The Prognostic Value of lncRNA SNHG3 in Cancer Patients: A meta-analysis

Jie Wang

The First People's Hospital of NeiJiang

Pingyong Zhong

The First People's Hospital of NeiJiang

Hao Hua (✉ 529065285@qq.com)

The First People's Hospital of NeiJiang <https://orcid.org/0000-0003-4560-9656>

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Abstract

Background: Small nucleolar RNA host gene 3 (SNHG3) is a promising long non-coding RNA that may possess prognostic value for different types of tumors. The objective of this meta-analysis is to evaluate the prognostic value of lncRNA SNHG3 in cancer patients.

Methods: A systematic literature search of the PubMed, Cochrane Library, EMBASE, Medline, Web of Science, CNKI, Weipu, and Wanfang electronic databases was carried out in this meta-analysis. The synthetic hazard ratios (HRs) or odd ratios (ORs) with 95% confidence intervals (CIs) were obtained to determine the prognostic and clinicopathological significance of SNHG3 expression in tumors.

Results: The final meta-analysis included 17 studies that contained 2072 patients. The pooled results provided evidence that SNHG3 overexpression predicted reduced overall survival (OS) (HR=2.15, 95%CI: 1.76–2.63, $P<0.00001$), recurrence-free survival (RFS) (HR=2.22, 95%CI: 1.04–4.76, $P=0.04$) and disease-free survival (DFS) (HR=2.04, 95%CI: 1.35–3.09, $P=0.0007$) for various cancers. Additionally, the SNHG3 overexpression was concerned with tumor node metastasis (TNM) stage (III/IV vs. I/II, OR=2.91, 95%CI: 1.60–5.29, $P=0.0005$), lymph node metastasis (LNM) (positive vs negative, OR=5.00, 95%CI: 2.82–8.87, $P<0.00001$), distant metastasis (DM) (positive vs negative, OR=2.29, 95%CI: 1.52–3.47, $P<0.0001$) and tumor size (larger vs smaller, OR=1.80, 95%CI: 1.04–3.11, $P=0.04$).

Conclusions: Our results indicated that SNHG3 overexpression was closely correlated with shorter OS in multiple cancer types, suggesting that SNHG3 might function as a promising predictor for clinical outcomes in cancer.

Background

Cancer from various systems and organs are one of the disease that poses a great threat to human health globally[1]. A substantial majority of cancers have the characteristics of occult onset, difficult diagnosis, and rapid progression, which are the major causes of the high rate of mortality. Meanwhile, tumors of different origins are not the same in terms of biological features, lesion involvement, clinical manifestations, efficacy, and prognosis[2]. Recently, multi-disciplinary treatment mode, a fixed expert group composed of multi-disciplinary experts, having been proposing appropriate treatment schemes for cancer patients [3]. Despite proper management of their disease, the prognosis for many cancer patients is still dismal, partly due to the lack of prognostic and diagnostic markers. Thus, it is necessary to identify effective prognostic markers that can provide urgently needed treatment strategies.

Non-coding RNA refers to RNA that is not translated into polypeptides [4]. These RNA can be divided into two categories based on length: small non-coding RNAs that are shorter than 200 nucleotides and long non-coding RNAs that are longer than 200 nucleotides [5]. LncRNAs have recently garnered more attention in the medical community for their potential prognostic value in cancer. Additionally, the relationship between lncRNAs, signal pathways in cancer, and cancer phenotypes has become a topical issues [6]. Previous studies identified the pivotal role of lncRNAs in biological processes, such as genomic

imprinting, histone modification, chromatin remodeling, and posttranscriptional regulation [7]. In recent years, lncRNAs have also been shown to be involved in tumor occurrence and progression. Moreover, it was reported that dysregulation of lncRNAs was significantly correlated with clinical characteristics and cancer prognosis. These data suggest that lncRNAs are novel biomarkers and therapeutic targets in cancer [8].

Small nucleolar RNA host gene 3 (SNHG3), a component of lncRNAs, has recently been investigated for its involvement in promoting cancer deterioration and progression, and the dysregulation of SNHG3 has been detected in different types of cancer [9, 10]. It has been reported that upregulated SNHG3 expression can induce specific biological phenotypes and poor prognosis [11]. Subsequently, another study demonstrated that increased SNHG3 expression played a vital role in promoting tumor cell proliferation and invasion, which was indicative of poor prognosis for cancer patients [12]. To date, there is no meta-analysis that provides an assessment of the effect of SNHG3 on the prognosis of cancer patients. Therefore, our aim was to evaluate the prognostic value of lncRNA SNHG3 expression in tumors.

Methods

Literature search

Two independent reviewers searched the PubMed, Cochrane Library, EMBASE, Medline, Web of Science, CNKI, Weipu, and Wanfang until June 4, 2020. The search was conducted irrespective of the region or language. The following keywords and Medical Subject Headings (MeSH) were included: "SNHG3", "Small nucleolar RNA host gene 3", "lncRNA", "long noncoding RNA", "cancer", "carcinoma", "neoplasm", "prognosis" and "survival".

The following criteria for inclusion in our meta-analysis to select eligible studies: (1) a definite diagnosis or histopathological diagnosis of cancer patients; (2) information about survival and clinical prognostic parameters of lncRNA SNHG3 in patients with cancer was reported; and (3) enough information were available for calculating the pooled hazard risk (HR) and 95% confidence interval (CI). exclusion criteria for the studies were as follows: (1) studies with absent information of prognostic outcomes; (2) duplicate publications; and (3) non-human studies, letters, case reports, review articles and other studies without original data.

Data Extraction And Quality Assessment

Data were extracted from each study by three authors independently and a consensus was reached. The following information was extracted: author, country, publication year, tumor type, cancer size, follow-up time, detection method and cut-off value. Patient number for each group was divided on the basis of the positive or negative lymph node metastasis, distant metastasis, tumor size, TNM stage, and patient number for high or low SNHG3 expression in each group.

When only Kaplan-Meier curves were available, HRs and 95% CIs were extracted from graphical survival plots by using Engauge Digitizer V4.1 (<https://sourceforge.net/projects/digitizer/>) [13]. If reported directly

in univariate or multivariate analyses, HRs with corresponding 95% CIs were extracted from multivariate analyses.

A quality assessment for all of the included studies depended on The Newcastle–Ottawa Quality Assessment Scale (NOS), which is composed of the following 3 dimensions: selection, comparability and exposure. Each study was scored from 0–9 according to these dimensions. A study with a NOS score ≥ 6 was considered to be of high quality [14].

Statistical Analyses

All statistical analyses of the data were calculated using Review Manager (RevMan) 5.3 software and Stata version 12.0 (Stata Corporation, College Station, TX, USA). Sensitivity analysis was performed by omitting literatures one by one to determine whether the results were stable and the publication bias of this meta analysis was evaluated by using the Beggs test according to Stata 12 software. The *Q* test and *I*² statistics were applied to estimate the heterogeneity of results. A fixed-effects model was choiced when *I*² < 50% was observed. The synthetic estimate was calculated depending on the random-effects model when the heterogeneity was obvious (*I*² > 50%). A two-tailed *p* value < 0.05 was considered as statistically significant.

Results

Literature search and selection

The literature selection process is shown in Fig. 1. Preliminarily, 151 relevant studies in total were yielded from the search of the PubMed, Cochrane Library, EMBASE, CNKI, Weipu, and Wanfang electronic databases. Among these, 89 studies were excluded as duplicate articles. Then we further excluded 34 studies by reviewing the title and, abstract. Subsequently, 11 more studies were not able to be included because of insufficient data and being unrelated to our study. Finally, 17 studies containing 1788 patients were eligible for this meta analysis and were highly consistent with the inclusion criteria. All of the included studies were published between 2017 and 2020 and came from China. Multiple forms of cancers were analyzed in the present meta-analysis, including gastric cancer [15], ovarian cancer [16], glioma [17, 18], colorectal cancer [19, 20], hepatocellular carcinoma [21, 22], breast cancer [23], renal cell carcinoma [24], osteosarcoma [11, 12], lung cancer [9, 25], acute myeloid leukemia [26], papillary thyroid carcinoma [27, 28]. The detailed information obtained from the studies is summarized in table 1.

Table1: The main characteristics of the included studies in the meta-analysis.

Study	Region	Tumor type	Sample size	TNM stage	SNHG3 expression		Cut-off Value	Detection Method	Outcome Measure	NOS
					high	low				
Xuan, et al 2019 ^[14]	China	GC	60	I-IV	30	30	Median	qRT-PCR	OS	5
Tian, et al 2019 ^[20]	China	ICC	52	I-IV	27	25	Median	qRT-PCR	OS	7
Shi, et al 2019 ^[24]	China	LC	32	I-IV	16	16	Median	qRT-PCR	OS	7
Zhang, et al 2019 ^[23]	China	KIRP	524	I-IV	262	262	Median	qRT-PCR	OS, DFS	7
Zeng, et al 2019 ^[11]	China	OS	54	I-IV	27	27	Median	qRT-PCR	OS	5
Chen, et al 2019 ^[12]	China	OS	126	I-IV	24	102	Median	qRT-PCR	OS	7
Liu, et al 2018 ^[9]	China	LC	120	I-IV	60	60	Median	qRT-PCR	OS	6
Huang, et al 2017 ^[18]	China	CRC	456	I-IV	117	339	Median	qRT-PCR	OS	7
Luo, et al 2018 ^[16]	China	glioma	70	I-IV	42	28	Median	qRT-PCR	OS, DFS	6
Wang, et al 2018 ^[22]	China	BRCA	74	I-IV	22	52	Median	qRT-PCR	NA	7
Sui, et al 2019 ^[26]	China	PTC	42	I-IV	24	18	Median	qRT-PCR	NA	7
Zhang, et al 2016 ^[21]	China	HCC	144	I-IV	91	53	Median	qRT-PCR	OS, DFS	7
Peng, et al 2018 ^[25]	China	AML	62	I-IV	32	30	Median	qRT-PCR	OS,	6
Fei, et al 2018 ^[17]	China	glioma	60	I-IV	30	30	Median	qRT-PCR	OS	7
Wen, et al 2020 ^[19]	China	CRC	58	I-IV	32	26	Median	qRT-PCR	OS	7
Duan, et al 2020 ^[27]	China	PTC	62	I-IV	24	38	Median	qRT-PCR	OS, RFS	5
Hong, et al 2018 ^[15]	China	OC	76	I-IV	40	36	Median	qRT-PCR	OS	7

NA, not available; DFS, disease-free survival; OS, overall survival; RFS, recurrence-free survival; GC, gastric cancer; KIRP, Kidney renal papillary cell carcinoma; OC, ovarian cancer; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; BRCA, breast cancer; LC, lung cancer; PTCs, papillary thyroid carcinoma; OS, osteosarcoma; AML, acute myeloid leukemia

SNHG3 expression highly correlated with OS, RFS and DFS

Overall, 15 of the 17 studies investigated cancer prognosis. A total of 2072 patients were assessed for the HR and 95% CI of OS. The random-effects model was performed to analyze the pooled HR and its 95% CI depended on no obvious heterogeneity ($P = 0.01, I^2 = 51\%$). We further elucidated the relationship between SNHG3 expression and the overall survival, as illustrated in Fig. 2. The pooled results revealed that the high expression of SNHG3 was related to poor prognosis of cancers (HR = 2.15, 95%CI: 1.76–2.63, $P < 0.00001$, Fig. 2A). In the subgroup analysis stratified by tumor type, we found that elevated SNHG3 could act as a prognostic predictor for patients with digestive system tumors (HR = 2.34, 95%CI: 1.53–3.57, $P = 0.003$) or patients with non-digestive system tumors (HR = 1.95, 95%CI: 2.43–2.67, $P = 0.0002$, Fig. 2B). Thus, the prognosis of cancer patients with SNHG3 overexpression was worse than those with low expression of SNHG3. In terms of DFS, only 3 studies were included, and the pooled results indicated that patients with high expression of SNHG3 had poor DFS (HR = 2.04, 95%CI: 1.35–3.09, $P = 0.0007$, Fig. 3A), Only one focus on the relationship between SNHG3 and tumor recurrence (HR = 2.22, 95%CI: 1.04–4.76, $P = 0.004$, Fig. 3B).

Independent prognostic value of SNHG3 in cancers

Multivariate analysis and a fixed-effects model were used in 5 studies ($P = 0.45, I^2 = 0\%$) calculate the independent prognostic value of SNHG3 in cancer. The combined HRs showed that the elevated expression of SNHG3 could be an independent prognostic factor for OS in patients with cancer(HR = 1.90, 95%CI: 1.59–2.27, $P < 0.00001$, Fig. 4).

Relationship between SNHG3 expression and clinicopathological characteristics

The merged results from 11 studies with 1204 patients demonstrated that patients with SNHG3 overexpression have a more advanced stage (III/IV) cancer (III/IV vs. I/II, OR = 2.91, 95%CI: 1.60–5.29, P = 0.0005, Fig. 5A). Here we used a random-effects model because of obvious heterogeneity ($P=0.0001$, $I^2 = 73\%$). In addition, these 5 studies contained 726 individuals showed correlation between SNHG3 and LNM in various cancers. A fix-effects model was utilized again because of obvious heterogeneity ($P = 0.17$, $I^2 = 37\%$), and the pooled results showed that lymph node metastasis was more susceptible to the upregulated SNHG3 expression group than the downregulated SNHG3 expression group (OR = 5.00, 95%CI:2.82–8.87, $P=0.00001$, Fig. 5B). Only 4 studies provided information for distant metastasis (DM). The pooled results indicated that patients with high SNHG3 expression have more metastasis to distant organs or tissues (OR = 2.29, 95%CI: 1.52–3.47, $P < 0.0001$, Fig. 5C). Again, a fixed-effects model was used ($P = 0.27$, $I^2 = 24\%$). 9 studies provided information for tumor size, which showed that patients with high SNHG3 expression have larger size (OR = 1.80, 95%CI: 1.04–3.11, $P = 0.04$, Fig. 5D). Furthermore, we did an investigation on the relationship between SNHG3 expression and age, gender, and differentiation. However, the pooled results suggested that SNHG3 expression was not positively associated with these characteristics (Fig. 6A–C). The details are shown in Table 2.

Table 2:Summary of the relationship between SNHG3 over-expressed and clinicopathological parameters.

Clinicopathological parameters	Studies	Patients	OR (95% CI)	P-value	I^2	Heterogeneity	
						P-value	Model
Age (older vs. younger)	12	1266	0.99 (0.79, 1.24)	0.92	10%	0.35	Fixed
Gender (male vs. female)	10	1106	1.14 (0.89, 1.46)	0.31	0%	0.87	Fixed
Tumor size (larger vs. smaller)	9	546	1.80 (1.04, 3.11)	0.04	51%	0.05	Random
Differentiation (poor vs. well)	5	858	1.19 (0.73, 1.93)	0.49	51%	0.09	Random
TNM stage (III+IV vs. I+II)	11	1204	2.91 (1.60, 5.29)	0.0005	73%	<0.0001	Random
LNM (Positive vs. Negative)	5	726	5.00 (2.82, 8.87)	<0.00001	37%	0.17	Fixed
DM (Positive vs. Negative)	4	780	2.29 (1.52, 3.47)	<0.0001	24%	0.27	Fixed

TNM, Tumor node metastasis;LNM, Lymph node metastasis; DM, Distant metastasis

Publication Bias And Sensitivity Analysis

The begg’s test was used to evaluate the publication bias in this meta-analysis. No significant publication bias for OS and independent factor for OS was found in this meta-analysis (Fig. 7A–B). As illustrated in Fig. 8A–B, we performed the sensitivity analysis to prove that the results were robust, and the summary HRs were not affected after removal of study one by one.

Discussion

While only 2% of human genomic sequences are found to encode proteins, most of the genome is transcribed into non-coding RNA that has no known biological function [29]. LncRNAs, a class of non-coding RNAs with more than 200 nucleotides in length but by no means encode protein [30], have been shown to be significantly involved in various essential cellular processes including cell cycle regulation, immune regulation, stem cells differentiation [4], insensitivity to radiation and drugs [31], and energy metabolism [32, 33] through interacting with DNA, RNA, or proteins. A growing number of studies have shown that the abnormal expression of lncRNAs plays an important role in the clinicopathological features and prognosis of cancers [34]. Furthermore, lncRNAs, which are easily detected in body fluids, have the potential to be accurate prognosis for cancer patients [35].

SNHG3 is a member of a cancer-associated lncRNA family, and is located in band 6 and region 3 of the short arm of chromosome 1. The upregulation of SNHG3 expression is detected in numerous cancer types and promotes the progression of cancers [18]. Recently, accumulating evidence demonstrated that SNHG3 overexpression was highly related to the poor prognosis of colorectal cancer patients and strongly promoted cell proliferation [19]. It has been confirmed that the up-regulation of SNHG3 could cause the apoptosis of lung adenocarcinoma cells and inhibited cells, implicating the link between high SNHG3 expression and the progression of cancer cells invasion [9]. In papillary thyroid carcinoma, Sui et al determined that PSMD10 had a significant connection with the cellular growth, proliferation, and invasion, this was attributed to the regulation of the miR-214-3p/PSMD10 axis by SNHG3 [27]. A study by Li et al demonstrated that the knockdown of SNHG3 prevented proliferation and metabolism of breast cancer cells by upregulating miR-330 and downregulating PKM [36]. In another study, SNHG3 was up-regulated in hepatocellular cancer (HCC) compared with normal tissue and regulated miR-139-5p expression, which was important for the development of hepatocellular cancer including proliferation, migration, and invasion [37]. Furthermore, Zhao et al proposed that SNHG3 overexpression significantly enhanced HCC proliferation and migration by activating SMAD3/ZEB1 signaling, providing potential targets for the diagnosis and treatment of HCC [38]. SNHG3 was also shown to be a crucial lncRNA expressed during the migration and invasion of laryngeal cancer cells through its regulation WEE1 by sponging miR-384, suggesting SNHG3 could help to identify effective treatment strategies for laryngeal carcinoma [39]. Meanwhile, Li et al also found a similar function for SNHG3 in facilitating AML cell growth via the regulation of the miR-758-3p/SRGN axis, indicating that SNHG3 had the high possibility of being a novel prognostic and therapeutic biomarker for AML [26]. Additionally, Liu et al determined that SNHG3 could function as a novel biomarker for oral squamous cell carcinoma, as SNHG3 overexpression results in acceleration of SNHG3 on proliferation and migration in oral squamous cell carcinoma by targeting nuclear transcription factor Y subunit gamma [18, 40, 41]. A research group also found that upregulation of SNHG3 could be suggested as an independent predictor to evaluate the prognostic of ovarian cancer patients and enhanced malignant progression of ovarian cancer [16]. Target drug therapy is an effective strategy to treat advance tumors, and there is evidence that SNHG3 is involved in drug resistance. The latest research found that knockdown of SNHG3 sensitize hepatocellular carcinoma cells to sorafenib by regulating epithelial-mesenchymal transition (EMT) via miR-128/CD51/Akt/PI3K feedback loop signaling, which imply that designing drugs to lower the SNHG3 expression could boost the value of

target drug therapy in the treatment of hepatocellular carcinoma[42]. Despite the well-identified link between SNHG3 and cancer, further studies are needed to validate the function of SNHG3 in cancer.

To further define the role of SNHG3 in different cancers, we conducted the first meta-analysis to elucidate the impact of abnormal SNHG3 expression levels on the prognostic value and clinicopathological characteristic of cancer patients. From merged results, we found that the patients with a high level of expression of SNHG3 had worse outcomes in terms of OS, RFS and DFS when in contrast to those with low SNHG3 expression, suggesting that elevated SNHG3 expression was highly related to poor prognosis and could act as an unfavorable prognostic predictor for patients with cancers. Also, the merged results suggest that the SNHG3 expression could be investigated as an independent predictive factor for OS in cancers. Moreover, the inferiority of high SNHG3 expression on LNM, DM, tumor size and advanced TNM stage was also exhibited, clearly indicating that the overexpression of SNHG3 had a connection with worse clinicopathological characteristics. However, no relationship was found between SNHG3 and age, gender, and differentiation.

Some limitations should be clearly delineated. The shortcomings of this meta-analysis are as follows: First, most studies were from China, which might be potentially suitable for China or Aisa. Second, the included studies were only from China, consequently the results might only capture the clinical characteristics of Asian populations. Third, the tumor types and number of patients and other prognostic indicators, such as RFS, were insufficient for a more comprehensive analysis. Therefore larger sample studies should be conducted to sustain the results. Fourth, the HRs were determined indirectly from survival curves by using available software, which might contribute to a calculation bias. Thus, more relevant high-quality studies that contain a large number of samples are needed to verify the findings.

Conclusion

In conclusion, our results provided novel insights into the correlation between SNHG3 expression, prognosis, and clinical outcomes in cancer patients. In the present meta-analysis, the results indicated that cancer patients with a high expression level of SNHG3 were at higher risk for poor OS compared with those with low SNHG3 expression. Our data strongly suggest that lncRNA SNHG3 might be capable of predicting poor prognosis of cancer patients as a novel biomarker. Taking the limitations of this study into account, more high-quality researches are needed to confirm the prognostic value of SNHG3 in tumors.

Abbreviations

lncRNA, long non-coding RNA; SNHG3, Small nucleolar RNA host gene 3; NA, not available; DFS, disease-free survival; OS, overall survival; GC, gastric cancer; KIRP, Kidney renal papillary cell carcinoma; OC, ovarian cancer; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; BRCA, breast cancer; LC: lung cancer; OS: osteosarcoma; TNM, Tumor node metastasis; LNM, lymph node metastasis; DM, distant metastasis; NOS, Newcastle–Ottawa Quality Assessment Scale

Declarations

Ethics approval and consent to participate

The study was approved by the Human Research Ethics Committees of the First People's Hospital of Neijiang, Neijiang, Sichuan

Consent for publication

All authors agree to publish.

Availability of data and materials

All data used to support the findings of this study are included within the article.

Competing interests

All authors have no conflict of interest in this meta-analysis

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Author's contributions

Conceptualization: HH

Data curation: HH, PYZ.

Formal analysis: HH, JW

Funding acquisition: HH

Investigation: HH

Project administration: JW

Software: HH, PYZ

Supervision: HH

Writing – original draft: JW.

Writing – review & editing: HH

All authors have read and approved the final manuscript

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Figures

Figure 1

Flow diagram of the study selection procedure in this meta-analysis.

A

B

Figure 2

Forest plots for the association between SNHG3 expression with overall survival (OS)(A) and subgroup analysis stratified by the cancer type(B).

A

B

Figure 3

Forest plots for the correlation between SNHG3 expression and DFS(A) and RFS(B).

Figure 4

Forest plots for the correlation between SNHG3 expression and independent predictive factor for OS.

Figure 5

Forest plots for the correlation between SNHG3 expression and clinicopathological characteristics. A: TNM stage; B: lymph node metastasis; C: distant metastasis; D: Tumor size.

A

B

C

Figure 6

Forest plots for the correlation between SNHG3 expression and clinicopathological characteristics. A:Age; B:Differentiation; C: Gender.

A

B

Figure 7

Begg's funnel plot of publication bias on the correlation between SNHG3 expression and OS(A), independent factor for OS(B).

A

B

Figure 8

Sensitivity analysis for OS(A) and independent factor for OS(B) in this meta-analysis.