Expression of small nucleolar RNA SNORA51 and its clinical significance in hepatocellular carcinoma

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Abstract. Small nucleolar RNA H/ACA Box 51 (SNORA51) is involved in progression of multiple cancers. However, its role in hepatocellular carcinoma (HCC) is still unclear. The aim of the present study was to analyze the expression of SNORA51 in HCC and its clinical significance. A total of 136 patients with HCC who underwent surgery from January 1, 2016 to December 31, 2018 were included. The expression of SNORA51 in cancer tissues and adjacent tissues was compared using reverse transcription-quantitative PCR and bioinformatics methods. Methylation of the SNORA51 promoter in cancer and adjacent tissues was compared using bioinformatics. The relationship between SNORA51 expression levels and clinicopathological characteristics of patients with HCC, in addition to prognosis, was analyzed. The expression of SNORA51 in HCC was significantly higher compared with that in adjacent tissues (P<0.05). starBase demonstrated that higher expression levels of SNORA51 were associated with a significantly worse prognosis of patients with HCC compared with those who had lower expression levels of SNORA51 (P<0.05). Bioinformatics analysis using The University of Alabama at Birmingham Cancer Data Analysis Portal demonstrated that methylation of the SNORA51 promoter region in HCC was significantly decreased compared with adjacent tissues (P<0.05). A high expression of SNORA51 was significantly associated with portal vein tumor thrombus, vascular invasion and TNM stage (P<0.05). The median survival time of patients with high SNORA51 expression was significantly lower compared with those who had low SNORA51 expression (P<0.05). Both uni- and multivariate Cox regression analysis demonstrated that SNORA51 expression was an independent risk factor that significantly worsened the prognosis of patients with HCC (P<0.05). The overexpression of SNORA51 in patients with HCC was significantly associated with a poor prognosis and may be related to the reduced methylation of the SNORA51 promoter region. Therefore, SNORA51 may be a promising biomarker for prediction of the prognosis of patients with HCC and may be a therapeutic target for the treatment of HCC in future.

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Introduction

Primary liver cancer (PLC) is one of the most common types of malignant tumor worldwide. PLC incidence and mortality rates rank sixth and third among malignant tumors globally, respectively (1). There were 906,000 new cases and 830,000 deaths globally from PLC in 2020, which highlights the worldwide healthcare burden caused by this condition (2). The most common histological type of PLC is hepatocellular carcinoma (HCC). The typical clinical manifestations of HCC include pain in the liver region, liver enlargement, ascites, etc. However, HCC has no obvious symptoms in its early stages and is often diagnosed in the mid to late stages of disease (3). Typically, at the time of diagnosis, liver function and immune system have been damaged, so the prognosis is poor (4,5). Therefore, the search for potential targets to predict the prognosis of patients with liver cancer is important to improve the prognosis of these patients. Small nucleolar RNA (snoRNA) is a type of small molecule RNA primarily expressed in the nucleolus with a length of 60-300 nucleotides (6). The role of snoRNA in the post-transcriptional modification and maturation of ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs) as well as other cellular RNAs has previously been reported (7). Due to the need for new ribosomes for cell growth, it is reasonable that tumor cells would exploit the mechanisms involved in ribosome biogenesis to support their fast growth (8). Recent studies reported that, in addition to participating in the normal biological functions of cells, snoRNA also serves an important role in the occurrence and progression of multiple cancers, including breast cancer (9), colorectal cancer (10), and pancreatic ductal adenocarcinoma (11). Previous studies have reported that abnormal methylation of snoRNA H/ACA Box 51 (SNORA51) gene is associated with an increased risk of lymphatic-hematopoietic cancer, including acute myelogenous leukemia (12,13). However, further research is required to elucidate the role of SNORA51 in HCC. Therefore, the present

study aimed to investigate expression of SNORA51 in HCC and its potential clinical significance.

Materials and methods

Patients and specimens. Liver cancer and paired adjacent liver (≥1 cm from the edge of the tumor) specimens were obtained from 136 patients (78 male and 58 female) with HCC (age, 35-84 years) who underwent hepatectomy at The First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) from January 1, 2016 to December 31, 2018. The inclusion criteria were as follows: Diagnosed with HCC by clinical evidence, image finding, and histologic examination; No serious heart, lung, kidney and coagulation dysfunction; With written informed consent for the study. The exclusion criteria were as follows: Metastatic tumors of the liver; radiotherapy, chemotherapy or other treatment before surgery; Declined to participate in this study.

Using the median expression of SNORA51 as the cut-off point, 136 patients were divided into high (n=68) and low expression (n=68) groups. Other clinical features measured included age, sex, cirrhosis, portal vein tumor thrombus, vascular invasion, tumor diameter, TNM stage, hepatitis B surface antigen (HBsAg) and α-fetoprotein (AFP) levels and overall patient survival. The final follow-up was December 31, 2021. The present study was approved by the Xi'an Jiaotong University Health Science Center Ethics Committee (Xi'an, China; approval no. XJTU-RE-2021644) and all patients provided written, informed consent for participation in the study.

RNA extraction and reverse transcription-quantitative (RT-q) PCR. Total RNA was extracted from tissue using TRIzol® (Invitrogen; Thermo Fisher Scientific, Inc.) and the purity and concentration of RNA were determined using a spectrophotometer (Thermo Fisher Scientific, Inc.). cDNA was obtained using the HiScript® II Reverse Transcriptase SuperMix (Vazyme Biotech Co., Ltd.) according to the manufacturer's instructions. The expression levels of SNORA51 in tissue samples were evaluated using FastStart Universal SYBR Green Master (Rox; Roche Diagnostics) according to the manufacturer's instructions. The thermocycling conditions were as follows: Initial denaturation at 95˚C for 1 min, followed by 40 cycles of 90˚C for 20 sec, 55˚C for 30 sec and 68˚C for 50 sec using the Bio-Rad CFX96 RT-qPCR system (Bio-Rad Laboratories, Inc.). Amplification specificity was assessed by melting curve analysis. U6 was used as an internal control for standardization. All assays were performed three times and data were analyzed using the comparative $2^{-\Delta\Delta Cq}$ method (14). The primer sequences were as follows: SNORA51 forward (F), 5'-GCCTCCTGGTGCTTACCACA-3' and reverse (R), 5'-GGGCCTGAGCTGAGGTGTAT-3' and U6 F, 5'-CTCGCTTCGGCAGCACA-3' and R, 5'-AACGCTTCACGAATTTGCGT-3'.

Database analysis. Data from patients with HCC from The Cancer Genome Atlas Program (TCGA) (15) database were analyzed using starBase 3.0 (starbase.sysu.edu.cn/) and The University of Alabama at Birmingham Cancer Data Analysis Portal (UALCAN; ualcan.path.uab.edu/index.html). A total of 362 patients with HCC were divided into high and low SNORA51 expression groups (both n=181) using the median of SNORA51 expression as the cut-off point. Spearman's correlation coefficient between SNORA51 expression and survival time of patients with HCC was analyzed using starBase. The methylation status of the SNORA51 promoter region in HCC (n=377) and adjacent tissues (n=50) (also from TCGA) was analyzed using UALCAN. The inclusion criteria were as follows: i) Name of the disease listed as HCC and ii) available data on expression levels of SNORA51.

Statistical analysis. SPSS software (version 16.0; SPSS, Inc.) was used for statistical analysis. Data are presented as the mean ± standard deviation (SD). A two-tail paired student's t test was used to compare the means of the two groups of patients and χ^2 test was applied to analyze categorical data. Cox regression model was used for univariate and multivariate analysis. Overall survival curves were plotted using the Kaplan-Meier method and log-rank test was utilized for examining the differences in survival rates between groups. All experiments were repeated three times independently. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Expression levels of SNORA51 are significantly increased in HCC tissues. The results of the RT-qPCR demonstrated that the expression levels of SNORA51 in HCC were significantly higher compared with those in adjacent tissue (Fig. 1A). Bioinformatics analysis of data from patients with HCC using starBase demonstrated an increased expression of SNORA51 in cancer compared with adjacent tissues (Fig. 1B).

High expression of SNORA51 was associated with portal vein tumor thrombus, vascular invasion and tumor stage. The association between SNORA51 expression levels and clinicopathological characteristics of patients with HCC was analyzed. These results demonstrated that high expression of SNORA51 was significantly associated with portal vein tumor thrombus, vascular invasion and tumor stage, but not with age, sex, tumor diameter, HBsAg and AFP levels or cirrhosis (Table I).

High expression of SNORA51 is associated with a worse prognosis of HCC patients. The relationship between SNORA51 expression and overall survival of patients with HCC was assessed using Kaplan-Meier curves. The median survival time of patients with HCC in the high SNORA51 expression group [16 months (95% CI, 12.475-18.135 months)] was significantly shorter compared with that in the low SNORA51 expression group [36 months (95% CI, 26.196-45.348 months)], which suggested that high expression of SNORA51 was negatively associated with prognosis of patients with HCC (Fig. 2A). Analysis of samples from TCGA using starBase demonstrated that high expression levels of SNORA51 were associated with poorer prognosis of patients with HCC compared with those with low expression of SNORA51 (Fig. 2B).

Analysis of factors affecting the prognosis of patients with HCC. Univariate and multivariate Cox regression analysis demonstrated that high SNORA51 expression levels, portal vein tumor thrombus, tumor diameter and TNM stage were

Table I. Association between SNORA51 expression and clinicopathological features of patients with hepatocellular carcinoma.

Clinicopathological feature	Total number of patients	SNORA51 expression		χ^2-value	P-value
		High	Low		
Age, years				0.472	0.606
>60	72	38	34		
≤60	64	30	34		
Sex				1.924	0.225
Male	78	43	35		
Female	58	25	33		
Cirrhosis				1.666	0.268
Present	43	18	25		
Absent	93	50	43		
Portal vein tumor thrombus				9.598	0.003
Present	45	31	14		
Absent	91	37	54		
Vascular invasion				15.308	<0.001
Present	86	54	32		
Absent	50	14	36		
Tumor diameter, cm				0.491	0.599
≤3	54	29	25		
>3	82	39	43		
TNM stage				15.562	<0.001
I-II	67	22	45		
III-IV	69	46	23		
Hepatitis B surface antigen				1.074	0.388
Positive	76	35	41		
Negative	60	33	27		
α-fetoprotein level (ng/ml)				0.319	0.779
≤20	14	6	8		
>20	122	62	60		

SNORA51, small nucleolar RNA H/ACA Box 51.

independent risk factors in predicting overall survival of patients with HCC (Table II).

Methylation of SNORA51 promoter is reduced in HCC tissue. Analysis using UALCAN demonstrated that the methylation of the SNORA51 promoter region in HCC tissue was significantly reduced compared with that in adjacent tissue (Fig. 3).

Discussion

HCC is the most common type of malignant tumor of the liver, accounting for >90% of PLC cases (16). The occurrence and development of HCC is a complex process involving multiple factors and genes and the mechanisms have not yet been fully elucidated. The early detection, diagnosis and treatment of patients with HCC are vital to increase the survival rate (17). Currently, the clinical treatment plan for patients with HCC and prognostic evaluation largely rely on tumor staging and there is a lack of specific molecular targets associated with treatment and prognosis of HCC (18).

snoRNAs are non-coding RNAs present in the nucleoli of eukaryotic cells. They are primarily divided into C/D box snoRNAs and H/ACA box snoRNAs. Both types of snoRNA combine with ribonucleoproteins to form stable and functional snoRNP complexes that participate in post-transcriptional maturation process of rRNA and other types of small RNA (19). Due to the unitary function of snoRNAs, their association with tumors is unclear. However, snoRNAs participate in the occurrence and development of tumors by regulating cell proliferation, differentiation and apoptosis (20,21). Yi *et al* (22) reported that SNORA42 increases viability of prostate cancer cells and promotes cancer cell migration and epithelial-mesenchymal transformation and high expression of SNORA42 is significantly associated with poor prognosis of patients with prostate cancer. Okugawa *et al* (23) reported that overexpression of SNORA42 enhances proliferation, migration and invasion of colon cancer cells and high expression of SNORA42 is an independent risk

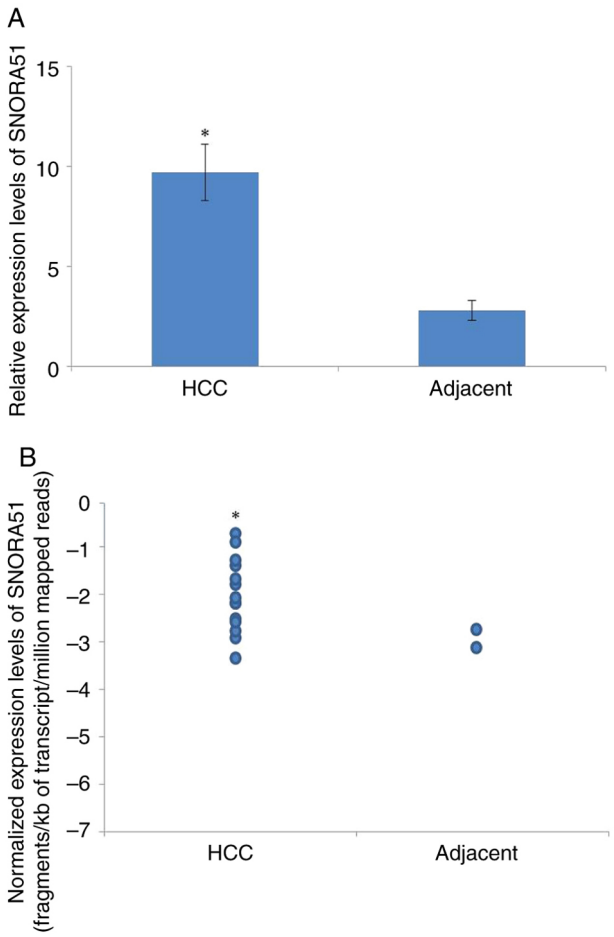

Figure 1. Relative expression of SNORA51 in HCC was higher than thain in adjacent tissue. (A) Expression levels of SNORA51 in HCC and adjacent tissue detected by reverse transcription-quantitative PCR. *P<0.05 vs. adjacent tissues. (B) Bioinformatics analysis of SNORA51 expression in HCC and adjacent normal tissue. HCC, hepatocellular carcinoma; SNORA51, small nucleolar RNA H/ACA Box 51. *P<0.05 vs. adjacent tissues.

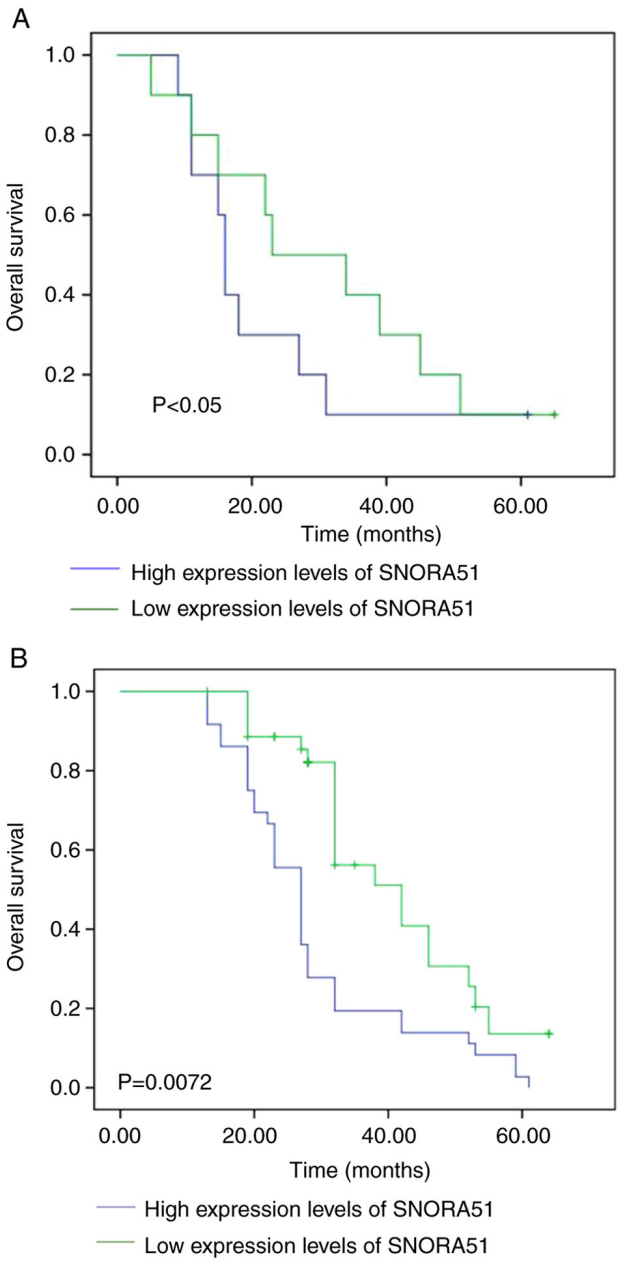

Figure 2. High expression of SNORA51 was associated with a worse prognosis of HCC patients. (A) Median survival time of HCC patients in high SNORA51 expression group was significantly shorter compared with the low SNORA51 expression group. The ticks in the Low expression curve indicated that the patient was missing at this time. (B) Bioinformatics analysis demonstrated that overexpression of SNORA51 was associated with poor prognosis in patients with HCC. The ticks in the Low expression curve indicated that the patient was missing at this time. HCC, hepatocellular carcinoma; SNORA51, small nucleolar RNA H/ACA Box 51.

factor affecting the survival of patients with colorectal cancer. In addition, snoRNA U50 is downregulated in breast cancer and overexpression of U50 inhibits colony formation of breast cancer cell lines (24). The specific expression of snoRNAs in tumor tissue suggests that these molecules may be a biomarker for tumor diagnosis and a potential therapeutic target. The expression of snoRNAs in tumor tissue is also closely related to the prognosis of patients, therefore, snoRNAs could be a potential biomarker for tumor prognosis (25).

A previous study reported that SNORA51 may be involved in progression of multiple myeloma (26). Bortezomib treatment and incubation with vitamin D and K have inhibitory effects on expression of SNORA51 in U266 myeloma cells and decrease tumor cell proliferation. Liang *et al* (27) reported that SNORA51 is highly expressed in breast cancer patients without non-sentinel lymph node invasion. Another clinical study reported that SNORD51 and SNORD57, in addition to small RNA fragments originating from their 3' ends, are detected in the plasma of patients with colorectal cancer, which suggested that these snoRNAs may act as potential biomarkers for the diagnosis of colorectal cancer (28). However, the role and mechanism of SNORA51 in HCC is still unclear.

Systematic treatment regimens have made significant progress in the treatment of advanced HCC. Nowadays, patients with stage III-IV advanced HCC receive systemic treatment rather than surgery (29); however, at time of patient recruitment, a number of patients with advanced HCC still received aggressive surgical treatment (30). In this study, liver cancer and paired adjacent liver specimens obtained from 136 HCC patients (including 69 III-IV advanced HCC) underwent hepatectomy were compared. The present study demonstrated that expression of SNORA51 in HCC was significantly higher

Table II. Uni- and multivariate Cox regression analysis of prognostic factors in patients with hepatocellular carcinoma.

	Univariate analysis		Multivariate analysis	
Factor	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (≤60 vs. >60 years)	0.852 (0.583-1.224)	0.154		
Sex (female vs. male)	0.947 (0.687-2.564)	0.322		
Cirrhosis (present vs. absent)	1.142 (0.864-2.953)	0.188		
Portal vein tumor thrombus (present vs. absent)	2.417 (1.346-4.023)	0.007	2.002 (1.159-3.873)	0.013
Vascular invasion (present vs. absent)	1.352 (0.808-2.193)	0.224		
Tumor diameter (>3 vs. ≤3 cm)	2.295 (1.611-3.618)	<0.001	1.956 (1.447-3.126)	0.009
TNM stage (III-IV vs. I-II)	2.515 (1.366-4.465)	<0.001	2.214 (1.482-3.996)	0.024
Hepatitis B surface antigen (negative vs. positive)	0.986 (0.698-1.422)	0.312		
α-fetoprotein (≤20 vs. >20 ng/ml)	1.755 (0.842-4.422)	0.256		
Small nucleolar RNA H/ACA Box 51 expression (high vs. low)	3.087 (1.690-5.214)	0.001	2.856 (1.354-4.463)	0.003

HR, hazard ratio.

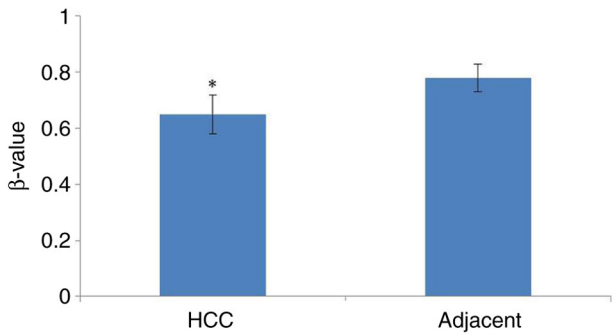

Figure 3. Methylation of the SNORA51 promoter was reduced in HCC tissue Bioinformatics analysis demonstrated that the methylation of SNORA51 promoter region in HCC was significantly lower compared with that in adjacent tissue. Data were presented as mean ± SD. *P<0.05 vs. adjacent. SNORA51, small nucleolar RNA H/ACA Box 51.

compared with that in adjacent tissue; data from patients with HCC using starBase demonstrated the same results. These results were consistent with the aforementioned studies. The present study also demonstrated that expression of SNORA51 was related to portal vein tumor thrombus, vascular invasion and TNM staging, which indicated that SNORA51 may be involved in tumor invasion and metastasis. The prognostic analysis demonstrated that the median survival time of patients with HCC with high SNORA51 expression was significantly shorter compared with that of patients with low SNORA51 expression; data from patients with HCC using starBase demonstrated the same results. Uni- and multivariate Cox regression analysis demonstrated that high SNORA51 expression was an independent risk factor affecting the prognosis of patients with HCC, which indicated that SNORA51 could be a biomarker for the prognosis of HCC and potentially be a future therapeutic target. UALCAN analysis demonstrated that methylation of the SNORA51 promoter region in HCC was significantly reduced compared with adjacent tissues, which indicated that upregulation of SNORA51 in HCC may be related to decreased methylation of its promoter region. This may serve as a future research direction for further study of the mechanism of SNORA51 in HCC.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LY, MZ and ZM analyzed and interpreted the data. ZM performed RT-qPCR and database analysis. LY wrote the manuscript. SW designed the experiments and reviewed the manuscript. LY and SW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Xi'an Jiaotong University Health Science Center Ethics Committee (Xi'an, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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