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Long non-coding RNA SNHG16 as a potential biomarker in hepatocellular carcinoma
A meta-analysis

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Abstract

Small nucleolar RNA host gene 16 (SNHG16) has recently been reported as a potential biomarker in various cancers. However, the prognostic value of SNHG16 in hepatocellular carcinoma (HCC) has not been investigated yet. Therefore, the purpose of this study was to reveal the association between SNHG16 expression and clinicopathological characteristics of HCC.

Standards-compliant literature was retrieved from multiple public databases, and data on overall survival, disease-free survival, and clinicopathological characteristics related to SNGH16 were extracted and meta-analysis was performed. Additionally, the Cancer Genome Atlas data were analyzed through the gene expression profiling interactive analysis database to verify previous results.

A total of 5 reports involving 410 patients with HCC were enrolled. The high expression of SNHG16 indicated worse overall survival (hazard ratio, 2.10; 95% CI, 1.22–3.60; $P = .007$) and disease-free survival (hazard ratio, 3.38; 95% CI, 1.10–10.40; $P = .03$). Additionally, the high expression of SNHG16 predicted a larger tumor size, metastasis, and advanced TNM stage.

SNHG16 could serve as a potential biomarker of poor prognosis in HCC.

Abbreviations: AFP = α-fetoprotein, DFS = disease-free survival, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HRs = hazard ratios, lncRNAs = long non-coding RNAs, OR = odds ratio, OS = overall survival, SNHG16 = small nucleolar RNA host gene 16.

Keywords: hepatocellular carcinoma, long non-coding RNA, meta-analysis, prognosis, SNHG16

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1. Introduction

Hepatocellular carcinoma (HCC), a disease that seriously endangers human health, is the sixth most common cancer worldwide according to the World Health Organization.[1] In 2018, 8,41,080 estimated new cases and 7,81,631 estimated deaths were reported worldwide, and the incidence of HCC is increasing faster than that of any other cancer.[2,3] HCC development is a complex multistep process that involves hepatocytic necrosis and regeneration,[4] and the major risk factors for HCC development are variable, including chronic hepatitis B or C virus infections.[5] Despite major advances in the treatment of HCC, such as resection, liver transplantation, tumor ablation, molecular targeted therapy, and immunotherapy, the current treatment fails to control HCC progression and death due to HCC to a great extent, and the 5-year survival rate remains at only 18%.[2,6,7] At present, the etiology and pathogenesis of HCC have not yet been fully clarified, and there is much anticipation in identifying novel targets and prognosis predictors.

Long non-coding RNAs (lncRNAs) are referred to RNAs longer than 200 nucleotides and have no protein-coding function.[8,9] Several studies have shown that lncRNAs are involved in many physiological and pathophysiological functions such as regulation of transcription, translation, localization, and function of proteins.[10] Accumulating evidence suggests that changes in the expression level of lncRNAs may play an important role in the development of a variety of carcinomas.[11]

Small nucleolar RNA host gene 16 (SNHG16), which was initially discovered in neuroblastoma, has recently been recognized

1

as an oncogenic lncRNA.[12] SNHG16 expression was upregulated in various cancers including laryngeal squamous cell carcinoma,[13] colorectal cancer,[14] cervical cancer,[15] and non-small cell lung cancer.[16] Additionally, high SNHG16 expression was detected in HCC and it was correlated with survival time, TNM stage, tumor size, metastasis, α-fetoprotein (AFP) level.[17–19] However, the number of samples in a single paper is not large enough, and the research parameters are different.

Therefore, the objective of this study was to conduct a quantitative meta-analysis to investigate the prognostic value of SNHG16 expression in HCC.

2. Material and methods

2.1. Search strategy

Electronic databases, such as PubMed-MEDLINE, Web of Science, and Cochrane Library, were screened for eligible studies by 2 researchers independently. The comprehensive search strategy included the terms 'SNHG16' and 'hepatocellular carcinoma' with appropriate synonyms. The publication date of the retrieved literature was from the inceptions of the databases up to June 22, 2020.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: histologically diagnosed HCC patients, SNHG16 expression examined in HCC tissues and adjacent normal tissues, inclusion of patient groups according to high or low expression of SNHG16, including the relationship between the expression of SNHG16 and prognosis, could obtain hazard ratios (HRs) or odds ratios (ORs), and published in English.

Exclusion criteria were as follows: non-human trials; studies only on the molecular function or mechanism of SNHG16; reviews, letters, case reports, or articles with bioinformatics analysis; insufficient data; duplicate data; and non-English articles. The ethical approval was not necessary because this article was a meta-analysis using published data.

2.3. Data extraction and quality control

Two investigators were blinded to each other while reviewing the trials and independently screened the reports. In case of any discrepancies, they negotiated to resolve them. If they could not be resolved, the senior investigator made the final decision. For each study, following information was extracted: first author, published year, country, tumor type, sample size, detection assay, clinical stage, outcome measures, survival analysis. In addition, the patients were divided into 2 groups according to the basis of age, sex, tumor size, lymph node metastasis, AFP level, TNM stage, and hepatitis B virus (HBV) infection, and the number of patients with high or low SNHG16 expression in each group were counted. Engauge Digitizer V 4.1 (Mark Mitchell) was used to estimate HR if only Kaplan–Meier survival curve was provided.[20] The Newcastle–Ottawa Scale was used by 2 authors to evaluate the quality of the literature, and we consider a score greater than 7 to be of high quality.[21]

2.4. Database analysis

Gene expression profiling interactive analysis was used to verify SNHG16 expression in HCC and its correlations with overall survival (OS) and disease-free survival (DFS).[22] The survival curves were plotted using Kaplan–Meier analysis and the log-rank test. The group cutoff was set as 'Median'.

2.5. Statistical analysis

All the statistical analyses in this study were performed using RevMan5.3 (Cochrane community, https://community.cochrane.org/help/tools-and software/revman-5/revman-5-download/). The heterogeneity between studies was examined by the Higgins I-squared (I^2) statistic and Cochran Q test. If $I^2 > 50\%$ and $P < .05$, heterogeneity was considered significant and the random-effects model was used for analysis. If $I^2 < 50\%$ and $P > .05$, heterogeneity was considered absent and the fixed-effect model was applied. Potential publication bias was evaluated using the Begg funnel-plot. $P < .05$ was considered statistically significant.

3. Results

3.1. Study identification and selection

A total of 10 articles were initially identified, of which 2 were excluded as duplicates. After reading the summary and full text carefully, 3 studies were further excluded because they were related to bioinformatics analysis or molecular structural analyses. Finally, 5 reports were included in this meta-analysis (Fig. 1).

These 5 reports, all published in 2019, contained 410 samples in total, having the lowest sample size as 50, largest sample size as 108, and average sample size as 82. The basic information of these reports is summarized in Table 1.

3.2. Association between SNHG16 and survival

A total of 3 articles reported the association between the expression level of SNHG16 and OS of HCC patients. As the heterogeneity was not obvious ($I^2 = 17\%$, $P = .30$), the fixed-effects model was performed and the pooled HRs indicated that the high expression level of SNHG16 was significantly associated with poor OS in patients with HCC (HR, 2.10; 95% CI, 1.22–3.60; $P = .007$) (Fig. 2A). Two studies were included to detect the association between the expression level of SNHG16 and DFS of patients with HCC. The random-effects model was performed because of heterogeneity ($I^2 = 84\%$,
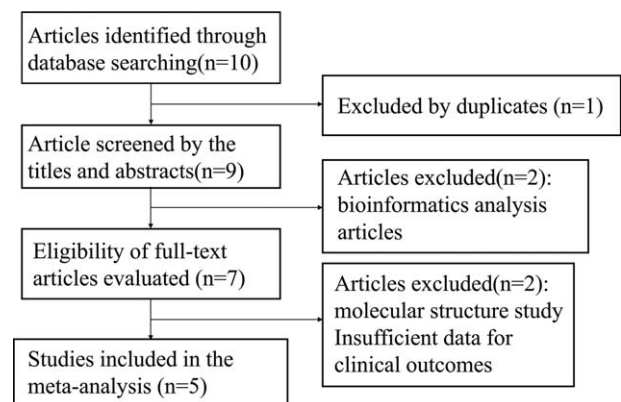

Figure 1. Flow chart of literature screening and inclusion.

Table 1

The main characteristics of the literature included in this meta-analysis.

Study	Year	Country	Tumor-type	Sample-type	Sample-size	Detection-assay	Clinical-stage	Outcome-measure	Survival-analysis	NOS
Guo Z	2019	China	HCC	Tissue	61	RT-PCR	I–IV	OS/DFS	Multivariate	8
Lin Q	2019	China	HCC	Tissue	88	RT-PCR	I–IV	OS	Multivariate	8
Ye J	2019	China	HCC	Tissue	103	RT-PCR	I–IV	N/A	N/A	7
Chen H	2019	China	HCC	Tissue	50	RT-PCR	I–IV	N/A	N/A	7
Zhong JH	2019	China	HCC	Tissue	108	RT-PCR	N/A	OS/DFS	N/A	7

DFS = disease free survival, HCC = hepatocellular carcinoma, N/A = not applicable, NOS = Newcastle–Ottawa Scale, OS = overall survival, RT-PCR = reverse transcription-polymerase chain reaction.

$P = .01$), and the results showed a significant association between the high expression level of SNHG16 and poor DFS in patients with HCC (HR, 3.38; 95% CI, 1.10–10.40, $P = .03$) (Fig. 2B).

3.3. Association between SNHG16 and clinicopathological parameters

The correlation between the expression level of SNHG16 and clinicopathological parameters was investigated using ORs and its 95% CIs. The results are presented in Figure 3 and Table 2. In addition to the random-effects model for analysis of the AFP level and HBV infection, the fixed-effect model was used for all other parameter analyses including age, sex, tumor size, metastasis, and TNM stage. The pooled OR values showed no significant correlation between the SNHG16 level and age, sex, AFP level or HBV infection. Notably, the high expression level of SNHG16 was significantly correlated with larger tumor size (OR, 3.18; 95% CI, 1.94–5.20, $P < .00001$), metastasis (OR, 3.12; 95% CI, 1.52–6.37, $P = .002$), and TNM stage (OR, 4.57; 95% CI, 2.51–8.31, $P < .00001$).

3.4. Publication bias

As shown in Figure 4, all the funnel plots were evenly distributed on both sides of the vertical axis and no obvious asymmetry was observed.

3.5. Bioinformatics validation

To further verify the results, the gene expression profiling interactive analysis dataset was used to investigate the expression level of SNHG16 in HCC (including 369 HCC samples and 160 normal tissue samples). As shown in Figure 5A, SNHG16 expression significantly increased in HCC tissues, compared with the normal control. Additionally, as shown in Figure 5B, the expression level of SNHG16 was significantly associated with the TNM stage in HCC. Moreover, the OS rates (log-rank; $P = .042$, HR = 1.4) (Fig. 5C) and DFS (log-rank; $P = .00046$, HR = 1.7) (Fig. 5D) with high expression of SNHG16 were significantly lower than those with low expression of SNHG16.

4. Discussion

According to eukaryotic whole-genome sequencing, only 2% genes are related to protein coding, whereas the rest are non-coding RNAs, which are further divided into lncRNAs and short non-coding RNAs according to their length.[23] Among them, lncRNAs are functionally defined as transcripts that are longer than 200 bp and have no protein-coding function.[8,9] Functionally, lncRNAs regulate gene expression at any level, including chromatin modification, transcription, and posttranscriptional processing. Numerous studies have shown that lncRNAs are involved in many physiological and pathophysiological functions, such as regulation of transcription, translation, localization, and function of
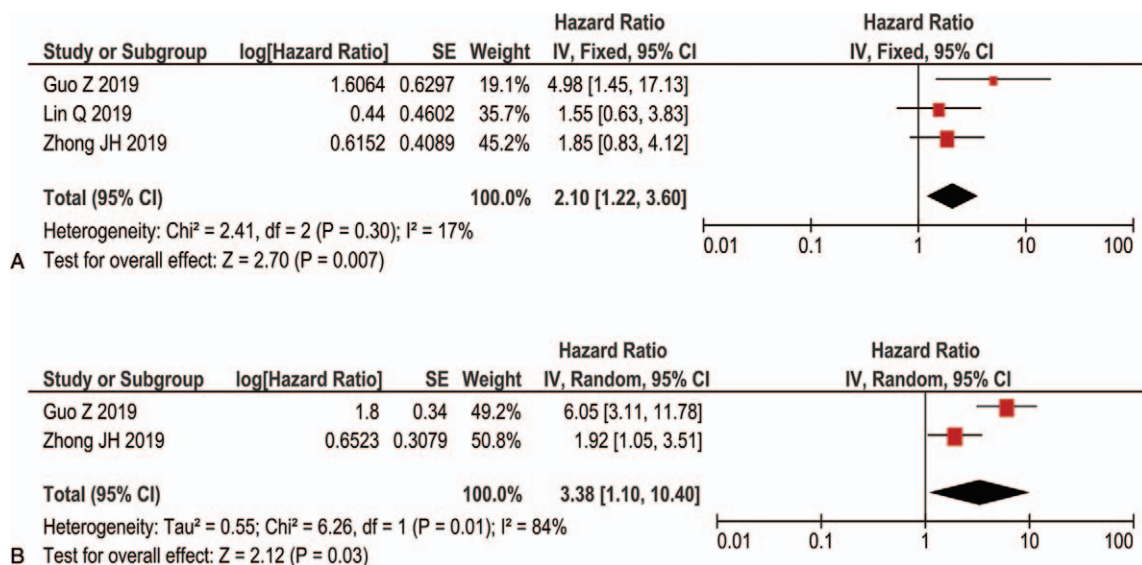

Figure 2. Forest plots evaluating the hazard ratios of high SNHG16 expression to (A) overall survival and (B) disease-free survival in HCC patients. HCC = hepatocellular carcinoma, SNHG16 = small nucleolar RNA host gene 16.
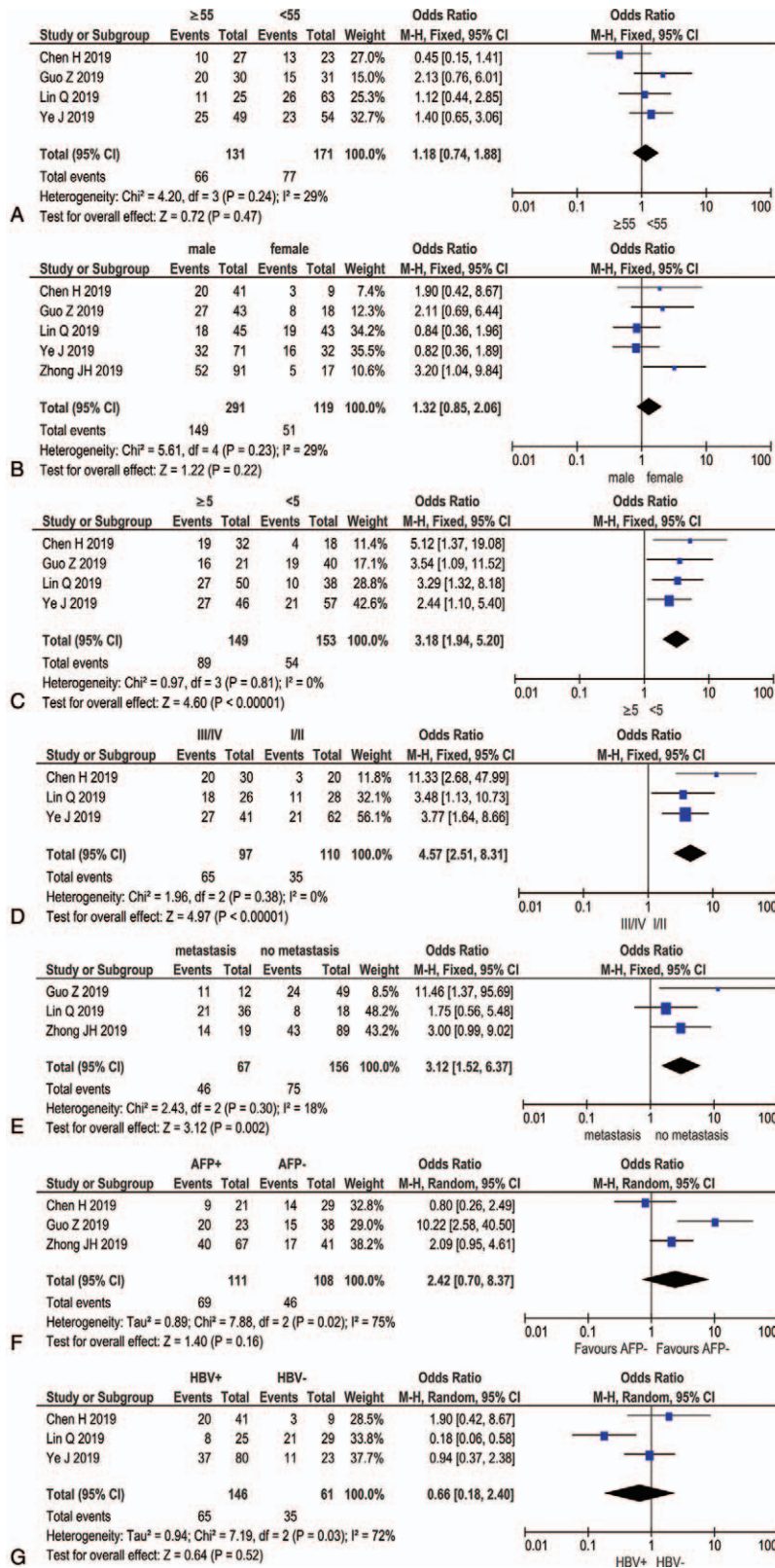
Figure 3. Forest plots evaluating the correlation between SNHG16 expression and clinicopathologic parameters, including (A) age, (B) sex, (C) tumor size, (D) TNM stage, (E) metastasis, (F) AFP level, and (G) HBV infection. AFP = α-fetoprotein, HBV = hepatitis B virus, SNHG16 = small nucleolar RNA host gene 16.

Table 2

The correlation between SNHG16 expression and clinicopathologic parameters in HCC.

Clinicopathologic parameters	No. of studies	No. of participants	Pooled OR (95% CI)	P	Model	Heterogeneity Chi^2, P, I^2 (%)
Age (≥55/<60)	4	302	1.18	.47	Fixed	4.20, .24, 29
Gender	5	410	1.32	.22	Fixed	5.61, .23, 29
Tumor size (≥5 cm/<5 cm)	4	302	3.18	.00001	Fixed	0.97, .81, 0
TNM stage	3	207	4.57	.00001	Fixed	1.96, .38, 0
Metastasis	3	223	3.12	.002	Fixed	2.43, .30, 18
AFP level	3	219	2.42	.16	Random	0.89, .02, 75
HBV infection	3	207	0.66	.52	Random	0.94, .03, 72

AFP = α-fetoprotein, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, OR = odds ratio, SNHG16 = small nucleolar RNA host gene 16.

proteins.[10] Aberrant expression or dysfunction of lncRNA is closely associated with various diseases.[24–26] Emerging evidence suggests that lncRNAs have a crucial role in the carcinogenesis process, for example, in case of glioma,[13] breast cancer,[27] lung cancer,[28] and HCC.[29]

SNHG16, located at chromosome 17q25.1, is a novel lncRNA observed in human cancers.[12] SNHG16 is overexpressed and could promote tumor development by acting as a competitive endogenous RNA in various cancers, including acute myeloblastic leukemia,[30] laryngeal squamous cell carcinoma,[31] colorectal cancer,[14] prostate carcinoma,[32] cervical cancer,[15] and HCC.[33] Downregulation of SNHG16 could inhibit cell proliferation, migration, invasion, and epithelial–mesenchymal transition in HCC and many other cancers.[31,33] However, SNHG16 overexpression inhibited HCC proliferation and chemoresistance.[34]

To further clarify the relationship between SNHG16 and HCC, we conducted this meta-analysis. The literature on SNHG16 and HCC published before June 22, 2020 was searched, and 10 articles, involving 410 samples in total, were included in this study. We found that an increase in SNHG16 expression predicts a decrease in OS and DFS. This correlation

was further verified through analysis using the Cancer Genome Atlas database.

Additionally, in this study, we analyzed the relationship between SNHG16 expression and clinicopathological characteristics of HCC. AFP is one of the most widely used biomarkers for HCC, but it has limited sensitivity and specificity, as many other non-malignant liver diseases can also result in a very high serum level of AFP.[35] In this study, the pooled results revealed no positive correlation between SNHG16 expression and the AFP level. HBV infection is regarded as the principal etiological risk factor for HCC,[36] and our pooled results also revealed no positive correlation between SNHG16 expression and HBV infection. However, the merged HRs indicated that the high expression of SNHG16 was significantly associated with larger tumor size, advanced TNM stage, and metastasis.

However, this study also has some limitations. First, all the literature included in the study was from Asia and lacked data from other regions. Second, the HR was not provided in some of the literature included in this study but was extracted from the survival curve, which might affect the accuracy of the data. Third, the number of reports included in the study was small, which might have a certain impact on the reliability of the conclusion; a
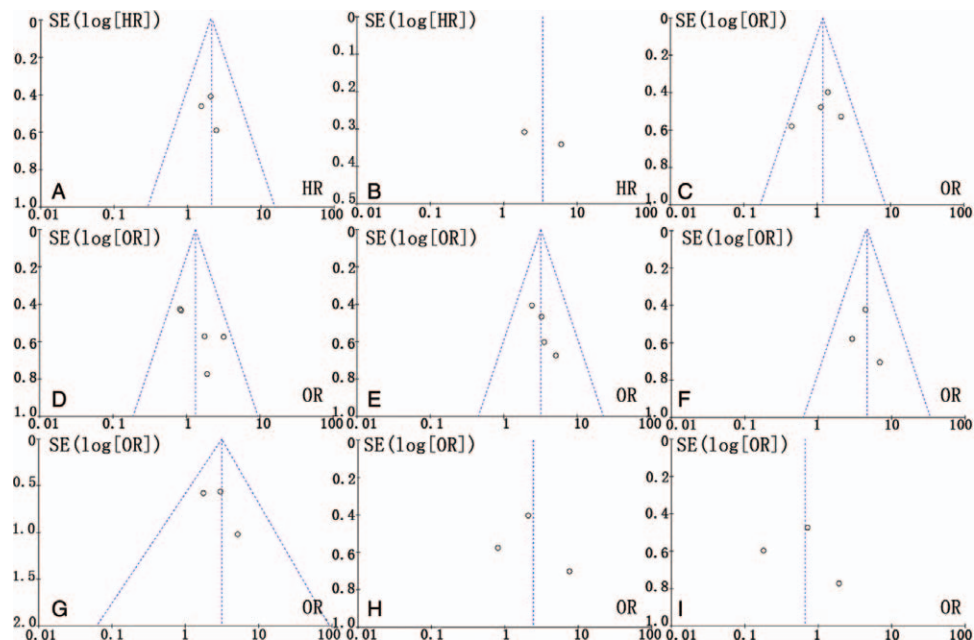

Figure 4. Funnel plot analysis of evaluating publication bias. Begg funnel plot of SNHG16 for (A) overall survival, (B) disease-free survival, (C) age, (D) sex, (E) tumor size, (F) TNM stage, (G) metastasis, (H) AFP level, and (I) HBV infection. AFP = α-fetoprotein, HBV = hepatitis B virus, SNHG16 = small nucleolar RNA host gene 16.
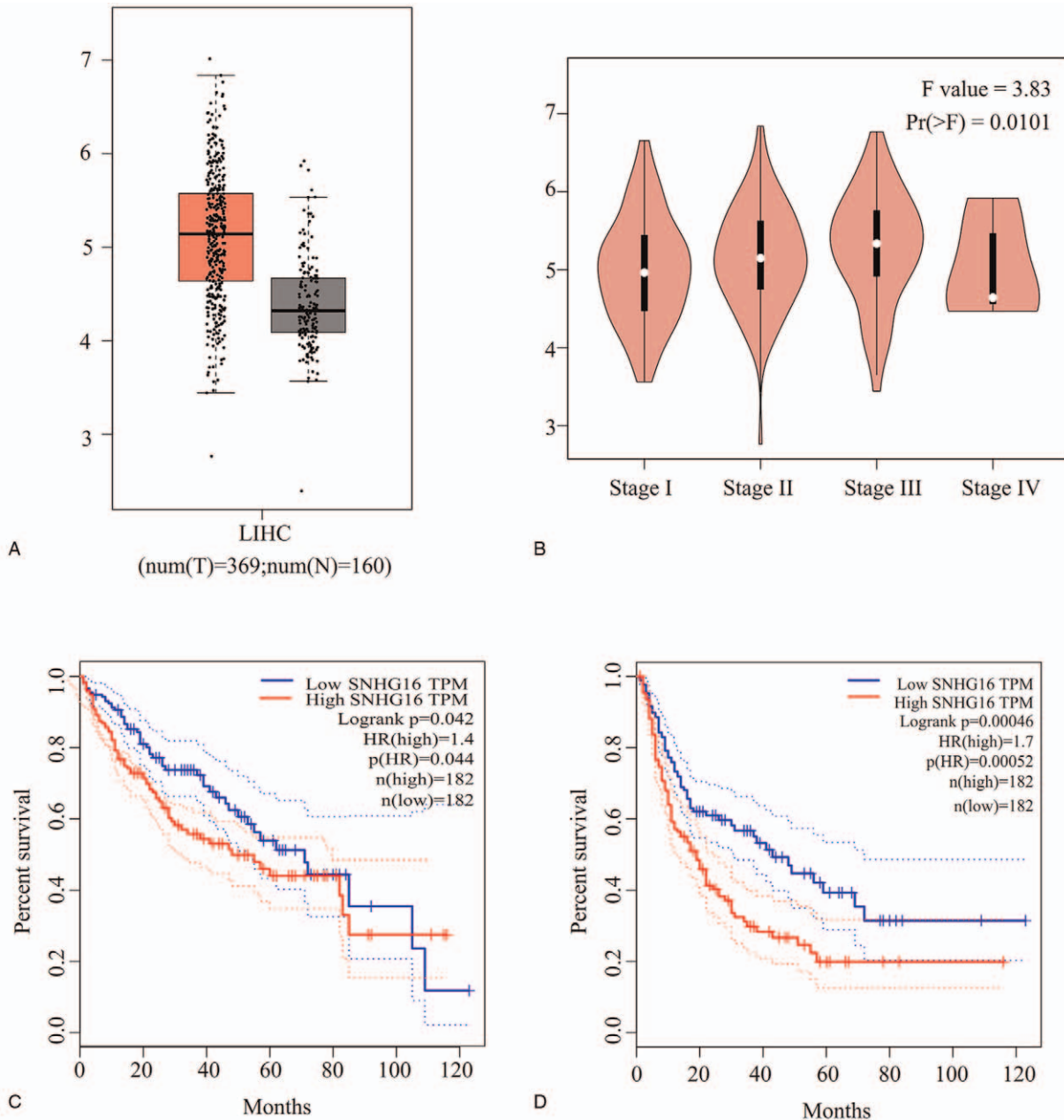
Figure 5. Validation of the expression of SNHG16 in HCC through GEPIA database. (A) The expression level of SNHG16 in LIHC (liver hepatocellular carcinoma). (B) The violin plot showing the expression of SNHG16 in samples of different clinical stages. (C) The association between the expression of SNHG16 and the overall survival in HCC. (D) The association between the expression of SNHG16 and the disease-free survival in HCC. GEPIA = gene expression profiling interactive analysis, HCC = hepatocellular carcinoma, SNHG16 = small nucleolar RNA host gene 16.

larger sample size is needed for further analysis. In addition, recent literatures have reported that molecular markers in serum can be used for non-invasive diagnosis,[37] prediction of survival and the treatment response in malignancies.[38,39] The expression level of serum SNHG16 and its role in the diagnosis, prognosis, and treatment of HCC should be further investigated.

5. Conclusions

Although our study had some limitations, it inferred that high SNHG16 expression was significantly correlated with poor OS and DFS, larger tumor size, advanced TNM stage and metastasis.

Therefore, SNHG16 might serve as a potential biomarker of poor prognosis in HCC.

Author contributions

Data curation: Po Gao, Jie Zhang.
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Investigation: Po Gao, Chao Xu, Kai Qu.
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Software: Qiuli Liu, Qingling Li, Chao Xu, Kai Qu, Jie Zhang.

Supervision: Qiuli Liu, Kai Qu.

Validation: Qiuli Liu.

Writing – original draft: Qiuli Liu.

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