Upregulation of LncRNA SNHG15 indicates an unfavourable prognosis and clinical features of patients in multiple malignancies: a meta-analysis and bioinformatics

Caizhi Chen
Department of Oncology, The Second Xiangya Hospital of Central South University, Changsha, Hunan410000, China  https://orcid.org/0000-0001-7865-685X

Yeqian Feng
Department of Oncology, The Second Xiangya Hospital of Central South University, Changsha, Hunan410000, China

Jingjing Wang
Department of Oncology, The Second Xiangya Hospital of Central South University, Changsha, Hunan410000, China

Ye Liang
Department of Oncology, The Second Xiangya Hospital of Central South University, Changsha, Hunan410000, China

Wen Zou (✉ zouwen29w@csu.edu.cn)
Department of Oncology, The Second Xiangya Hospital of Central South University, Changsha, Hunan410000, China  https://orcid.org/0000-0001-6398-0649

Research article

Keywords: LncRNA SNHG15, prognosis, meta-analysis, bioinformatics

DOI: https://doi.org/10.21203/rs.3.rs-29350/v1

License: ©  This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background: A snoRNA host gene named SNHG15 which produces a short half-lived IncRNA has been reported to be dysregulated in multiple cancers and correlated with tumor progression in published researches recently. So this meta-analysis was performed to evaluate the generalized prognostic effect of SNHG15 on malignancies because of the discrepant data amongst different studies.

Methods: Four public databases were utilized for identifying eligible studies. The association between prognostic indicators and clinical features were extracted and pooled for estimation of the hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs). Publication bias and the stability of pooled results were measured by Begg's test, Egger's test and sensitivity analysis respectively. Additionally, Online database based on The Cancer Genome Atlas (TCGA) was screened and further validate our results.

Results: Totally eleven studies including 1087 patients were ultimately enrolled in our paper. Promoted SNHG15 expression was associated with worse OS and DFS. Moreover, increased SNHG15 expression suggested advanced TNM stage and LNM but not correlated with age, gender and tumor size. No publication bias and instability of result were observed. SNHG15 was significantly upregulated in seven cancers and elevated expression of SNHG15 indicated shorter OS and DFS in five malignancies according to the validation using GEPIA (Gene Expression Profiling Interactive Analysis).

Conclusions: Promoted expression of IncRNA SNHG15 was markedly related to worse prognosis and clinical features, suggesting that SNHG15 might serve as a novel factor in various cancers.

Background

Cancer has become a severe health problem and ranked as the leading cause of death worldwide with the increasingly incidence and mortality every year. According to the latest statistics publishing on CA cancer journal, it is projected that 1,806,590 new cancer cases and 606,520 cancer deaths will be occurred in the United States in 2020[1]. Although multidisciplinary treatments such as surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy of malignancies have been improved greatly these years, the prognosis and earlier diagnosis are still extremely challenging[2]. For this reason, there is an urgent need to identify innovative and effective targets so as to investigate the signaling pathways in tumors, which may play an indispensable role in the therapeutic decision-making of cancer patients.

Long non-coding RNAs (IncRNAs), which are initially speculated as transcriptional noise with no specific biological functions, are emerging as a novel category of ncRNAs with a length longer than 200 nucleotides that are transcribed by RNA polymerase II but does not encode proteins for lack of open reading frame[3]. Nonetheless, growing researches have demonstrated that aberrant expression of IncRNAs are intently correlated with biological process including tumor progression, angiogenesis, metastasis and invasion, which indicates that its roles serve as tumor suppressors or oncogenes for cancer control[4, 5]. Recently, SNHG6 (small nucleolar RNA host gene 6), linc00152 and OIP5-AS1(opa-
interacting protein 5 antisense RNA 1) have been identified as potential prognostic biomarkers which were involved in modulation of tumor-related genes and molecular mechanism in human cancers[6-8].

Small nucleolar RNA host gene 15 (SNHG15), which is located at 7p13 with a length of 860 bp, was initially reported as a short half-life lncRNA in the research of Tani et al [9]. As a tumor oncogene, lncRNA SNHG15 functions as ceRNAs to sponge miR-153, miR-381, miR-141, miR-141-3p in regulation to promote cell proliferation, migration, invasion, autophagy and cisplatin resistance in glioma, breast cancer, osteosarcoma and hepatocellular carcinoma[10-13]. Furthermore, SNHG15 enhances the tumor development or drug resistance in glioblastoma multiforme, colorectal carcinoma and prostate cancer through SNHG15/CDK6/miR-627, SNHG15/miR-141/SIRT1/Wnt/β-catenin, SNHG15/miR-338-3p/FKBP1A and SNHG15/miR-338-3p/FOS-RAB14 axis[14-17]. Additionally, the research of Morvarid Saeinasab et al well elucidated that SNHG15 could facilitate cell proliferation, invasion and drug resistance in colorectal cancer functioned as a bifunctional MYC-regulated noncoding locus encoding a lncRNA by interacting with AIF. Similarly, Jiang et al demonstrated that in colon cancer, SNHG15 promoted tumor progression via stabilizing transcription factor Slug[18, 19]. However, as a tumor suppressor, only Liu et al reported that SNHG15 was downregulated in thyroid cancer tissue samples and cells and its inhibited expression positively enhanced cell proliferation, migration, invasion in vitro[20].

Collectively, most studies have demonstrated that SNHG15 pervasively involved in gene modulation via acting as an oncogene in various malignancies and its elevated expression might be dramatically associated with prognosis and clinicopathological parameters of gastric cancer[21], hepatocellular carcinoma[22], lung cancer[23], non-small cell lung cancer[24, 25], renal cell carcinoma[26], pancreatic ductal adenocarcinoma[27], breast cancer[28], papillary thyroid carcinoma[29], colorectal cancer[30] and epithelial ovarian cancer[31].

However, owing to inconsistency existed amongst those published studies, small number of patient samples and different detection methods, the prognostic value of SNHG15 remains discrepant and indefinite. Therefore, we conducted this meta-analysis and bioinformatic validation to identify whether SNHG15 could characterize as a noninvasive predictor of tumors and tried to reach consensus on the prognostic value of this gene.

**Methods**

**Search strategies for eligible literatures**

Potential relevant articles that investigate the association between SNHG15 expression and clinical outcomes of cancers were thorough searched using PubMed, Web of science, Embase and the Cochrane Library up to February 26, 2020. There domains of keywords in multiple combinations were utilized as searched subjects as follows: ("long noncoding RNA" OR "lncRNA") AND ("SNHG15" OR "small nucleolar RNA host gene 15") AND ("Cancer" OR "Cancers" OR "Tumors" OR "Tumor" OR "Malignancy" OR "Malignancies" OR "Neoplasm" OR "Neoplasia" OR "Neoplasias" OR "Neoplasm" OR "Malignant Neoplasms" OR "Malignant Neoplasm" OR "Neoplasm, Malignant" OR "Neoplasms, Benign" OR "Benign Neoplasm" OR...
“Neoplasms, Malignant” OR “Benign Neoplasms” OR “Neoplasm, Benign”). Further manual search was conducted to avoid the ellipsis of eligible papers by screening the title and abstracts of references list in pertinent articles.

**Inclusion and exclusion criteria**

All enrolled researches were assessed by two independent investigators and disagreements were solved by reaching a consensus after discussing with the third author. Articles that met the following criteria would be enrolled in our study: (1) original articles investigated the roles of SNHG15 in cancers which were definitively diagnosed by histopathology; (2) samples were cancer tissue and adjacent normal tissue; (3) Detection method was qRT-PCR; (4) clinical features including age, gender, tumor size, TNM stage, lymph node metastasis or distant metastasis and prognostic indicators like OS, DFS or PFS were both reported in paper. (5) patients were categorized into promoted SNHG15 expression group and decreased SNHG15 expression group on the basis of the cut-off value and the number of these two groups was illustrated explicitly. (6) HRs and 95% CIs were reported by multivariate analysis from the articles or were available to be calculated via the Kaplan-Meier curves indirectly. (7) The language of articles was English.

Exclusion criteria: (1) studies explored other lncRNAs or were not related to cancers; (2) duplicate articles; (3) other literature type like review, letter, conference abstract, meta-analysis, case report, retraction; (4) articles focused on biological functions; (5) lack of sufficient data for HR and 95% CI extraction.

**Data extraction and quality evaluation**

The main informations from eligible studies were extracted as follows: first author, publication year, country, cancer type, sample type, sample size (high/low), cut-off value of SNHG15 expression, assay method, survival (OS/RFS/PFS), HR availability, HR (95% CI) with its P value, follow-up months and NOS scores. If survival rates were not obtained from multivariate analysis, the survival HR (95% CI) were indirectly retrieved from K-M curves via Engauge Digitiser software. The quality of enrolled studies was assessed by Newcastle-Ottawa Scale (NOS) with a range from 0 to 9 and a score more than 6 was considered as qualified literature.

**Validation of bioinformatics database**

Gene Expression Profiling Interactive Analysis (GEPIA), which is based on The Cancer Genome Atlas (TCGA), was performed to further verify the abnormal expression of SNHG15 between cancer tissues and match TCGA normal and GTEx data amongst various neoplasms, using p<0.01 as cut-off value. Moreover, survival plots of the correlation between SNHG15 expression and overall survival (OS) and disease-free survival (DFS) were retrieved as Kaplan–Meier (K–M) curves on the basis of different cancer datasets online.

**Statistical analysis**
Stata (Version 12.0) was employed to analyze all the datas extracted from articles included and P value < 0.05 indicated the existence of significant difference. The hazard ratio (HR) and odds ratio (OR) with their corresponding 95% CIs were utilized to analyse the association between SNHG15 expression and prognostic indicators (OS/DFS), clinical features respectively. And when HR/OR > 1 and 95% CI did not include 1 were observed in the results, it implied that patients with promoted SNHG15 expression had the worse prognosis and advanced clinicopathological parameters. Cochran's Q and I² statistics were carried out to measure the heterogeneity across all enrolled studied. A random-effect model was applied with the existence of markedly heterogeneity as I² > 50% and P < 0.10 otherwise adopting the fix-effect model. Begg’s and Egger’s tests were quantitatively conducted for detection of underlying publication bias. Accordingly, sensitivity analysis was used to evaluate the stability of results.

Results

Screening process of publication literatures

The systematically databases search of literatures including initially pertinent publication about the correlation between SNHG15 and cancers in PubMed (n=36), Web of science (n=35), Embase(n=75) and the Cochrane Library(n=0). After originally removing the duplications(n=49), the remained studies(n=97) were browsed for titles and abstracts. 72 studies were removed due to irrelvant topics, reviews, case reports, conference abstracts. Next, 25 full-text articles were assessed for eligibility. Among them, nine were removed owing to only focusing on functional exploration of SNHG15, two were excluded for lacking of prognostic data and three articles were precluded due to unclear group number. Ultimately, 11 articles containing sufficient datas of both survivals and clinical features were enrolled in our meta-analysis. Figure 1 presented the detailed selection process for qualified publications.

Characteristic description of enrolled studies

Eleven studies with a total of 1087 patients were all performed in China and the published year was from 2016 to 2019. With respect to cancer types, three studies explored lung carcinoma including one lung cancer and two NSCLC, others were respectively gastric cancer, hepatocellular carcinoma, renal cell carcinoma, pancreatic ductal adenocarcinoma, breast cancer, papillary thyroid cancer, colorectal cancer, epithelial ovarian cancer. All samples were cancer tissues and adjacent normal tissues and the detection assay was qRT-PCR. Patients were classified as high SNHG15 expression group and low SNHG15 expression group and most studies used median value for cut-off values except one utilizing mean value and one missing. All studies reported overall survival while only two referred to disease-free survival and one mentioned progression-free survival. In terms of HR with 95% CI availability, five studies could obtain from papers directly and the remaining cohorts were retrieved from K-M curves via Engauge Digitiser software. The follow-up time was ranged from 40 to 180 months. The quality of involved studies was assessed by NOS with a range from 6 to 8 scores. The main features of enrolled studies were listed in Table 1.
The association between SNHG15 expression and clinical outcomes

The correlation between SNHG15 expression and clinical features was investigated via calculating the pooled OR with its CI of age, gender, tumor size TNM stage and LNM. The results showed that promoted SNHG15 expression was not significantly related with age (<60 vs ≥60, OR = 0.98, 95% CI: 0.65-1.48, P=0.912, Figure 2(a)), gender (male vs female, OR = 0.95, 95% CI: 0.73-1.25, P=0.728, Figure 2(b)), tumor size (large vs small, OR = 1.88, 95% CI: 0.91-3.89, P=0.087, Figure 2(c)). However, significantly association was observed between increased SNHG15 expression and advanced clinical features including TNM stage (III-IV vs I-II, OR = 3.01, 95% CI: 2.15-4.23, P<0.001, Figure 2(d)) and LNM (positive vs negative, OR = 3.20, 95% CI: 2.30-4.45, P<0.001, Figure 2(e)). Four fix-effect models were adopted for the low heterogeneity (0%-35.7%) and only one random-effect model was employed with a significant heterogeneity of 78.4%. The details were characterized in Table 2.

To further demonstrate whether SNHG15 could act as a prognostic predictor of cancers, we explore the association between elevated SNHG15 expression and survival indicators (OS/DFS). All enrolled studies reported the overall survival and forest plot revealed that the pooled HR and 95% CI was 1.95 (1.53-2.49) using fixed-effect model (I²=0%, p=0.778), suggesting promoted SNHG15 expression indicated worse OS (P<0.001, Figure 3(a)). Similarly, as shown in Figure 3(b), no significant heterogeneity was observed in two studies for DFS (I²=0%, p=0.822), so the fixed-effect model was employed. The pooled result revealed that increased SNHG15 expression emerged to be dramatically associated with unfavorable DFS (HR = 2.31, 95% CI = 1.48-3.61, P<0.001, Figure 3(b)). Because no obvious heterogeneity was observed in the results so we didn't performed subgroup analysis. Additionally, we only conducted publication bias for OS due to only two studies reporting DFS. More detailed informations were integrated in Table 2.

Publication bias and sensitivity analysis for prognosis

The pooled HR for OS and DFS was not influenced after removing any study one by one in sensitivity analysis, which meant the reliability and stability of our results (Figure 4(a-b)). Furthermore, Begg's and Egger's test (P=0.938 and P=0.970) both quantitatively revealed that there was no significant publication bias of OS (Figure 4(c-d)).

Validation of the results in GEPIA database

GEPIA database was utilized to further validate our results. In terms of SNHG15 dysregulation, promoted SNHG15 expression was found in colon adenocarcinoma (COAD), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), kidney renal clear cell carcinoma (KIRC), pancreatic adenocarcinoma (PAAD), rectum adenocarcinoma (READ), testicular germ cell tumors (TGCT), Thymoma (THYM) (Figure 5). Furthermore, increased SNHG15 expression was correlated to unfavourable OS in adrenocortical carcinoma (ACC), kidney renal clear cell carcinoma (KIRC), mesothelioma (MESO), uveal melanoma (UVM) and worse DFS in adrenocortical carcinoma (ACC), prostate adenocarcinoma (PRAD), uveal melanoma (UVM) (log-rank P<0.05) (Figure 6-7). These results certified our conclusions in our paper and indicated that SNHG15 could characterized as a novel prognostic biomarker for cancers.
The Association Between Snhg15 Expression And Clinical Outcomes

The correlation between SNHG15 expression and clinical features was investigated via calculating the pooled OR with its CI of age, gender, tumor size TNM stage and LNM. The results showed that promoted SNHG15 expression was not significantly related with age(< 60 vs ≥ 60, OR = 0.98, 95% CI: 0.65–1.48, P = 0.912, Fig. 2(a)), gender (male vs female, OR = 0.95, 95% CI: 0.73–1.25, P = 0.728, Fig. 2(b)), tumor size (large vs small, OR = 1.88, 95% CI: 0.91–3.89, P = 0.087, Fig. 2(c)). However, significantly association was observed between increased SNHG15 expression and advanced clinical features including TNM stage (III-IV vs I-II, OR = 3.01, 95% CI: 2.15–4.23, P < 0.001, Fig. 2(d)) and LNM (positive vs negative, OR = 3.20, 95% CI: 2.30–4.45, P < 0.001, Fig. 2(e)). Four fix-effect models were adopted for the low heterogeneity (0%-35.7%) and only one random-effect model was employed with a significant heterogeneity of 78.4%. The details were characterized in Table 2.
Table 2
Results of the association between SNHG15 and clinicopathological outcomes

| Outcome                          | Studies (n) | OR     | 95% CI     | P value | Model | Chi2 | I2  | P Value |
|----------------------------------|-------------|--------|------------|---------|-------|------|-----|---------|
| Age (< 60 vs ≥ 60)               | 4           | 0.98   | 0.65–1.48  | 0.912   | Fixed | 1.84 | 0%  | 0.607   |
| Gender (male vs female)          | 9           | 0.95   | 0.73–1.25  | 0.728   | Fixed | 12.44| 35.7%| 0.133   |
| TNM stage (III-IV vs I-II)       | 6           | 3.01   | 2.15–4.23  | 0.000   | Fixed | 2.76 | 0%  | 0.737   |
| Lymph node metastasis (positive vs negative) | 8           | 3.20   | 2.30–4.45  | 0.000   | Fixed | 3.20 | 0%  | 0.866   |
| Tumor size (large vs small)      | 7           | 1.88   | 0.91–3.89  | 0.087   | Random| 27.76| 78.4%| 0.000   |
| Overall survival                 | 11          | 1.95   | 1.53–2.49  | 0.000   | Fixed | 6.43 | 0%  | 0.778   |
| Disease-free survival            | 2           | 2.31   | 1.48–3.61  | 0.000   | Fixed | 0.05 | 0%  | 0.822   |

To further demonstrate whether SNHG15 could act as a prognostic predictor of cancers, we explore the association between elevated SNHG15 expression and survival indicators (OS/DFS). All enrolled studies reported the overall survival and forest plot revealed that the pooled HR and 95% CI was 1.95 (1.53–2.49) using fixed-effect model (I² = 0%, p = 0.778), suggesting promoted SNHG15 expression indicated worse OS (P < 0.001, Fig. 3(a)). Similarly, as shown in Fig. 3(b), no significant heterogeneity was observed in two studies for DFS (I² = 0%, p = 0.822), so the fixed-effect model was employed. The pooled result revealed that increased SNHG15 expression emerged to be dramatically associated with unfavorable DFS (HR = 2.31, 95% CI = 1.48–3.61, P < 0.001, Fig. 3(b)). Because no obvious heterogeneity was observed in the results so we didn't performed subgroup analysis. Additionally, we only conducted publication bias for OS due to only two studies reporting DFS. More detailed informations were integrated in Table 2.
Discussion

LncRNAs were primitively acknowledged as “transcriptional noise” or “junk DNA” and did not draw investigators’ attention in the last few decades[32]. However, research results suggest that aberrant IncRNAs expression may emerge tumor promoting or suppressing efficacy leading to carcinogenesis and cancer progression owing to next-generation genome wide sequencing and microarray widely applying in clinic in recent years[33, 34]. For instance, some IncRNAs like NOC2L-4.1, TUG1, MALAT1 are well established as tumor promoters[35-37], while other IncRNAs including ASMTL-AS1,LINC02381 LINC02499 could inhibit tumor progression[38-40].

SNHG15, a new promising cancer-related IncRNA, has been proved upregulated in diverse malignant tumors. Ma et al demonstrated its elevated expression was significantly related to tumor size, TNM stage and lymph node metastasis of pancreatic cancer patients[41]. But the definite prognostic role of this gene was not inconclusive. In our meta-analysis, we investigated the potential association between SNHG15 expression and prognostic attributes and clinicopathological parameters by integrating the data of 11 studies. It was identified that promoted SNHG15 expression enhanced the risk of shorter OS as well as DFS with no conspicuous heterogeneity. Simultaneously, we demonstrated that patients with increased SNHG15 expression were more likely to develop advanced TNM stage and positive lymphnode metastasis while these possibilities were not observed in age, gender and tumor size. Additional, no evident publication bias of OS was noticed throughout the study and the robustness of the results was verified via sensitivity analysis. Furthermore, the validation of TCGA datasets showed that high SNHG15 expression level was observed in COAD,DLBC,KIRC,PAAD,READ,TGCT and THYM. With respect to prognosis, promoted SNHG15 expression was indicated shorter OS in ACC,KIRC,MESO,UVM compared with decreased SNHG15 expression. Moreover, survival plots revealed that patients with SNHG15 upregulation had worse DFS in ACC,PRAD and UVM. Taken together, all these results intensely proofed SNHG15 could act as a biological modulator and novel biomarker of cancer patients with poor prognosis.

Accordingly, the potential molecular modulation participated in the tumor progression may be through investigate to better understand the interaction between altered SNHG15 expression and poor prognosis (Table 3). In gastric cancer, SNHG15 upregulation promoted cell proliferation and invasion via modulating the expression of MMP2/MMP9[21]. In terms of lung cancer, the research of Cui et al reported that promoted SNHG15 expression enhanced tumor occurrence and development by targeting miRNA-211-3p via regulating proliferation and migration in vitro[23]. Similarly in non-small cell lung cancer, two studies demonstrated that knockdown of SNHG15 could suppress tumorigenesis via inhibiting the expression of EMT,MMP2,MMP9 and regulating the miR-486/CDK14 axis[24, 25]. Meanwhile, Du et al identified that SNHG15 facilitated renal cell carcinoma invasion and migration through involving NF-κB signaling pathway and inducing EMT process[26]. With respect to breast cancer, Kong et al acknowledged that SNHG15 served as a ceRNA to sponge miR-211-3p contributing to the promotion of proliferation, migration and invasion and the inhibition of apoptosis[28]. Besides, SNHG15 acted as a ceRNA to modulate miR-200a-3p/YAP1-Hippo molecular mechanism in papillary thyroid carcinoma according to the study of Wu et al[29]. Consistently, function assays revealed that upregulation of SNHG15 facilitated
migration, invasion, proliferation, and chemoresistance of epithelial ovarian cancer[31]. However, the thorough investigation of the signaling pathways were still insufficient in HCC, PDAC and colorectal cancer so more studies should be performed to explore the potential mechanisms of SNHG15 expression in predicting survival in diverse malignancies[22, 27, 30]

Several highlights should be mentioned in our paper, Firstly, our meta-analysis was the first study exhaustively investigated the association between SNHG15 expression and clinical outcomes so far. Secondly, only one random-effect model was employed in most of our analysis so the results were quite credible and accurate. Thirdly, we formulated the rigorous inclusion and exclusion criteria to select the enrolled studies for the high-quality of literatures.

Nonetheless, few limitations which should be taken into consideration still exist in our study. First, the region of included subjects were all from China with the small cases of cancer types and sample size, which led to our results only applying in Asia. So we further validated these results via GEPIA database to support our conclusion as far as possible. Second, HR with its 95% CIs were retrieved from K-M curves in six studies which may inevitably exaggerate the prognostic value of SNHG15 and produce bias. Third, lack of articles with negative results may overestimate the clinical value of this gene. Fourth, the inconsistent cut-off values may introduce heterogeneity amongst the studies.

Conclusions

Taken together, in spite of above limitations, our study initial indicated that promoted SNHG15 expression was significantly associated with unfavorable prognosis and advanced clinical features. However, high-quality researches with standardized methods and larger sample size from different country are still in need to further certify our results.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All datas are included in our paper.

Competing interests

The authors declare no potential conflicts of interest.
Funding

The authors declare that our study is not supported by any fundings.

Author Contributions

WZ designed the concept of study. YL collected and analyzed the data. CZC wrote the manuscript and arranged the tables and figures; JJW and YQF revised the paper. All authors reviewed and approved the final manuscript.

Acknowledgements

We are grateful to all researchers of enrolled studies.

References

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2020. CA Cancer J Clin 2020, 70(1):7-30.
2. Siegel RL, Miller KD, Jemal A: Cancer Statistics, 2017. CA Cancer J Clin 2017, 67(1):7-30.
3. Zhang Y, Tao Y, Liao Q: Long noncoding RNA: a crosslink in biological regulatory network. Brief Bioinform 2018, 19(5):930-945.
4. Geisler S, Coller J: RNA in unexpected places: long non-coding RNA functions in diverse cellular contexts. Nat Rev Mol Cell Biol 2013, 14(11):699-712.
5. Chen X, Yan CC, Zhang X, You ZH: Long non-coding RNAs and complex diseases: from experimental results to computational models. Brief Bioinform 2017, 18(4):558-576.
6. Zhao S, Zhu H, Jiao R, Wu X, Ji G, Zhang X: Prognostic and clinicopathological significance of SNHG6 in human cancers: a meta-analysis. BMC Cancer 2020, 20(1):77.
7. Wang H, Liu Y, Tang A: Prognostic Values of Long Noncoding RNA linc00152 in Various Carcinomas: An Updated Systematic Review and Meta-Analysis. Oncologist 2020, 25(1):e31-e38.
8. Ren X, He J, Qi L, Li S, Zhang C, Duan Z, Wang W, Tu C, Li Z: Prognostic and clinicopathologic significance of long non-coding RNA opa-interacting protein 5-antisense RNA 1 in multiple human cancers. Artificial cells, nanomedicine, and biotechnology 2020, 48(1):353-361.
9. Tani H, Torimura M: Identification of short-lived long non-coding RNAs as surrogate indicators for chemical stress response. Biochemical and biophysical research communications 2013, 439(4):547-551.
10. Ma Y, Xue Y, Liu X, Qu C, Cai H, Wang P, Li Z, Li Z, Liu Y: SNHG15 affects the growth of glioma microvascular endothelial cells by negatively regulating miR-153. Oncology reports 2017, 38(5):3265-3277.
11. Mi H, Wang X, Wang F, Li L, Zhu M, Wang N, Xiong Y, Gu Y: SNHG15 Contributes To Cisplatin Resistance In Breast Cancer Through Sponging miR-381. OncoTargets and therapy 2020, 13:657-666.
12. Liu K, Hou Y, Liu Y, Zheng J: LncRNA SNHG15 contributes to proliferation, invasion and autophagy in osteosarcoma cells by sponging miR-141. *Journal of biomedical science* 2017, 24(1):46.

13. Ye J, Tan L, Fu Y, Xu H, Wen L, Deng Y, Liu K: LncRNA SNHG15 promotes hepatocellular carcinoma progression by sponging miR-141-3p. *Journal of cellular biochemistry* 2019, 120(12):19775-19783.

14. Li Z, Zhang J, Zheng H, Li C, Xiong J, Wang W, Bao H, Jin H, Liang P: Modulating IncRNA SNHG15/CDK6/miR-627 circuit by palbociclib, overcomes temozolomide resistance and reduces M2-polarization of glioma associated microglia in glioblastoma multiforme. *Journal of experimental & clinical cancer research: CR* 2019, 38(1):380.

15. Sun X, Bai Y, Yang C, Hu S, Hou Z, Wang G: Long noncoding RNA SNHG15 enhances the development of colorectal carcinoma via functioning as a ceRNA through miR-141/SIRT1/Wnt/beta-catenin axis. *Artificial cells, nanomedicine, and biotechnology* 2019, 47(1):2536-2544.

16. Zhang Y, Zhang D, Lv J, Wang S, Zhang Q: LncRNA SNHG15 acts as an oncogene in prostate cancer by regulating miR-338-3p/FKBP1A axis. *Gene* 2019, 705:44-50.

17. Li M, Bian Z, Jin G, Zhang J, Yao S, Feng Y, Wang X, Yin Y, Fei B, You Q et al: LncRNA-SNHG15 enhances cell proliferation in colorectal cancer by inhibiting miR-338-3p. *Cancer medicine* 2019, 8(5):2404-2413.

18. Saeinasab M, Bahrami AR, Gonzalez J, Marchese FP, Martinez D, Mowla SJ, Matin MM, Huarte M: SNHG15 is a bifunctional MYC-regulated noncoding locus encoding a lncRNA that promotes cell proliferation, invasion and drug resistance in colorectal cancer by interacting with AIF. *Journal of experimental & clinical cancer research: CR* 2019, 38(1):172.

19. Jiang H, Li T, Qu Y, Wang X, Li B, Song J, Sun X, Tang Y, Wan J, Yu Y et al: Long non-coding RNA SNHG15 interacts with and stabilizes transcription factor Slug and promotes colon cancer progression. *Cancer letters* 2018, 425:78-87.

20. Liu Y, Li J, Li F, Li M, Shao Y, Wu L: SNHG15 functions as a tumor suppressor in thyroid cancer. *Journal of cellular biochemistry* 2019, 120(4):6120-6126.

21. Chen SX, Yin JF, Lin BC, Su HF, Zheng Z, Xie CY, Fei ZH: Upregulated expression of long noncoding RNA SNHG15 promotes cell proliferation and invasion through regulates MMP2/MMP9 in patients with GC. *Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine* 2016, 37(5):6801-6812.

22. Zhang JH WH, Yang HG.: Long Noncoding RNA SNHG15, a Potential Prognostic Biomarker for Hepatocellular Carcinoma. *Eur Rev Med Pharmacol Sci* 2016, 20(9):1720-1724.

23. Cui HX ZM, Liu K, Liu J, Zhang ZL, Fu L.: LncRNA SNHG15 Promotes Proliferation and Migration of Lung Cancer via Targeting microRNA-211-3p. *Eur Rev Med Pharmacol Sci* 2018, 22(20):6838-6844.

24. Dong YZ MX, Li GS.: Long non-coding RNA SNHG15 indicates poor prognosis of non-small cell lung cancer and promotes cell proliferation and invasion. *Eur Rev Med Pharmacol Sci* 2018, 22(9):2671-2679.

25. Jin B, Jin H, Wu HB, Xu JJ, Li B: Long non-coding RNA SNHG15 promotes CDK14 expression via miR-486 to accelerate non-small cell lung cancer cells progression and metastasis. *Journal of cellular
26. Du Y, Kong C, Zhu Y, Yu M, Li Z, Bi J, Li Z, Liu X, Zhang Z, Yu X: Knockdown of SNHG15 suppresses renal cell carcinoma proliferation and EMT by regulating the NF-kappaB signaling pathway. *International journal of oncology* 2018, 53(1):384-394.

27. Guo XB, Wang JY.: Evaluating the diagnostic and prognostic value of long non-coding RNA SNHG15 in pancreatic ductal adenocarcinoma. *Eur Rev Med Pharmacol Sci* 2018, 22(18):5892-5898.

28. Kong Q, Qiu M: Long noncoding RNA SNHG15 promotes human breast cancer proliferation, migration and invasion by sponging miR-211-3p. *Biochemical and biophysical research communications* 2018, 495(2):1594-1600.

29. Wu DM, Wang S, Wen X, Han XR, Wang YJ, Shen M, Fan SH, Zhang ZF, Shan Q, Li MQ et al: LncRNA SNHG15 acts as a ceRNA to regulate YAP1-Hippo signaling pathway by sponging miR-200a-3p in papillary thyroid carcinoma. *Cell death & disease* 2018, 9(10):947.

30. Huang L, Lin H, Kang L, Huang P, Huang J, Cai J, Xian Z, Zhu P, Huang M, Wang L et al: Aberrant expression of long noncoding RNA SNHG15 correlates with liver metastasis and poor survival in colorectal cancer. *Journal of cellular physiology* 2019, 234(5):7032-7039.

31. Qu C, Dai C, Guo Y, Qin R, Liu J: Long noncoding RNA SNHG15 serves as an oncogene and predicts poor prognosis in epithelial ovarian cancer. *OncoTargets and therapy* 2019, 12:101-111.

32. Adams BD, Parsons C, Walker L, Zhang WC, Slack FJ: Targeting noncoding RNAs in disease. *J Clin Invest* 2017, 127(3):761-771.

33. Muller S, Raulefs S, Bruns P, Afonso-Grunz F, Plotner A, Themann R, Jager C, Schlitter AM, Kong B, Regel I et al: Next-generation sequencing reveals novel differentially regulated mRNAs, lncRNAs, miRNAs, sdRNAs and a piRNA in pancreatic cancer. *Mol Cancer* 2015, 14:94.

34. Serrati S, De Summa S, Pilato B, Petriella D, Lacalamita R, Tommasi S, Pinto R: Next-generation sequencing: advances and applications in cancer diagnosis. *OncoTargets and therapy* 2016, 9:7355-7365.

35. Wang Q, Ding J, Nan G, Lyu Y, Ni G: LncRNA NOC2L-4.1 functions as a tumor oncogene in cervical cancer progression by regulating the miR-630/YAP1 pathway. *Journal of cellular biochemistry* 2019, 120(10):16913-16920.

36. Lei H, Gao Y, Xu X: LncRNA TUG1 influences papillary thyroid cancer cell proliferation, migration and EMT formation through targeting miR-145. *Acta Biochim Biophys Sin (Shanghai)* 2017, 49(7):588-597.

37. Wu L, Wang X, Guo Y: Long non-coding RNA MALAT1 is upregulated and involved in cell proliferation, migration and apoptosis in ovarian cancer. *Exp Ther Med* 2017, 13(6):3055-3060.

38. Feng Z, Chen R, Huang N, Luo C: Long non-coding RNA ASMTL-AS1 inhibits tumor growth and glycolysis by regulating the miR-93-3p/miR-660/FOXO1 axis in papillary thyroid carcinoma. *Life Sci* 2020, 244:117298.

39. Jafarzadeh M, Soltani BM, Soleimani M, Hosseinkhani S: Epigenetically silenced LINC02381 functions as a tumor suppressor by regulating PI3K-Akt signaling pathway. *Biochimie* 2020, 171-
40. Ma X, Mo M, Tan HJJ, Tan C, Zeng X, Zhang G, Huang D, Liang J, Liu S, Qiu X: LINC02499, a novel liver-specific long non-coding RNA with potential diagnostic and prognostic value, inhibits hepatocellular carcinoma cell proliferation, migration, and invasion. *Hepatol Res* 2020.

41. Ma Z HH, Wang J, Zhou Y, Pu F, Zhao Q, Peng P, Hui B, Ji H, Wang K: Long Non-Coding RNA SNHG15 Inhibits P15 and KLF2 Expression to Promote Pancreatic Cancer Proliferation Through EZH2-mediated H3K27me3. *Oncotarget* 2017, 8(48):84153-84167.

**Tables**

Table 1 Characteristics of the included studies
| First author | Year | Country | Cancer type | Sample tissue | Sample size (high/low) | Cut-off value | Method | Survival | HR availability | HR (95% CI) | P value | Follow-up months | NOS |
|--------------|------|---------|-------------|---------------|------------------------|--------------|--------|----------|----------------|-------------|---------|----------------|-----|
| Chen         | 2016 | China   | gastric cancer | 106 (53/53) | Median qRT-PCR | OS/DFS | reported | 2.92 (1.304–6.575) | 0.009 | 40 | 8 |
| Zhang        | 2016 | China   | HCC tissue | 152 (77/75) | Median qRT-PCR | OS | reported | 2.24 (1.331–6.255) | 0.001 | 70 | 7 |
| Cui          | 2018 | China   | lung cancer | 55 (27/28) | NM qRT-PCR | OS | reported | 2.23 (1.033–4.829) | 0.041 | 80 | 7 |
| Dong         | 2018 | China   | NSCLC tissue | 49 (23/26) | Mean qRT-PCR | OS/DFS K-M curve | 1.87 (0.840–4.200) | 0.125 | 120 | 7 |
|              |      |         |             |               |            |     |         | 2.15 (1.010–4.590) |         | 80 |     |    |
| Study  | Year | Country | Tissue Type | Median qRT-PCR | OS | K-M curve |
|--------|------|---------|-------------|----------------|----|-----------|
| Du     | 2018 | China   | RCC tissue  | 96(48/48)      | Med | 1.02      |
| Guo    | 2018 | China   | PDA tissue  | 171(82/89)     | Med | 3.25      |
| Jin    | 2018 | China   | NSCLC tissue| 35(20/15)      | Med | 1.41      |
| Kong   | 2018 | China   | Breast cancer| 58(29/29)   | Med | 2.12      |
| Wu     | 2018 | China   | PTC tissue  | 92(50/42)      | Med | 1.08      |
| Huang  | 2019 | China   | Colorectal cancer | 91(46/45) | Med | 2.73      |

Note: OS refers to Overall Survival, and K-M curve represents the Kaplan-Meier survival curve.
### Table 2 Results of the association between SNHG15 and clinicopathological outcomes

| Qu  | China | EOC tissue | 182 (73/109) Mean qRT-PCR OS/PFS K-M curve | 1.91 (1.210-3.040) 0.00 6/ |
|-----|-------|------------|---------------------------------------------|-----------------------------|
| 2019|       |            |                                             |                             |

HCC: hepatocellular carcinoma; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; PDAC: pancreatic ductal adenocarcinoma; PTC: papillary thyroid cancer; EOC: epithelial ovarian cancer; NM: not mention; OS: overall survival; DFS: disease-free survival; PFS: progression-free survival; K-M curve: Kaplan–Meier curve; qRT-PCR: quantitative real time polymerase chain reaction; NOS: Newcastle-Ottawa Scale.
### Table 3 Summary of SNHG15 with their aberrant expression, biological functions, and related signaling pathways.

| Outcome                                                 | Studies (n) | OR    | 95% CI    | P value | Model  | Chi²  | I²   | P Value |
|---------------------------------------------------------|-------------|-------|-----------|---------|--------|-------|------|---------|
| Age (<60 vs ≥60)                                        | 4           | 0.98  | 0.65-1.48 | 0.912   | Fixed  | 1.84  | 0%   | 0.607   |
| Gender (male vs female)                                 | 9           | 0.95  | 0.73-1.25 | 0.728   | Fixed  | 12.44 | 35.7%| 0.133   |
| TNM stage (III-IV vs I-II)                              | 6           | 3.01  | 2.15-4.23 | 0.000   | Fixed  | 2.76  | 0%   | 0.737   |
| Lymph node metastasis (positive vs negative)            | 8           | 3.20  | 2.30-4.45 | 0.000   | Fixed  | 3.20  | 0%   | 0.866   |
| Tumor size (large vs small)                             | 7           | 1.88  | 0.91-3.89 | 0.087   | Random | 27.76 | 78.4%| 0.000   |
| Overall survival                                        | 11          | 1.95  | 1.53-2.49 | 0.000   | Fixed  | 6.43  | 0%   | 0.778   |
| Disease-free survival                                   | 2           | 2.31  | 1.48-3.61 | 0.000   | Fixed  | 0.05  | 0%   | 0.822   |
| Study   | Cancer                      | Expression | biological functions                                                                 | related signaling pathways          |
|---------|-----------------------------|------------|--------------------------------------------------------------------------------------|-------------------------------------|
| Chen2016 | gastric cancer              | upregulation | promote cell proliferation and invasion, inhibit apoptosis                              | MMP2/MMP9                           |
| Cui2018  | lung cancer                 | upregulation | promote cell proliferation, invasion                                                  | microRNA-211-3p                      |
| Dong2018 | non-small cell lung cancer  | upregulation | promote cell proliferation, invasion and metastasis, inhibit apoptosis.                | EMT/MMP2/MMP9                        |
| Du2018   | renal cell carcinoma        | upregulation | promote cell proliferation, invasion and migration                                     | EMT/NF-κB                           |
| Jin2018  | non-small cell lung cancer  | upregulation | promote cell proliferation, induce apoptosis and cycle arrest at G0/G1 phase          | miR-486/CDK14                       |
| Kong2018 | breast cancer               | upregulation | promote cell proliferation, migration, invasion and induce apoptosis                   | miR-211-3p/EMT                       |
| Wu2018   | papillary thyroid cancer    | upregulation | promote cell growth and migration                                                     | miR-200a-3p/YAP1-Hippo               |
| Qu2019   | epithelial ovarian cancer   | upregulation | promote cell migration, invasion, proliferation and                                   |                                     |
Figures

Figure 1

Flow diagram of this meta-analysis.
Figure 2

Forest plots evaluating the association between SNHG15 expression and clinical features. (a) age, (b) gender, (c) tumor size, (d) TNM stage, (e) lymph node metastasis.
Figure 3

Forest plots assessing the association between SNHG15 expression and prognosis. (a) overall survival (OS), (b) disease-free survival (DFS).
Figure 4

Forest plots of sensitivity analysis and publication bias. (a) sensitivity analysis for OS, (b) sensitivity analysis for DFS; (c) Begg’s test of OS; (d) Egger’s test of OS.

Figure 5

SNHG15 expression in seven types of cancer vs. normal tissue. “*” Log2FC > 1 and P < 0.01. Abbreviations: COAD: Colon Adenocarcinoma; DLBC: Lymphoid Neoplasm Diffuse Large B-cell Lymphoma; KIRC: Kidney Renal Clear Cell Carcinoma; PAAD: Pancreatic Adenocarcinoma; READ: Rectum Adenocarcinoma; TGCT: Testicular Germ Cell Tumors; THYM: Thymoma.
Figure 6

Verification of the prognostic value of SNHG15 based the TCGA database. (a) OS plots of SNHG15 in ACC. (b) OS plots of SNHG15 in KIRC. (c) OS plots of SNHG15 in MESO. (d) OS plots of SNHG15 in UVM. Abbreviations: TCGA: The Cancer Genome Atlas; ACC: Adenocarcinoma; Carcinoma; KIRC: Kidney Renal Clear Cell Carcinoma; MESO: Mesothelioma; UVM: Uveal Melanoma.
Figure 7
Validation of the prognostic value of SNHG15 based the TCGA database. (a) DFS plots of SNHG15 in ACC. (b) DFS plots of SNHG15 in PRAD. (c) DFS plots of SNHG15 in UVM. Abbreviations: TCGA: The Cancer Genome Atlas; ACC: Adrenocortical Carcinoma; PRAD: Prostate Adenocarcinoma; UVM: Uveal Melanoma.