

# The tissue expression levels of SUMO1P 3 may be a reliable prognostic biomarker to predict the clinical outcomes in patients with HCC

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## Abstract

Small ubiquitin-like modifier 1 pseudogene 3 (SUMO1P3) is a novel identified long non-coding RNA that is upregulated in several cancers and exerts its oncogenic effects via multiple pathways. SUMO1P3 was significantly higher in HCC tissues and cells than in non-cancerous specimens and normal cells. SUMO1P3 knockdown inhibited the proliferation, migration, and invasion of HCC cells. In the present study, we investigated the clinical significance and prognostic value of SUMO1P3 in HCC.

A total of 123 patients were pathologically diagnosed as primary HCC and underwent surgical resection at the Department of Hepatopancreatobiliary Surgery, The Second Affiliated Hospital of Kunming Medical University from March 2014 to November 2019. The expression differences between HCC tissues and matched normal tissues were analyzed using paired Student's *t* test. Chi-squared test was used for correlation analysis. Survival curves were plotted using the Kaplan–Meier method and were compared via the log-rank test. The independent prognostic value of SUMO1P3 expression was evaluated using results from univariate and multivariate Cox regression models.

As revealed by quantitative RT-PCR analysis, SUMO1P 3 expression level was significantly higher in HCC cancer tissues compared with normal adjacent tissues (mean±SD: 4.341±1.320 vs 1.000±0.3666,  $P < .001$ ). The  $\chi^2$  test showed that the SUMO1P 3 expression level was significantly associated with tumor size ( $P = .031$ ), capsular invasion ( $P = .011$ ), vascular invasion ( $P = .004$ ), Edmondson–Steiner grade ( $P = .002$ ), and TNM stage ( $P = .001$ ). The patients with high SUMO1P 3 expression showed shorter 5-year overall survival than those with low SUMO1P 3 expression ( $P = .034$ ; log-rank test). Multivariate regression analysis showed that the status of SUMO1P 3 expression was an independent prognostic factor for overall survival (HR=2.107, 95% CI: 1.478–9.014,  $P = .031$ ).

The expression levels of SUMO1P 3 may be a reliable prognostic biomarker to predict the clinical outcomes in patients with HCC.

**Abbreviations:** cDNA = complementary DNA, HCC = hepatocellular carcinoma, lncRNAs = long non-coding RNAs, SD = standard deviation, SUMO1P 3 = small ubiquitin-like modifier 1 pseudogene 3, TNM = tumor-node-metastasis.

**Keywords:** HCC, liver cancer, lncRNA, prognosis, SUMO1P 3

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The authors have no conflicts of interest to disclose.

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

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## 1. Introduction

Hepatocellular carcinoma (HCC) has been reported to be the most common type of primary liver cancer. It accounts for the second leading cause of cancer-related deaths.<sup>[1]</sup> Hepatocarcinogenesis is a complex process, which is associated with the accumulation of genetic and epigenetic changes during the HCC progression.<sup>[2,3]</sup> At present, because of the poor understanding of pathological molecular mechanisms in HCC, the effective therapy for this cancer is very limited.<sup>[4,5]</sup> Therefore, it is essential to identify the mechanisms that underlie HCC metastasis for the development of novel sensitive and effective therapies.

Long non-coding RNAs (lncRNAs) are non-coding transcripts more than 200bp in length. Accumulating evidences indicated that lncRNAs are extensively participated in physiological processes such as cell proliferation, cell differentiation, and cell cycle.<sup>[6]</sup> In addition, lncRNAs play an important role in regulating proliferation, invasion and metastasis, angiogenesis, and viability in different tumors.<sup>[7]</sup> lncRNA expression has also been shown to be clinically relevant to cancer diagnosis and prognosis determination.

Small ubiquitin-like modifier 1 pseudogene 3 (SUMO1P3) is a novel identified long non-coding RNA that was originally identified as a potential prognostic and therapeutic target for gastric cancer.<sup>[8]</sup> SUMO1P3 is a lncRNA that is upregulated in several cancers and exerts its oncogenic effects via multiple pathways. Previously, Wu et al found that the expression of SUMO1P3 was significantly higher in HCC tissues and cells than in non-cancerous specimens and normal cells. SUMO1P3 knockdown inhibited the proliferation, migration, and invasion of HCC cells. SUMO1P3 enhances Wnt/ $\beta$ -catenin pathway through sponging miR-320a, thus contributing to aggressive progression of HCC.<sup>[9]</sup> Zhou et al found that knockdown of SUMO1P3 repressed tumor growth and invasion and enhanced radiosensitivity in HCC.<sup>[10]</sup> In the present study, we investigated the clinical significance and prognostic value of SUMO1P3 in HCC.

## 2. Materials and methods

### 2.1. Patients and samples

A total of 123 patients were pathologically diagnosed as primary HCC and underwent surgical resection at the Department of hepatopancreatobiliary surgery, The Second Affiliated Hospital of Kunming Medical University from March 2014 to November 2019. In addition, the adjacent normal liver tissues were collected as controls (separated from  $\geq 2$  cm from the tumor margin and were confirmed without tumor cells under a microscope). All fresh tissues collected from surgery were stored immediately at  $-80^{\circ}\text{C}$  for use. None of the patients received radiotherapy, biotherapy, or systemic chemotherapy. The primary clinical and pathological features (including age, gender, tumor volume, distant metastasis, and TNM stage) were obtained from the medical records. HCC stage was classified according to the modified tumor-node-metastasis (TNM) cancer staging system published by the International Union Against Cancer (UICC, 2009). Written informed consent was obtained from all the patients in this study. We obtained the consent of the Research Ethics Committee of The Second Affiliated Hospital of Kunming Medical University. The clinicopathological information is summarized in Table 1.

### 2.2. RNA extraction and quantitative real-time PCR

TRIzol reagent (Invitrogen, Carlsbad, CA) was utilized to separate total RNA in tissues. First-strand complementary DNA (cDNA) was synthesized using 1  $\mu\text{g}$  of total RNA and the PrimeScript RT reagent Kit (Promega, Madison, WI). qRT-PCR was applied to measure the relative RNA level using the TaqMan Power SYBR Green PCR Mix kit (Thermo Fisher Scientific, Waltham, MA). qPCR was performed using Applied Biosystems 7500 Real Time PCR System (Applied Biosystems, Foster City, CA). The thermal cycle was as follows: pre-denaturation at  $95^{\circ}\text{C}$  for 1 min, followed by 40 cycles at  $95^{\circ}\text{C}$  for 15 s,  $60^{\circ}\text{C}$  for 30 s, and  $72^{\circ}\text{C}$  for 30 s. The threshold cycle was determined after the reactions. The relative miRNA and lncRNA expression levels were calculated based on comparative threshold cycle (Ct) technique ( $2^{-\Delta\Delta\text{Ct}}$ ). The expression level was normalized to GAPDH levels of each sample. The primer sequences were as follows: SUMO1P3 primers, forward: 5'-ACTGGAATGGAGGAAGA-3', reverse: 5'-TGAGAAAG-GATTGAGGAAAAG-3'; GAPDH primers, forward: 5'-

**Table 1**

**Summary of clinicopathologic features of the patients with HCC.**

Variables	Cases (n)	SUMO1P3 expression		P
		High (n=63)	Low (n=60)	
Age (years)				
<60	56	28	28	.857
$\geq 60$	67	35	32	
Sex				
Female	44	20	24	.354
Male	79	43	36	
AFP (ng/mL)				
<20	49	23	26	.466
$\geq 20$	74	40	34	
Liver cirrhosis				
Yes	78	42	36	.461
No	45	21	24	
Tumor size (cm)				
<5	57	23	34	.031
$\geq 5$	66	40	26	
Tumor number				
Solitary	91	45	46	.543
Multiple	32	18	14	
Capsular invasion				
Yes	29	21	8	.011
No	94	42	52	
Vascular invasion				
Yes	31	23	8	.004
No	92	40	52	
Edmondson–Steiner grade				
I/II	64	24	40	.002
III/IV	59	39	20	
TNM stage				
I/II	90	38	52	.001
III	33	25	8	

CGCTCTCTGCTCCTCCTGTTC-3', reverse: 5'-ATCCGTT-GACTCCGACCTTAC-3'.

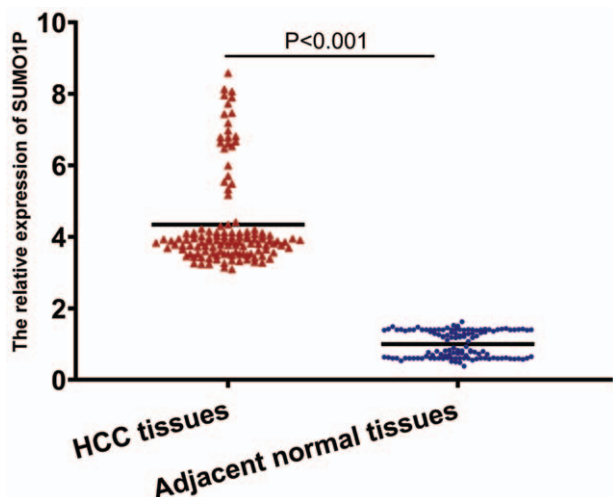
### 2.3. Statistical analysis

The statistical analyses were performed using SPSS 19.0 (SPSS Inc, Chicago, IL) and GraphPad Prism 7 (GraphPad Software, CA). The expression differences between HCC tissues and matched normal tissues were analyzed using paired Student's *t* test. Chi-squared test was used for correlation analysis. Survival curves were plotted using the Kaplan–Meier method and were compared via the log-rank test. The independent prognostic value of SUMO1P3 expression was evaluated using results from univariate and multivariate Cox regression models.  $P < .05$  was considered as statistically significant.

## 3. Results

### 3.1. Expression level of SUMO1P3 in human HCC tissues and adjacent normal liver tissues

We analyzed the expression levels of SUMO1P3 in primary HCC samples and normal adjacent liver samples from 123 patients with HCC. As revealed by quantitative RT-PCR analysis, SUMO1P3 expression level was significantly higher in HCC cancer tissues compared with normal adjacent tissues (mean  $\pm$  SD:  $4.341 \pm 1.320$  vs  $1.000 \pm 0.3666$ ,  $P < .001$ , shown in Fig. 1).



**Figure 1.** As revealed by quantitative RT-PCR analysis, SUMO1P3 expression level was significantly higher in HCC cancer tissues compared with normal adjacent tissues (mean  $\pm$  SD: 4.341  $\pm$  1.320 vs 1.000  $\pm$  0.3666,  $P < .001$ ).

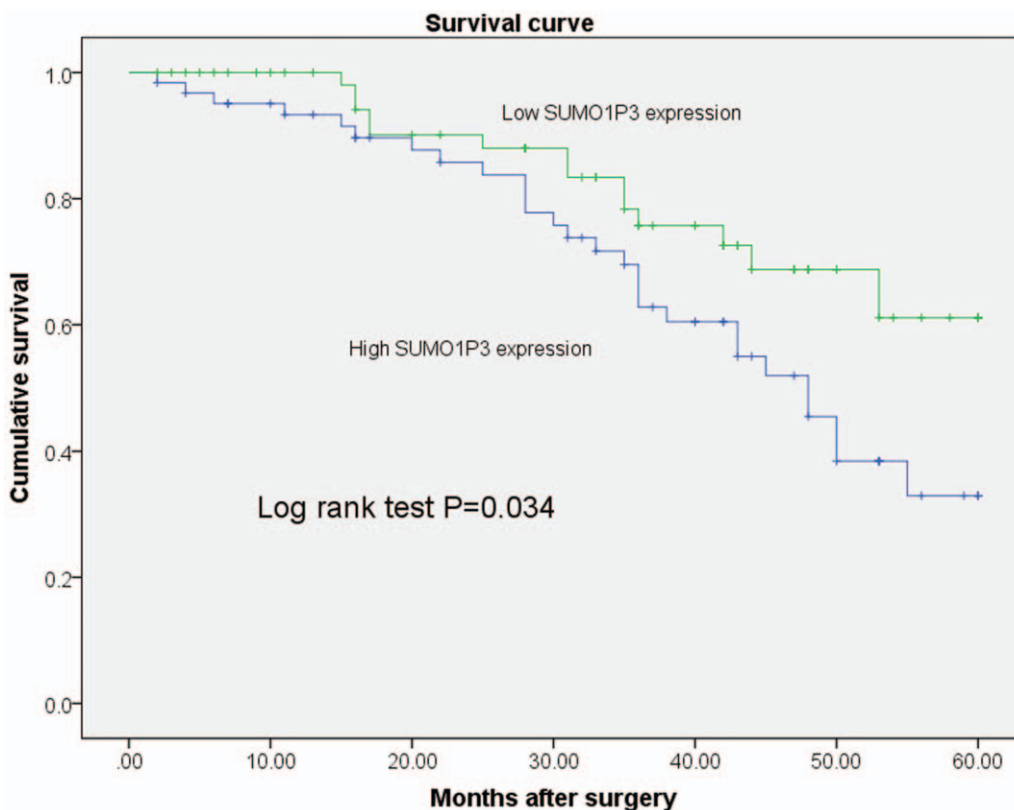
The 123 HCC patients were classified into two groups according to the median of SUMO1P3 expression level as determined by quantitative RT-PCR. Sixty-three cases were placed in the high SUMO1P3 expression group and 60 in the low SUMO1P3 expression group.

**3.2. The correlation between SUMO1P3 and clinicopathological features of patients with HCC**

In order to better understand the potential roles of tissue SUMO1P3 in HCC development and progression, the correlation between the tissue SUMO1P3 levels and the clinicopathological factors of the HCC patients were also assessed. The  $\chi^2$  test showed that there was no significant correlation between the SUMO1P3 levels and factors such as age, gender, AFP level, liver cirrhosis, and tumor number (all  $P > .05$ , shown in Table 1). However, the SUMO1P3 expression level was significantly associated with tumor size ( $P = .031$ ), capsular invasion ( $P = .011$ ), vascular invasion ( $P = .004$ ), Edmondson–Steiner grade ( $P = .002$ ), and TNM stage ( $P = .001$ , shown in Table 1).

**3.3. The prognostic value of SUMO1P3 in HCC**

To assess whether the expression of SUMO1P3 was a tumor prognostic biomarker, the overall survival was investigated with respect to expression levels of SUMO1P3 in primary HCC. A total of 123 HCC patients included in the study during the follow-up period and the survival curves plotted by Kaplan–Meier method were shown. As shown in Figure 2, the patients with high SUMO1P3 expression showed shorter 5-year overall survival than those with low SUMO1P3 expression ( $P = .034$ ; log-rank test). Table 2 showed the multivariate analysis of the clinicopathological factors related to patient prognosis. Multivariate regression analysis showed that the status of SUMO1P3 expression was an independent prognostic factor for overall survival (HR = 2.107, 95% CI: 1.478–9.014,  $P = .031$ ). Thus,



**Figure 2.** Analysis of SUMO1P3 expression in the prognosis of HCC patients using a Kaplan–Meier plotter.

**Table 2**  
**Multivariate analysis of overall survival in patients with HCC.**

Variable	Hazard ratio	95% CI	P
Age	1.672	0.472–4.293	.418
Sex	1.283	0.374–3.662	.522
AFP	2.394	0.772–5.384	.071
Liver cirrhosis	2.634	0.555–3.494	.077
Tumor size	2.399	0.772–5.912	.069
Tumor number	1.293	0.372–2.294	.178
Capsular invasion	2.889	2.391–10.374	.005
Vascular invasion	3.102	2.816–11.228	.003
Edmondson–Steiner grade	3.191	2.117–13.471	<.001
TNM stage	2.891	2.291–19.203	.005
SUMO1P3 expression level	2.107	1.478–9.014	.031

high SUMO1P3 expression was correlated with the poorer overall survival of patients with HCC.

#### 4. Discussion

HCC is one of the most common diagnosed malignancies and the second leading cause of tumor-related deaths worldwide.<sup>[11]</sup> HCC is characterized by a high degree of aggressiveness and rapid growth. HBV or HCV infection, alcoholic, or non-alcoholic steatohepatitis are the leading causes of HCC. At present, surgical resection and liver transplantation are the main radical therapies for HCC.<sup>[12]</sup> Despite advances in the methods of examination and treatment of HCC, its prognosis is still unsatisfactory, the 5-year overall survival rate of all stages is 15% and the recurrence rate of patients with HCC is more than 80%.<sup>[13]</sup> Therefore, it is critical to identify new therapeutic targets for treatment of HCC.

Accumulating data demonstrated that lncRNAs play vital roles in various biological processes, such as cell growth and differentiation, immune activation/inactivation, and transcriptional and posttranscriptional regulation.<sup>[14,15]</sup> Recently, the function of lncRNAs in tumor has been widely explored. Growing evidences show lncRNAs exert important roles in the development and progression of various cancers, including HCC.<sup>[16,17]</sup>

SUMO1P3 is a novel identified long non-coding RNA that was originally identified as a potential prognostic and therapeutic target for gastric cancer. SUMO1P3 is a lncRNA that is upregulated in several cancers and exerts its oncogenic effects via multiple pathways. For example, Mei et al found that SUMO1P3 was significantly up-regulated in gastric cancer tissues compared with paired-adjacent nontumorous tissues ( $P < .01$ ). Its expression level was significantly correlated with tumor size ( $P = .003$ ), differentiation ( $P = .002$ ), lymphatic metastasis ( $P = .001$ ), and invasion ( $P = .039$ ). The area under the ROC curve of SUMO1P3 was up to 0.666. These results indicated, for the first time, that pseudogene-expressed lncRNA SUMO1P3 may be a potential biomarker in the diagnosis of gastric cancer.<sup>[8]</sup> Zhan et al found that SUMO1P3 was significantly up-regulated in bladder cancer tissues compared with paired-adjacent nontumorous tissues in a cohort of 55 bladder cancer patients. Moreover, up-regulated SUMO1P3 expression was positively correlated with greater histological grade ( $P < .05$ ) and advanced TNM stage ( $P < .05$ ). Furthermore, they found cell proliferation/migration inhibition and apoptosis induction were also observed in SUMO1P3 siRNA-transfected bladder cancer cells. These data

suggest that SUMO1P3 plays oncogenic roles in bladder cancer and can be used as a potential prognostic and therapeutic target.<sup>[18]</sup> Liu et al found that SUMO1P3 expression was higher in breast cancer tissues when compared to adjacent normal tissues and they found that high levels of SUMO1P3 expression associated significantly with tumor progression and poor survival of breast cancer patients. Moreover, they found that knockdown of SUMO1P3 suppressed proliferation, migration, and invasion of breast cancer cells. Bioinformatics analysis and luciferase reporter assays confirmed that SUMO1P3 binds to miR-320a, which has been identified as a tumor suppressor in various cancers, including breast cancer. They also confirmed that the tumor-promoting effects of SUMO1P3 in breast cancer are partly mediated by negative regulation of miR-320a. These data indicates that SUMO1P3 functions as an oncogenic lncRNA in breast cancer and may serve as a novel diagnostic and biological target for breast cancer diagnosis and treatment.<sup>[19]</sup> Tian et al found that SUMO1P3 expression was elevated in pancreatic tissues compared with the corresponding adjacent normal tissues. Additionally, the data indicated that the increased expression of SUMO1P3 is significantly associated with tumor progression and the poor survival of patients with pancreatic cancer. Furthermore, they identified that SUMO1P3 knockdown may suppress the proliferation, migration, and invasion of pancreatic cancer cells. Additionally, downregulation of SUMO1P3 suppressed the epithelial–mesenchymal transition (EMT) and increased the expression of epithelial cadherin, and decreased the expression of neuronal cadherin, vimentin, and  $\beta$ -catenin. Taken together, the results demonstrated that SUMO1P3 may participate in EMT and pancreatic cancer progression, thus suggesting that it may be a novel diagnostic and therapeutic biological target for pancreatic cancer.<sup>[20]</sup> Zhang et al found that SUMO1P3 expression was significantly higher in colon cancer tissues and cell lines than the corresponding non-tumor samples and normal colonic epithelial cells, respectively. The upregulation of SUMO1P3 was positively correlated with the advanced histological stages, metastases, angiogenesis, and poor prognosis of colon cancer patients. SUMO1P3 knockdown repressed the proliferation, migration, invasion, and pro-angiogenesis of colon cancer cells in vitro. SUMO1P3 silencing reduced the growth, liver metastasis, and vascularization of colon cancer in vivo. Mechanistically, SUMO1P3 depletion decreased the levels of cyclin D1, Vimentin, and VEGFA while increased E-cadherin expression in xenograft tumor tissues. Overall, these results indicate that SUMO1P3 expedites the malignant behaviors of colon cancer and may be as a potential therapeutic target.<sup>[21]</sup> Zhang et al found that SUMO1P3 expression was increased in both lung squamous cell carcinoma and lung adenocarcinoma. Then, they confirmed that SUMO1P3 expression was significantly increased in NSCLC cancer tissues and cell lines. Meanwhile, the expression levels of SUMO1P3 expression in metastatic lymph node specimens were strikingly elevated in comparison to primary NSCLC tissue specimens. Then, they found high SUMO1P3 expression was correlated with late clinical stage, lymph node metastasis, distant metastasis, and poor differentiated degree. In the survival analysis of TCGA, they observed that SUMO1P3 expression had no association with overall survival and disease free survival in NSCLC patients. There was a statistically negative correlation between SUMO1P3 expression and miR-136 expression in NSCLC tissues. Moreover, miR-136 directly bound to SUMO1P3, and SUMO1P3 negatively regulated miR-136 expression in NSCLC cells. Furthermore, SUMO1P3 promoted

NSCLC cell migration and invasion via regulating miR-136. In conclusion, SUMO1P3 functions as metastasis-associated lncRNA in NSCLC.<sup>[22]</sup>

The role of SUMO1P3 has also been investigated in HCC. Previously, Wu et al found that the expression of SUMO1P3 was significantly higher in HCC tissues and cells than in non-cancerous specimens and normal cells. SUMO1P3 knockdown inhibited the proliferation, migration, and invasion of HCC cells. SUMO1P3 enhances Wnt/ $\beta$ -catenin pathway through sponging miR-320a, thus, contributing to aggressive progression of HCC.<sup>[9]</sup> Zhou et al found that knockdown of SUMO1P3 repressed tumor growth and invasion and enhanced radiosensitivity in HCC.<sup>[10]</sup> However, until now, the prognostic value of SUMO1P3 in HCC has not been investigated. In the present study, we investigated the clinical significance and prognostic value of SUMO1P3 in HCC. We analyzed the expression levels of SUMO1P3 in primary HCC samples and normal adjacent liver samples from 123 patients with HCC. As revealed by quantitative RT-PCR analysis, SUMO1P3 expression level was significantly higher in HCC cancer tissues compared with normal adjacent tissues. In order to better understand the potential roles of tissue SUMO1P3 in HCC development and progression, the correlation between the tissue SUMO1P3 levels and the clinicopathological factors of the HCC patients were also assessed. The  $\chi^2$  test showed that the SUMO1P3 expression level was significantly associated with tumor size, capsular invasion, vascular invasion, Edmondson–Steiner grade, and TNM stage. To assess whether the expression of SUMO1P3 was a tumor prognostic biomarker, the overall survival was investigated with respect to expression levels of SUMO1P3 in primary HCC. A total of 123 HCC patients included in the study during the follow-up period and the survival curves plotted by Kaplan–Meier method were shown. As shown in Figure 2, the patients with high SUMO1P3 expression showed shorter 5-year overall survival than those with low SUMO1P3 expression. Multivariate regression analysis showed that the status of SUMO1P3 expression was an independent prognostic factor for overall survival. The present study reported the relationship between SUMO1P3 expression and the prognosis of HCC patients the first time. There are several limitations in our research. First of all, we only investigated the clinical significance of tissue SUMO1P3 expression in Asian population, further investigation should be performed in other race. Secondly, we have not investigated its expression level in serum of HCC patients, and also the relationship between its serum expression and the diagnosis and prognosis of HCC patients.

In conclusion, the tissue expression levels of SUMO1P3 may be a reliable prognostic biomarker to predict the clinical outcomes in patients with HCC.

### Author contributions

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