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Downregulated Expression of Tropomyosin 1 in Intrahepatic Cholangiocarcinoma: A Predictor of Recurrence and Prognosis

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Background: The downregulation of tropomyosin 1 (*TPM1*) has been observed in various tumors, but few studies have focused on the clinical significance of *TPM1* in intrahepatic cholangiocarcinoma (ICC). In the present study, we investigated the prognostic significance of *TPM1* in ICC.

Material/Methods: A total of 124 patients with ICC were enrolled in this study. Quantitative real-time polymerase chain reaction (qRT-RCR) was performed to examine the mRNA levels of *TPM1* in ICC tissue samples and adjacent noncancerous tissue specimens, while the protein level of *TPM1* in tissue specimens were investigated using immunohistochemistry assay. The correlation of *TPM1* with clinicopathological features of ICC was analyzed by chi-square test. Survival analysis was performed with Kaplan-Meier method. The Cox proportional hazards model was used to evaluate the prognostic value of *TPM1* in patients with ICC.

Results: *TPM1* expression was significantly downregulated in ICC tissues at mRNA and protein levels ($P<0.001$ for both). Downregulated *TPM1* mRNA was negatively associated with tumor size ($P=0.001$) and TNM stage ($P=0.007$). Moreover, survival analysis demonstrated that patients with low *TPM1* expression had a shorter overall survival (OS) ($P<0.001$) and recurrence-free survival (RFS) ($P<0.001$) than those with high *TPM1* expression. Additionally, multivariate analysis showed that *TPM1* could be a potential biomarker for predicting the recurrence (HR=4.632, 95% CI: 3.832–10.368, $P<0.001$) and survival outcome (HR=5.320, 95% CI: 2.627–11.776, $P<0.001$) of ICC.

Conclusions: *TPM1* may serve as a useful biomarker for predicting tumor recurrence and prognosis in patients with ICC.

MeSH Keywords: Biological Markers • Cholangiocarcinoma • Prognosis • Tropomyosin

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Background

Cholangiocarcinoma (CCA), originating from the bile duct epithelium, is known as one of the most aggressive malignant tumors, with high risk of recurrence and metastasis [1]. CCA can be classified into 3 broad categories: intrahepatic, perihilar, and distal tumors [2]. Intrahepatic cholangiocarcinoma (ICC) accounts for around 20% to 25% of all CCA cases [3]. Although the incidence of ICC is relatively low, it has been progressively and significantly increasing over the last 30 years [4]. Surgical resection offers the only hope of cure for patients with ICC and can improve median survival compared with conservative therapy alone (1.8 months), but the outcome is still poor [5–7]. The dismal prognosis of ICC may be attributed to various reasons, including late onset of symptoms, heterogeneous tumor differentiation, aggressive infiltration, and rapid metastasis, delay in early diagnosis [8]. Therefore, identification of novel biomarkers for predicting tumor recurrence and patient outcomes is crucial to finding effective therapeutic strategies for ICC.

Tropomyosin proteins (TMs) belong to a family of highly conserved actin-binding proteins that are generated by 4 distinct genes designated as tropomyosin 1 (*TPM1*), TPM2, TPM3, and TPM4 [9]. As a member of the TM family, *TPM1* encodes isoforms of the high molecular weight (HMW) TMs [10], which can regulate the proliferation, invasion, metastasis, and motility of tumor cells [11]. Research shows that the expression of *TPM1* is downregulated in numerous carcinomas, such as breast carcinoma [12], neuroblastoma [13], and bladder cancer [14].

Previous studies have identified *TPM1* as a tumor suppressor and a potential candidate biomarker for multiple malignancies. However, the clinical significance of *TPM1* in ICC remains unclear. Therefore, the aim of the present study was to determine the expression of *TPM1* in ICC as well as its clinical and prognostic values in ICC patients.

Material and Methods

Patients and specimens

The study was approved by the Ethics Committee of Beijing 302 Hospital, and all patients signed informed consent. From February 2010 to January 2013, 124 ICC tissue specimens and matched adjacent noncancerous tissue samples were obtained from patients who underwent curative surgery at Beijing 302 Hospital. All patients were histologically confirmed to have ICC by 2 pathologists, and none of them had received any prior treatment (chemotherapy and radiotherapy). Clinical tumor stage was determined according to the American Joint Committee on Cancer (AJCC) 7th TNM staging system. The median follow-up period for these patients was 15 months (range, 1–60 months). All the clinical information obtained is summarized in Table 1.

RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted using TRIzol (Invitrogen) reagent according to the manufacturer's protocol. For measurement of the *TPM1* transcript from total RNA, cDNA was synthesized using the PrimeScript RT Master Mix (Takara). The qRT-PCR was carried out using the Power SYBR Green PCR Master Mix based on the manufacturer's instructions, and glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) was used as the endogenous control. The relative expression level of *TPM1* normalized to *GAPDH* was calculated by the $2^{\Delta\Delta CT}$ method. Experiments were repeated at least 3 times.

Immunohistochemistry assay

We detected TPM1 protein expression in isolated tissue specimens using immunohistochemistry (IHC) assay. Samples were cut into 4-μm-thick sections and baked at 65°C for 1 h. Then, deparaffinization and rehydration were performed with gradient series alcohol. Next, the sections were incubated with 0.01M citric acid buffer (pH 6.0) at 98°C for 10 min and then air-dried at room temperature, after which the sections were mixed with primary antibody at 37°C for 1 h or at 4°C overnight. PBS buffer was used to wash the sections 3 times. After that, biotin-labeled secondary antibody was added to each section at 37°C for 30 min. Finally, staining signaling was conducted with DAB. The IHC results are expressed as the staining percentage of cells (0% to 100%). Staining of under 10% of the cells or no staining was considered to be negative. Staining of 10% to 20% of the cells indicated moderate immunopositivity and staining of more than 20% of cells showed strong immunopositivity. Both moderate and strong immunopositivity were classified as positive. The sections were blocked and preserved for further use.

Statistical analyses

Statistical analyses were carried out using SPSS Statistical Software version 18.0 (SPSS, Inc.) and GraphPad Prism 5.0 (GraphPad Software, Inc.). All descriptive statistical variables are presented as mean ± standard deviation (SD). The differences between variable was tested using the *t* test and the chi-square test was applied to measure the differences between quantitative variables. The Kaplan-Meier method with log-rank test was used to estimate survival rates and the Cox proportional hazards model for multivariate survival analysis was used to evaluate the predictive value of markers for survival and recurrence. For each analysis, a *P* value less than 0.05 was considered statistically significant.

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Table 1. The relationship between *TPM1* expression and the clinicopathological characteristics in ICC.

Variables	N	TPM1 mRNA level		*P* value
		High	Low	
Age				0.472
≥60	63	35	28	
<60	61	29	32	
Gender				0.281
Male	63	36	27	
Female	61	28	33	
Tumor size				0.001
≥3 cm	81	33	48	
<3cm	43	31	12	
Lymph node metastasis				0.063
Absent	78	35	43	
Present	46	29	17	
Differentiation				0.470
Well or moderate	72	35	37	
Poor	52	29	23	
TNM stage				0.007
III, IV	71	29	42	
I, II	53	35	18	

Results

Decreased *TPM1* expression levels in ICC

The mRNA level of *TPM1* expression was assessed in 124 ICC tissue specimens and matched adjacent noncancerous tissue samples using qRT-PCR method. As shown in Figure 1, the expression of *TPM1* was significantly decreased in ICC tissues compared to that in noncancerous samples (0.340±0.151 *vs.* 0.821±0.303, *P*<0.001). The results of IHC showed that the positive expression rate of TPM1 was only 16.1% in ICC tissues, but was 79.0% in the adjacent normal tissues (Table 2, Figure 2). The above results indicate that *TPM1* can act as a tumor-suppressor gene in the development of ICC.

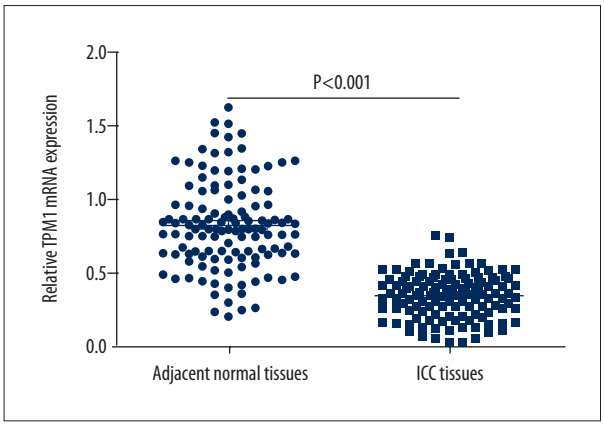

Figure 1. Relative *TPM1* mRNA expression levels detected by qRT-PCR. *TPM1* expression was significantly decreased in ICC tissue samples compared to that in adjacent noncancerous tissue specimens (*P*<0.001).

Expression levels of *TPM1* and clinicopathological characteristics of ICC

To test the hypothesis that *TPM1* plays an important role in the progression and development of ICC, we further examined the association of *TPM1* expression with its clinicopathological characteristics. As shown in Table 1, the *TPM1* levels were classified into 2 groups (high and low) according to the mean value. Low expression of *TPM1* was obviously correlated with tumor size (*P*=0.001) and TNM stage (*P*=0.007). However, no significant relationship was observed between *TPM1* expression and age, sex, lymph node metastasis, or differentiation.

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Table 2. Different TPM1 expression in ICC tissues and normal tissues.

Tissue	No.	Expression		Positive rate	*P* value
		Positive	Negative		
ICC tissues	124	20	104	16.1%	P<0.001
Adjacent normal tissues	124	98	26	79.0%	

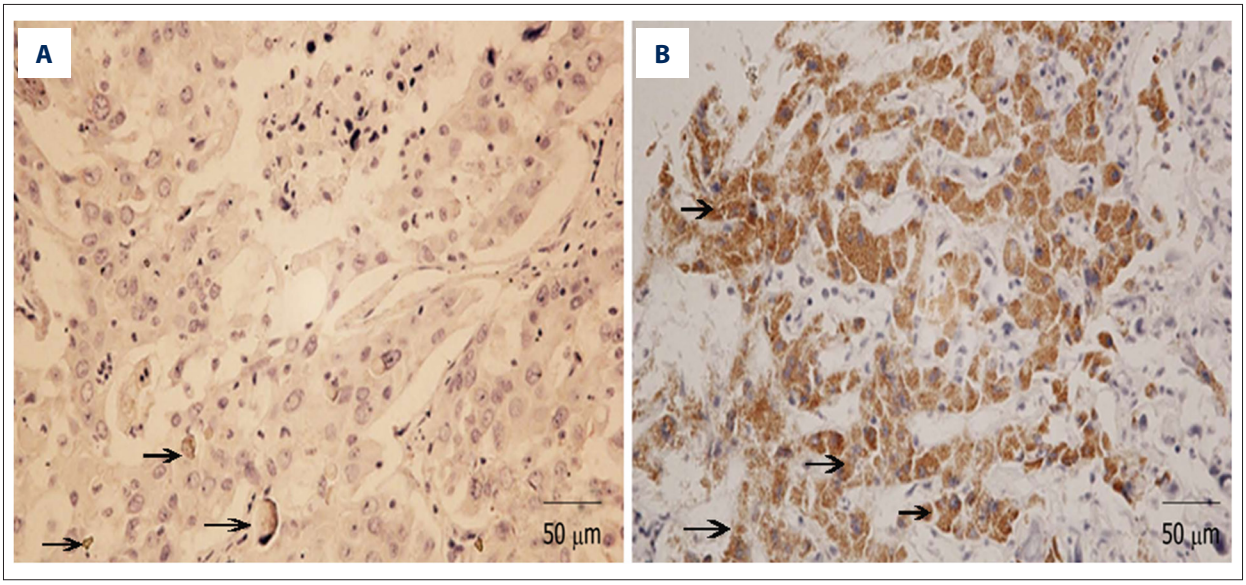

Figure 2. The expression of TPM1 protein in ICC tissue specimens detected using IHC. (**A**) The expression of TPM1 in ICC tissues. (**B**) The expression of TPM1 in adjacent noncancerous tissues. The expression of TPM1 was lower in ICC tissues than in adjacent normal tissues. Arrows represent the signal of TPM1.

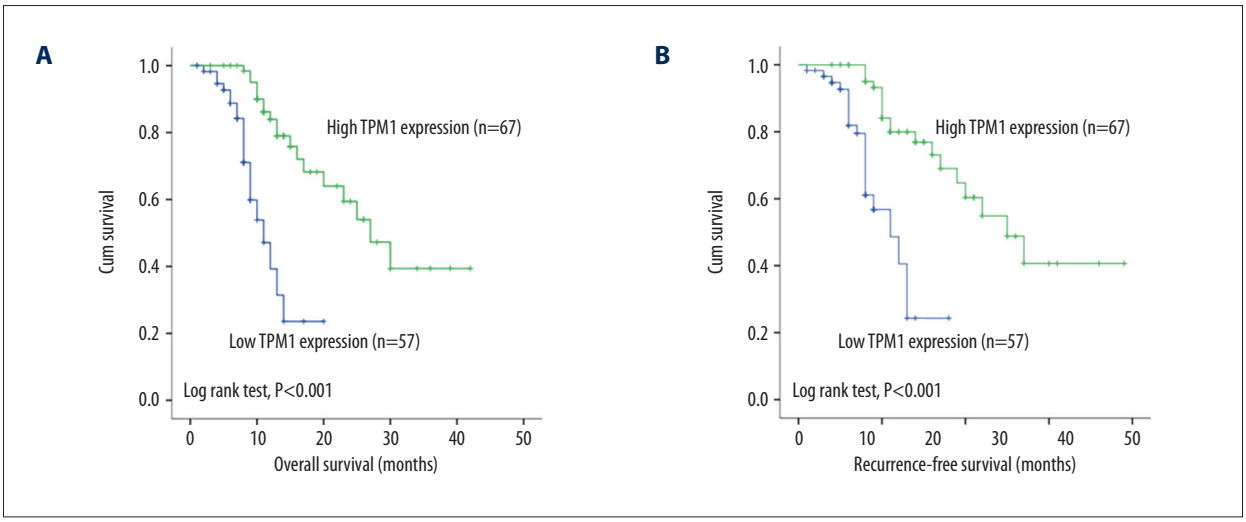

Figure 3. Survival analysis of *TPM1* in ICC. (**A**) Patients with high *TPM1* levels had better OS than those with low *TPM1* expression (*P*<0.001). (**B**) Patients with high *TPM1* expression had longer RFS than those with low *TPM1* expression (*P*<0.001).

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Table 3. Univariate and multivariate analysis of variables associated with OS in patients with ICC.

Variables	Univariate analysis			Multivariate analysis		
	HR (95% CI)		*P* value	HR (95% CI)		*P* value
Age	1.195	(0.638–2.237)	0.264	–		–
Gender	1.921	(1.019–3.621)	0.084	–		–
Tumor size	2.613	(1.932–3.438)	0.013	–		–
TNM stage	1.936	(0.841–4.754)	0.008	1.521	(1.271–2.005)	0.012
Lymph node metastasis	1.582	(1.020–3.533)	0.048	1.211	(0.963–2.163)	0.036
Differentiation	1.544	(1.288–4.360)	0.036	–		–
TPM1 expression	5.153	(2.544–10.436)	<0.001	5.320	(2.627–11.776)	<0.001

Table 4. Univariate and multivariate analysis of variables associated with recurrence in patients with ICC.

Variables	Univariate analysis			Multivariate analysis		
	HR (95% CI)		*P* value	HR (95% CI)		*P* value
Age	1.266	(0.676–2.372)	0.464	–		–
Gender	1.926	(1.021–3.632)	0.053	–		–
Tumor size	1.919	(1.488–2.729)	0.012	–		–
TNM stage	2.636	(1.841–5.754)	0.003	1.963	(1.265–4.327)	0.024
Lymph node metastasis	2.701	(2.020–4.344)	0.098	–		–
Differentiation	1.570	(1.296–3.098)	0.056	–		–
TPM1 expression	3.653	(2.252–8.746)	<0.001	4.632	(3.832–10.368)	<0.001

Correlation of *TPM1* expression with overall survival and recurrence in ICC patients

As *TPM1* level was significantly decreased in patients with ICC, we assessed the association between *TPM1* expression and survival situation. The mean overall survival (OS) of the 124 ICC patients was 12 months, while the mean recurrence-free survival (RFS) was 10 months. Patients with high *TPM1* expression exhibited a significantly longer OS than those with low expression ($P<0.001$; Figure 3A). Univariate survival analysis showed various factors were associated with tumor OS, including tumor size ($P=0.013$), TNM stage ($P=0.008$), lymph node metastasis ($P=0.048$), and differentiation ($P=0.036$) (Table 3). RFS was similar to OS in that the *TPM1* high-expression group showed a significantly longer RFS ($P<0.001$; Figure 3B). Other factors significantly related to RFS were tumor size ($P=0.012$) and TNM stage ($P=0.003$) (Table 4). Furthermore, the subgroup analyses of *TPM1* expression stage revealed that patients with high *TPM1* expression had better OS, not only in the tumor size ≥3 cm group ($P<0.001$; Figure 4A), but also in the tumor size <3 cm group ($P=0.011$; Figure 4B), whereas patients with high *TPM1* showed a longer OS in stages III–IV ($P<0.001$; Figure 4C) but not in stages I and II ($P=0.103$; Figure 4D).

TPM1 as an independent prognostic factor in ICC patients

Based on multivariate analysis with the Cox proportional hazards model for the significant clinical features in univariate analysis, low *TPM1* level was identified as an independent prognostic factor (HR=5.320; 95% CI: 2.627–11.776, $P<0.001$; Table 3) and an independent predictive factor of recurrence (HR=4.632; 95% CI 3.832–10.368, $P<0.001$; Table 4). Moreover, the results demonstrated that both TNM stage ($P=0.012$) and lymph node metastasis ($P=0.036$) were independent prognostic factors, and TNM stage ($P=0.024$) was also identified as an independent predictive factor of recurrence. Therefore, all these results suggest that *TPM1* is a potential biomarker for predicting the recurrence and survival outcome of ICC.

Discussion

In the present study we observed that the expression of *TPM1* was downregulated in ICC tissues compared with matched adjacent noncancerous tissues and that *TPM1* expression can be an independent prognostic indicator of OS and recurrence for ICC patients.

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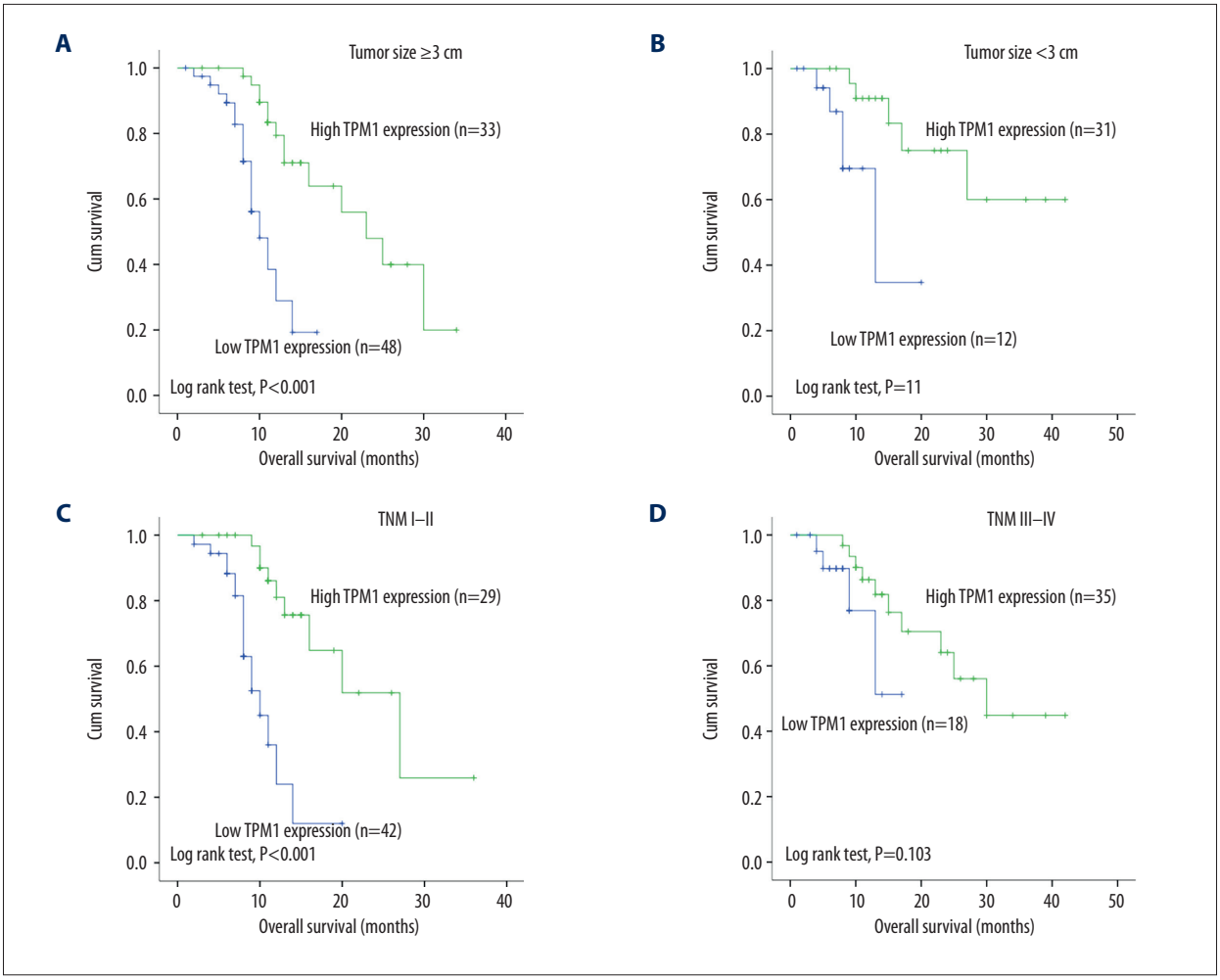

Figure 4. Subgroup survival analysis of *TPM1*. (**A, B**) Patients with high *TPM1* expression had a better OS, not only in the size ≥3 cm group (P<0.001), but also in the size <3 cm group (P=0.011). (**C, D**) Patients with high *TPM1* expression had a better OS in stages III–IV (P<0.001), but not in stages I–II (P=0.103).

ICC is an aggressive tumor that continues to be one of the most common causes of cancer-related mortality. There are various available treatments for patients with ICC, but the therapeutic effects are unsatisfactory [15]. To improve the survival outcome of ICC patients, it is essential to identify prognostic indicators to guide treatments and to predict disease progression in ICC. The tumorigenesis of ICC is a complex process regulated by multiple genetic and environmental factors and their interactions. With the development of molecular sequencing techniques, various studies have explored novel molecular biomarkers for management of ICC. For example, a study by Wu et al. reported that *miR-122* regulates ICC cell proliferation and apoptosis via the p53 pathway, which might be a potential therapeutic target [16]. Although various molecular biomarkers have been identified for ICC, few of them had been used clinically. Thus, novel and reliable molecular biomarkers are urgently needed for ICC.

As a microfilament-associated protein, *TPM1* can be abundantly expressed in different human cells, such as epithelia, fibroblasts, and smooth muscle cells [17,18]. Previous studies have found that the expression of *TPM1* is decreased in many transformed cell lines and multiple carcinomas, including breast carcinoma [12,19,20], neuroblastoma cancer [13], bladder cancer [14], tongue squamous cell carcinoma [21], and high-metastatic Lewis lung carcinoma [22]. In ICC, *TPM1* expression has been found to be significantly downregulated in ICC cells (HuCCT1) compared with normal intrahepatic biliary epithelial cells (HIBEC) [2]. In the present study, we found that *TPM1* expression in ICC tissues was significantly decreased compared to adjacent noncancerous tissues, which was consistent with the above-mentioned study. Furthermore, the downregulation of TPM1 was negatively associated with TNM stage and tumor size. All our data revealed that TPM1 acts as a tumor suppressor, and its decreased expression might contribute to aggressive progression of ICC. An increasing number of studies

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have suggested that *TPM1* can suppress anchorage-independent growth and restore anoikis in cancer cells, which has been generally regarded as a tumor suppressor [12,23,24]. Growing evidence has demonstrated that the decreased expression of *TPM1* in carcinogenesis is regulated by microRNAs or several growth factors such as vascular endothelial cell growth factor (VEGF) and fibroblast growth factor (FGF) [24–27]. In ICC, it had been reported that downregulation of *TPM1* might be regulated by DNA methylation, histone deacetylation, and upregulating of miR-21 [2]. All these studies can guide further research on the specific molecular mechanisms underlying the regulatory roles of *TPM1* in ICC.

Li et al. reported that tongue squamous cell carcinoma patients with high *TPM1* expression had better survival [21], and Wang et al. demonstrated *TPM1* expression was associated with prognosis in patients with renal cell carcinoma (RCC) [28]. However, the potential significance of *TPM1* for survival evaluation in patients with ICC remained unclear. In the present study, our results showed that patients with low *TPM1* expression had shorter OS n and RFS than those with high *TPM1* expression. Our results also show that the OS of patients with high *TPM1* expression was significantly better in different sizes (size ≥3 cm or size <3 cm) than that of the patients with low *TPM1* expression. However, according to TNM staging, patients with high *TPM1* expression had better OS in stages III–IV, but not in stages I and II, suggesting that *TPM1* was more sensitive in advanced stages of ICC. Both univariate and multivariate analyses indicated that low *TPM1* expression increased the risk of death in ICC patients, and *TPM1* could be an independent predictor for the recurrence and survival outcome of ICC. Recent evidence supports that *TPM1* expression is correlated with some clinical features such as tumor size, smoking status, and tumor grade [28]. In our study, the low expression of *TPM1* was found to be correlated with tumor size and TNM stage. Although we studied the clinical role of *TPM1* in ICC patients, there are several limitations to our study. First, this was a single-center study with a relatively small sample size. Second, the underlying mechanism of *TPM1* in ICC was not explored, and this needs further research.

Conclusions

In summary, *TPM1* expression was significantly decreased in human ICC tissues, and survival analysis demonstrated that *TPM1* could be a promising biomarker for predicting recurrence and OS in patients with ICC.

Conflict of interest

None.

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