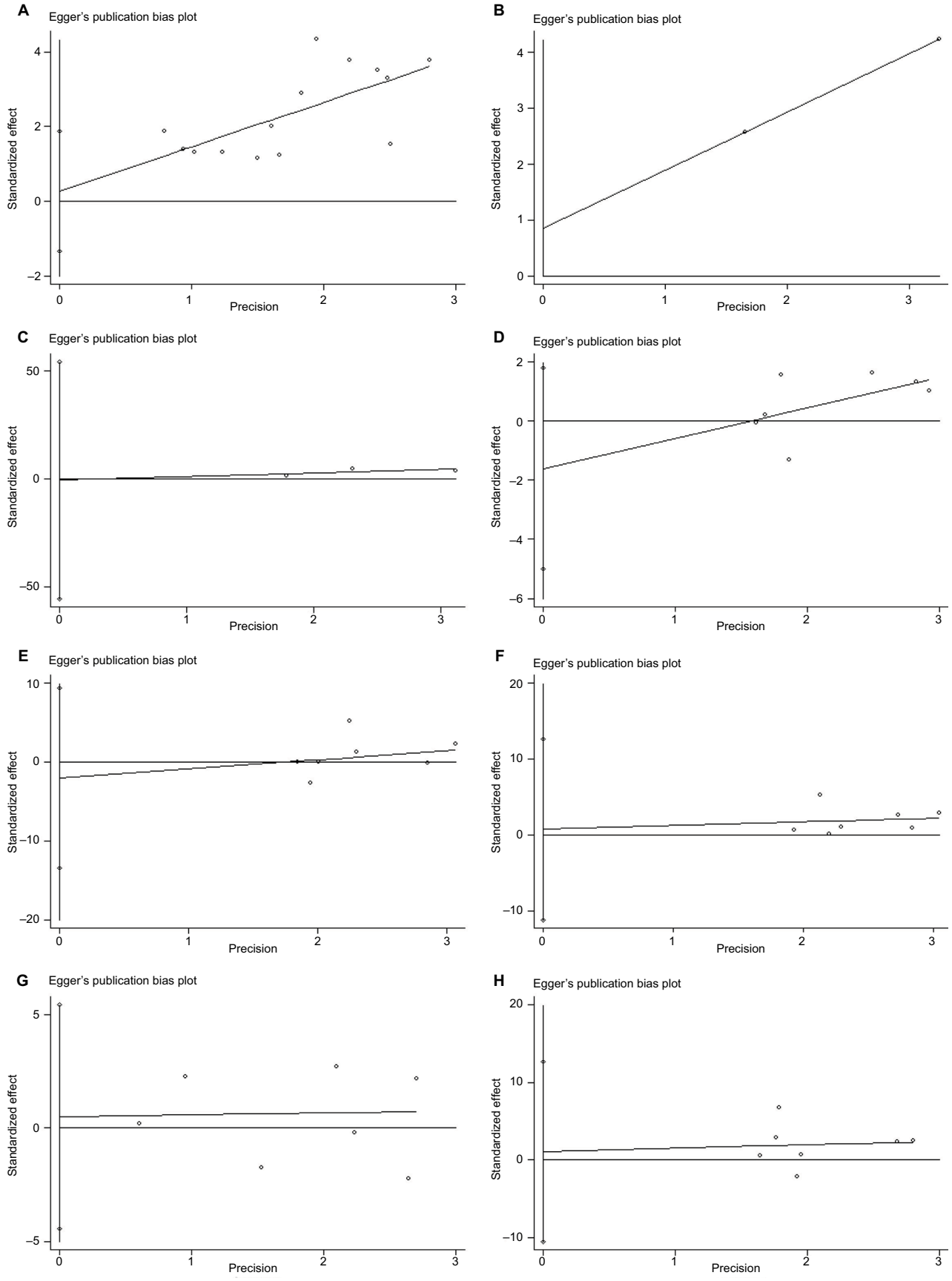


Figure S3 Egger's test for publication bias.
Notes: (**A**) Overall survival; (**B**) disease-free survival; (**C**) recurrence-free survival; (**D**) gender; (**E**) tumor classification; (**F**) lymph node status; (**G**) metastasis; (**H**) TNM stage.

Table S1 Characteristics of studies (included and excluded) in this meta-analysis

Author	Year	lncRNAs	Biotype (Ensembl)/ length (bp)	Method	Case number (high/low)	Outcome	Cut-off	Follow-up months
Nie et al[1]	**2013**	**HOTAIR**	**Antisense RNA/2421**	**qRT-PCR and ISH**	**91/69**	**OS, DFS, and RFS**	**SI =6**	**Median of 69**
Zhang et al[9]	2013	LINC00312	Misc RNA/2887	qRT-PCR and ISH	169/160	OS and DFS	NA	100
Bo et al[2]	**2015**	**AFAP1-AS1**	**Antisense RNA/6795**	**qRT-PCR and ISH**	**23/55**	**OS and RFS**	**1.5-Fold**	**120**
Sun et al[3]	**2015**	**LET**	**Sense intronic/2283**	**qRT-PCR**	**34/34**	**OS and RFS**	**Median**	**100**
Zhang et al[19]	2015	LOC84740	NA	qRT-PCR	23/82	DFS	Fold-change	48
Zhang et al[19]	2015	ENST00000498296	Processed pseudogene/909	qRT-PCR	64/42	DFS	Fold-change	48
Zhang et al[19]	2015	AL359062	NA/1762	qRT-PCR	58/48	DFS	Fold-change	48
Zhang et al[19]	2015	ENST00000438550	Processed pseudogene/371	qRT-PCR	81/25	DFS	Fold-change	48
Jin et al[4]	**2016**	**MALAT1**	**lincRNA/8708**	**qRT-PCR and ISH**	**66/65**	**OS**	**SI =6**	**60**
Lu et al[5]	**2016**	**NEAT1**	**lincRNA/22743**	**qRT-PCR and ISH**	**66/65**	**OS**	**SI =6**	**60**
Song et al[10]	**2016**	**XIST**	**lincRNA/19275**	**qRT-PCR**	**76/32**	**OS**	**2.31-Fold**	**140**
Song and Yin[11]	**2016**	**EWSAT1**	**lincRNA/2498**	**qRT-PCR**	**76/32**	**OS**	**2.36-Fold**	**140**
Zou et al[6]	**2016**	**ANRIL**	**Antisense RNA/3835**	**qRT-PCR**	**44/44**	**OS and DFS**	**Median**	**100**
Guo et al[12]	2017	LINC0086	Protein coding/5230	qRT-PCR and ISH	44/68	OS	NA	80
Jiang and Liu[7]	**2017**	**HULC**	**lincRNA/556**	**qRT-PCR**	**78/42**	**OS**	**2.5-Fold**	**50**
Liu et al[13]	**2017**	**PCAT7**	**Retained intron/1164**	**qRT-PCR**	**38/12**	**OS**	**NA**	**140**
Su et al[14]	**2017**	**CASC9**	**lincRNA/1164**	**qRT-PCR**	**45/45**	**OS**	**2.5-Fold**	**60**
Sun et al[17]	2017	LOC100129148	Misc RNA/461	qRT-PCR	39/43	OS	Mean	80
Tang et al[8]	**2017**	**AFAP1-AS1**	**Antisense RNA/6795**	**qRT-PCR and ISH**	**68/28**	**OS**	**NA**	**120**
Wang et al[15]	**2017**	**NEAT1**	**lincRNA/22743**	**qRT-PCR and AM**	**39/31**	**OS**	**2-Fold**	**50**
Yang et al[18]	2017	LINC01420	Misc RNA/694	qRT-PCR and ISH	65/45	OS	1.2-Fold	125
Kong et al[16]	**2018**	**LINC00460**	**lincRNA/739**	**qRT-PCR**	**25/25**	**OS**	**Median**	**140**

Note: Bold fonts represent the included studies.

Abbreviations: AM, affymetrix microarray; DFS, disease-free survival; ISH, in situ hybridization; lincRNA, long intergenic noncoding RNA; lncRNAs, long noncoding RNAs; NA, not available; NPC, nasopharyngeal carcinoma; OS, overall survival; qRT-PCR, quantitative real time polymerase chain reaction; RFS, recurrence-free survival; SI, staining index.

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