The Prognostic Value of Long Non-Coding RNA SNHG7 in Human Cancer: A Meta-Analysis.

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Abstract

**Background:** The long non-coding RNA SNHG7 is upregulated in many types of cancer and plays a role as an oncogene. However, its overall predictive ability in human cancer prognosis has not been assessed using existing databases. Therefore, further study of its prognostic value and clinical significance in human malignancies is warranted.

**Methods:** We systematically collected relevant literature from multiple electronic document databases about the relationship between SNHG7 expression level and prognosis in patients with solid cancers. We further screened them for eligibility. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess the prognostic value. Odds ratios (ORs) and their 95% CIs were collected to evaluate the relationship between the expression of SNHG7 and clinicopathological features, including lymph node metastasis (LNM), tumour size, tumour node metastasis (TNM) stage and histological grade.

**Results:** Fourteen original studies involving 971 patients were enrolled strictly following the inclusion and exclusion criteria. The meta-analysis showed that SNHG7 expression was significantly correlated with poor overall survival (HR = 1.93, 95% CI: 1.64−2.26, \(p<0.001\)) in human cancer patients. In addition, the pooled OR indicated that overexpression of SNHG7 was associated with earlier LNM (OR = 1.83, 95% CI: 1.44−2.32; \(P<0.001\)), and advanced TNM stage (OR = 1.82, 95% CI: 1.44−2.30; \(P<0.001\)). Meanwhile, there was no significant heterogeneity between the selected studies, proving the reliability of the meta-analysis results.

**Conclusions:** High SNHG7 expression may predict poor oncological outcomes in patients with multiple human cancers, which could be a novel prognostic biomarker of unfulfilled clinicopathological features. However, further high-quality studies are needed to verify and strengthen the clinical value of SNHG7 in different types of cancer.

**Background**

Human pleomorphic solid carcinoma is a malignant disease with complicated pathogenesis. The high incidence and mortality rate of solid cancer remains a serious health problem worldwide, causing a huge burden on families and countries\[1\]. It has been reported that more than 1,000,000 colorectal cancer (CRC) cases are confirmed annually, and nearly 700,000 of them die of the disease \[2\]. Furthermore, the estimated number of new hepatocellular cancer (HCC) cases and deaths in China in 2015 were 466,100 and 422,100, respectively \[3\]. Although great progress has been made in diagnosis and treatment technology, the five-year survival rate of most malignant tumours is still extraordinarily low \[4\] \[5\]. The main reason for the decrease in the five-year survival rate is the lack of early clinical symptoms and the presence of early lymph node metastasis \[6\]. Therefore, recent studies have focused on finding new biomarkers for early diagnosis of cancer \[7\] \[8\]. However, the sensitivity and specificity of most tumour biomarkers in clinical applications have not achieved the expected results. For this reason, it is of great significance to explore reliable biomarkers for diagnosis and treatment at the gene and molecular level.
Long noncoding RNAs (lncRNAs) are mRNA-like transcripts, with a length of more than 200 nucleotides, lacking an obvious open reading framework[9]. Although lncRNAs cannot directly encode proteins, they are involved in the regulation of gene expression via the regulation of chromatin modification, alternative splicing, and nuclear substance transport [10] [11]. Their abnormal expression is closely related to oncogenesis and drug resistance, and they exert their effects by regulating tumour oncogenes or suppressor genes at multiple levels [12] [13]. In addition, functional experiments have shown that many lncRNAs play an important role in the proliferation, invasion, and metastasis of cancer cells by regulating the expression of downstream signalling molecules through the formation of an action axis. [14] [15]. In the future, they may serve as credible biomarkers or therapeutic targets for the diagnosis and prediction of the prognosis of human cancer[16].

Small nucleolar RNA host gene 7 (SNHG7) is a novel lncRNA with 2,157 base pairs [17], which is located 9q34.3, and has a strong correlation with the development of multiple cancers [18]. The upregulated expression of SNHG7 in a variety of malignant tumours is related to the incidence of CRC, breast cancer (BC), and gastric cancer (GC) [19] [20] [21], and its expression level in cancer tissues is higher than in matched adjacent tissues [22]. Accumulated evidence demonstrated that increased SNHG7 expression was associated with unfavourable clinicopathological parameters and poor prognosis. However, most research results were limited by the level of dispersion and the number of samples. There is a lack of relevant meta-analysis articles to evaluate the relationship between SNHG7 expression level and clinical prognosis of miscellaneous human solid neoplasms. Therefore, in strict accordance with the pre-set inclusion and exclusion criteria, we searched and evaluated the relevant literature, and conducted a systematic review and comprehensive meta-analysis, to further investigate whether the expression of SNHG7 is related to prognosis and pathological characteristics. Consequently, the main purpose of this study was to explore the clinical prognostic value of SNHG7 expression as a biomarker or therapeutic target in patients with various solid cancers.

**Methods**

**Literature Search Strategies**

This meta-analysis was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23] (Supplementary Table S1). Systematic literature search and retrieval of all relevant studies were conducted in PubMed, Web of Science, Embase, Cochrane Library database, CNKI. Searches were conducted for items reporting the relationship between anomalous expression of SNHG7 and prognostic value in various solid cancers. We searched between the dates of the database establishment to 28 June, 2020. The key words used for the searches were as follows in [Title/Abstract]: (“long non-coding RNA” OR “lncRNA” OR “noncoding RNA” OR “small nucleolar RNA host gene 7” OR “SNHG7”) AND (“prognosis” OR “prognostic,” OR “survival” OR “outcome”) AND (“tumour” OR “cancer,” OR “neoplasm” OR “carcinoma”). When the preliminary search was completed, we first excluded articles unrelated to human cancers, and then selected qualified research according to the criteria in the section below. A manual search of the reference list of related literature to find other eligible
articles and only articles published in English were included. This is a retrospective study of published research and therefore did not require ethical approval or patient consent.

**Inclusion and Exclusion Criteria**

The inclusion criteria for the collected studies were as follows: (1) the role of SNHG7 in the development of human solid cancer was discussed, SNHG7 expression was measured in tissue samples; (2) patients were divided into high and low expression groups for SNHG7; (3) the relationship between the expression of SNHG7 and prognosis [overall survival (OS)] or clinicopathological characteristics is described; (4) there is sufficient survival data to estimate the hazard ratio (HR) and its 95% confidence interval (95% CI); and (5) clear diagnosis of specimens by histopathology was provided. The exclusion criteria for the collected studies were as follows: (1) reviews, case reports, conference abstracts, duplicate publications, letters, and expert opinions; (2) research data that was not statistically significant or data obtained from animal experiments; (3) the structure or function of SNHG7 was the focus of the study, and prognostic outcome was not measured.

**Data Extraction**

Information on the prognosis value of SNHG7 was extracted from the original data and two researchers (KXY and CHH) independently collected raw data that met the inclusion and exclusion criteria using data tables for each design. If there were discrepancies between their evaluations, the researchers either decided on a consensus or consulted the third investigator (WJY) before analysis. The data and information collected from all eligible studies were as follows: the name of the first author, year of publication, country of patient data, tumour type, total number of patients, detection method, number of patients in high and low expression groups, follow-up duration, survival outcomes such as OS, 95% CI of elevated SNHG7 for hazard ratio (HR), and clinicopathological features including LNM, tumour size, histological grade, and TNM stage. If both multivariate and univariate analyses were reported in a study, we chose the former method for data analysis.

**Quality Assessment**

The quality of the included studies was evaluated according to the Newcastle-Ottawa Scale standard (NOS score) [24], which was composed of 3 parameters of quality, including selection (max: 4-points), comparability (max: 2-points), and outcome (max: 3-points), with a total score ranging from 0 to 9 points on the assessment scale. A study with an NOS score $\geq 6$ was considered high quality. When there were differing opinions in the quality assessment process, they were resolved through consultation and discussion.

**Statistical Analysis**

Statistical analysis was performed using Stata statistical software version 16.0 (Stata Corporation, College Station, TX, USA). We then used the reliable HRs and 95% CIs obtained from the original data for OS to measure the relationship between the expression of SNHG7 and the prognosis of patients with solid cancers. In addition, the pooled odds ratios (ORs) and their 95% CIs were used to estimate the association between SNHG7 expression and clinicopathological features, including tumour size, LNM,
TNM stage, and differentiation grade. When the original article's data provides information about HRs and 95% CIs, we used the relevant data directly for analysis. Otherwise, we extracted the HR values from a Kaplan–Meier curve using Engauge Digitizer (version 12.1) software according to the method described in the previous literature [25]. In order to determine the heterogeneity of the study, we used chi-square-based $Q$ and $I^2$ tests to quantify the included studies. When calculated $I^2$ values > 50% or $P_h < .1$, indicating significant differences in heterogeneity, the random-effects model was used for analysis. If there was no significant heterogeneity among studies ($I^2$ values < 50% or $P_h > .1$), the fixed effects model would be used to analyse the results. Sensitivity analysis was conducted to determine the potential sources of heterogeneity in any individual study. Begg's bias test and funnel plot were used to evaluate potential publication bias [26]. A $P$ value less than 0.05 was considered statistically significant.

Results

Data Selection and Their Characteristics

The literature retrieval procedure is presented in Fig. 1. Initially, a total of 96 studies were identified from PubMed, Web of Science, Cochrane Library, Embase, and CNKI. Then, 44 articles were eliminated due to duplication. In the remaining 52 studies, after screening titles and abstracts, 6 studies were excluded because they were review articles, letters, conference abstracts, or animal experiments. Furthermore, 32 studies were excluded because of incomplete data or the absence of a prognosis outcome. Based on the inclusion and exclusion criteria, a total of 14 studies involving a total of 971 patients were selected for this meta-analysis [27] [28] [29] [30] [31] [32] [17] [33] [22] [34] [35] [36] [37] [38]. The main characteristics of the included studies are summarized in Table 1 and Table 2. The study samples with a mean sample size of 69.4, which ranged from 40 to 127. All patients were from China, and ten types of cancer were recruited in this meta-analysis, including HCC, CRC, cervical cancer (CC), prostate cancer (PRC), pancreatic cancer (PC), hypopharyngeal cancer (HC), bladder cancer (BLC), synchronous colorectal liver metastasis (SCLM), neuroblastoma (NB), and breast cancer (BC). Quantitative real-time polymerase chain reaction (qRT-PCR) was used to detect the expression of $SNHG7$ in tissue samples. According to the test results, the patients were divided into high and low expression groups. All eligible samples were confirmed by pathology, and were qualified tissue specimens without any preoperative treatments. All of the NOS scores for the included studies ranged from 6 to 8, with a mean value of 7, indicating that these included articles were of high quality.

Association Between High $SNHG7$ Expression and Overall Survival (OS)

A total of 13 studies included the relationship between $SNHG7$ and OS in 899 patients with solid tumours by reporting the HRs and 95% CIs for OS. Subsequently, we evaluated the relationship between expression and prognosis. The comprehensive analysis results of these studies are displayed in Fig. 2. The pooled results indicated that high $SNHG7$ expression in cancer tissues was significantly associated with poor long-term OS, compared to patients with low levels of $SNHG7$ expression (pooled HR = 1.86, 95% CI: 1.60–2.16). In addition, the heterogeneity test revealed no significant heterogeneity in these qualified
studies ($I^2 = 36.9\%; P_h = 0.088$), so the fixed effects model was used to estimate the pooled HRs and 95% CIs. Ultimately, according to the results of this meta-analysis, high $SNHG7$ expression in patients with solid cancer was associated with lower OS, and $SNHG7$ might be an independent prognostic factor of OS for patients with solid cancer.

**Association Between High $SNHG7$ Expression and the clinicopathological Parameters**

The association between $SNHG7$ expression and clinicopathological features was calculated using the pooled ORs and in the form of forest plots. For a specific clinical feature, there are different numbers of eligible included literatures to provide data, which we collected and analysed based on. In the calculation process, owing to the absence of significant heterogeneity detected among the included studies ($I^2 = 0.0\%$), a fixed-effect model was applied to calculate the pooled OR and their corresponding 95% CI. The pooled data suggested that the high expression of $SNHG7$ significantly correlated with LNM (yes vs. no OR = 1.83, 95% CI: 1.44–2.32; $P < 0.001$) (Fig. 3c), and TNM stage (III/IV vs. I/II OR = 1.82, 95% CI: 1.44–2.30; $P < 0.001$) (Fig. 3a). However, the pooled ORs results revealed that high $SNHG7$ expression was not associated with larger tumour size (large vs. small OR = 1.24, 95% CI 0.96–1.62, $P = 0.104$) (Fig. 3b), and poor tumour differentiation (poorly vs. well/moderately OR = 1.20, 95% CI: 0.91–1.58; $P = 0.195$) (Fig. 3d). Therefore, according to the results of the meta-analysis, we can conclude that high $SNHG7$ expression had a higher risk of early LNM and advanced tumour progression than those with low $SNHG7$ expression. In summary, high $SNHG7$ expression was associated with unfavourable clinicopathological characteristics in multiple cancers.

**Publication Bias**

The potential publication bias was estimated by funnel plot and Begg’s bias test in this meta-analysis study. Owing to the limited number of studies included, there was no published bias in assessing clinicopathological features. Therefore, we focused on the potential publication bias on connection between $SNHG7$ expression levels and OS. The visible funnel plots of Begg’s test are shown in Fig. 4. The distribution of data points in the funnel plot did not show obvious asymmetry among the studies investigating the effect of $SNHG7$ expression on OS. In addition, the $P$ values were determined using the Begg test for OS ($Pr > |z| = 0.502$). These results suggested that there was no significant publication bias in the studies, and that our meta-analysis results were reliable.

**Sensitivity Analysis**

Sensitivity analysis was performed to estimate the stability of pooled results by omitting each single study at a time for the meta-analysis on the relationship between the $SNHG7$ expression level and pooled HR. When each study was excluded, we explored the impact of deleted datasets on overall HR. When the analytical result was not significantly changed after removing each of the studies, the results of the current meta-analysis were relatively steady (Fig. 5).

**Discussion**
The incidence of solid cancers has risen considerably, and they represent a substantial threat to human health and major cause of mortality [39]. The occurrence and development of cancers are related to many factors, one of the most perilous factors is mutation at the gene level and abnormal expression of epigenetic regulatory factors. Although great progress has been made in the treatment field, including the development of precise chemotherapy drugs and improved surgery, the five-year survival rate of multiple cancers is still very low[40]. In the majority of cases, solid cancers continue to be tremendously harmful to human health. This means there is an urgent need to find more promising biomarkers to diagnose cancer sooner and achieve targeted treatment as a target of action.

In recent years, many studies have focused on the application of lncRNAs in the clinical treatment of cancer. Relevant evidence shows that lncRNAs participate in many physiological processes such as gene expression and DNA damage response in cancer cells. As an important lncRNA, numerous studies have shown that up regulation of $SNHG7$ expression may be an important prognostic factor for cancer patients by promoting the growth, migration and invasion of cancer cells. Similar increased oncogenesis has been observed in many types of cancer, including renal cell cancer (RCC)[41], HCC [42], and ovarian cancer (OC) [43]. The mechanism by which upregulation of $SNHG7$ expression relates to carcinogenesis is not well understood. Chen et al. found that the expression of $SNHG7$ was significantly increased in glioblastoma and could be used as a molecular sponge to negatively regulate the expression of miR-449b-5p. At this time, the expression of MYCN protein increased and reversed the antitumour effect of miR-449b-5p, thus promoting the proliferation, migration, and invasion of glioblastoma [44]. In another study, Wang et al. found that $SNHG7$ was upregulated in non-small-cell lung cancer (NSCLC) and played an oncogenic role in their experiment. The overexpression of $SNHG7$ decreased the expression of miR-181a-5p and promoted the expression of downstream target protein E2F transcription factor 7 ($E2F7$), as well as advanced the malignant behaviour phenotype of cancer cells through the $SNHG7$ /miR-181a-5p / $E2F7$ axis. However, when the $SNHG7$ gene is knocked out, these processes can be clearly inhibited [45]. Furthermore, Sun et al. also found that $SNHG7$ was significantly upregulated in BC tissues and cell lines, and $SNHG7$ could inhibit the expression of miR-34a through sponge binding. Experiments on the mechanism showed that upregulated $SNHG7$ promotes the proliferation and migration of cancer cells by activating epithelial mesenchymal transition (EMT) and Notch-1 signalling pathway [46]. Subsequently, it has been reported that the upregulation of $SNHG7$ is related to poor clinical outcome of various cancers, which indicates that $SNHG7$ may be a biomarker for predicting the prognosis of human cancers [27] [47]. In the past, literature reports only focused on a single aspect of $SNHG7$ with small sample sizes, which could not definitively show the prognostic value of abnormal expression of $SNHG7$ in various malignant tumours. For this reason, we conducted a comprehensive meta-analysis based on previously published single-center sample studies.

The purpose of this meta-analysis was to analyse the relationship between high $SNHG7$ expression and cancer prognosis as well as clinicopathological characteristics of various solid cancers. This large-scale meta-analysis provides direct evidence for the prognostic value of high $SNHG7$ expression in patients with human solid cancers. A total of fourteen recent articles, including 971 patients with different types of cancers, were fitted into the meta-analysis. Our combined analysis showed that patients with high
expression of SNHG7 had shorter OS than those with low expression. In addition, we also studied the
relationship between high expression of SNHG7 and clinicopathological features. The results showed
that the high expression of SNHG7 was related to advanced TNM stage and earlier LNM of human
malignant tumour, but the high expression of SNHG7 was not significantly correlated with larger tumour
size and poor tumour differentiation. The process of this meta-analysis was carried out in strict
accordance with the PRISMA statement, so the results obtained from the analysis data are relatively
reliable.

This meta-analysis comprehensively and systematically studied the relationship between SNHG7
expression and prognosis for multiple cancers, however, there are still several limitations that should not
be ignored. First, although this meta-analysis included 14 qualified articles, the number of studies and
sample size were still relatively small, so multi-ethnic clinical research is needed to reinforce the
conclusions. Second, all the studies in this article were retrospective, and all of them were from China, so
the results may not be applicable to patients with multiple solid cancers in the world. Some studies did
not provide HRs and their corresponding 95% CIs, so we extracted data from the Kaplan-Meier survival
curve, which may lead to errors in the acquired data. Finally, since negative results were rarely published,
the results of this study may overestimate the role of SNHG7 in the prognosis of human cancer to some
extent. Although the results of publication bias analysis are relatively stable, potential publication bias
may still exist.

Although there are aforementioned limitations in this meta-analysis, it has included all the latest
qualifying published articles for comprehensive and systematic analysis. The analysis reveals a lot of
instructive information, such as the association between the upregulated expression of SNHG7 and poor
prognosis of patients with human solid cancer. Ultimately, we expect that SNHG7 will play an important
role as a biomarker in the clinical diagnosis and treatment of manifold cancer types.

Conclusions

In conclusion, following our meta-analysis of the latest published articles, the results indicated that high
SNHG7 expression levels were significantly associated with detrimental clinical outcomes in human solid
cancers, and increased SNHG7 expression was also strongly correlated with advanced TNM stage and
earlier LNM. Furthermore, previous studies have demonstrated that SNHG7 plays an important role in the
occurrence and development of various cancers, therefore, it is a potential biomarker for improving
tumour prognosis and clinical diagnosis ability. In the future, additional high-quality studies are needed to
verify the prognostic value of SNHG7 in human solid cancers.

Declarations

Data Availability
All the literature included in this meta-analysis can be cited in the electronic database, and the use and processing of the data in the literature have been approved by the corresponding authors.

**Conflicts of Interest**

The authors declare that there is no conflict of interest regarding the publication of this paper.

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**Author contributions**

KXY, ZHC and LC conceived and designed this meta-analysis. KXY, CHH, WJY, ZHC, and LC performed this study. KXY, RXX, LX, PWZ, and LC collected and analysed the data. CHH, PWZ, and LX contributed analysis tools. KXY, LC, and ZHC wrote the paper. KXY, LC, CHH, and ZHC prepared tables and figures. All authors have read and approved the final manuscript.

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**Ethics Approval and Consent**

Because all the data were extracted from published retrospective studies, this study did not require ethical approval.

**Consent to Publish**

NA.

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Tables

Table 1  Baseline characteristics of included studies in this meta-analysis
RS: Retrospective Study; HR: Hazard Ratio; OS: Overall Survival; KM: Kaplan-Meier; NOS: Newcastle-Ottawa Scale

Table 2  Clinicopathological features of included studies in this meta-analysis

| Study     | Year | Country | Type  | Study design | Method | Sample size | Follow-up (month) | survival outcomes | HRs 95% CI | NOS score |
|-----------|------|---------|-------|--------------|--------|-------------|-------------------|-------------------|-------------|-----------|
| Shen et al| 2020 | China   | HCC   | RS           | RT-PCR | 100         | >50               | OS                |             |           |
| Zhang et al| 2020 | China   | SCLM  | RS           | RT-PCR | 96          | >96               | OS                |             |           |
| Shan et al| 2018 | China   | CRC   | RS           | RT-PCR | 48          | >60               | OS                |             |           |
| Zhao et al| 2020 | China   | CC    | RS           | RT-PCR | 45          | >40               | OS                |             |           |
| Wu et al  | 2020 | China   | CC    | RS           | RT-PCR | 51          | >60               | OS                |             |           |
| Xia et al | 2020 | China   | PC    | RS           | RT-PCR | 127         | >60               | OS                |             |           |
| Zeng et al| 2019 | China   | CC    | RS           | RT-PCR | 60          | >40               | OS                |             |           |
| Cheng et al| 2019| China   | PRC   | RS           | RT-PCR | 40          | >40               | OS                |             |           |
| Wu et al  | 2019 | China   | HC    | RS           | RT-PCR | 71          | >60               | OS                |             |           |
| Xu et al  | 2019 | China   | BLC   | RS           | RT-PCR | 72          | —                 | —                 |             |           |
| Chi et al | 2019 | China   | NB    | RS           | RT-PCR | 92          | >60               | OS                |             |           |
| Luo et al | 2018 | China   | BC    | RS           | RT-PCR | 72          | >60               | OS                |             |           |
| Li et al  | 2018 | China   | CRC   | RS           | RT-PCR | 51          | >60               | OS                |             |           |
| Qi et al  | 2018 | China   | PC    | RS           | RT-PCR | 42          | >50               | OS                |             |           |

TNM: Tumour Node Metastasis; LNM: lymph node metastasis