Int J Clin Exp Pathol 2018;11(1):367-374
www.ijcep.com /ISSN:1936-2625/IJCEP0067961

Original Article

Expression of LAMP3 and its correlation with clinicopathologic characteristics and prognosis in hepatocellular carcinoma

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Received October 26, 2017; Accepted November 10, 2017; Epub January 1, 2018; Published January 15, 2018

Abstract: Lysosome-associated membrane protein (LAMP) 3 is one of members of lysosome-associated membrane protein family, which has been reported to play an important role in multiple malignant tumors. However, there is less research about the expression of LAMP3 in hepatocellular carcinoma (HCC). The purpose of this study was to investigate the expression of LAMP3 and explore its roles in HCC.The expression of LAMP3 in 99 cases of HCC tissues was performed by immunohistochemistry. In addition, the expression of LAMP3 in 20 pairs of HCC tissues and pericarcinomatous tissues was determined by quantitative real-time polymerase chain reaction and Western blotting. Immunohistochemical staining showed that LAMP3 was mainly expressed in the cytoplasm. And the expression of LAMP3 in HCC tissues (64/99, 64.6%) was significantly lower than that in pericarcinomatous tissues (23/99, 23.2%). In addition, the expression of LAMP3 mRNA and protein in HCC tissues was also significantly lower than that in pericarcinomatous tissues for 20 pairs of HCC samples. Low expression of LAMP3 was correlated with age, tumor-node-metastasis (TNM) staging, Edmondson grade, alpha-fetoprotein (AFP). Kaplan-Meier analysis showed that patients with low expression of LAMP3 had worse overall survival (OS) and disease-free survival (DFS). Multivariate analysis revealed that low expression of LAMP3 was an independent prognostic factor of OS and DFS for HCC patients.The results suggested that LAMP3 may play an important role in the development and progression of hepatocellular carcinoma, and serve as an independent prognostic predictor for HCC patients after surgical resection.

Keywords: LAMP3, hepatocellular carcinoma, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant disease and the third leading cause of cancer death [1]. The statistics showed that China has accounted for nearly 50% of the total number of new liver cancer cases and deaths in 2012 [2]. It has been showed that multiple factors are related with HCC development such as genomic alterations, molecular metabolic abnormalities, and signaling transduction dysfunction [3, 4]. Despite new diagnostic and therapeutic methods have been developed in recent years, because of the high degree of malignancy and being prone to recurrence and metastasis, the average survival time of patients with HCC is 6 to 20 months [5]. Most of the patients have been diagnosed in the middle and late phase. So the discovery of effective molecular biology diagnostic indicators for early diagnosis and treatment is the key to improve the prognosis of patients with HCC.

Lysosome-associated membrane protein (LAMP) 3, which belongs to the LAMP protein family, was first found specifically expressed in lung tissues and named as TSC403 [6]. LAMP3 has been investigated as a molecular marker of mature dendritic cells [7]. Recent researches have reported that LAMP3 may play an important role in multiple malignant tumors, including breast cancer [8], gastrointestinal cancer [9], cervical cancer [10], oral squamous cell carcinoma [11], esophagus cancer [12], and head and neck squamous cell carcinomas [13].

Table 1. Correlation between LAMP3 expression and clinicopathological characteristics

Variables	Total	LAMP3 expression		*P*-value
		Low	High	
Gender				
Male	85	57	28	0.216
Female	14	7	7	
Age (year)				
≤50	51	28	23	0.037
>50	48	36	12	
AFP (ng/ml)				
≤20	46	24	22	0.016
>20	53	40	13	
Tumor size (cm)				
≤5	37	22	15	0.404
>5	62	42	20	
Capsule				
Complete	60	40	20	0.602
Incomplete	39	24	15	
Edmondson grade				
I-II	60	34	26	0.039
III-IV	39	30	9	
TNM stage				
I-II	26	12	14	0.022
III-IV	73	52	21	
Liver cirrhosis				
Yes	61	38	23	0.535
No	38	26	12	
Vascular invasion				
Yes	72	49	23	0.247
No	27	15	12	

Moreover, recent study also indicated that LAMP3 was related to hypoxia-induced metastasis [14] and resistance to chemotherapy [15]. However, there is less research about the role of LAMP3 in HCC patients. In this study, we determined the expression of LAMP3 mRNA and protein in HCC and pericarcinomatous tissues and assessed the relationship between LAMP3 expression and clinicopathologic parameters of patients with HCC.

Materials and methods

Patients and tissue samples

A total of 99 patients with HCC who had undergone curative surgery from 2006 to 2011 at the Department of Hepatic Surgery at Anhui Provincial Hospital Affiliated to Anhui Medical University, Hefei, China were recruited. These patients included 85 males and 14 females, whose median age was 46 years (range: 19-74 years). All of the patients had received any types of treatments (adjuvant chemotherapy, radiation therapy or immunotherapy) before surgery. Clinical characteristics of all the patients were collected retrospectively from medical records, such as age, sex, tumor size, tumor capsule, vascular invasion, tumor-node-metastasis (TNM) staging, Edmondson grade, alpha-fetoprotein (AFP) and cirrhosis. The detailed information of patients waslisted in **Table 1**. All of the patients were followed up until December 2016. Median follow-up time was 21 months.

Tumor samples were randomly collected from patients after surgery at Anhui Provincial Hospital Affiliated to Anhui Medical University, from March 2017 to June 2017. 20 pairs of HCC tissues and pericarcinomatous tissues were collected immediately after surgery, transported in liquid nitrogen, and stored at -80°C.

All patients had signed the informed consents before surgery, and the study protocol was approved by the Research Ethics Committee of Anhui Provincial Hospital.

Immunohistochemistry (IHC)

Immunohistochemical staining was carried out by a two-step protocol according to the manufacturer instructions. HCC tissue sections, which were fixed by formalin and paraffin-embedded, were deparaffinized in xylene, rehydrated through the gradient concentration of ethanol, and subjected to autoclave antigen retrieval in citric acid buffer at 100°C for 5 minutes, and then incubated in 3% hydrogen peroxide for 10 minutes to recover endogenous peroxidase activity. Next, the tissue sections were incubated with rabbit anti-LAMP3 antibody (orb 136854, Biorbyt, Cambridge, UK) at a dilution of 1:200 overnight at 4°C. Then washed with PBS and incubated with horseradish peroxidase-conjugated goat anti-rabbit secondary antibody (Zhongshan Golden Bridge Biotechnology, Beijing, China) for 30 minutes. Subsequently, all tissue sections were visualized with DAB kit (Zhongshan Golden Bridge Biotechnology, Beijing, China) and the nucleus was counterstained with hematoxylin. In addition, PBS was used as a negative control for the primary antibody under the same conditions.

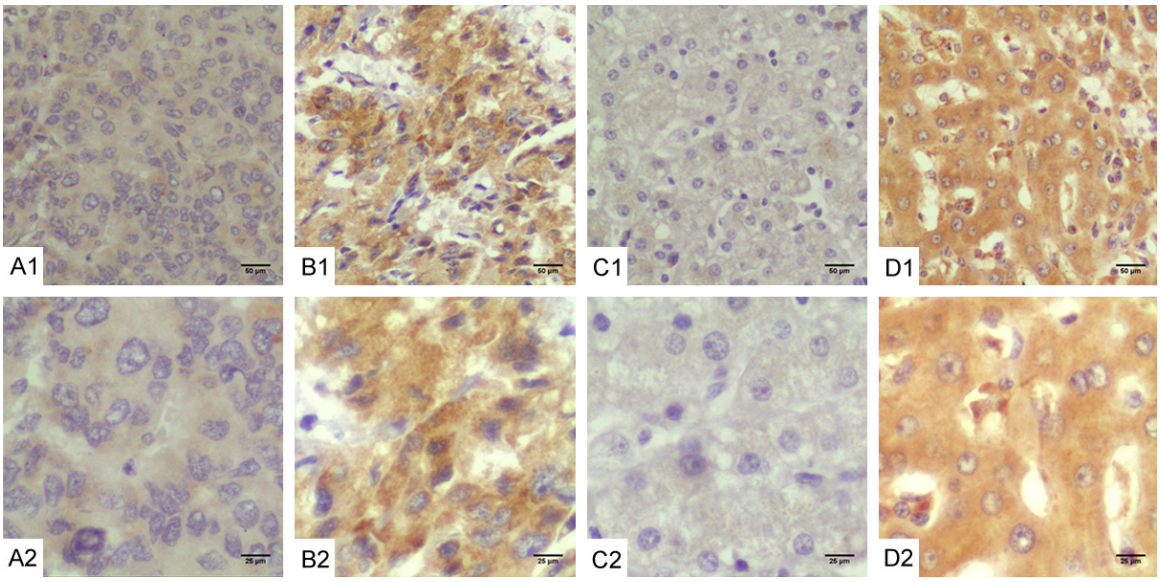

Figure 1. Immunohistochemical staining of LAMP3 in HCC and pericarcinomatous tissues. (A) Low expression of LAMP3 in HCC tissues. (B) High expression of LAMP3 in HCC tissues. (C) Low expression of LAMP3 in pericarcinomatous tissues. (D) High expression of LAMP3 in pericarcinomatous tissues. (A1, B1, C1 and D1-original magnification: 200×; A2, B2, C2 and D2-original magnification: 400×).

The results of IHC were independently evaluated by two experienced pathologists who had nothing to do with this experiment. And the expression of LAMP3 was scored according to the following criteria [12]: (1) staining intensity: 0 (negative), 1 (weak), 2 (moderate) and 3 (strong); (2) percentage of positive cells: 1 (≤25%), 2 (25%-50%), 3 (50%-75%), 4 (>75%). The final IHC score was calculated by multiplying the staining intensity score by the score of positive cells (range 0-12). The samples were grouped into high and low groups by the median score (4 scores) of tumors as the cutoff value. Samples score lower than 4 was regarded as low expression and the score higher than 4 was regarded as high expression.

Western blotting

HCC tissues and pericarcinomatous tissues were lysed in lysis buffer of radioimmunoprecipitation assay (Beyotime Biotechnology, Shanghai). Protein concentrations were measured by BCA assay (Beyotime Biotechnology, Shanghai). 10 μl of each protein was separated on 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and then transferred to polyvinylidene difluoride (PVDF) membranes (Millipore, USA). After washed by PBS, the membranes were incubated at 4°C overnight with rabbit anti-LAMP3 antibody (Biorbyt, Cambridge, UK) at a dilution of 1:500 or mouse anti-GAPDH antibody (Santa Cruz Biotechnology, USA) at a dilution of 1:1000. Next, the membranes were incubated at the room temperature for 1.5 hours with horseradish peroxidase (HRP)-labeled secondary antibodies (Kangwei Biotech, Beijing). The results were observed with enhanced chemiluminescence (ECL; Thermo Fisher, USA) by chemiluminescence detection system.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA extraction from 20 pairs of HCC tissues and pericarcinomatous tissues was using TRIzol reagent (Invitrogen, USA) followed manufacture's protocol. The cDNA were synthesized with the miRcute Plus miRNA First-Strand cDNA Synthesis Kit (Tiangen Biotech, Beijing) according to the experimental guide. The qRT-PCR was preformed on 7500 Fast Real-Time PCR system (Applied Biosystems, USA) in the following conditions: the first denaturation step at 95°C for 30 seconds, followed by 40 cycles at 95°C for 5 seconds and 60°C for 34 seconds. The amplification primers of LAMP3 were designed as followings: F: 5'-CTTTGGAAATGTGGATGAGTGCT-3', R: 5'-GACACCCATACCCATAAGGCA-3' and the

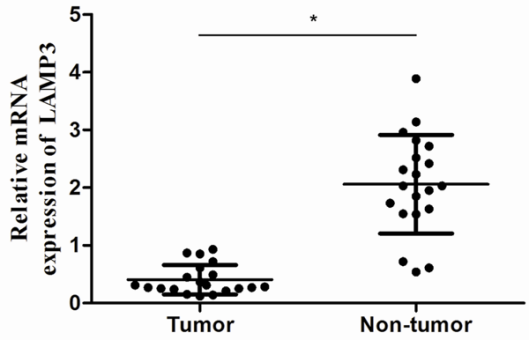

Figure 2. qRT-PCR analysis of LAMP3 mRNA expression in fresh tissues. Total RNAs of 20 pairs of HCC and the corresponding nontumorous tissues were subjected to qRT-PCR assay to examine the mRNA expression of LAMP3. *P<0.05.

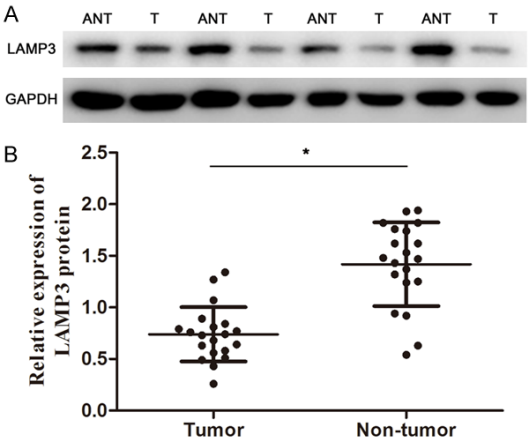

Figure 3. Western blotting analysis of LAMP3 protein expression in fresh tissues. A: Representative results of LAMP3 protein expression in paired HCC tissues (T) and the corresponding nontumorous tissues (ANT) from four patients. LAMP3 protein expression was normalized to GAPDH. B: All of the paired HCC tissues and the corresponding nontumorous tissues from 20 patients. *P<0.05.

primers of GAPDH were designed as follows: F: 5'-GCCGCATCTTCTTTTGCGTC-3', R: 5'-TACGACCAAATCCGTTGACTCC-3'. GAPDH was used as an endogenous reference to standardize the differences in the amounts of total RNA in each sample. The $2^{-\Delta\Delta Ct}$ method was used to analyze the relative gene expression of LAMP3 comparing to the relative gene expression of GAPDH for each sample.

Statistical analysis

SPSS20 (SPSS Inc., USA) was used for statistical analysis. Paired-Samples t test was used to determine the significance of LAMP3 expression in HCC and pericarcinomatous tissues. Pearson chi-squared (χ^2) test was performed for comparing the expression of LAMP3 and clinicopathological parameters of patients with HCC. The Kaplan-Meier method was used to estimate the cumulative patient survival and the survival curve was compared by log-rank test. Cox proportional hazard ratios model was used to analyze factors of survival. P value <0.05 was defined as statistical significance.

Results

Immunohistochemical analysis of LAMP3 expression

We detected the expression of LAMP3 in 99 HCC tissue sections and the positive staining was mainly found in the cytoplasm (**Figure 1**). Low expression of LAMP3 was detected in 64.6% (64/99) of HCC tissues and 23.2% (23/99) of pericarcinomatous tissues.

qRT-PCR analysis of LAMP3 mRNA expression

qRT-PCR was carried out to detect the LAMP3 mRNA expression in 20 pairs of HCC tissues and pericarcinomatous tissues. As shown in **Figure 2**, the mean of relative LAMP3 mRNA expression in HCC and pericarcinomatous tissues was 0.40±0.26 and 2.06±0.85, respectively. The results showed the expression of LAMP3 mRNA in HCC tissues was significantly lower than that in pericarcinomatous tissues (P<0.05).

Western blot analysis of LAMP3 protein expression

LAMP3 protein level in the same 20 pairs of HCC tissues and pericarcinomatous tissues was examined by Western blotting. 17 paired samples (17/20) showed expression of LAMP3 protein in HCC tissues was significantly lower than that in pericarcinomatous tissues, which was consistent with the results of qRT-PCR. LAMP3 relative protein expression in HCC tissues and adjacent pericarcinomatous tissues was 0.74±0.26 and 1.42±0.41, respectively (**Figure 3**).

Relations between expression of LAMP3 and HCC prognosis

All of the patients in this study had complete follow-up date, the median follow-up time was

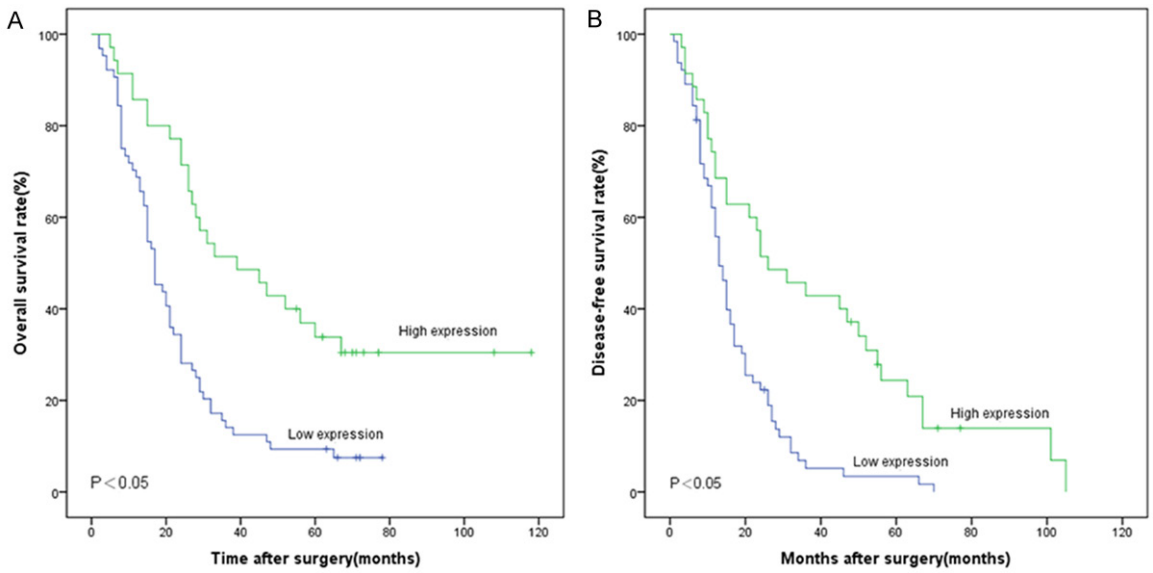

Figure 4. Kaplan-Meier analysis of OS and DFS curves of HCC patients based on LAMP3 as low or negative. A: OS curve of patients with HCC based on LAMP3 expression; B: DFS curve of patients with HCC based on LAMP3 expression. HCC patients with high expression of LAMP3 had better OS and DFS rate than those with low expression of LAMP3.

21 months. Statistical analysis revealed that low expression of LAMP3 was significantly correlated with age (*P*=0.037), AFP (*P*=0.016), Edmondson grade (*P*=0.039), TNM stage (*P*=0.022). However, there were no obviousrelationships to the other parameters, and the details were listed in **Table 1**. Kaplan-Meier analysis showed that patients with low expression of LAMP3 had a worse overall survival (OS) time than that of patients with high expression of LAMP3. Similarly, compared to the patients with high expression of LAMP3, the patients who had low expression of LAMP3 had a shorter disease-free survival (DFS) time (**Figure 4**). Univariate analysis revealed that LAMP3 expression, tumor size, vascular invasion, AFP, Edmondson grade and TNM stage were prognostic factors of OS and DFS in patients with HCC (**Table 2**). Furthermore, multivariate survival analysis showed that expression of LAMP3, TNM stage and vascular invasion were the independent predictors of poor prognosis for OS of HCC patients, while expression of LAMP3, Edmondson grade, TNM stage and vascular invasion were the independent predictors of poor prognosis for DFS of HCC patients (**Table 3**).

Discussion

LAMP3 is a highly glycosylated membrane protein [16], and located in the 3q chromosome [6]. It is regarded as a genomic region that is frequently amplified in many kinds of human cancers tissues and plays a major role in the progression of cancers [17]. Such as gene *PIK3CA*, was reported located in the 3q chromosome, and its mutations were strongly correlated with tumor size and the poor prognosis of patients with HCC [18].

High expression of LAMP3 was correlated with the degree of tumor differentiation and TNM stage of oral squamous cell carcinoma (OSCC), as well as an independent prognostic marker in OSCC [11]. The expression of LAMP3 in esophageal squamous cell carcinoma (ESCC) tissues was higher than that in the paired normal tissues, and the ESCC patients with higher expression level of LAMP3 had a worse prognosis [12]. Overexpression of LAMP3 in ovarian cancer was associated with poor survival outcome [19]. In our study, the expression of LAMP3 was lower in HCC tissues compared with pericarcinomatous tissues, and the data analysis suggested that patients with low expression of LAMP3 had a worse prognosis compared with those with high LAMP3 expression. Further multivariate analysis showed low expression of LAMP3 may be a promising biomarker for the prognosis of patients with HCC.

Recently, a lot of researches have revealed that LAMP3 was a metastasis-associated gene. For

Table 2. Univariate analysis of parameters associated with OS and DFS

Parameters	OS		*P*	DFS		*P*
	Median survival time (months)	95% CI		Median survival time (months)	95% CI	
LAMP3						
Low expression	17	13.75-20.25	<0.001	13	10.68-15.32	<0.001
High expression	39	18.14-59.86		26	10.93-41.07	
Gender						
Male	24	20.74-27.26	0.779	16	11.11-20.89	0.680
Female	15	11.33-18.67		12	4.67-19.33	
Age (years)						
≤50	21	14.7-27.3	0.858	13	9.94-16.06	0.867
>50	22	17.47-26.53		16	11.47-20.53	
AFP (ng/ml)						
≤20	24	14.03-33.97	0.044	17	7.18-26.82	0.016
>20	21	17.96-24.04		13	10.86-15.14	
Tumor size (cm)						
≤5	30	13.31-46.69	0.036	26	2.04-49.96	0.036
>5	17	11.21-22.79		15	12.7-17.3	
Tumor capsule						
Complete	24	18.32-29.68	0.354	15	11.21-18.79	0.681
None	20	14.56-25.44		16	12.99-19.01	
Edmondson grade						
I-II	26	17.14-34.86	0.011	20	9.88-30.12	0.001
III-IV	17	9.66-24.34		12	10.51-13.49	
TNM stage						
I-II	47	22.57-71.43	0.001	36	5.4-66.6	0.001
III-IV	20	16.2-23.8		14	11.51-16.49	
Liver cirrhosis						
Present	24	18.91-29.09	0.643	16	11.68-20.32	0.628
Absent	19	12.1-25.9		15	13.5-16.5	
Vascular invasion						
Yes	17	11.8-22.2	0.002	15	12.7-17.3	0.009
No	32	16.73-47.27		26	2.04-19.96	

Table 3. Multivariate analysis of parameters associated with OS and DFS

Parameters	OS			DFS		
	HR	95% CI	*P*	HR	95% CI	*P*
LAMP3 (high vs low)	1.989	1.186-3.337	0.009	1.867	1.122-3.105	0.016
AFP (ng/mL) (≤20 vs >20)	1.373	0.850-2.220	0.195	1.477	0.937-2.326	0.093
Tumor size (cm) (≤5 vs >5)	0.860	0.504-1.468	0.582	0.820	0.476-1.414	0.476
Edmondson grade (I/II vs III/IV)	1.394	0.876-2.218	0.161	1.794	1.124-2.864	<0.001
TNM stage (I/II vs III/IV)	2.567	1.488-4.426	<0.001	2.378	1.438-3.932	0.014
Vascular invasion (yes vs no)	2.666	1.512-4.700	0.001	2.069	1.212-3.530	0.008

example, Nagelkerke et al [20] indicated that abnormal expression of LAMP3 was correlated with hypoxia stimulates migration of breast cancer cells via unfolded protein response. Kanao et al [10] found that overexpression of LAMP3 promoted metastatic potential of uter-

ine cervical cancer. Mujcic et al [14] identified LAMP3 as a novel hypoxia-inducible gene regulated by the unfolded protein response and mediated the hypoxia-induced metastasis.In this study, we detected the expression of LAMP3 in 99 cases of HCC tissues by IHC staining, and the results suggested that LAMP3 was low expression in HCC tissues, and significantly associated with age, AFP, Edmondson grade and TNM stage. Otherwise, expression of LAMP3 in 20 pairs of HCC tissues and pericarcinomatous tissues was detected by qRT-PCR and Western blot, and the results were the same as those by IHC staining. As we all know, the metastasis of liver cancer is a complex process of common regulation by various genes, proteins and cytokines. Our data showed that LAMP3 was related to the invasion and metastasis characteristics of HCC. Further study will carry out to investigate the specific mechanism of cancerogenic function of LAMP3 in HCC.

In conclusion, our study revealed the expression of LAMP3 in HCC and its prognostic value for patients with HCC. The results suggested that LAMP3 may play an important role in the development and progression of hepatocellular carcinoma, and serve as an independent prognostic predictor for HCC patients after surgical resection.

Acknowledgements

This project was supported by the National Natural Science Foundation of China (No. 81272398).

Disclosure of conflict of interest

None.

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