Prognostic and clinical significance of long non-coding RNA SNHG12 expression in various cancers

**CURRENT STATUS:** UNDER REVIEW

Chenghao Zhang  
The Second Xiangya Hospital

Chao Tu  
The Second Xiangya Hospital

Xiaolei Ren  
The Second Xiangya Hospital

Wenchao Zhang  
The Second Xiangya Hospital

Lile He  
The Second Xiangya Hospital

Lin Qi  
The Second Xiangya Hospital

Ruiqi Chen  
The Second Xiangya Hospital

Zhihong Li  
The Second Xiangya Hospital, Central South University

**Corresponding Author**  
lizhihong@csu.edu.cn

**ORCiD:** https://orcid.org/0000-0002-1944-9671

**DOI:** 10.21203/rs.3.rs-18849/v1

**SUBJECT AREAS**  
Oncology  
Cancer Biology

**KEYWORDS**  
LncRNA, cancer, sarcoma, SNHG12, prognosis
Abstract

Background: Recently, dysregulation of IncRNA SNHG12 has been determined in kinds of cancers. However, definite prognostic value of SNHG12 remains unclear. We conducted this meta-analysis to evaluate the association between SNHG12 expression levels and cancer prognosis.

Methods: A literature retrieval was conducted by searching kinds of databases. The meta-analysis of prognostic and clinicopathological parameters was performed by using Revman 5.2 and Stata 12.0 software. Besides, The Cancer Genome Atlas dataset was analyzed to validate the results in our meta-analysis via using Gene Expression Profiling Interactive Analysis.

Results: High SNHG12 expression significantly predicted worse overall survival (HR=1.97, 95%CI 1.56-2.48, P<0.01) and recurrence-free survival (HR=1.71, 95%CI 1.05-2.78, P<0.01). Tumor type, sample size, survival analysis method, and cut-off value did not alter SNHG12 prognosis value according to stratified analysis results. Additionally, patients with elevated SNHG12 expression were more prone to unfavorable clinicopathological outcomes, including larger tumor size, lymph node metastasis, distant metastasis, advanced clinical stage. Online cross-validation in TCGA dataset further proved that cancer patients with upregulated SNHG12 expression had worse overall survival and disease-free survival.

Conclusion: Elevated SNHG12 expression was associated with poor survival and unfavorable clinicopathological features in various cancers, and therefore might be a potential prognostic biomarker in human cancers.

Background

Nowadays, cancer has been a leading cause of mortality worldwide and has brought huge burdens to patients, families and society(1). Despite numerous achievements in surgical resection, radiotherapy, chemotherapy, and immunotherapy(2–4), cancer patients suffer from disappointing survival outcomes and life quality, especially for patients with advanced clinical stage or metastatic cancer(5). The insufficiency of effective prognosis biomarkers is supposed to be a crucial reason for this. Consequently, there remains a need to identify new prognostic biomarkers and therapeutic targets.

LncRNAs is a class of noncoding RNA that are more than 200 nucleotides (nt) long(6). Previous studies
suggest that lncRNAs play important roles in regulating chromatin dynamics, gene expression, protein ubiquitination and protein degradation(7). Long noncoding RNAs (lncRNAs) have been proved to play vital roles in chromatin dynamic regulation, protein ubiquitination, protein degradation and genomic imprinting in oncogenesis(7). Recently, accumulating evidences have showed that large number of lncRNAs are aberrantly expressed or mutated in various cancers, and are closely linked to tumorigenesis, tumor stage, metastasis and recurrence(8–11). Therefore, these evidences implicated the potential of lncRNAs serving as prognostic biomarkers and therapeutic targets for human cancers. Small nucleolar RNA host gene 12 (SNHG12) is a newly identified lncRNA with aberrant expression in various human cancers(12–14). Recent published studies have shown that SNHG12 may play important roles in the tumorigenesis and progression of cancers such as proliferation, migration, invasion, and apoptosis(15, 16). Furthermore, emerging evidence has implicated the significance of lncRNA SNHG12 in multiple cancer-related pathways, including Slug/zinc finger E-box-binding homeobox 2 (ZEB2), Notch2/Notch, PI3K/AKT, and Wnt/β-catenin signaling pathway(17–20). Also, upregulated SNHG12 expression was closely linked to reduced survival in multiple cancers(21). Among these cancers, elevated SNHG12 expression levels were significantly correlated with unfavorable clinicopathological outcomes, such as tumor size, lymph nodes metastasis (LNM), distant metastasis (DM), clinical stage, and drug resistance. Collectively, SNHG12 may act as a risk biomarker and therapeutic target for multiple kinds of human malignancies.

However, majority of studies evaluating the prognostic potential of SNHG12 in cancer survival outcomes have been limited by their small sample size and discrete outcomes, leading to the uncertainty in the prognostic value of SNHG12. In our meta-analysis, we quantitatively evaluate the correlation between SNH12 expression, survival, and clinicopathological outcomes in human pan-cancers, which may provide newly promising biomarkers for cancer prognosis and therapeutic strategy.

Methods

Search strategy

We rigorously projected, reviewed and reported this meta-analysis in line with the PRISMA
checklist (Supplementary Table 1) (22, 23). A systematic literature searching was conducted in several electronic databases, including PubMed, Web of Science, Embase, Scopus, the Cochrane Library, and China National Knowledge Infrastructure (CNKI) and Wanfang databases for eligible studies published by December 25, 2019. The search strategy was as follows: “small nucleolar RNA host gene 12 OR SNHG12” AND “cancer OR tumor OR carcinoma OR sarcoma OR malignancy”. Two authors independently completed the literature search, selection, and had discussion to solve any disagreement. Moreover, we checked the citations of retrieved articles for potentially relevant studies.

**Inclusion and exclusion criteria**

All eligible studies were critically reviewed and evaluated by two independent investigators (CHZ and XLR). The study would be included in the meta-analysis if it met the following standards: (a) the level of SNHG12 was examined in cancer tissues and adjacent normal tissues; (b) patients were divided into high and low expression groups according to the cut-off value of SNHG12 expression; (c) correlation between SNHG12 expression and survival or clinicopathological features were implicated; and (d) available hazard ratios (HRs) with 95% confidence interval (CI) for OS or RFS could be extracted directly or indirectly.

While the studies meeting following criteria should be excluded: (a) case reports, reviews, letters, meta-analysis and conference reports; (b) irrelevant to human cancer and SNHG12; (c) focused on the function and molecular mechanisms of SNHG12 rather than its association with cancer survival; and (d) animal studies and duplicate publications.

**Data extraction and quality control**

Two independent investigators (CHZ and XLR) extracted the following data from each included study: first author name, publication year, tumor type, sample size, number of high SNHG12 expression and low expression groups, follow-up months, detection assay, clinical stage, metastasis, cut-off value, survival outcomes including overall survival (OS), recurrence-free survival (RFS), and disease-free survival (DFS). The missing data regarding survival outcomes was obtained by contacting the corresponding author of eligible articles. If only Kaplan-Meier (K-M) curves were available in the study,
the Engauge Digitizer (Version 10.8) was used to synthesize the pooled HRs and corresponding 95%CI via indirect extraction from the curves(24, 25). Since all studies included in this meta-analysis were cohort studies, the study quality was assessed in line with the Newcastle-Ottawa Scale (NOS) by two investigators (WCZ and LQ)(26). NOS scores ranged from 0 to 9, and studies with score ≥ 6 were considered of high methodological quality (Supplementary Table 2).

**Online cross-validation in TCGA datasets**

We used Gene Expression Profiling Interactive Analysis (GEPIA) to verify the association with OS and DFS and examine SNHG12 expression levels in multiple kinds of cancers. The matched normal data in The Cancer Genome Atlas (TCGA) was used in the validation(27). The survival analysis was evaluated by Kaplan-Meier method and log-rank test, and the HR and p value were shown in the K-M curves.

**Statistical analysis**

Extracted data was analyzed by using RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 (Stata, College Station, TX). Pooled HRs and corresponding 95%CI were utilized to assess the correlation between SNHG12 and prognosis. ORs and 95%CI were applied to evaluate the association between SNHG12 expression and clinicopathological features. Chi square-based Q test and Higgins $I^2$ statistics were employed to determine the heterogeneity across the included studies. $I^2$ value>50% or p-value<0.05 were considered statistically significant and the random-effect model was adopted, otherwise, the fixed-effect model was applied. Sensitivity analysis was conducted by sequentially omitting each single study in order to assess the stability of results. Additionally, Egger’s regression test and Begg’s funnel plot were conducted to evaluate potential publication bias. All p-value were two-sided and a p-value<0.05 was considered significant.

**Results**

**Characteristics and eligible studies**

A total of 182 studies were initially identified as potential articles, and 103 studies were excluded as duplicates. After reviewing titles and abstracts, 44 studies were excluded since they were non-comparative studies or irrelevant topics. Then, 35 potentially eligible articles were selected for full-text assessed, and 17 studies were excluded due to the lack of survival data. Thus, 18 studies
compromising 1290 patients were considered eligible in the light of the inclusion and exclusion criteria. The screen procedure was thoroughly implicated via a flow diagram in Figure 1.

The characteristics of the eligible studies are presented in Table 1. These studies were published between 2017 and 2020, and their sample size ranged from 20 to 199. A total of ten different cancer types were included in our meta-analysis, including prostate cancer, gastric cancer, colorectal cancer, renal cell carcinoma, osteosarcoma, nasopharyngeal carcinoma, glioblastoma, cervical cancer, breast cancer, and hepatocellular carcinoma. Among these 18 studies, quantitative real-time polymerase chain reaction (qRT-PCR) was used as detection assay in 17 studies, and fluorescence in situ hybridization (FISH) analysis was performed in one study. As for survival outcomes, association between SNHG12 expression level and OS were reported in all studies except for three studies only reporting RFS and clinicopathological outcomes respectively. In all included studies, patients were divided into high or low SNHG12 expression groups according to the cut-off value. Moreover, the follow-up months ranged from 45 to 160 months, and univariate or multivariate analysis were used in each survival analysis. As for clinical stage, there were four kinds of clinical stage classification system, including tumor node metastasis (TNM) classification system, the International Federation of Gynecology and Obstetrics (FIGO) stage, Enneking stage, and The World Health Organization (WHO) grade. Additionally, all eligible studies were considered as high methodological quality with their NOS scores ≥7.

**Association between IncRNA SNHG12 and OS/ RFS**

A total of 15 studies were included for OS analysis. Since no obvious heterogeneity was observed among these studies ($I^2=0.0\%, \ p=0.967$), fixed-effects model was employed to synthesize pooled HR and corresponding 95% CI. The aggregated data suggested that high expression level of SNHG12 was significantly correlated to poor OS (HR=1.97, 95%CI 1.56-2.48, $p<0.001$) (Figure 2A), indicating that lower SNHG12 expression in cancer patients may predict a better survival outcome.

Two studies regarding prostate cancer and hepatocellular carcinoma provided related data for RFS analysis. In the absence of apparent heterogeneity among these studies ($I^2=0.0\%, \ p=0.380$), fixed-
effects model was applied to calculate the HR and its 95%CI. As demonstrated in Figure 2B, the pooled results indicated that high SNHG12 expression level predicted unfavorable RFS in prostate cancer and hepatocellular carcinoma (HR=1.71, 95%CI 1.05-2.78, p<0.05).

Sensitivity analysis
Sensitivity analysis was performed in order to assess whether any individual study would affect the result of pooled OS. By removing each included study, we found that the pooled result had a slight fluctuation when “Zhang, R 2019” was removed (Figure 2C). Thus, the pooled HR was analyzed again after omitting “Zhang, R 2019”, and the result demonstrated that high expression of SNHG12 was still correlated to worse OS in different kinds of cancers (HR=2.02, 95%CI 1.57-2.59, p<0.00001, and \( I^2 = 0.0\%, p=0.957 \), fixed model), indicating the stability and reliability of this meta-analysis.

Publication bias
Begg`s funnel plot and Egger`s regression test were employed to evaluate potential publication bias. As shown in Figure 2D, no apparent asymmetry was observed in the Begg`s funnel plot and the result of Egger`s regression further proved it (\( p>|t|=0.160 \)). Therefore, no significant publication bias existed in this meta-analysis.

Subgroup analysis of association between SNHG12 and OS
Even though the study heterogeneity was low in OS analysis (\( I^2 = 0.0\%, p=0.967 \)), several stratified analyses were performed based on tumor type (digestive system tumor or others), sample size (more or less than 60), survival analysis method (univariate or multivariate analysis), and cut-off value (mean or median). As shown in Figure 3 and Table 2, all subgroup analyses based on different stratified factors did not alter the association between SNHG12 and OS in multiple kinds of cancers.

Association between SNHG12 and clinicopathologic characteristics
ORs and corresponding 95%CI were applied to investigate the association between SNHG12 and clinicopathologic features including age, gender, tumor size, Gleason score, TNM stage, WHO grade, LNM and DM. Fixed-effect model was applied in all analyses and no statistically significant correlation was detected between SNHG12 and age, gender (Supplementary Figure 1, Table 3). Recognizing, as
demonstrated in Figure 4 and Table 3, high SNHG12 expression had significant association with larger tumor size (OR=5.05, 95%CI 2.67-9.55, p<0.00001), LNM (OR=3.32, 95%CI=2.32-4.75, p<0.00001), DM (OR=2.35, 95%CI 1.46-3.78, p=0.005), poorer TNM stage (OR=3.61, 95%CI 2.51-5.17, p<0.00001), higher WHO grade (OR=11.34, 95%CI 4.60-27.95, p<0.00001) and higher Gleason score in prostate cancer (OR=2.69, 95%CI 1.59-4.53, p=0.0002). We could not assess the association between SNHG12 expression and other clinicopathological parameters owing to insufficient data.

**Online cross-validation in TCGA dataset**

We used TCGA dataset to evaluate SNHG12 expression levels in multiple kinds of cancers in order to further validate the pooled results. As depicted in Figure 5, SNHG12 showed aberrant expression levels in breast invasion carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), liver hepatocellular carcinoma (LIHC), colon adenocarcinoma (COAD), rectum adenocarcinoma (READ), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), sarcoma (SARC), and stomach adenocarcinoma (STAD) when compared with normal control. Moreover, the violin plot implicated that SNHG12 expression level was significantly correlated with pathological stage in human pan-cancers. Additionally, the survival plots in GEPIA indicated that high expression of SNHG12 predicted worse OS (HR=1.1, p<0.05) and DFS (HR=1.1, p<0.05), which verified our results in this meta-analysis.

**Discussion**

LncRNAs were previously regarded as “transcriptional noise” without any coding effects and did not get much attention among investigators over the past decades(28). Recently, increasing evidence of next-generation genome wide sequencing and single-cell RNA-sequencing has revealed that lncRNAs have aberrant expressions and mutations in human pan-cancers(29–31). More and more studies have showed that abnormally expressed lncRNAs are emerging as important regulators in tumorigenesis and show a significant association with cancer prognosis(32–35). SNHG12 is dysregulated in multiple kinds of human cancers, including prostate cancer(12), gastric cancer(19), cervical cancer(36), hepatocellular carcinoma(37), renal cell carcinoma(38), nasopharyngeal carcinoma(39), glioma(40), breast cancer(41), non-small cell lung cancer(17), ovarian cancer(14), colorectal cancer(42), and
osteosarcoma(18). Additionally, upregulated SNHG12 expression levels play important roles in the cellular process of tumorigenesis, including cancer cell proliferation(12, 19, 39, 43), migration(18, 37), invasion(36, 38), apoptosis(16, 44), epithelial-mesenchymal transition (EMT) (17) and chemo resistance(45).

In order to determine the prognostic value of SNHG12 in human cancers, for the first time, we carried out this meta-analysis. The synthesized results implicated that high expression levels of SNHG12 predicted worse OS and RFS, and the stratified analyses of OS indicated similar results. Moreover, one study reported that gastric cancer patients with upregulated SNHG12 expression had a worse DFS after surgery(15). Therefore, SNHG12 overexpression was closely associated with poor prognosis in cancer patients. The pooled results also showed that patients with higher SNHG12 expression level were more exposed to worse clinicopathological outcomes including larger tumor size, higher Gleason score in prostate cancer, advanced TNM stage, higher WHO grade in glioma, LNM and DM. Besides, some clinically meaningful parameters only reported in a single study or presented by divergent cut-off values were not included in the pooled results. For instance, prostate cancer patients with high SNHG12 expression were more prone to higher serum prostate-specific antigen (PSA) value (p = 0.0349), residual tumor (p = 0.002), and bone metastasis (p < 0.001)(12, 44). Additionally, patients with SNHG12 upregulation had more possibility developing advanced Enneking stage (p = 0.038) in osteosarcoma and vascular invasion in hepatocellular carcinoma (p = 0.0093) (5, 18). Therefore, our results suggested that high SNHG12 expression level might be an unfavorable biomarker for cancer prognosis. Further, we conducted GEPIA online analyses to validate the prognostic value of SNHG12 in human cancers based on TCGA dataset, and the online validation indicated similar results. Taken together, SNHG12 could act as a functional regulator in cancer progression and promising prognostic biomarker in pan-cancer patients.

Even though many studies have revealed the prognostic significance of SNHG12 in human cancers, the further mechanisms remain indistinct. The present evidence revealed that SNHG12 could function as ceRNA by directly binding to miRNA and thereby regulating target genes in human cancers. For instance, SNHG12 upregulation increased the expression of hypoxia-inducible factor 1 α (HIF1α) by
targeting miR-199a-5p, which induced cell proliferation, migration, and invasion in renal cell carcinoma(38). Moreover, doxorubicin resistance in osteosarcoma was promoted by SNHG12 via targeting miR-320a to upregulate myeloid cell leukemia 1 (MCL1)(45). Similar mechanism was also reported in other human cancers, such as miR-133b or miR-195/cyclin E1 (CCNE1) in prostate cancer (12, 44), miR-199a/b-5p/ mixed-lineage protein kinase 3 (MLK3) in hepatocellular carcinoma (37), miR-424-5P or miR-125b/ signal transducer and activator of transcription 3 (STAT3) in cervical cancer (36, 46), miR-16 or miR-320 in gastric cancer(13, 15), miR-218/Slug/ZEB2 in non-small cell lung cancer (17), miR-129/SRY-box transcription factor 4 (SOX4) in ovarian cancer (14), miR-16 in colorectal cancer (42), miR-129-5p/ WW domain-containing E3 ubiquitin protein ligase 1 (WWP1) in laryngeal squamous cell carcinoma (47), and miR-195/SRY-box transcription factor 5 (SOX5) in glioma (48). Besides, SNHG12 could be involved into cancer progression by interacting with various kinds of signaling pathways. SNHG12 overexpression promoted cell invasion, migration and EMT in non-small cell lung cancer via engaging into Slug/ZEB signaling pathway to regulate expression of E-cadherin, matrix metalloproteinase 9 (MMP-9) and vimentin(17). Similarly, SNHG12 was found to have cross-talk with other crucial signaling pathways in tumorigenesis including PI3K/Akt/mTOR (19), Notch (39), Wnt/β-catenin(20). Therefore, more studies are still needed to thoroughly explore the underlying mechanisms of SNHG12 in human cancers.

Recognizing, some limitations to this study should be addressed. First, all the eligible studies were carried out in Chinese population, thus caution must be noticed since these results might not be broadly applied to other population. Second, some HR values were computed according to software reconstruction of K-M curves rather than directly obtaining original data, which might lead to bias. Third, the pooled result of SNHG12 expression on RFS should be given caution when the result is generalized to other cancers, since only two studies containing hepatocellular carcinoma and prostate cancer were included. Fourth, mean or median value was set as cut-off value in all eligible studies without a consensus standard or detailed description on the calculation process and original data. Thus, the uncertainty about cut-off values across all eligible studies might bring about potential bias. Conclusions
Upregulated expression of SNHG12 was markedly associated with worse survival and clinicopathological outcomes in multiple cancers, and therefore might be applied as a promising prognosis predictor and potential therapeutic target in human cancers. However, studies with a larger sample size, broader spectrum of cancers, or even prospective design are still needed to verify these results.

**Abbreviations**

Akt: protein kinase B; BRCA: breast invasion carcinoma; CESC: cervical squamous cell carcinoma and endocervical adenocarcinoma; ceRNA: competitive endogenous RNA; CNKI: China National Knowledge Infrastructure; CI: confidence interval; CCNE1: cyclin E1; COAD: colon adenocarcinoma; DM: distant metastasis; DFS: disease-free survival; EMT: epithelial–mesenchymal transition; FISH: fluorescence in situ hybridization; FIGO: the International Federation of Gynecology and Obstetrics; GEPIA: Gene Expression Profiling Interactive Analysis; HR: hazard ratio; HIFα: hypoxia-inducible factor 1 α; KIRC: kidney renal clear cell carcinoma; KIRP: kidney renal papillary cell carcinoma; LIHC: hepatocellular carcinoma; LNM: lymph node metastasis; mTOR: mechanistic target of rapamycin kinase; MMP-9: matrix metalloproteinase 9; MCL1: myeloid cell leukemia 1; MLK3: mixed-lineage protein kinase 3; N/A: not available; NOS: Newcastle-Ottawa Scale; OR: odd ratio; OS: overall survival; PSA: prostate-specific antigen; PI3K: phosphoinositide 3-kinase; qRT-PCR: quantitative real-time polymerase chain reaction; READ: rectum adenocarcinoma; RFS: recurrence-free survival; SARC: sarcoma; SNHG12: small nucleolar RNA host gene 12; STAT3: signal transducer and activator of transcription 3; SOX4: SRY-box transcription factor 4; SOX5: SRY-box transcription factor 5; STAD: stomach adenocarcinoma; TCGA : The Cancer Genome Atlas; TNM: tumor node metastasis; WWP1: WW domain-containing E3 ubiquitin protein ligase 1; WHO grade: World Health Organization grade; ZEB2: zinc finger E-box-binding homeobox 2.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**
Not applicable.

**Availability of data and materials**

The data used and analyzed in the study is available from the corresponding author on reasonable request.

**Competing interests**

Chao Tu and Zhihong Li are the member of the editorial board of BMC Cancer. The authors declare that they approve this article and have no competing interests.

**Funding**

This work was supported by the National Natural Science Foundation of China under Grant 81902745; Natural Science Foundation of Hunan Province, under Grant 2018JJ3716 and 2018JJ3759; Fundamental Research Funds for the Central Universities of Central South University (No. 2017zzts231); and Central South University Innovative Program for Undergraduates (No. 20190034020002). The funding parties had no role in the study design, data collection and analysis, and interpretation of data, or in the manuscript writing.

**Author’s contributions**

ZHL and CT conceived the project. CHZ and XLR carried out data extraction and analysis. WCZ and LQ performed the literature search, screen and quality assessment. LLH an RQC contributed to the manuscript drafting. ZHL and CT supervised the project and revised the manuscript. All author carefully read and approved the final manuscript.

**Acknowledgements**

We would like to thank the investigators and participants of each included study for their contributions.

**References**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.

2. Jiang J, Zhou H, Ni C, Hu X, Mou Y, Huang D, et al. Immunotherapy in pancreatic cancer: New hope or mission impossible? Cancer Letters. 2019;445:57-64.
3. Keane FK, Hong TS. Role and Future Directions of External Beam Radiotherapy for Primary Liver Cancer. Cancer Control. 2017;24(3):1073274817729242.

4. Teno JM, Curtis JR. Family Perspectives on Aggressive Cancer Care Near the End of Life. JAMA Oncology. 2016;2(7):957-8.

5. Zhang C, Ren X, He J, Wang W, Tu C, Li Z. The prognostic value of long noncoding RNA SNHG16 on clinical outcomes in human cancers: a systematic review and meta-analysis. Cancer cell international. 2019;19:261.

6. Schmitt AM, Chang HY. Long Noncoding RNAs in Cancer Pathways. Cancer cell. 2016;29(4):452-63.

7. Bhan A, Mandal SS. LncRNA HOTAIR: A master regulator of chromatin dynamics and cancer. Biochimica et biophysica acta. 2015;1856(1):151-64.

8. Bhan A, Mandal SS. Long noncoding RNAs: emerging stars in gene regulation, epigenetics and human disease. ChemMedChem. 2014;9(9):1932-56.

9. Vitiello M, Tuccoli A, Poliseno L. Long non-coding RNAs in cancer: implications for personalized therapy. Cell Oncol (Dordr). 2015;38(1):17-28.

10. Bartonicek N, Maag JLV, Dinger ME. Long noncoding RNAs in cancer: mechanisms of action and technological advancements. Mol Cancer. 2016;15(1):43-.

11. Tu C, Ren X, He J, Zhang C, Chen R, Wang W, et al. The Value of LncRNA BCAR4 as a Prognostic Biomarker on Clinical Outcomes in Human Cancers. J Cancer. 2019;10(24):5992-6002.

12. Cheng G, Song Z, Liu Y, Xiao H, Ruan H, Cao Q, et al. Long noncoding RNA SNHG12 indicates the prognosis of prostate cancer and accelerates tumorigenesis via sponging miR-133b. Journal of cellular physiology. 2020;235(2):1235-46.

13. Zhao G, Wang S, Liang X, Wang C, Peng B. Oncogenic role of long non-coding RNA SNHG12 in gastric cancer cells by targeting miR-16. Experimental and therapeutic
14. Sun D, Fan XH. LncRNA SNHG12 accelerates the progression of ovarian cancer via absorbing miRNA-129 to upregulate SOX4. European review for medical and pharmacological sciences. 2019;23(6):2345-52.

15. Zhang H, Lu W. LncRNA SNHG12 regulates gastric cancer progression by acting as a molecular sponge of miR-320. Molecular medicine reports. 2018;17(2):2743-9.

16. Wang JZ, Xu CL, Wu H, Shen SJ. LncRNA SNHG12 promotes cell growth and inhibits cell apoptosis in colorectal cancer cells. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas. 2017;50(3):e6079.

17. Huang X, Zhang Z, Qing X, Zhang W, Zhong B, Deng X, et al. Dysregulated Expression of Circular RNAs Serve as Prognostic and Clinicopathological Markers in Cancer. J Cancer. 2019;10(8):1825-32.

18. Zhou S, Yu L, Xiong M, Dai G. LncRNA SNHG12 promotes tumorigenesis and metastasis in osteosarcoma by upregulating Notch2 by sponging miR-195-5p. Biochemical and biophysical research communications. 2018;495(2):1822-32.

19. Wang L, Zhang G-C, Kang F-B, Zhang L, Zhang Y-Z. hsa_circ0021347 as a Potential Target Regulated by B7-H3 in Modulating the Malignant Characteristics of Osteosarcoma. Biomed Res Int. 2019;2019:9301989-.

20. Song J, Wu X, Ma R, Miao L, Xiong L, Zhao W. Long noncoding RNA SNHG12 promotes cell proliferation and activates Wnt/beta-catenin signaling in prostate cancer through sponging microRNA-195. Journal of cellular biochemistry. 2019;120(8):13066-75.

21. Tamang S, Acharya V, Roy D, Sharma R, Aryaa A, Sharma U, et al. SNHG12: An LncRNA as a Potential Therapeutic Target and Biomarker for Human Cancer. Frontiers in oncology. 2019;9:901-.

22. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The
PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700-b.

23. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1-.

24. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16-.

25. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17(24):2815-34.

26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5.

27. Tang Z, Li C, Kang B, Gao G, Li C, Zhang Z. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. Nucleic Acids Res. 2017;45(W1):W98-W102.

28. Struhl K. Transcriptional noise and the fidelity of initiation by RNA polymerase II. Nat Struct Mol Biol. 2007;14(2):103-5.

29. Li M, Liu Y, Zhang X, Liu J, Wang P. Transcriptomic analysis of high-throughput sequencing about circRNA, IncRNA and mRNA in bladder cancer. Gene. 2018;677:189-97.

30. Serrati S, De Summa S, Pilato B, Petriella D, Lacalamita R, Tommasi S, et al. Next-generation sequencing: advances and applications in cancer diagnosis. OncoTargets and therapy. 2016;9:7355-65.
31. Li X, Meng X, Wei C, Zhou Y, Chen H, Huang H, et al. Dissecting LncRNA Roles in Renal Cell Carcinoma Metastasis and Characterizing Genomic Heterogeneity by Single-Cell RNA-seq. Mol Cancer Res. 2018;16(12):1879-88.

32. Chen C, Feng Y, Wang X. LncRNA ZEB1-AS1 expression in cancer prognosis: Review and meta-analysis. Clinica chimica acta; international journal of clinical chemistry. 2018;484:265-71.

33. Wang J, Su Z, Lu S, Fu W, Liu Z, Jiang X, et al. LncRNA HOXA-AS2 and its molecular mechanisms in human cancer. Clinica chimica acta; international journal of clinical chemistry. 2018;485:229-33.

34. Zhang H, Huang H, Xu X, Wang H, Wang J, Yao Z, et al. LncRNA HCG11 promotes proliferation and migration in gastric cancer via targeting miR-1276/CTNNB1 and activating Wnt signaling pathway. Cancer cell international. 2019;19:350-.

35. Ren X, He J, Qi L, Li S, Zhang C, Duan Z, et al. Prognostic and clinicopathologic significance of long non-coding RNA opa-interacting protein 5-antisense RNA 1 in multiple human cancers. Artif Cells Nanomed Biotechnol. 2020;48(1):353-61.

36. Dong J, Wang Q, Li L, Xiao-Jin Z. Upregulation of Long Non-Coding RNA Small Nucleolar RNA Host Gene 12 Contributes to Cell Growth and Invasion in Cervical Cancer by Acting as a Sponge for MiR-424-5p. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2018;45(5):2086-94.

37. Lan T, Ma W, Hong Z, Wu L, Chen X, Yuan Y. Long non-coding RNA small nucleolar RNA host gene 12 (SNHG12) promotes tumorigenesis and metastasis by targeting miR-199a/b-5p in hepatocellular carcinoma. Journal of experimental & clinical cancer research : CR. 2017;36(1):11.

38. Chen Q, Zhou W, Du S-q, Gong D-x, Li J, Bi J-b, et al. Overexpression of SNHG12
regulates the viability and invasion of renal cell carcinoma cells through modulation of HIF1. Cancer cell international. 2019;19.

39. Liu Z-B, Tang C, Jin X, Liu S-H, Pi W. Increased expression of IncRNA SNHG12 predicts a poor prognosis of nasopharyngeal carcinoma and regulates cell proliferation and metastasis by modulating Notch signal pathway. Cancer Biomarkers. 2018;23(4):603-13.

40. Lei W, Wang Z-L, Feng H-J, Lin X-D, Li C-Z, Fan D. Long non-coding RNA SNHG12 promotes the proliferation and migration of glioma cells by binding to HuR. International journal of oncology. 2018;53(3):1374-84.

41. Wang O, Yang F, Liu Y, Lv L, Ma R, Chen C, et al. C-MYC-induced upregulation of IncRNA SNHG12 regulates cell proliferation, apoptosis and migration in triple-negative breast cancer. American journal of translational research. 2017;9(2):533-45.

42. Liu Y, Zhou J, Wang S, Song Y, Zhou J, Ren F. Long non-coding RNA SNHG12 promotes proliferation and invasion of colorectal cancer cells by acting as a molecular sponge of microRNA-16. Experimental and therapeutic medicine. 2019;18(2):1212-20.

43. Yang BF, Cai W, Chen B. LncRNA SNHG12 regulated the proliferation of gastric carcinoma cell BGC-823 by targeting microRNA-199a/b-5p. European review for medical and pharmacological sciences. 2018;22(5):1297-306.

44. Wang X, He C, Yang Z, Li S, Qiao L, Fang L. Dysregulation of long non-coding RNA SNHG12 alters the viability, apoptosis, and autophagy of prostate cancer cells by regulating miR-195/CCNE1 axis. International Journal of Clinical and Experimental Pathology. 2019;12(4):1272-83.

45. Zhou B, Li L, Li Y, Sun H, Zeng C. Long noncoding RNA SNHG12 mediates doxorubicin resistance of osteosarcoma via miR-320a/MCL1 axis. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2018;106:850-7.
46. Jin XJ, Chen XJ, Zhang ZF, Hu WS, Ou RY, Li S, et al. Long noncoding RNA SNHG12 promotes the progression of cervical cancer via modulating miR-125b/STAT3 axis. Journal of cellular physiology. 2019;234(5):6624-32.

47. Li J, Sun S, Chen W, Yuan K. Small Nucleolar RNA Host Gene 12 (SNHG12) Promotes Proliferation and Invasion of Laryngeal Cancer Cells via Sponging miR-129-5p and Potentiating WW Domain-Containing E3 Ubiquitin Protein Ligase 1 (WWP1) Expression. Medical Science Monitor. 2019;25:5552-60.

48. Liu X, Zheng J, Xue Y, Qu C, Chen J, Wang Z, et al. Inhibition of TDP43-Mediated SNHG12-miR-195-SOX5 Feedback Loop Impeded Malignant Biological Behaviors of Glioma Cells. Molecular therapy Nucleic acids. 2018;10:142-58.

Tables

TABLE 1. Summary of the main characteristics of the studies included in the meta-analysis.

DFS: disease-free survival; DM: distant metastasis; FISH: fluorescence in situ hybridization; FIGO: the International Federation of Gynecology and Obstetrics; LNM: lymph node metastasis; N/A: not available; NOS: Newcastle-Ottawa Scale; OS: overall survival; RFS: recurrence-free survival; SNHG12: small nucleolar RNA host gene 12; TNM: tumor node metastasis; WHO grade: World Health Organization grade

CI: confidence interval; HR: hazard ratio
| Study                  | Year | Tumor type               | Sample Size | SNHG12 expression | Follow-up months | Detection assay |
|------------------------|------|--------------------------|-------------|-------------------|------------------|-----------------|
| Cheng, G et al         | 2020 | Prostate cancer          | 199         | High: 99          | 160              | qRT-PCR         |
|                       |      |                          |             | Low: 100          |                  |                 |
| Zhao, G et al          | 2019 | Gastric cancer           | 56          | High: 25          | 60               | qRT-PCR         |
|                       |      |                          |             | Low: 31           |                  |                 |
| Zhang, R et al         | 2019 | Gastric cancer           | 75          | High: 48          | 80               | FISH            |
|                       |      | Prostate cancer          |             | Low: 27           |                  |                 |
| Wang, X et al          | 2019 | Prostate cancer          | 56          | High: 22          | 60               | qRT-PCR         |
|                       |      | Prostate cancer          |             | Low: 34           |                  |                 |
| Song, J et al          | 2019 | Prostate cancer          | 89          | High: 44          | N/A              | qRT-PCR         |
|                       |      | Colorectal cancer        |             | Low: 45           |                  |                 |
| Liu, Y et al           | 2019 | Renal cell carcinoma     | 53          | High: 26          | 60               | qRT-PCR         |
|                       |      |                          |             | Low: 27           |                  |                 |
| Zhou, S et al          | 2018 | Osteosarcoma             | 31          | High: 16          | 60               | qRT-PCR         |
|                       |      |                          |             | Low: 15           |                  |                 |
| Zhou, B et al          | 2018 | Osteosarcoma             | 64          | High: 32          | 80               | qRT-PCR         |
|                       |      |                          |             | Low: 32           |                  |                 |
| Yang, B et al          | 2018 | Gastric cancer           | 54          | High: 27          | 45               | qRT-PCR         |
|                       |      |                          |             | Low: 27           |                  |                 |
| Liu, Z et al           | 2018 | Nasopharyngeal carcinoma | 129         | High: 62          | 60               | qRT-PCR         |
|                       |      |                          |             | Low: 67           |                  |                 |
| Liu, X et al           | 2018 | Glioblastoma             | 39          | High: 31          | 50               | qRT-PCR         |
| Lei, W et al           | 2018 | Glioblastoma             | 79          | Low: 39           | 60               | qRT-PCR         |
| Dong, J et al          | 2018 | Cervical cancer          | 76          | Low: 38           | 80               | qRT-PCR         |
| Wang, O et al          | 2017 | Breast cancer            | 102         | High: 51          | N/A              | qRT-PCR         |
| Wang, J et al          | 2017 | Colorectal cancer        | 60          | Low: 30           | 60               | qRT-PCR         |
|                       |      |                          |             | Low: 30           |                  |                 |
| Lan, T et al           | 2017 | Hepatocellular carcinoma | 48          | High: 24          | 48               | qRT-PCR         |
|                       |      |                          |             | Low: 24           |                  |                 |
| Zhang, H et al         | 2017 | Gastric cancer           | 60-         | High: 30          | 60               | qRT-PCR         |
|                       |      |                          |             | Low: 30           |                  |                 |

SNHG12: small nucleolar RNA host gene 12; WHO grade: World Health Organization grade

Additional File

**Supplementary Figure 1.** Forest plots evaluating the association between SNHG12 expression, age
Supplementary Table 1. PRISMA Checklist.

Supplementary Table 2. Study quality and bias in the retrospective cohort studies judged by the Newcastle-Ottawa Scale (NOS) checklist.

Figures

and gender. No statistically significant correlation was detected between SNHG12, age(A), and gender(B).
Figure 1

Flow diagram of the literature selection procedure.
Figure 2

Forest plots of studies assessing the HRs of high SNHG12 expression in human cancers for (A) overall survival and (B) recurrence-free survival. (C) sensitivity analysis of pooled Hazard ratio for overall survival. (D) Begg’s funnel plot for publication bias of SNHG12 on overall survival.
Stratified analyses of SNHG12 expression on overall survival according to subgroups: (A) tumor type, (B) sample size, (C) survival analysis method and (D) cut-off value.

**A**

| Study ID | HR (95% CI) | % Weight |
|----------|-------------|----------|
| Wang, O 2017 | 3.18 [0.31, 31.09] | 10.9% |
| Yang, B 2018 | 3.02 [1.54, 5.94] | 11.8% |
| Zhang, H 2017 | 1.90 [0.97, 3.81] | 9.2% |
| Zhao, G 2019 | 1.80 [0.72, 4.62] | 9.2% |
| Total (95% CI) | 5.05 [2.67, 9.55] | 100.0% |

**B**

| Study ID | HR (95% CI) | % Weight |
|----------|-------------|----------|
| Wang, O 2017 | 2.73 [1.26, 5.92] | 24.1% |
| Liu, Y 2019 | 4.40 [1.28, 15.18] | 7.2% |
| Song, J 2019 | 2.69 [1.23, 7.09] | 17.2% |
| Wang, O 2017 | 2.35 [1.03, 5.36] | 21.8% |
| Yang, B 2018 | 7.19 [1.95, 26.51] | 5.2% |
| Zhang, H 2017 | 13.00 [3.55, 47.60] | 3.9% |
| Zhang, R 2019 | 1.13 [0.40, 3.22] | 19.4% |
| Zhao, G 2019 | 18.46 [1.01, 337.51] | 1.2% |

---

Figure 3
Forest plots evaluating the association between SNHG12 expression and clinicopathological parameters, including (A) tumor size (>5cm/≤5cm), (B) lymph node metastasis, (C) distant metastasis, (D) TNM stage, (E) WHO grade, and (F) Gleason score (>7/≤7).
Figure 5

Validation of SNHG12 expression level in multiple cancers in TCGA cohort. (A) The expression level of SNHG12 in breast invasion carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), liver hepatocellular carcinoma (LIHC), colon adenocarcinoma (COAD), rectum adenocarcinoma (READ), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), sarcoma (SARC), and stomach adenocarcinoma (STAD). (B) Violin plot implicating SNHG12 expression levels in different pathological stage of human pan-cancers in TCGA cohort. (C) Overall survival plot of SNHG12 in TCGA cohort (n=9497). (D) Disease-free survival plot of SNHG12 in TCGA cohort (n=9497).

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

Figure S1.tif
Supplementary Table 1.doc
Supplementary Table 2.docx