

Prognostic value of lncRNA SNHG20 as a biomarker in human cancers: a systematic review and meta-analysis

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Abstract

Background: Long noncoding RNA small nucleolar RNA host gene 20 (SNHG20) is a novel oncogene and dysregulated in a variety of human cancers. It has been revealed to be associated with the clinicopathological features and prognosis. However, the prognostic value of SNHG20 in various cancers remains unclear. Therefore, we performed this meta-analysis to evaluate the relationship between SNHG20 expression and clinical outcomes in human cancers.

Methods: Comprehensive literature search was performed in PubMed, Web of Science, CNKI and Wangfang databases, and eligible studies were obtained according to the inclusion and exclusion criteria. The pooled hazard ratios (HRs) and odds ratios (ORs) were applied to assess the clinical value of SNHG20 expression for overall survival (OS) and clinicopathological features.

Results: A total of 16 articles including 1190 cancer patients were included in the study. The pooled results demonstrated that evaluated SNHG20 expression was positively related to a poorer OS of cancers (HR=2.36, 95%CI: 1.85-2.87, P<0.001). Subgroup analysis revealed that SNHG20 overexpression was closely related to the low OS of patients with the digestive system cancer (HR=2.92, 95%CI: 1.96-3.88, P<0.001), sample size >80 (HR=2.42, 95%CI: 1.69-3.14, P<0.001), direct HR estimation method (HR=2.65, 95%CI: 1.78-3.52, P<0.001), and median ratio as cut-off value (HR=2.21, 95%CI: 1.60-2.83, P<0.001). In addition, the pooled data also showed that SNHG20 was positively linked to lymph node metastasis (LNM) (OR=1.65, 95%CI: 1.21-2.26, P=0.002), distant metastasis (DM) (OR=1.76, 95%CI: 1.10-2.83, P=0.02), and advanced TNM stage (OR=1.79, 95%CI: 1.34-2.39, P<0.001). Moreover, the results of the trim and fill analysis confirmed the reliability of our finding.

Conclusions: Upregulation of SNHG20 was associated with advanced TNM stage, worse LNM and DM, and shorter OS, suggesting that SNHG20 may serve as a biomarker for prognosis and clinicopathological characteristics in human cancers.

Introduction

Cancer has already become a major threat for human health in the world, and it has been the leading cause of death in China since 2010[1]. Cancer is a complex disease caused by a variety of molecular change, including chromosomal translocations, deletions and amplification, epigenetic alterations and genetic mutations [2-4]. Although numerous progress has been achieved in the diagnosis and treatment of human cancers over the past decade, the clinical prognosis remains relatively worse in most cancer patients, mainly owing to the lack of effective biomarker to early diagnose cancer and predict clinical prognosis of cancer patients.

LncRNAs are a typical kinds of ncRNAs with more than 200 nucleotides, which have been proved to play a crucial role in tumorigenesis and tumor progression. Except for a few lncRNAs translate into proteins to involve in cellular and physiological processes, most lncRNAs transcripts directly or indirectly modulate transcriptional and posttranscriptional processes [5]. Moreover, many lncRNAs could serve as enhancers [6], splicing regulators [7], chromatin remodelers [8], and so on. Notably, growing evidence suggested that dysregulated lncRNAs occurred in a broad spectrum of human cancers [9, 10], and participated in cancer initiation and progression, indicating the potential value as clinical biomarkers and therapeutic targets. Recently, a new discovered lncRNA NSHG20 has drawn increasing attention.

LncRNA small nucleolar RNA host gene 20 (SNHG20), localized at 17q25.2, is dysregulated in broad ranges of cancers. Increasing evidence from fundamental and clinical studies demonstrated that SNHG20 involved in tumorigenesis and exhibits poor prognostic value in many cancers, such as hepatocellular carcinoma [9, 10], non-small cell lung cancer [12], and epithelial ovarian cancer [13]. However, most studies reported the prognostic value of SNHG20 in cancer patients was limited by small sample size and discrete clinical outcome. Therefore, we conducted this systematic review and quantitative meta-analysis to investigate the prognostic value of SNHG20 in human cancers.

Methods

Search strategy

We comprehensively searched in PubMed, Web of Science, CNKI and Wangfang database for eligible studies which reported the relationship between lncRNA SNHG20 and OS before August 26, 2019. A combination of the following subjects were applied for the online search: ("carcinoma" OR "cancer" OR "tumor" OR "neoplasm") AND ("prognosis" OR "outcome" OR "diagnosis" OR "survival")

AND ("SNHG20" OR "small nucleolar RNA host gene 20"). The reference lists of primary publications were also manually searched to obtain potential eligible studies.

Inclusion And Exclusion Criteria

We used the following inclusion criteria for eligible studies: 1) Studies reported the relationship between SNHG20 and prognosis in human cancers; 2) Available data for HRs and corresponding 95%CI extraction; 3) patients were divided into high and low expression groups based on the expression of SNHG20. The following articles were excluded from the study: 1) reviews, letters, or case reports; 2) non-human studies; 3) duplicated publication.

Data Extraction And Quality Assessment

The essential information were screened and extracted from each eligible study by two researchers (Li and Rui) independently, including the name of first author, year of publication, origin country, cancer type, sample size, detection method of SNHG20, HR and corresponding 95%CI for OS, as well as clinicopathological features. The HRs with 95%CIs were obtained directly from eligible studies carried out the multivariate analysis. For those studies without multivariate analysis, HRs and 95%CIs were calculated based on the survival curve according to the method described in the previous publication [14]. The Newcastle-Ottawa Scale (NOS) was applied to evaluate the quality of the included study.

Statistical analysis

The present meta-analysis was performed with Stata SE15.0 (Stata Corporation). HR and corresponding 95%CI for OS were applied to determine the pooled effect, and the odds ratio (OR) were used as the outcome estimation for data pooling. The fixed-effect model was selected while heterogeneity exists ($I^2 > 50\%$ and $p < 0.05$), otherwise, the random-effect model was applied. Begg's funnel plot and Egger's regression test were used to assess the publication bias. P-value < 0.05 was considered as statistical significance.

Results

Summary of eligible studies

The detailed literature selection is shown in Fig. 1. A total of 55 potentially relevant articles were identified in this meta-analysis. 15 duplicate articles and 15 irrelevant articles were excluded after screening the titles and abstracts. Finally, 16 eligible studies were included owing to the lack of sufficient data in the other 9 articles. The characteristics of the included 16 studies were summarized in Table 1. A total of 1190 patients from 16 studies between 2016 and 2019 were included [14]. All of the included studies were conducted in China and published in English. The study sample size ranged from 32 to 144 patients, and 5 studies enrolled more than 80 patients. The types of carcinoma included NSCLC ($n = 2$), GC ($n = 1$), OSCC ($n = 1$), Glioblastoma ($n = 1$), CRC ($n = 1$), glioma ($n = 1$), LSCC ($n = 1$), HCC ($n = 2$), NC ($n = 1$), EOC ($n = 1$), Osteosarcoma ($n = 2$), Bladder cancer ($n = 1$), ESCC ($n = 1$). The level of SNHG20 expression was detected by quantitative real-time polymerase chain reaction (qRT-PCR) in all included studies. Multivariate analysis was performed in 6 studies. Clinical outcomes were recorded including 16 studies for OS, 2 for DFS, 1 for PFS, and 1 for RFS. HRs with corresponding 95% CIs were extracted from the original data in 6 studies, and calculated from survival curves in the other 10 studies. Clinicopathologic features were also recorded in 15 studies including TNM stages, lymph node metastasis (LNM) and distant metastasis (DM). In addition, all studies were more than 6 according to the NOS score criteria, indicating a high quality for the studies.

Table 1
Characteristics of the included eligible studies.

Author	Year	Country	Tumor	Sample size	Cut-off value	Detection method	Outcomes	HR estimation method	HR(95%CI)	NOS
Chen ZY	2017	China	NSCLC	42	median ratio	qRT-PCR	OS/PFS	Indirectly	3.38(1.00–11.51)	8
Cui N	2018	China	GC	56	median ratio	qRT-PCR	OS/DFS	Indirectly	2.83(1.14–7.05)	8
Gao PJ	2019	China	OSCC	40	median ratio	qRT-PCR	OS	U/M	2.077(1.39–3.24)	7
Gao XF	2018	China	Glioblastoma	78	other	qRT-PCR	OS	Indirectly	2.06(1.00–4.20)	6
Li C	2016	China	CRC	107	median ratio	qRT-PCR	OS	U/M	2.97(1.51–5.82)	8
Li XS	2019	China	Glioma	108	median ratio	qRT-PCR	OS/RFS	U/M	4.722(2.19–19.19)	8
Li Y	2019	China	LSCC	56	median ratio	qRT-PCR	OS	Indirectly	4.62(1.04–20.49)	8
Jin LL	2019	China	NSCLC	42	median ratio	qRT-PCR	OS	Indirectly	3.72(1.06–13.10)	7
Liu JX	2017	China	HCC	96	other	qRT-PCR	OS	Indirectly	2.70(1.67–4.36)	7
Sun CB	2018	China	NC	55	median ratio	qRT-PCR	OS	Indirectly	3.33(1.08–10.30)	6
Wang DD	2018	China	EOC	60	other	qRT-PCR	OS	U/M	9.17(2.71–31.25)	7
Wang WK	2018	China	Osteosarcoma	32	other	qRT-PCR	OS	Indirectly	4.64(1.06–20.36)	8
Zhang DY	2016	China	HCC	144	other	qRT-PCR	OS/DFS	U/M	3.985(1.98–8.02)	8
Zhang J	2018	China	Osteosarcoma	140	median ratio	qRT-PCR	OS	U/M	1.94(1.19–3.17)	7
Zhao QS	2018	China	Bladder cancer	54	other	qRT-PCR	OS	Indirectly	3.37(1.00–11.42)	7
Zhang CR	2018	China	ESCC	80	other	qRT-PCR	OS	Indirectly	2.94(1.12–7.71)	7

Notes: NSCLC: non-small cell lung cancer; GC: gastric cancer; OSCC: oral squamous cell carcinoma; CRC: colorectal cancer; LSCC: laryngeal squamous cell carcinoma; HCC: hepatocellular carcinoma; NC: nasopharyngeal carcinoma; EOC: epithelial ovarian cancer; ESCC: esophageal squamous cell carcinoma; OS: overall survival; DFS: disease-free survival; PFS: Progression-free survival; RFS: recurrence-free survival

Prognostic Value Of Snhg20

A total of 16 studies with 1190 patients were available to evaluate the effects of SNHG20 expression on OS in human cancers. As shown in Fig. 2, the pooled results suggested that elevated SNHG20 expression predicted a poor OS for cancers (HR = 2.36, 95%CI: 1.85–2.87, $P < 0.001$) with no heterogeneity ($\chi^2 = 0\%$, $P = 0.989$) (Fig. 2). Furthermore, subgroup analysis was also performed to explore the association between HRs and OS including cancer type, sample size, HR estimation method, and cut-off value. Stratified analysis revealed that there was a negatively relationship between SNHG20 expression and OS in the studies with respiratory system (HR = 2.22, 95%CI: 1.33–3.10, $P < 0.001$), digestive system cancers (HR = 2.92, 95%CI: 1.96–3.88, $P < 0.001$), and other cancers (HR = 2.08, 95%CI: 1.25–2.90, $P < 0.001$) (Fig. 3A). Higher SNHG20 expression predicted poorer OS in the studies using the median ratio as the cut-

off value ($HR = 2.21$, 95%CI: 1.60–2.83, $P < 0.001$), as well as those using the mean value as the cat-off value ($HR = 2.69$, 95%CI: 1.78–3.61, $P < 0.001$) (Fig. 3B). And we also found that upregulation of SNHG20 expression significantly associated with short OS in the studies with indirect estimation method subgroup ($HR = 2.65$, 95%CI: 1.78–3.52, $P < 0.001$), as well as those with direct method (U/M) subgroup ($HR = 2.21$, 95%CI: 1.58–2.84, $P < 0.001$). In addition, the effect of SNHG20 overexpression on predicting short OS occurred in the studies with sample size ≤ 80 ($HR = 2.31$, 95%CI: 1.59–3.03, $P < 0.001$), as well as those with sample size > 80 ($HR = 2.42$, 95%CI: 1.69–3.14, $P < 0.001$) (Fig. 2C).

Association Between Snhg20 And Clinicopathological Features

The correlation between SNHG20 expression and clinicopathological characteristics were examined with OR analysis in 15 studies with 1148 cancer patients. 9 studies with 615 patients were included to analysis the link between SNHG20 and TNM stage, and the pooled data found an obvious association between SNHG20 overexpression and advanced TNM stage ($OR = 1.79$, 95%CI: 1.34–2.39, $P < 0.001$) (Fig. 4A). As shown in Fig. 4B, 495 cancer patients from 8 studies were included to evaluate the correlation between SNHG20 and LNM, and the results indicated that the patients with elevated SNHG20 expression were more susceptibility to develop LNM ($OR = 1.65$, 95%CI: 1.21–2.26, $P = 0.002$). In addition, 3 studies with 218 patients were included to analyze the link between SNHG20 and DM, the results revealed an obvious association between SNHG20 expression and DM ($OR = 1.76$, 95%CI: 1.10–2.83, $P = 0.02$) (Fig. 4C).

Publication Bias And Sensitivity Analysis

To evaluate the publication bias, the Begg's funnel plot and Egger's linear regression tests were applied in this meta-analysis. In the analysis of evaluating the association between SNHG20 expression on OS, visual inspection of the Begg's funnel plot revealed asymmetry (Fig. 5A), and Egger's test suggested the probable evidence of publication bias ($t = 27.76$, $p < 0.001$). Furthermore, to assess the impact of potential publication bias, the trim and fill analysis were performed with the fixed-effect model. Seven which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry. The imputed studies produce a symmetrical funnel plot (Fig. 5A). The pooled analysis incorporation the hypothetical studies continued to show a statistically significant association between SNHG20 expression and OS in human cancers (corrected $HR = 2.39$, 95%CI: 2.01–2.84, $P < 0.001$). We also detected the heterogeneity through sensitivity analysis, and the pooled HR was not significantly changed after removing each study, suggesting that the results were stable (Fig. 5B).

Discussion

Collective evidence has indicated that lncRNA SNHG20 is closely related to cancer. Initially, lncRNA SNHG20 was identified as an overexpressed oncogene in hepatocellular carcinoma[11]. Its overexpression is associated with tumor size, clinical stage, and poor prognosis in patients with hepatocellular carcinoma. Currently, lncRNA SNHG20 has been confirmed as a dysregulated oncogene in other several malignancies, such as gastric cancer [11], glioblastoma [17], NSCLC [18]. Moreover, the silence of SNHG20 significantly suppressed cell proliferation, migration, and invasion in a variety of human cancers. It has drawn great attention as carcinogenic lncRNA in many kinds of cancers. Many researchers focused on the clinical potential value in predicting cancer prognosis. However, inconsistency regarding the predictive value of lncRNA SNHG20 in some prognostic parameters, e.g., TNM stage, LNM, and DM, arise from a wide range of studies due to heterogeneity.

In the present meta-analysis, we found that patients with elevated SNHG20 expression tended to have poorer OS in cancer patients. Namely, high lncRNA SNHG20 expression may serve as an independent predictive factor for the prognosis of cancer patients. Meanwhile, this study also revealed that SNHG20 overexpression significantly associated with more advanced TNM stage, higher risk of LNM and DM. To sum up, our finding suggested that lncRNA could serve as a potential independent prognostic factor for predicting clinical outcomes for cancer patients. However, the underlying molecular mechanism of aberrant SNHG20 expression correlated with poor clinical prognosis remains elusive.

Many studies have investigated the functional mechanism of lncRNA SNHG20 on tumorigenesis and tumor progression in various cancers (Table 2). Previous studies have reported that SNHG20 could provide specific functional scaffolds for regulatory complexes, such as EZH2. SNHG20 acted/function as an oncogene to interact with EZH2 to inhibit the expression of E-cadherin and p21 in the GC

and NSCLC cells [12, 28]. Wnt/β-catenin signal pathway has been revealed to be involved in the regulation of cell proliferation, migration, and invasion in certain cancers [29, 30]. It was reported that lncRNA SNHG20 could promote the proliferation, migration, and invasion of bladder cancer and ovarian cancer by activating the Wnt/β-catenin signal pathway [27, 31]. Moreover, several important pathway was confirmed to be modulated by SNHG20 in various cancers, including GSK-3β/β-catenin signaling pathway in gastric cancer [28], MDM2-p53 pathway and PTEN/PI3K/AKT signaling pathway in glioma [32, 33], PI3K/Akt/mTOR signaling pathway in glioblastoma [17], ATM-JAK-PD-L1 pathway in ESCC [25], and MEK/ERK pathway in cervical cancer [34]. Furthermore, SNHG20 could promote vasculogenic mimicry formation of glioma cells by activating FOXK1 [35] and accelerate the proliferation of hepatocellular carcinoma by upregulate HBx and downregulate PTEN [36].

Table 2
Molecular mechanism of SNHG20 in cancer initiation and progression.

Cancer type	Molecular Mechanism	Functions	References
GC	Downregulate miR-140-5p to increase NDRG3;downregulate miR-295-3p to inhibit ZFX,inhibit p21 to regulate GSK-3β/β-catenin signaling pathway	promote cell proliferation to mediate resistance to 5-FU in gastric cancer, prognostic biomarker and associated with tumor size and lymphatic metastasis, promote epithelial-mesenchymal transition (EMT)	[15][28][37]
Glioma	Sponge miR-4486 to regulate the MDM2-p53 pathway;increase POXK1;activate PTEN/PI3K/AKT signaling pathway	promote cell proliferation, migration, decrease the apoptosis percentage;promote vasculogenic mimicry formation of glioma cells	[32][33][35]
LSCC	Suppress miR-140 expression	Promote cell proliferation, prognostic biomarker and correlated with tumor stage.	[21]
Glioblastoma	Activate PI3K/Akt/mTOR signaling pathway	Promote cell proliferation, decrease cell apoptosis and remain stem properties	[17]
EOC	NA	Prognostic biomarker and correlated with histological grade and lymph node status, promote cell proliferation, migration, and invasion	[13]
NSCLC	Suppress miR-154 and elevating ZEB2 and RUNX2 expression,repress P21	Promote cell proliferation, migration, invasion and decrease apoptosis. Prognostic biomarker and correlate with advanced tumor, lymph node and metastases (TNM) stage and tumor size	[12][18]
ESCC	Modulate ATM-JAK-PD-L1 pathway	Promote cell proliferation, migration, invasion, EMT, and decrease apoptosis.Prognostic biomarker and correlate with tumor size, lymph node metastasis, TNM stage, and tumor grade	[25]
HCC	Upregulate HBx and downregulate PTEN, increase ZEB1, ZEB2, N-cadherin and Vimentin expression and down-regulated E-cadherin	Promote proliferation,invasion and decrease apoptosis, prognostic biomarker and correlate with tumor size and advanced TNM stage	[11][22][36]
OSCC	Downregulate miR-197 to increase LIN28	Prognostic biomarker and associate with tumor differentiation and Tumor-Node-Metastasis stage,promote proliferation.	[16][38]
Osteosarcoma	Downregulate miR-139 to increase RUNX2	Prognostic biomarker and associate with Enneking stage, distant metastasis, and histological grade, Promote proliferation, invasion and decrease apoptosis	[24][26]
Bladder cancer	Activate the Wnt/β-catenin signalling pathway	Prognostic biomarker and associate with advanced clinical stage, lymph node metastasis	[27]
Cervical cancer	Downregulate miR-140-5p to increase ADAM10 and inhibit MEK/ERK pathway	Promote proliferation and invasion	[34]
Breast cancer	Downregulate miR-495 to increase HER2	Promote proliferation, invasion, and migration	[39]
Ovarian cancer	Activate the Wnt/β-catenin signalling pathway	Promote ovarian cancer progression	[31]
Colorectal cancer	NA	Prognostic biomarker and associate with advanced TNM stage	[19]
NC	Upregulate TGF-β1	Prognostic biomarker and associate with distant tumor metastasis.	[23]

Notes:GC: gastric cancer; LSCC: laryngeal squamous cell carcinoma; EOC: epithelial ovarian cancer;NSCLC: non-small cell lung cancer; ESCC: esophageal squamous cell carcinoma; HCC: hepatocellular carcinoma; OSCC: oral squamous cell carcinoma; NC: nasopharyngeal carcinoma

In addition, growing evidence has demonstrated that SNHG20 function as competitive endogenous RNA (ceRNA) to regulate miRNAs, and plays a key role in the initiation, development, and chemoresistance of cancer. In gastric cancer, Yu *et al.* demonstrated that SNHG20 contribute to 5-fluorouracil resistance through SNHG20/miR-140-5p/NDRG3 regulatory pathway, providing a brand new

insight for the 5-fluorouracil resistance of gastric cancer [37]. Recently, miR-295-3p was found to be a target of SNHG20 in gastric cancer by Cui *et al.* [15]. In cervical cancer, Guo *et al.* also demonstrated that SNHG20 could function as an oncogenic lncRNA by regulating miR-140-5p/ADAM10 axis [34]. Furthermore, SNHG20 function as a ceRNA to promote malignant progression of human cancers through competitive sponging of miR-4486 in glioma [32], miR-140 in LSCC [21], miR-154 in NSCLC [18], miR-197 in OSCC [38], miR-139 in osteosarcoma [24], and miR-495 in breast cancer [39].

Several limitations existed in this meta-analysis owing to the discrete data across these clinical studies. First, all included studies were performed in China, which might limit the applicability of our results for other ethnic population. Second, the cut-off values are different among the included articles. Third, some of the HRs were calculated by reconstructing survival curves, which might result in a calculation bias. Finally, only studies published in English or Chinese were obtained in this meta-analysis, and the data collection may be incomplete.

Conclusion

In conclusion, this meta-analysis demonstrated that SNHG20 overexpression was significantly correlated with poorer overall survival in patients with human cancers, and related to lymph node metastasis, distant metastasis, and advanced TNM stage. Thus, lncRNA SNHG20 might serve as a novel effective prognostic biomarker in cancer patients. Further high-quality studies are required to explore the role of SNHG20 in cancers and support this study.

Abbreviations

SNHG20:small nucleolar RNA host gene 20; HRs:hazard ratios; ORs:odds ratios; LNM:lymph node metastasis; DM:distant metastasis; NOS:Newcastle-Ottawa Scale; ceRNA:competitive endogenous RNA; NSCLC:non-small cell lung cancer; GC:gastric cancer; OSCC:oral squamous cell carcinoma; CRC:colorectal cancer; LSCC:laryngeal squamous cell carcinoma; HCC:hepatocellular carcinoma; NC:nasopharyngeal carcinoma; EOC:epithelial ovarian cancer; ESCC:esophageal squamous cell carcinoma; OS:overall survival; DFS:disease-free survival; PFS:Progression-free survival; RFS:recurrence-free survival

Declarations

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YFL, XMR, DBC, HJX, HJY, XLM

Conceived and designed the experiments: YFL and XMR. Performed the experiments: YFL, XMR, DBC. Analyzed the data: DBC and HJX. Contributed analysis tools/materials:HJX and HJY. Wrote the paper: YFL, HJY, XLM. All authors have read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data analyzed during this study are included in this published article.

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Figures

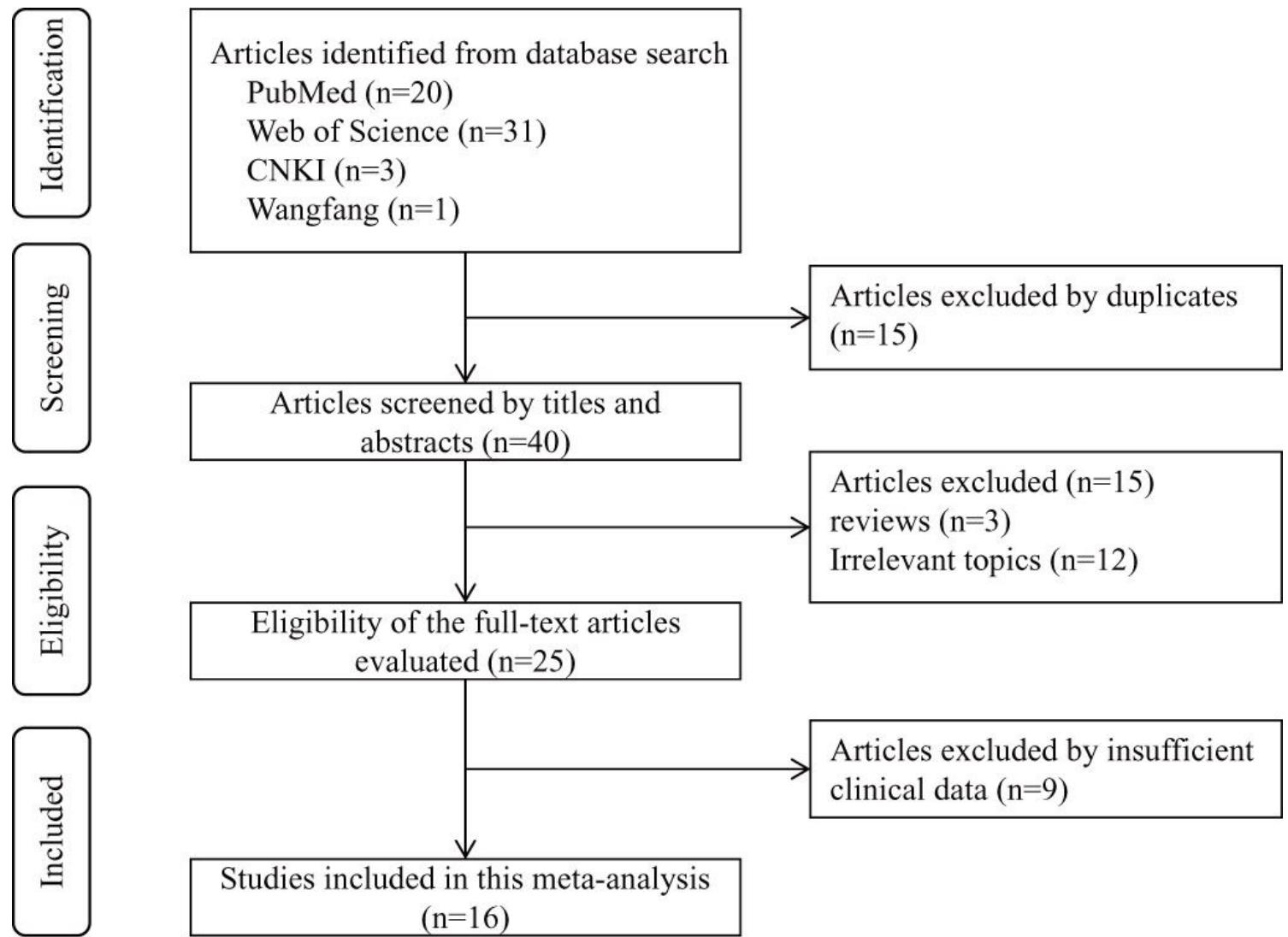


Figure 1

Flow chart of literature search

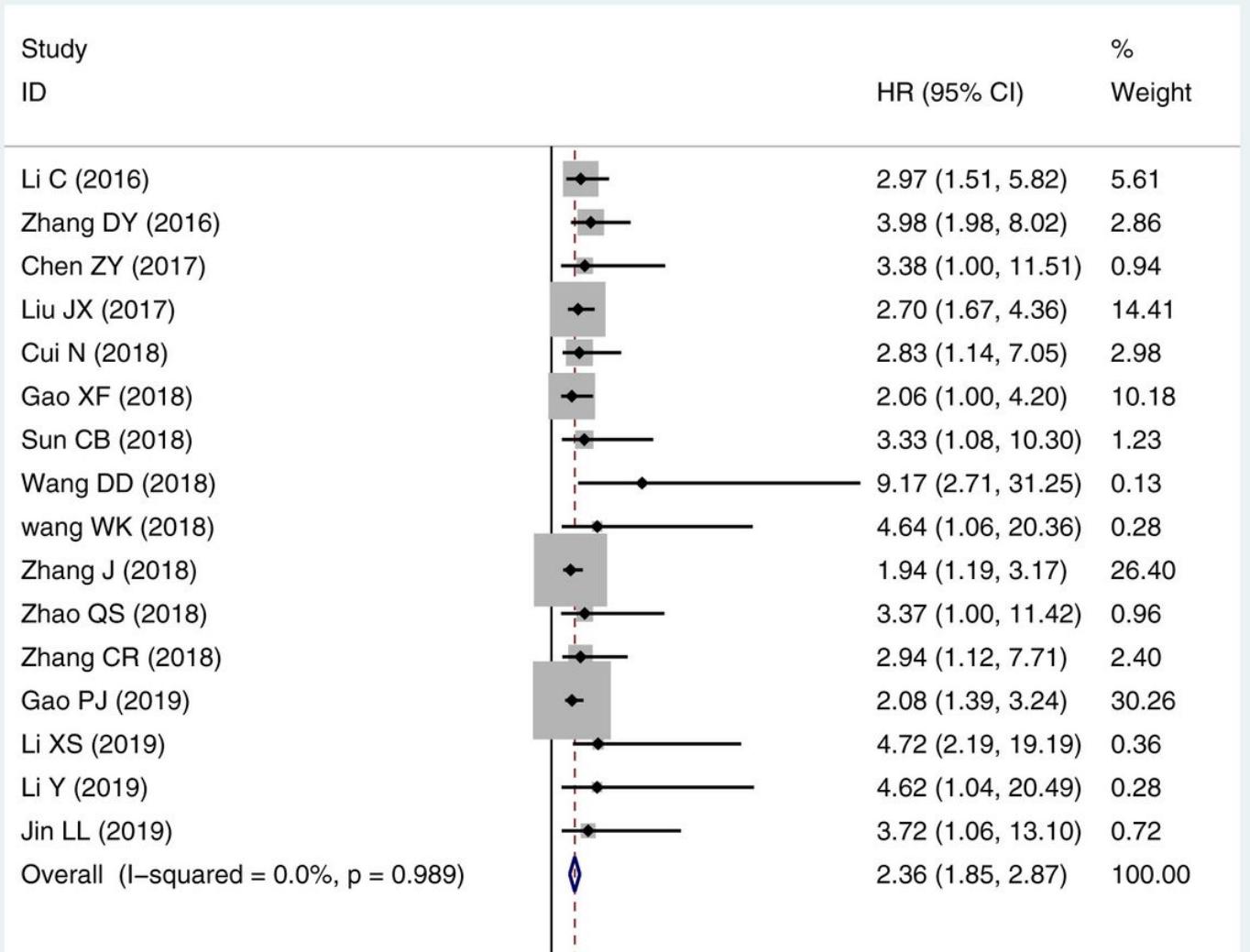
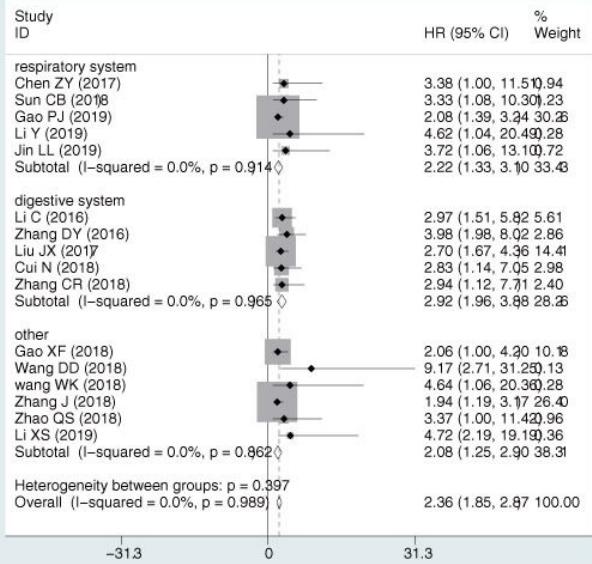


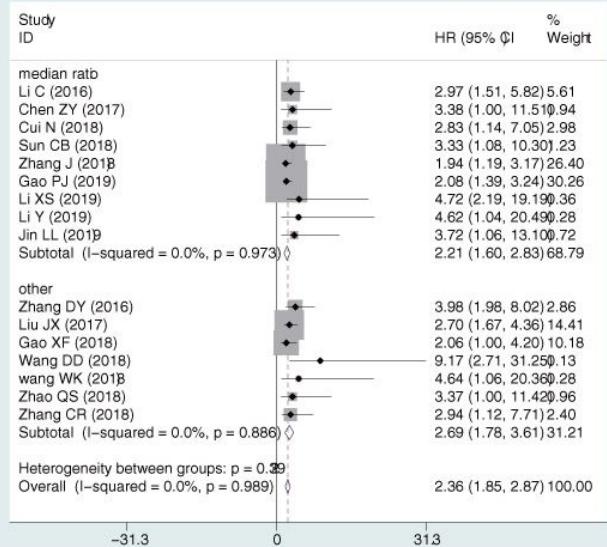
Figure 2

Forest plot of studies evaluating the association between SNHG20 expression and overall survival (OS).

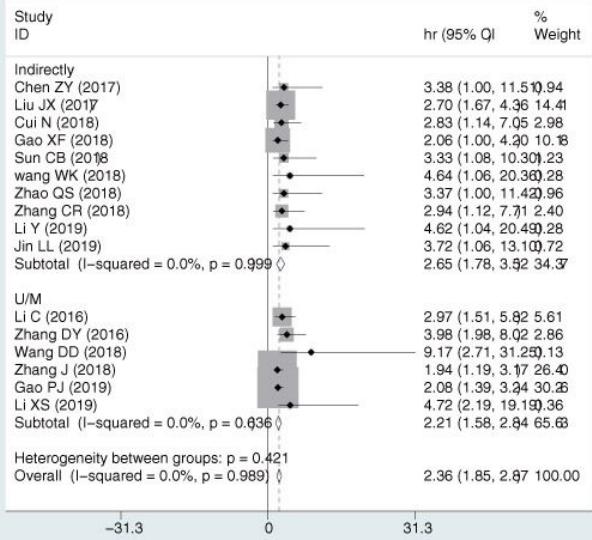
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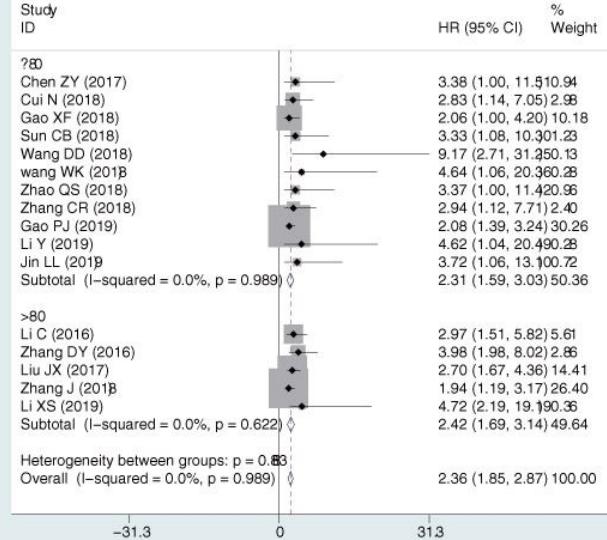
B



B



D

**Figure 3**

Forest plots of subgroup analysis for the HRs of OS by (A) tumor type, (B) cut-off value, (C) HR estimation method, and (D) sample size.

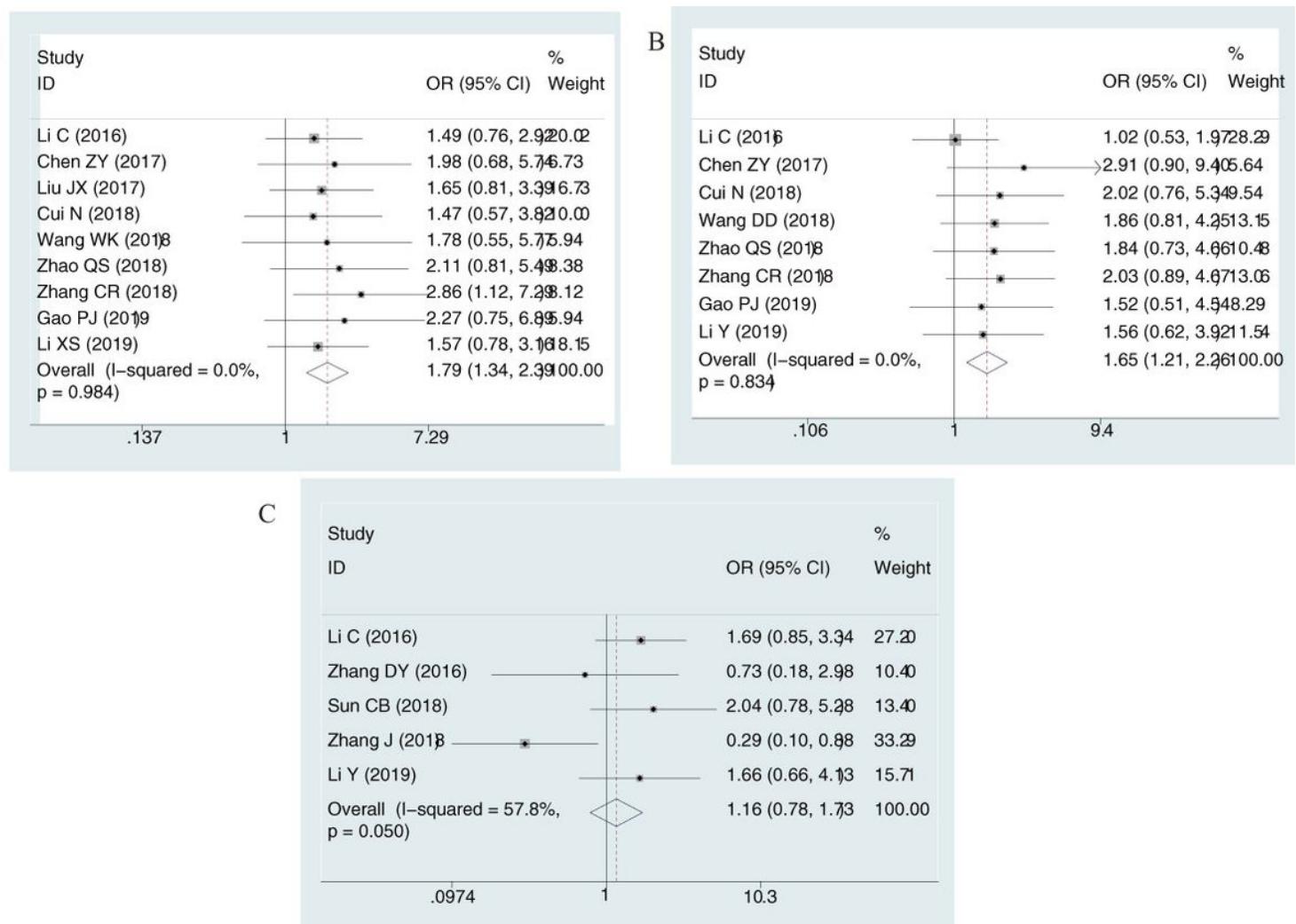


Figure 4

Meta-analysis for the association between SNHG20 expression with clinicopathological parameters. The investigated clinicopathological parameters are: (A) TNM stage, (B) lymph node metastasis (LNM), and (C) distant metastasis (DM)

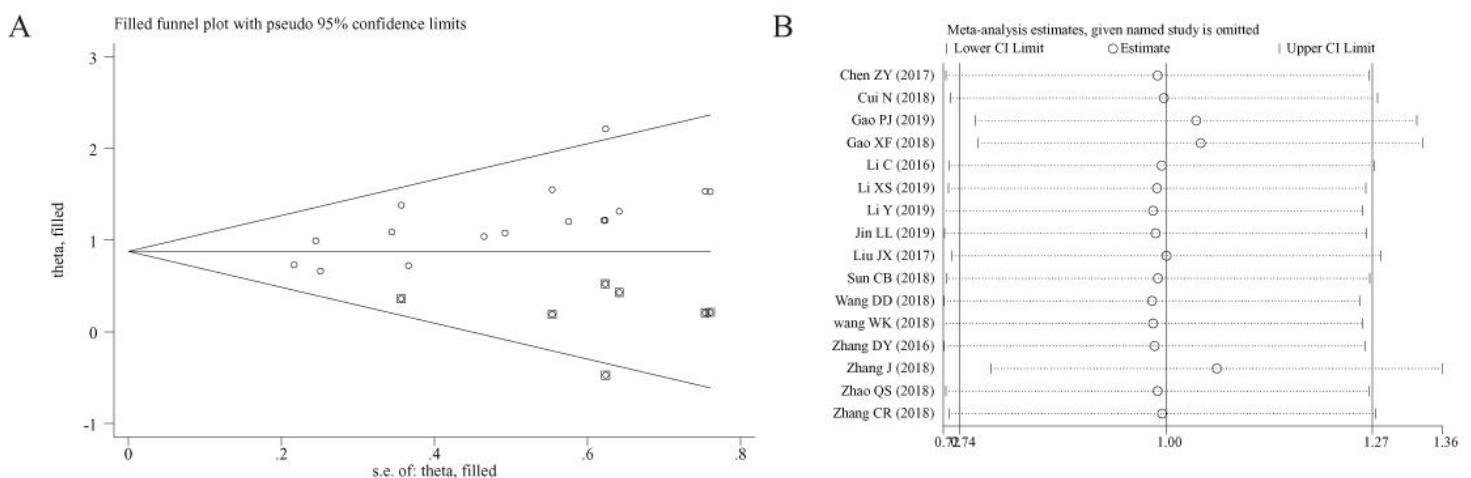


Figure 5

Begg's funnel plot and sensitivity analysis