Clinicopathological significance and prognosis of long noncoding RNA SNHG14 expression in human cancers: A Meta-Analysis and bioinformatics analysis

Bin Liu  
The First Clinical Medical School, Lanzhou University, Lanzhou, Gansu Province, 730000

Tingting Lu  
Institution of Clinical Research and Evidence Based Medicine, Gansu Provincial Hospital, Lanzhou, Gansu Province, 730000,

Yongfeng Wang  
The First Clinical Medical College of Gansu University of Chinese Medicine, Lanzhou, Gansu Province, 730000,

Yaqiong Chen  
General Surgery Clinical Medical Center, Gansu Provinical Hospital, Lanzhou, Gansu Province, 730000,

Shixun Ma  
General Surgery Clinical Medical Center, Gansu Provinical Hospital, Lanzhou, Gansu Province, 730000,

Yajun Jiao  
General Surgery Clinical Medical Center, Gansu Provinical Hospital, Lanzhou, Gansu Province, 730000,

Kehu Yang  
Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu Province, 730000,

Hui Cai  (caialonteam@163.com)  
General Surgery Clinical Medical Center, Gansu Provinical Hospital, Lanzhou, Gansu Province, 730000,

Research Article

Keywords: IncRNA, SNHG14, cancer, meta-analysis, prognostic

Posted Date: December 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1209386/v1

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

Background

SNHG14 is a recently found long non-coding RNA (IncRNA) with a strong link to cancer. However, it is uncertain if the expression of SNHG14 is linked to the prognosis of individuals with various forms of cancer. We conducted a meta-analysis of the available literature to evaluate the association between SNHG14 and clinicopathological characteristics and patient prognosis.

Methods

The databases PubMed/Medline, Web of Science, Cochrane Library, and Embase were combed for relevant papers published till November 2021. The odds ratio (OR) and 95% confidence interval (CI) were used to analyze dichotomous variables, while the hazard ratio (HR) and 95% CI were employed as a summary statistic for survival outcomes. In addition, the Cancer Genome Atlas TCGA (TCGA) and gene expression omnibus (GEO) database were utilized to investigate SNHG14 differential expression in pan-cancers. Cox regression and Kaplan-Meier analysis were used to investigate the prognostic significance of SNHG14 in pan-cancer. The association between the degree of SNHG14 expression in pan-cancer and immune infiltration, tumor mutational burden (TMB), and microsatellite instability (MSI) was measured using Spearman correlations.

Results

A total of 21 studies with 1,080 patients, mainly from China, were included. Our results showed that elevated SNHG14 expression was significantly associated with poor overall survival (OS) (HR = 1.39; 95% CI: 1.06-1.83; \( P = 0.017 \)). In addition, increased SNHG14 expression was associated with tumor size (OR = 1.60; 95% CI: 1.20-2.14; \( P = 0.001 \)), TNM staging (OR = 0.54; 95% CI: 0.40-0.71; \( P < 0.001 \)), lymph node metastasis (OR = 1.86; 95% CI: 1.35-2.55; \( P < 0.001 \)), differentiation grade (OR = 1.95; 95% CI: 1.36-2.80; \( P < 0.001 \)), and distant metastasis (OR = 2.44; 95% CI: 1.30-4.58; \( P = 0.005 \)). However, there was no significant difference in age (OR = 1.02; 95% CI: 0.77-1.33; \( P = 0.863 \)) and gender (OR = 0.98; 95% CI: 0.72-1.35; \( P = 0.915 \)).

Conclusion

This study revealed that overexpression of SNHG14 is associated with low OS rate and clinicopathological characteristics. SNHG14 can be considered as a new tumor marker that aids in early tumor diagnosis, thus improving the prognosis of patients.

Introduction

Cancer is one of the leading causes of human death worldwide and a major public health problem[1]. In recent years, cancer research has progressed by leaps and bounds but the clinical outcome is still not optimistic. The main reason is that cancers have not been effectively diagnosed and treated early, resulting in unsatisfactory clinical curative effects, which significantly affect the prognosis of patients[2]. As a result, there is a pressing need to identify biomarkers that might aid in the early detection and prognostication of tumor patients[3].

Researchers have found that most genomic DNA is present in processed translation scripts as a consequence of the advancement of whole-genome and transcriptome sequencing capabilities and the ENCODE project. These non-coding ribonucleic acid (ncRNA) translation scripts may not be translated into functional proteins[4, 5]. LncRNA (long non-coding ribonucleic acid) is a kind of non-coding ribonucleic acid with more than 200 nucleotides[6]. Despite their lack of capacity to code for proteins, IncRNA have been demonstrated to play a critical role in the control of gene expression at various stages of the transcription/translation process[7–9]. They are considered promising markers for cancer prognosis, diagnosis, and development. The link between IncRNA and the carcinogenesis of many types of cancer has been well established [10, 11].

The human chromosome 15q11.2 contains the small nucleolar RNA host gene 14 (SNHG14), which has been shown to accelerate tumor formation in a variety of malignant tumors[12]. It has been shown to play a role in the activation of inflammatory microglia, sepsis-induced acute kidney damage, and LPS-induced acute kidney injury in a number of malignancies, including lung cancer and cervical cancer[13–16]. SNHG14 modulates E-cadherin expression by interacting with EZH2, facilitating pancreatic ductal adenocarcinoma progression[17]. Liu et al. recently revealed that SNHG14 may be employed as a ceRNA to increase clearance start and progression[18]. Furthermore, SNHG14 has also been discovered to operate as a competitive endogenous RNA for microRNA-382-5p (miR-382-5p), which controls SPIN1 expression in...
It can bind to the whole UBE3A gene and promoter, preventing UBE3A production and resulting in neurogenetic disorders including Angelman syndrome. The regulating mechanism of SNHG14, on the other hand, is extremely complex and unknown.

There is no obvious article to conform the relationship between SNHG14 and cancer prognosis. In addition, many studies on SNHG14 have only obtained independent results due to limitations, such as a short follow-up. We conducted a meta-analysis of the available literature to evaluate the association between SNHG14 and clinicopathological characteristics and patient prognosis in the current study to give better clinical guidance to physicians.

**Materials And Methods**

This meta-analysis was designed, conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidance.

**Registration number**

This study has been registered in PROSPERO (No. CRD42021287397).

**Search strategy**

The databases PubMed/Medline, Web of Science, Cochrane Library, and Embase were combed for relevant papers published till November 2021. The following freewords and MeSH terms were used: (“small nucleolar RNA host gene 14” or “SNHG14” or “115HG” or “IC-SNURF-SNRPN” or “LNCA” or “NCRNA00214” or “U-UBE3A-ATS” or “UBE3A-AS” or “UBE3A-AS1” or “UBE3A-ATS” or “UBE3AATS”) and (“cancer” or “carcinoma” or “neoplasm” or “tumor”). The search strategy (for PubMed) is presented in the Supplementary Appendix (Item 1).

**Inclusion and exclusion criteria**

The inclusion criteria were as follows: (1) Topic of study: human cancer, (2) Diagnosis method: pathology or histology, (3) Patients divided into “high SNHG14” and “low SNHG14” groups, and (4) Clearly reported Association between SNHG16 and clinicopathological (age, gender, tumor size, TNM staging, lymph node metastasis, differentiation grade, and distant metastasis) and odds ratio (OR), (5) Acquired or estimated the HR and 95% CIs. The exclusion criteria were as follows: (1) Literature type: reviews, case reports, meeting abstracts, and basic experimental research literature, (2) Duplicate articles or data, (3) Data extraction of non-English language and animal studies.

**Data extraction and quality assessment**

Two reviewers (BL and YFW) independently assessed the eligibility of each trial and extracted the relevant data (first author name, publication date, country/region, tumor type, sample type, sample size, testing method, cut-off value, outcome measure, and follow-up). The main outcomes were OS (HR with 95% CI) and clinicopathological characteristics (age, gender, tumor size, TNM stage, lymph node metastasis, differentiation grade, and distant metastasis).

The studies’ quality was assessed using the Newcastle-Ottawa Scale (NOS). We looked at the following domains: research group selection, comparability, exposure (case–control study), and outcome (cohort study). Studies having a score of 6 were regarded to be of excellent quality in general. Any discrepancies were worked out with the help of the senior investigator through conversation and consultation.

**Data synthesis and statistical analysis**

The dichotomous outcomes were evaluated using OR and 95% CI. The data from the Kaplan-Meier (KM) curve was extracted using the Engauge Digitizer V.4.1 software, and the HR and 95 % CI were calculated. The was used to determine the degree of study heterogeneity. When >50%, indicating considerable heterogeneity between trials, a random-effects model was utilized. A fixed-effects model was utilized in the other cases. For data processing and statistical analysis, the Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark, and Stata version 15.0 software (Stata Corporation, College Station, TX, United States) were used. P<0.05 was deemed statistically significant.

**Survival analysis of SNHG14 gene expression difference in human cancer**
The Cancer Genome Atlas (TCGA) data portal (https://portal.gdc.cancer.gov/) was used to gather gene expression data and clinical information, and the connection between SNHG14 expression and clinical outcomes was examined, with OS as the primary indicator. The Kaplan-Meier technique was utilized to conduct a risk score-based survival study. The cutoff value for the human cancer dichotomy was chosen as the median value of SNHG14 expression level, separating each patient into a high-risk or low-risk category. The survival curve was outlined using the R packages "survminer" and "survival" according to their high and low-risk values. Furthermore, COX analysis was used to look into the association between SNHG14 expression and cancer prognosis. The findings were plotted using the R packages "limma" and "ggpubr" were mostly used for clinicopathological analysis.

The relationship between the expression of SNHG14 and TMB or MSI in cancer

We analyzed tumor mutational burden (TMB), microsatellite instability (MSI), and SNHG14 expression using Spearman's correlation analysis. The data were obtained from the TCGA database, downloaded through the Genomic Data Commons (GDC) data portal website (https://portal.gdc.cancer.gov/), and statistically analyzed using R software v4.0.3.

Correlation of SNHG14 expression in cancer with tumor microenvironment (TME) and immune cell infiltration

The ESTIMATE method in R-packages "estimate" and "limma"[24], which were used to predict tumor purity and the presence of infiltrating stromal/immune cells in pan-cancer tissues, was utilized to calculate immune and stromal cell scores (using SNHG14 expression data). Newman and colleagues created CIBERSORT, which is used to quantify immune cell infiltration in all malignancies by estimating the number of certain cell types in mixed cell populations using gene expression data[25]. The R packages "ggplot2," "ggpubr," and "ggExtra" were used to investigate the relationship between SNHG14 expression and tumor immune microenvironment and immune cell infiltration ($P<0.001$ was used as the cut-off value).

Results

Studies characteristics and quality assessment

A total of 208 studies were found. After removing duplication, we further screened 113 studies based on their title, abstract. 51 studies need to read the full text, and eventually 21[19, 26-45] were included in this meta-analysis (Figure 1). This study included 1,080 patients, all from China. Each included study had a minimum sample size of 24 and a maximum sample size of 99. The included studies consisted of 11 types of cancer, including colorectal cancer, hepatocellular carcinoma, bladder cancer, non-small cell lung cancer, endometrial carcinoma, acute myeloid leukemia, retinoblastoma, prostate cancer, cervical cancer, pancreatic cancer, and ovarian cancer. The expression of SNHG14 was detected by qPCR in 21 studies. Among the included studies, 16[19, 27, 28, 31-33, 35-39, 41-45] reported on OS and 17[19, 26-40, 43] on clinical outcomes. The NOS scores for all included studies were $\geq 7$, which indicates that the methodological quality of included studies was high. The details are listed in Table 1.

Association between the expression level of SNHG14 and OS

Among the 21 studies included in this study, 16 involved 1578 patients. In these studies, OS was linked to expression levels in cancer patients. Our meta-analysis revealed a statistically significant difference (HR = 1.39; 95% CI: 1.06-1.83; $P = 0.017$) (Figure 2a). In the high SNHG14 expression group, the number of patients with low survival rates increased significantly, indicating that SNHG14 is an independent factor in the survival of patients with malignant tumors. A subgroup analysis was also performed to look into the relationship between SNHG14 expression and the operating system based on the following factors: analysis method (multivariate and univariate analysis) (Figure 2b), cancer type (digestive system, female reproductive system, or others) (Figure 2c), follow-up time (60 or 60 months) (Figure 2d), and sample size (60 or 60 tissues) (Figure 2e). The follow-up duration was $\geq 60$ months, the sample size was 60 tissues, and the multivariate analysis approach and the female reproductive system were statistically significant, according to subgroup analysis. These analysis results are shown in Table 2.

Association between SNHG14 and clinicopathological features

Among the 21 studies, 17 reported a link between clinicopathological characteristics and SNHG14. These analysis results are shown in Figure 3 and Table 3. High SNHG14 expression was found to be significantly correlated with TNM Staging (OR = 0.54; 95% CI: 0.40-0.71; $P<0.001$) (Figure 3c), tumor size (OR = 1.60; 95% CI: 1.20-2.14; $P = 0.001$) (Figure 3d), lymph node metastasis (OR = 1.86; 95% CI: 1.35-2.55; $P<0.001$) (Figure 3e), differentiation grade (OR = 1.95; 95% CI: 1.36-2.80; $P<0.001$) (Figure 3f), and distant metastasis (OR = 2.44; 95% CI: 1.30-4.58; $P = 0.005$) (Figure 3g). However, meta-analysis revealed that SNHG14 expression was unrelated to age (OR = 0.98; 95% CI: 0.72-1.35; $P = 0.915$) (Figure 3a) and gender (OR = 0.98; 95% CI: 0.72-1.35; $P = 0.915$) (Figure 3b).
Publication bias and sensitivity analysis

The publication bias of the papers in our meta-analysis was investigated using Begg and Egger regression tests, and a funnel plot was created to measure publication bias. [Begg funnel plot (Pr > |z| = 0.528) (Figure 4a) and Egger funnel plot (P>|t| = 0.480) (Figure 4b)] revealed no publication bias, indicating that our pooled results were reliable. A sensitivity analysis was also utilized to investigate their possible source and analyze the validity of these results. The results of OS remained steady following testing after disregarding each included study in turn for each outcome. Therefore, the operating system's anticipated aggregated results based on SNHG14 expression were accurate (Figure 5).

Prognostic value of SNHG14 in cancer

The predictive significance of SNHG14 in cancer was investigated using a variety of online database resources. SNHG14 expression is associated to the prognosis of various malignancies from the TCGA database, according to the Kaplan-Meier cumulative curve. Patients with greater SNHG14 expression showed a better survival rate than those with lower SNHG14 expression, such as those with brain lower grade glioma (LGG) (OS: N = 529, P = 0.017) (Figure 6a) and pancreatic adenocarcinoma (PAAD) (OS: N = 182, P = 0.022). (Figure 6b). SNHG14, on the other hand, showed a negative effect on mesothelioma (MESO) (OS: N=86, P=0.026) (Figure 6c), with patients with increased SNHG14 expression having a poorer survival rate.

COX analysis was used to look at the survival rate linked with SNHG14, and PrognoScan was used as the primary database retrieved from the GEO. The researchers discovered that SNHG14 expression was related to LGG (HR = 0.644; 95 % CI: 0.442-0.939; P = 0.022), PAAD (HR = 0.502; 95 % CI: 0.298-0.854; P= 0.009), and skin cutaneous melanoma (SKCM) (HR = 0.777; 95 % CI: 0.622-0.971; P = 0.027), while liver hepatocellular carcinoma (LIHC) (Figure 6d).

The relationship between SNHG14 expression in cancer and TMB and MSI

TMB and MSI are essential determinants in tumor incidence and progression, thus we used a bubble diagram to show the relationship between SNHG14 expression and TMB or MSI to assess its immunogenicity[46]. Our findings revealed that SNHG14 expression is associated with TMB in a representative number of malignancies (n = 14; P<0.05), with TMB positively associating with colon adenocarcinoma (COAD), thymoma (THYM), and acute myeloid leukemia (AML) (LAML). In eleven other cancer types, however, SNHG14 expression is negatively correlated with TMB: esophageal carcinoma (ESCA), lung adenocarcinoma (LUAD), PAAD, stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), bladder urothelial carcinoma (BLCA), head and neck squamous cell carcinoma (HNSC), LGG, LIHC, rectum adenocarcinoma (READ) (Figure 7a).

The next step was to see if SNHG14 expression is linked to MSI in certain cancers. Our findings revealed that SNHG14 expression is strongly connected with MSI in nine cancer types, with four cancer types (LUAD, cholangiocarcinoma (CHOL), LGG, lung squamous cell carcinoma (LUSC)) positively correlating with MSI. In ESCA, STAD, COAD, lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), and PAAD, however, SNHG14 expression is negatively linked with MSI (Figure 7b).

Correlation of SNHG14 expression in cancer with (TME) and immune cell infiltration

The concentration of immunosuppressive cell subsets inside the TME appears to impact cancer prognosis and therapeutic benefit, according to growing research. [47]. SNHG14 expression is related with the OS of various malignancies, according to Kaplan-Meier and Cox survival analyses (LGG, PAAD, MESO, SKCM, LIHC). For these cancer types, the ESTIMATE method was used to determine stromal and immune cell scores. The immunological scores of PAAD (Figure 8c) are favorably connected, but the immune scores of LGG (Figure 8a) and SKCM (Figure 8d), as well as the stromal scores of the LGG, are negatively correlated (Figure 8b).

SNHG14 expression is also favorably connected with infiltrating active mast cells and monocytes in LGG, but negatively correlated with infiltrating M0 macrophages, M1 macrophages, and CD8 T cells, according to our findings. SNHG14 expression is favorably connected with naive B cells and CD8 T cells infiltrated in PAAD, and negatively correlated with memory B cells, M0 macrophages, and activated NK cells infiltrated in PAAD. The expression of SNHG14 in infiltrating M0 macrophages is favorably connected with infiltrating M0 macrophages and negatively correlated with infiltrating CD8 T cells in LIHC. SNHG14 expression is favorably connected with invading resting memory CD4 T cells and regulatory T cells (Tregs) in SKCM, but negatively correlated with CD8 T cells (Figure 9).

Discussion
Cancer is a severe health concern to humans. Despite significant advancements in cancer detection and treatment, cancer incidence has gradually increased in recent years[48]. IncRNA is dysregulated in cancer and plays a crucial role in tumor growth and progression, according to several studies. Overexpression of IncRNA-XIST, for example, has been linked to poor prognosis and clinicopathological features, suggesting that IncRNA-XIST might be a potential non-invasive biomarker for prognosis and clinical pathology[49].

SNHG14 is extensively expressed in a variety of malignancies and has been shown to accelerate tumor growth[50]. Colorectal cancer, hepatocellular carcinoma, bladder cancer, non-small cell lung cancer, endometrial carcinoma, acute myeloid leukemia, retinoblastoma, prostate cancer, cervical cancer, pancreatic cancer, and ovarian cancer all have elevated levels of SNHG14. Furthermore, via interacting with the RNA-binding protein Lin28A, SNHG14 plays a role in altering glucose metabolism and carcinogenesis in gliomas. Silencing SNHG14 decreases glioma cell glycolysis and proliferation while increasing cell apoptosis[51]. In contrast to the previous study, another one found that SNHG14 inhibits glioma cell growth and invasion while also encouraging apoptosis. Because the role of SNHG14 in many malignancies is still debated[52]. Therefore, this meta-analysis was conducted to look into the association between SNHG14 expression and clinicopathological characteristics as well as patient prognosis.

According to the results of meta-analysis, high expression of the SNHG14 gene is associated with a poor operating system. Subgroup analysis showed that the female reproductive system was statistically significant. A study by Zhang on the digestive system showed that low expression of SNHG14 is associated with poor prognosis, which may have led to biased results[31]. However, the overall results revealed that high SNHG14 expression is correlated with poor tumor prognosis. Increased SNHG14 expression was found to associate with tumor size, TNM staging, lymph node metastasis, differentiation grade and distant metastasis but not with age and gender. Despite data have shown SNHG14 to be an important prognostic factor for different type of tumors, the molecular mechanism of how it affects cancer remains unknown. SNHG14 promotes the progression of DLBCL by isolating miR-152-3p, preventing it from inhibiting the PD-1/PD-L1 checkpoint[53]. LncRNA SNHG14 is upregulated and activated by SP1 regulators in ccRCC cells. SNHG14 can promote renal cancer cell migration and invasion through sponge miR-203 and release N-WASP as ceRNA[54]. Furthermore, the transfer of IncRNA SNHG14 mediated by exosomes induces breast cancer cell resistance to trastuzumab, and exosomal IncRNA SNHG14 in human serum is a potential breast cancer diagnostic biomarker that enhances the clinical benefit of trastuzumab therapy[55]. Table 4 summarizes SNHG14 and its roles, as well as associated genes, in order to further investigate the association between SNHG14 and other malignancies.

Bioinformatics analysis was utilized to investigate the survival analysis of SNHG14 expression variations in cancer and the association with TMB, TSI, and TME in order to discover the role of IncRNA SNHG14 in cancer. The link between PDCD1 expression levels and pan-cancer prognosis was investigated using independent data sets from TCGA, Kaplan-Meier plotter, and PrognoScan. A higher level of SNHG14 expression is related with a better prognosis in LGG and PAAD, according to our findings. Zhang discovered that SNHG14 may sponge miR-101 to improve PDAC cell growth and identify the particular axis of SNHG14/miR-101/autophagy underpinning PDAC cell chemoresistance to gemcitabine, potentially advancing PDAC treatment [56]. High levels of SNHG14 expression, on the other hand, are linked to a poor MESO prognosis.

This is the first study that analyzed the relationship between the expression level of SNHG14 and the prognosis and clinical characteristics of cancer patients. Shen et al. previously explored SNHG14's expression profile, biological function, and molecular mechanism in cancer, laying a molecular foundation for SNHG14's potential therapeutic use.[57]. We used a meta-analysis to evaluate the relationship between SNHG14 expression, OS, and clinicopathological significance of different types of cancer. Compared to previous studies, this study included more original studies, detailed subgroup and sensitivity analyses, and the use of bioinformatics to analyze the correlation between SNHG14 and other malignancies.

There are several limitations to our research. First, the HR in the survival analysis was calculated based on the KM curve from the literature, which may result in errors. Second, the patients included in the study were all Asian, thus interpretation and application of the results requires caution. Third, this study mainly focused on the bioinformatics analysis of SNHG14 expression and patient survival using different databases, with no in vivo or in vitro experiments. Finally, the individual differences of various of cancer patients, as well as their different lifestyles, may also contribute to heterogeneity.

**Conclusion**

This meta-analysis demonstrated that high expression of the SNHG14 gene is associated with poor operating systems of cancer patients. Furthermore, differentially expressed SNHG14 can be used as an oncogene or cancer suppressor to improve cancer prognosis, as well as to identify potential therapeutic targets. In addition, more well-designed studies with a larger sample size are expected to further confirm our findings.
Abbreviations

lncRNA
Long noncoding RNA
ceRNA
Competing endogenous RNAs
SNHG14
small nucleolar RNA host gene 14
HR
Hazard ratio
OR
Odds ratio
OS
Overall survival
95% CI
95% Confidence interval
qRT-PCR
Quantitative real-time polymerase chain reaction
NOS
The Newcastle–Ottawa Quality Assessment Scale
TCGA
The Cancer Genome Atlas
GEO
gene expression omnibus.

Declarations

Acknowledgements:
The authors thank Key Laboratory of Molecular Diagnostics and Precision Medicine for Surgical Oncology in Gansu Province and the DaVinci Surgery System Database (DSSD, www.davincisurgerydatabase.com) and for their help and support in the methodology and meta-analysis process.

Funding:
This study was supported by the Natural Science Foundation of Gansu Province, China, No. 18JR3RA052; Gansu Province Da Vinci robot high end diagnosis and treatment personnel training project, No. 2020RCXM076; Reversing the EMT process to promote the differentiation of cancer stem cells and improve the relevant mechanisms and strategies of gastric cancer chemotherapy sensitivity.

Availability of data and materials
All data are included in this manuscript.

Authors’ contributions
Liu B, Lu TT, KH Yang and Cai H designed the research; Liu B, Wang YF, and Jiao YJ conducted the literature search; Liu B and Wang YF collected and retrieved the data; Liu B, Chen YQ, and Ma SX analyzed the data; Liu B and Lu TT wrote and revised the manuscript; All authors approved the final version.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.
Competing interests

The authors proclaim that they have no competing interests.

Author information

1 The First Clinical Medical College of Lanzhou University, Lanzhou, Gansu, 730000, China. 2 The First Clinical Medical College of Gansu University of Chinese Medicine, Lanzhou, Gansu, 730000, China. 3 Institute of Clinical Research and Evidence Based Medicine, Gansu Provincial Hospital, Lanzhou, Gansu, 730000, China. 4 General Surgery Clinical Medical Center, Gansu Provincial Hospital, Lanzhou, Gansu, 730000, China.

References


Table 1 Characteristics of included studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Cancer type</th>
<th>Sample type</th>
<th>Sample size</th>
<th>Detection Method</th>
<th>Cut-off value</th>
<th>Outcome measure</th>
<th>Hazard ratios</th>
<th>Follow-up (month)</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al[26]</td>
<td>2021</td>
<td>China</td>
<td>Colorectal cancer</td>
<td>Tissue</td>
<td>30</td>
<td>qRT-PCR</td>
<td>Mean</td>
<td>CP</td>
<td>NA</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Liao et al[27]</td>
<td>2021</td>
<td>China</td>
<td>Hepatocellular carcinoma</td>
<td>Tissue</td>
<td>66</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>80</td>
<td>8</td>
</tr>
<tr>
<td>Feng et al[28]</td>
<td>2021</td>
<td>China</td>
<td>Bladder cancer</td>
<td>Tissue</td>
<td>62</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Wang et al[29]</td>
<td>2021</td>
<td>China</td>
<td>Acute myeloid leukaemia</td>
<td>Bone marrow</td>
<td>57</td>
<td>qRT-PCR</td>
<td>Mean</td>
<td>CP</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
</tr>
<tr>
<td>Chen et al[19]</td>
<td>2020</td>
<td>China</td>
<td>Non-small cell lung cancer</td>
<td>Tissue</td>
<td>50</td>
<td>qRT-PCR</td>
<td>NA</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>Zhang et al[31]</td>
<td>2020</td>
<td>China</td>
<td>Colorectal cancer</td>
<td>Tissue</td>
<td>92</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td>Zhang et al[32]</td>
<td>2020</td>
<td>China</td>
<td>Endometrial Carcinoma</td>
<td>Tissue</td>
<td>53</td>
<td>qRT-PCR</td>
<td>Mean</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>Zhang et al[33]</td>
<td>2020</td>
<td>China</td>
<td>Hepatocellular carcinoma</td>
<td>Tissue</td>
<td>40</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Xu et al[34]</td>
<td>2020</td>
<td>China</td>
<td>Hepatocellular carcinoma</td>
<td>Tissue</td>
<td>55</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>CP</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
</tr>
<tr>
<td>Sun et al[35]</td>
<td>2020</td>
<td>China</td>
<td>Retinoblastoma</td>
<td>Tissue</td>
<td>43</td>
<td>qRT-PCR</td>
<td>Mean</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>Wang et al[36]</td>
<td>2020</td>
<td>China</td>
<td>Endometrial Carcinoma</td>
<td>Tissue</td>
<td>52</td>
<td>qRT-PCR</td>
<td>Mean</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>72</td>
<td>8</td>
</tr>
<tr>
<td>Luo et al[37]</td>
<td>2020</td>
<td>China</td>
<td>Prostate cancer</td>
<td>Tissue</td>
<td>60</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>Zhang et al[38]</td>
<td>2019</td>
<td>China</td>
<td>Non-small cell lung cancer</td>
<td>Tissue</td>
<td>99</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>60</td>
<td>9</td>
</tr>
<tr>
<td>Ji et al[39]</td>
<td>2019</td>
<td>China</td>
<td>Cervical cancer</td>
<td>Tissue</td>
<td>80</td>
<td>qRT-PCR</td>
<td>Mean</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>Deng et al[40]</td>
<td>2019</td>
<td>China</td>
<td>Pancreatic cancer</td>
<td>Tissue</td>
<td>45</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>CP</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
</tr>
<tr>
<td>Zhao et al[41]</td>
<td>2019</td>
<td>China</td>
<td>Ovarian cancer</td>
<td>Tissue</td>
<td>24</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>OS</td>
<td>K-M curve</td>
<td>72</td>
<td>7</td>
</tr>
<tr>
<td>Zhao et al[42]</td>
<td>2019</td>
<td>China</td>
<td>Ovarian cancer</td>
<td>Tissue</td>
<td>56</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>OS</td>
<td>K-M curve</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>Zhang et al[43]</td>
<td>2019</td>
<td>China</td>
<td>Cervical cancer</td>
<td>Tissue</td>
<td>30</td>
<td>qRT-PCR</td>
<td>Median</td>
<td>OS CP</td>
<td>K-M curve</td>
<td>80</td>
<td>8</td>
</tr>
</tbody>
</table>
Table 2 Result of SNHG14 expression with overall survival.

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>Patients (n)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity ($I^2$, P)</th>
<th>Model</th>
<th>Begg’s test (P)</th>
<th>Egger’s test (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=60 month</td>
<td>708</td>
<td>1.53(1.12-2.07)</td>
<td>0.007</td>
<td>12.5%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 month</td>
<td>155</td>
<td>0.87(0.46-1.66)</td>
<td>0.677</td>
<td>0.0%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=60</td>
<td>459</td>
<td>1.22(0.77-1.94)</td>
<td>0.394</td>
<td>39.5%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>404</td>
<td>1.57(1.07-2.29)</td>
<td>0.020</td>
<td>0.0%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis method</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate</td>
<td>381</td>
<td>1.60(1.07-2.40)</td>
<td>0.022</td>
<td>0.0%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>482</td>
<td>1.30(0.81-2.07)</td>
<td>0.274</td>
<td>41.0%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digestive system</td>
<td>230</td>
<td>0.97(0.49-1.94)</td>
<td>0.942</td>
<td>48.5%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female reproductive system</td>
<td>242</td>
<td>1.97(1.18-3.30)</td>
<td>0.009</td>
<td>0.0%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>391</td>
<td>1.49(0.99-2.11)</td>
<td>0.055</td>
<td>0.0%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>863</td>
<td>1.39(1.06-1.83)</td>
<td>0.017</td>
<td>9.0%</td>
<td>Fixed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Result of SNHG14 expression with clinicopathological feature.

<table>
<thead>
<tr>
<th>Clinicopathological parameters studies (n)</th>
<th>Patients (n)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity ($I^2$, P)</th>
<th>Model</th>
<th>Begg’s test (P)</th>
<th>Egger’s test (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (elderly vs non-elderly)</td>
<td>944</td>
<td>1.02(0.77-1.33)</td>
<td>0.863</td>
<td>0.0%</td>
<td>Fixed</td>
<td>0.934</td>
<td>0.538</td>
</tr>
<tr>
<td>Gender (male vs female)</td>
<td>679</td>
<td>0.98(0.72-1.35)</td>
<td>0.915</td>
<td>27.8%</td>
<td>Fixed</td>
<td>0.493</td>
<td>0.756</td>
</tr>
<tr>
<td>Tumor size (large size vs small size)</td>
<td>764</td>
<td>1.60(1.20-2.14)</td>
<td>0.001</td>
<td>53.9%</td>
<td>Fixed</td>
<td>0.174</td>
<td>0.405</td>
</tr>
<tr>
<td>TNM stage (III + IV vs I + II)</td>
<td>820</td>
<td>0.54(0.40-0.71)</td>
<td>&lt;0.001</td>
<td>61.1%</td>
<td>Random</td>
<td>0.586</td>
<td>0.723</td>
</tr>
<tr>
<td>Lymph node metastasis (positive vs negative)</td>
<td>653</td>
<td>1.86(1.35-2.55)</td>
<td>&lt;0.001</td>
<td>63.7%</td>
<td>Random</td>
<td>0.938</td>
<td>0.349</td>
</tr>
<tr>
<td>Differentiation grade (poorly vs moderately and well)</td>
<td>525</td>
<td>1.95(1.36-2.80)</td>
<td>&lt;0.001</td>
<td>60.3%</td>
<td>Fixed</td>
<td>0.532</td>
<td>0.335</td>
</tr>
<tr>
<td>Distant metastasis (presence vs absence)</td>
<td>172</td>
<td>2.44(1.30-4.58)</td>
<td>0.005</td>
<td>0.0%</td>
<td>Random</td>
<td>1.000</td>
<td>0.743</td>
</tr>
</tbody>
</table>

Table 4 Summary of lncRNA SNHG14 functional role and related gene.
<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Expression</th>
<th>Functional role</th>
<th>Related gene</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>Upregulate/downregulate</td>
<td>Cell proliferation, apoptosis, invasion migration, metastasis, EMT</td>
<td>miR-519b-3p/DDX5, miR-92b-3p, miR-944/KRAS</td>
<td>Wang[26], Zhang[31], Pei[44]</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Upregulate</td>
<td>Cell proliferation, apoptosis, invasion migration, metastasis</td>
<td>miR-876-5p/SSR2, PABPC1, miR-217</td>
<td>Liao[27], Zhang[33], Xu[34]</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Upregulate</td>
<td>Cell proliferation, apoptosis, invasion migration</td>
<td>miR-211-3p/ESM1, miR-150-5p</td>
<td>Feng[28], Li[45]</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>Upregulate</td>
<td>Cell proliferation, apoptosis, invasion migration</td>
<td>miR-382-5p, miR-340</td>
<td>Zhou[30], Chen[19], Zhang[38]</td>
</tr>
<tr>
<td>Endometrial Carcinoma</td>
<td>Upregulate/downregulate</td>
<td>Cell proliferation, apoptosis, invasion migration, metastasis</td>
<td>miR-93-5p/ ZBTB7A, miR-655-3p</td>
<td>Zhang[32], Wang[36]</td>
</tr>
<tr>
<td>Acute myeloid leukaemia</td>
<td>Upregulate</td>
<td>Cell proliferation, apoptosis</td>
<td>miR-193b-3p/MCL1</td>
<td>Wang[29]</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Upregulate</td>
<td>Cell proliferation, apoptosis, invasion migration</td>
<td>miR-124</td>
<td>Sun[35]</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Upregulate</td>
<td>Cell proliferation, apoptosis, invasion</td>
<td>miR-5590-3p/YY1</td>
<td>Luo[37]</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Upregulate</td>
<td>Cell proliferation, apoptosis, invasion migration, EMT</td>
<td>miR-206/YWHAZ</td>
<td>Ji[39]</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Upregulate</td>
<td>Cell proliferation, apoptosis, invasion</td>
<td>miR-613</td>
<td>Deng[40]</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Upregulate</td>
<td>Cell proliferation, invasion migration</td>
<td>miR-125a-5p, DGCR8</td>
<td>Zhao[41], Zhao[42]</td>
</tr>
</tbody>
</table>

**Figures**
Figure 1

Flow diagram of this meta-analysis.
Figure 2

Forest plots for the association of SNHG14 expression with overall survival and subgroup analysis of SNHG14 expression with overall survival. (a) Forest plots for the association of SNHG14 expression with overall survival. (b) Subgroup analysis stratified by analysis method. (c) Subgroup analysis stratified by cancer type. (d) Subgroup analysis stratified by follow-up time. (e) Subgroup analysis stratified by sample size.
Figure 3

Forest plots for association of SNHG14 expression with clinicopathological features: Age (a), Gender (b), TNM staging (c), Tumor size (d), Lymph node metastasis (e), Differentiation grade (f), Distant metastasis (g).
Figure 4

Begg's publication bias plots (a) and Egger funnel regression test (b) of overall survival.
Figure 5

Sensitivity analysis for studies about OS by omitting each study sequentially.
Kaplan-Meier survival curves comparison of high and low expression of SNHG14 gene for OS of LGG (A), PAAD (B), MESO (C) and Correlation analysis of SNHG14 expression with survival using the COX method for different types of cancers in TCGA (D).

**Figure 6**

Kaplan-Meier survival curves comparison of high and low expression of SNHG14 gene for OS of LGG(A), PAAD (B), MESO (C) and Correlation analysis of SNHG14 expression with survival using the COX method for different types of cancers in TCGA (D).
Figure 7

Relationships between SNHG14 gene expression and TMB(a), MSI(b) in different types of cancers.
Figure 8

Correlation of SNHG14 gene expression with immune score: LGG(a), PAAD (c), SKCM(d) and stromal score: LGG(b).
Figure 9

Relationship between SNHG14 gene expression and infiltrating levels of immune cells in LGG, PAAD, MESO, SKCM, LIHC.

Supplementary Files

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

- SupplementaryAppendixItem1.docx