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Original contribution

Overexpression and clinical relevance of the RNA helicase DHX15 in hepatocellular carcinoma☆,☆☆

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Summary DHX15 is an outstanding member of the DEAH-box RNA helicase family. A few studies suggest that DHX15 contributes to carcinogenesis in several tumor cell lines. However, whether DHX15 acts as an oncogene or tumor suppressor and its association with hepatocellular carcinoma (HCC) prognosis are still poorly understood. To address this question, we used immunohistochemistry to evaluate DHX15 expression patterns and their association with clinicopathological factors and the prognosis of patients with HCC. Our results showed that DHX15 expression was significantly higher in cancerous tissues than that in nontumor tissues ($P < .0001$). DHX15 expression in HCC patients was associated with differentiation status ($P = .018$), tumor number ($P = .048$), intrahepatic or extrahepatic metastasis ($P = .001$), serum α-fetoprotein ($P = .006$), hepatitis B virus level ($P = .018$), and recurrence ($P < .001$). In addition, the survival analysis revealed that the DHX15-high group had significantly decreased overall survival time ($P = .004$) and lower 1-year survival rates ($P = .002$) compared with the DHX15-low group. Furthermore, multivariate analysis identified DHX15 expression as an independent factor associated with poor prognosis in HCC ($P = .036$). In summary, these findings demonstrate, for the first time, that DHX15 is significantly upregulated in HCC and its high expression was correlated with poor prognosis, suggesting its pivotal role in the progression of HCC. The present results suggest that DHX15 may serve as a potential prognostic biomarker for HCC patients.
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1. Introduction

Hepatocellular carcinoma (HCC) is ranked as the sixth most common malignancy and the third leading cause of cancer-related mortality worldwide [1]. Recent advances in HCC diagnosis and treatment have resulted in a gradual decrease in HCC mortality. However, the long-term prognosis of patients with HCC remains unsatisfactory. The mortality

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rate of HCC is similar to its incidence rate, which reflects its poor prognosis [2]. The poor clinical outcome of HCC patients is mainly due to the high incidence of recurrence and metastasis [3]. A recentstudyreportedthattherecurrencerateafterresectionisapproximately50%inthefirst2 years, increasing to 75% within 5 years [4]. There are currently no specific biomarkers for reliably predicting recurrence and the long-term prognosis of HCC; therefore, the identification of new biomarkers for effective prognosis prediction is necessary and may contribute to improving postoperative quality of life in HCC patients.

DHX15, an outstanding member of the DEAH-box RNA helicase family, localizes to the nucleus and is involved in different substantive cellular processes, including pre-mRNA splicing and ribosome biogenesis, in addition to mediating the innate immune sensing of viral RNA [5-7]. DHX15 interacts with the G-patch protein NF-κB–repressing factor and XRN2 to form a preribosomal subcomplex and plays a critical role in the processing of pre-rRNAs and the turnover of excised spacer fragments [8]. Furthermore, DHX15 can bind to and be activated by Gno1p/PINX1, which is important for ribosome biogenesis [9]. DHX15 induces the production of type I interferon and proinflammatory cytokines in response to dsRNA and RNA viruses in a mitochondrial antiviral signaling–dependent manner. In addition, it stimulates the NF-κB and MAPK pathways, further contributing to mitochondrial antiviral signaling–mediated cytokine production and apoptosis [10,11].

Recent evidence suggests that DHX15 contributes to carcinogenesis in several tumor cell lines, although its expression levels are variable. DHX15 is overexpressed in lung adenocarcinoma samples and breast cancer cells [12-14]. In addition, DHX15 is commonly overexpressed in acute myeloid leukemia patients and associated with poor overall survival, and knockdown of DHX15 in Jurkat cells leads to impaired cell proliferation and increased apoptosis [15]. Recent research indicates that ETS1 and SP1 bind to the DHX15 promoter and promote its transcription in acute lymphoblastic leukemia [16]. DHX15 downregulation inhibits breast cancer cell proliferation, and co-overexpression of DHX15 and GPATCH2 enhances breast cancer cell growth [14]. DHX15 is upregulated in prostate cancer specimens, and its expression is correlated with Gleason scores and prostate-specific antigen recurrence. A mechanistic study revealed that DHX15 increases androgen receptor transcriptional activity and contributes to prostate cancer progression through Siah2 [17]. By contrast, Ito et al [18] showed that DHX15 acts as a tumor suppressor gene in glioma by inhibiting NF-κB pathway activity. Xiao et al [19] reported that DHX15 activates the p38 MAPK signaling pathway, leading to the inhibition of proliferation and metastasis in gastric cancer in vitro and in vivo. Moreover, DHX15 is involved in the promotion of apoptosis through interactions with cytoplasmic and mitochondrial G-patch protein 1 [20]. However, whether DHX15 acts as an oncogene or tumor suppressor and its association with HCC development and progression remains unclear. To address this question, we used immunohistochemistry (IHC) to evaluate DHX15 expression patterns and their association with clinicopathological factors and the prognosis of patients with HCC.

In the present study, we showed that DHX15 was markedly upregulated in HCC tissues, and high expression of DHX15 was closely associated with aggressive clinicopathological features, poor prognosis, and early recurrence in HCC patients. The present results indicate that DHX15 may contribute to HCC carcinogenesis and could serve as a prognostic predictor and therapeutic target in HCC.

2. Materials and methods

2.1. Patients and samples

A total of 104 patients diagnosed as having HCC from 2012 to 2016 in the Department of Hepatobiliary Surgery, Zhongshan Hospital Xiamen University, were included in our present study. All of them were diagnosed as having primary HCC and did not receive chemotherapy or radiotherapy before surgical operation but treated with commonly surgical resection at our hospital, so that we had complete clinical records and follow-up data. Follow-up time was from the date of pathological diagnosis to the date of death or last communication. Specimen collection was performed after informed consent was obtained from each patient, and the utilization of the tumor materials for research purposes was carried out in accordance with the approved guidelines and licensed by the Ethics Committee of Zhongshan Hospital Xiamen University (approved date: November 9, 2011; No. XMZSH-2011-079). This studies have also been performed according to the Declaration of Helsinki.

2.2. Patient characteristics

The clinical characteristics of the 104 HCC patients analyzed are summarized as follows: the mean age was 53 years (range, 20-90 years), and the male-to-female ratio was 3.7. All patients were Chinese. Of them, 16.35% (n = 17) had poor differentiation according to the pathologist's diagnosis, and 59.61% (n = 62) had a tumor diameter of greater than 5 cm; 29.81% (n = 31) of the patients presented with multifocal tumors, and intrahepatic and extrahepatic metastases were detected in 59.61% (n = 62) of the patients. Moreover, 47.00% (n = 47) and 67.00% (n = 67) had serum α-fetoprotein (AFP) and hepatitis B virus (HBV) levels of greater than 200 ng/mL and greater than 1000 IU/mL, respectively. During the median follow-up of 24 months (range, 1-58 months), 34 (32.69%) patients died and 27 (25.96%) developed recurrence.

2.3. Hematoxylin-eosin and IHC staining

Formalin-fixed, paraffin-embedded tissues from primary tumor were cut into serial 4-μm-thick sections by the pathological technologist and prepared for hematoxylin eosin and IHC

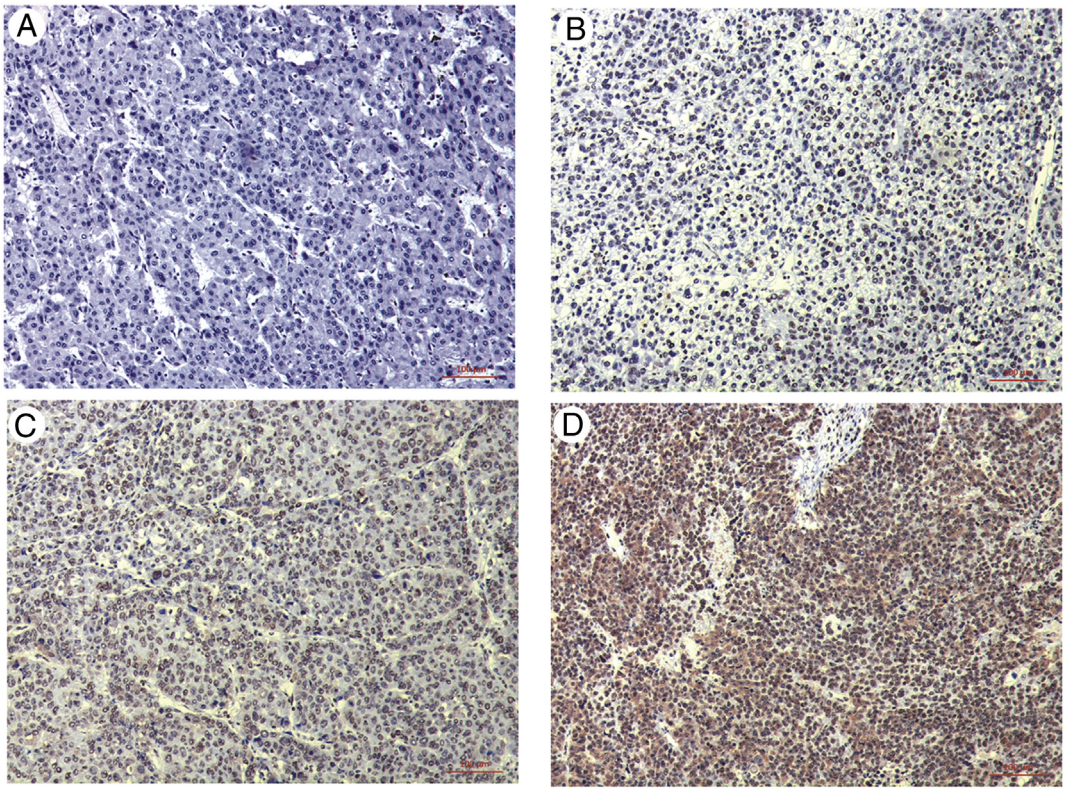

Fig. 1 Representative immunohistochemical staining of DHX15 in HCC tissues. DHX15 expression was classified into 4 categories according to the intensity of immunohistochemical staining as follows: A, negative; B, weak; C, moderate; and D, strong nuclear staining. Scale bars, 100 μm.

staining. For hematoxylin eosin staining, sections were deparaffinized and hydrated with a gradient alcohol. After soaking in phosphate-buffered saline solution, sections were stained with hematoxylin and eosin, respectively. For IHC staining, sections were stained via the streptavidin-peroxidase method. In brief, sections were deparaffinized, hydrated, and soaked in 3% H_2O_2 for 15 minutes at room temperature, and then incubated with DHX15 polyclonal antibody (1:800, sc-271 686; Santa Cruz) at room temperature for 1 hour. Meanwhile, negative control was incubated with nonimmune rabbit IgG at the same dilution as for the primary antibody. Biotinylated secondary antibody and diaminobenzidine were purchased from Maixin Biotechnology (Fuzhou, China).

Table 1 IHC scoring system for DHX15 expression

Intensity	Score	Percentage of staining positive cells (%)	Score
Negative	0	Negative	0
Weak	1	≤25	1
Moderate	2	26-50	2
Strong	3	51-75	3
		≥76	4

NOTE. For both scores, any stromal and inflammation cells or necrotic regions were excluded from analysis.

2.4. Immunostaining evaluation

As reported previously, the intensity was scored as 0 (no expression), 1 (weak expression), 2 (moderate expression), and 3 (strong expression; seen in Fig. 1) [21]. The percentage of positive staining was scored as 0 (no stain), 1 (≤25%), 2 (26%-50%), 3 (51%-75%), or 4 (≥76%). As shown in Table 1, the percentage and intensity of DHX15 expression were multiplied to generate a final score ranging from 0 to 12. The score was used to dichotomize the samples. Assessments were performed independently by 2 researchers blinded to the clinical data. Discrepant scores between researchers (a difference in composite score of ≥3 or a difference in high versus low outcome score) triggered a third researcher to obtain a final expression score. Based on the previously published IHC evaluation approach, low DHX15 expression was defined as a score of 4 or lower (n = 42), and high DHX15 expression was defined as a score of higher than 4 (n = 62) [22].

2.5. Statistical analysis

Data were analyzed using the software of SPSS version 21.0 for Windows (SPSS, Chicago, IL). The Pearson x^2 test was used to analyze the relationship between DHX15 expression and various clinicopathological parameters. Differences in DHX15 immunostaining score between cancer and noncancer tissues were evaluated using the Wilcoxon matched pairs

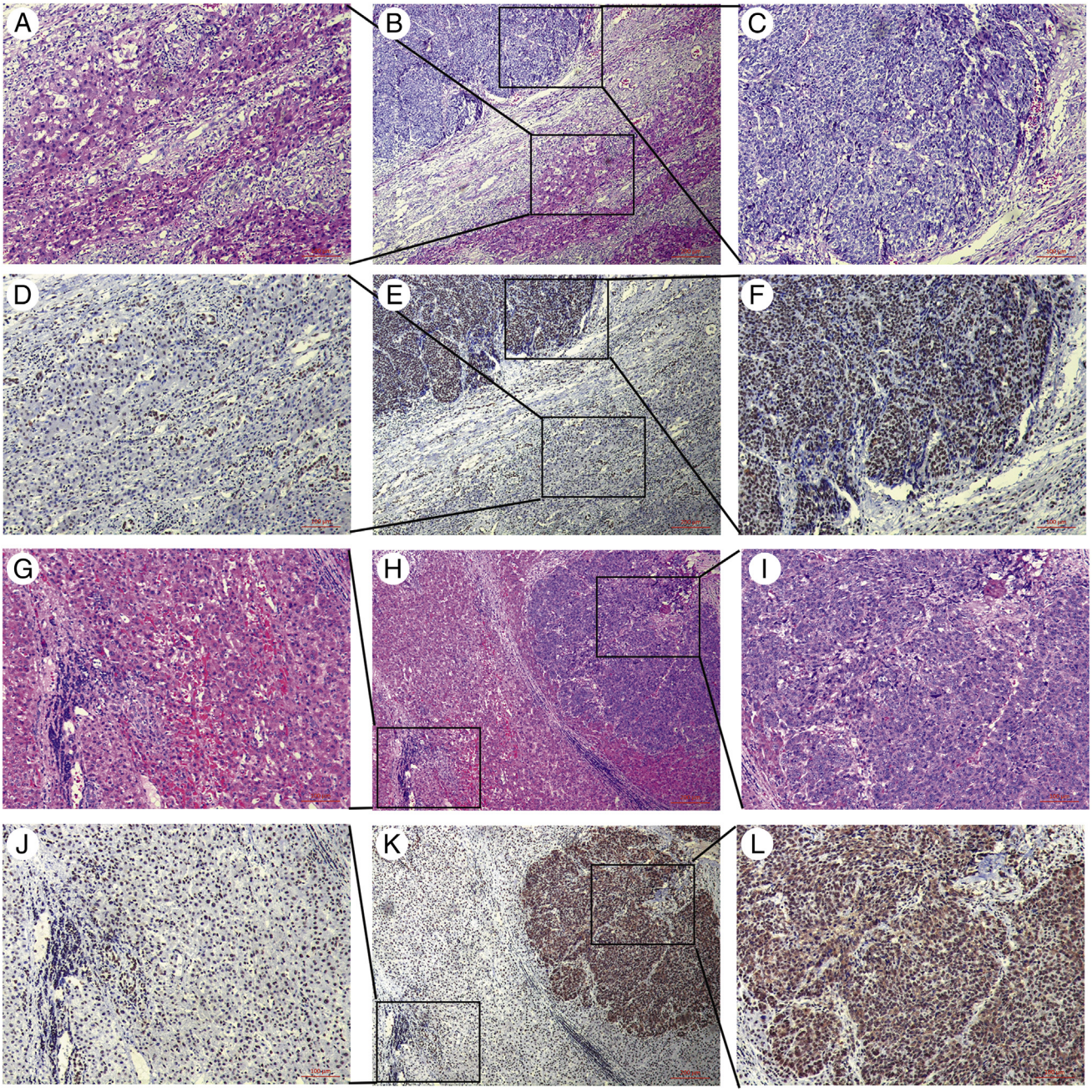

Fig. 2 Representative expression pattern of DHX15. The representative expression pattern of DHX15 in 2 paired tumor and nontumor liver tissues (A-C and G-I, H&E; D-F and J-L, IHC). DHX15 was weakly expressed in noncancerous liver tissues (A and G, H&E; D and J, IHC), whereas it was expressed at relatively higher levels in cancer tissues (C and I, H&E; F and L, IHC). H&E, hematoxylin and eosin. Scale bars, 200 μm (lane 1) and 100 μm (lanes 2 and 3).

test. Kaplan-Meier survival function was calculated and compared using the log-rank test. The Cox proportional hazard regression model was used for multivariate analyses to explore the effects of the clinicopathological variables and DHX15 expression on patient survival. All statistical tests were 2-tailed, and a *P* value of less than .05 was considered statistically significant.

3. Results

3.1. DHX15 is highly expressed in HCC tissues

To understand the possible role of DHX15 in the development and progression of HCC, we first explored the expression pattern of this protein in paired clinical tissue samples. As

Table 2 Correlation between DHX15 expression and clinicopathological characteristics

Characteristics	DHX15 high (IHC score >4)	DHX15 low (IHC score ≤4)	x^2	*P*
Sex				
Male	48	34	0.187	.665
Female	14	8		
Age (y)				
>53	30	19	0.100	.752
≤53	32	23		
Tumor size (cm)				
>5	39	23	0.689	.406
≤5	23	19		
Differentiation				
Poor	15	2	5.566	.018 *
Moderate-well	47	40		
Tumor number				
Multiple	23	8	3.899	.048 *
Single	39	34		
Intrahepatic and external hepatic metastases				
Yes	45	17	10.719	.001 *
No	17	25		
Serum AFP level (ng/mL) [a]				
>200	34	13	7.486	.006 *
≤200	24	29		
Serum HBV level (IU/mL) [a]				
>1000	45	22	5.594	.018 *
≤1000	14	19		
Recurrence [b]				
Yes	22	5	13.599	<.001 *
No	13	27		

[a] Four missing data points.
[b] Thirty-seven missing data points.
* Statistically significant, $P < .05$.

shown in Fig. 2, DHX15 was undetectable (31/104) or expressed very weakly (67/104) in noncancerous liver tissues. Its expression was higher in HCC tissues than in adjacent normal tissues, and it showed a predominantly diffuse nuclear staining pattern. Among the 104 noncancer tissue samples, 94.23% (98/104) of cases scored lower than 5, whereas 39.42% of tumor tissues showed relatively lower DHX15 expression (41/104). Overall, cancer tissues showed a significantly higher expression level of DHX15 than did noncancer tissues ($P < .0001$, Supplementary Fig. S1). Taken together, these results suggested that DHX15 maybe act as a tumor promoter in HCC.

Table 3 The 1-year survival rate among differential expressions of DHX15

DHX15 expression status	Survival time (mo)		Case no.	1-y survival ratio (%)	*P*
	>12	≤12			
DHX15 high	25	21	46	54.35	.002 *
DHX15 low	28	4	32	87.50	

* Statistically significant, $P < .05$.

3.2. DHX15 upregulation is associated with an aggressive phenotype of HCC

Next, we evaluated the association between DHX15 expression and clinicopathological parameters in HCC patients. As shown in Table 2, DHX15 expression in HCC was not correlated with certain clinicopathological features, including age, sex, and tumor size. However, the rate of high DHX15 expression was higher in patients with poor differentiation (15/17; 88.24%) than in those with moderate to well-differentiated tumors (47/87; 54.02%) ($P = .018$). The rate of high DHX15 expression was higher in patients with multiple tumors (23/31; 74.19%) than in those with a single tumor (39/73; 53.42%) ($P = .048$). In addition, the rate of high DHX15 expression was higher in patients with intrahepatic and extrahepatic metastases (45/62; 72.58%) than in those without metastasis (17/42; 40.48%) ($P = .001$). Analysis of the association between DHX15 expression in cancer tissues and serum HBV DNA and AFP levels showed that DHX15 expression was positively related to serum HBV ($P = .018$) and AFP levels ($P = .006$). Moreover, higher expression of DHX15 was significantly associated with recurrence ($P < .001$). These results

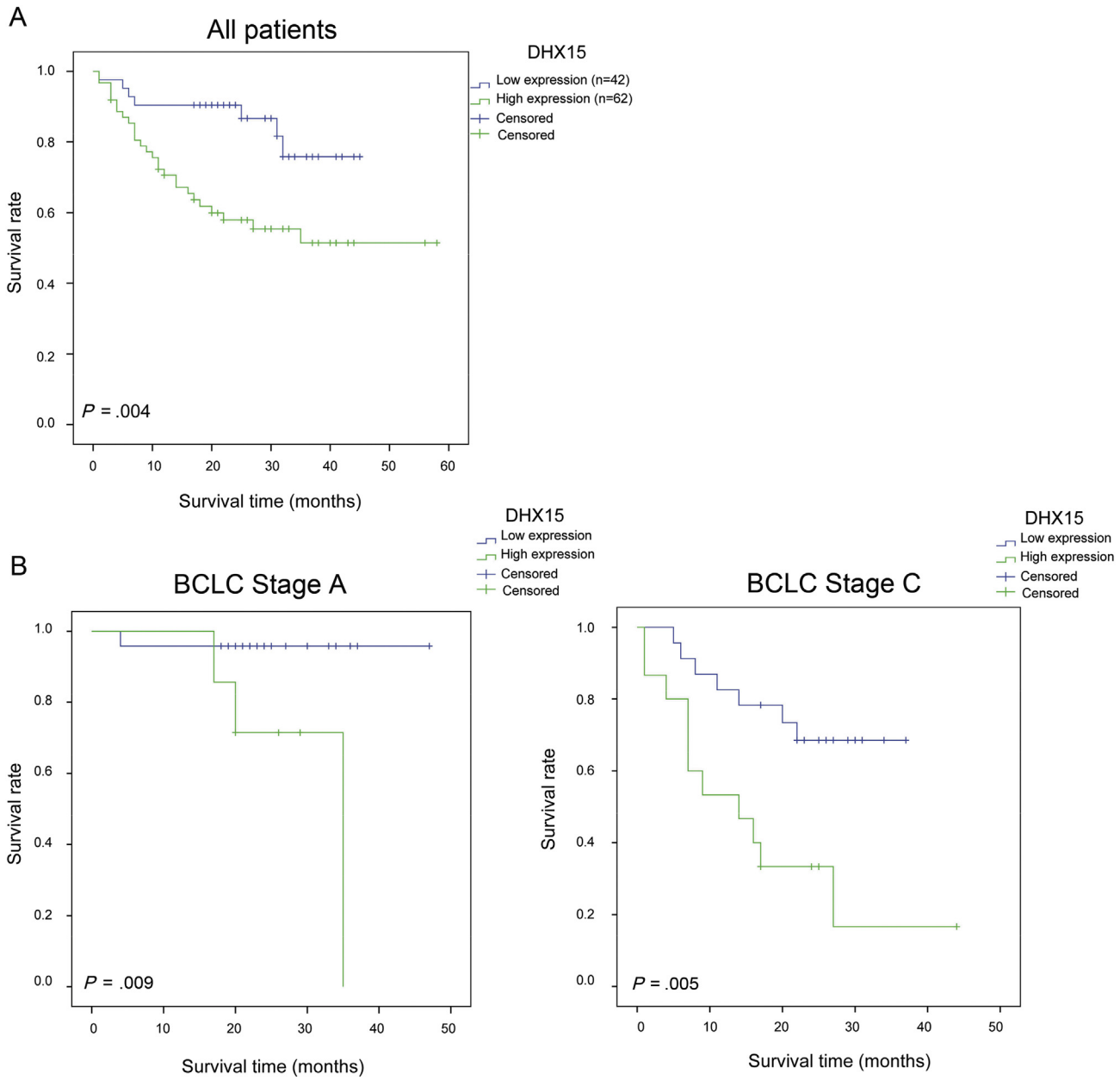

Fig. 3 DHX15 expression is correlated with poor survival. Kaplan-Meier curves of HCC patients with high (IHC score >4) and low (IHC score ≤4) DHX15 expression. Patients with high DHX15 expression had decreased overall survival both in all patients (A) and the BCLC stage subgroup (B). The *P* values were calculated using the log-rank test.

indicate that DHX15 expression may be correlated with the development and progression of HCC.

3.3. High expression of DHX15 predicts an unfavorable prognosis in HCC patients

To further evaluate whether DHX15 expression is linked to survival, HCC patients with complete follow-up information (n = 104) were classified into the DHX15-low (n = 42) and DHX15-high groups (n = 62) according to the IHC score of DHX15 expression. Statistical analysis showed that the 1-year survival rates were 87.50% for DHX15-low patients and 54.35% for DHX15-high patients (*P* = .002, Table 3). Kaplan-Meier analysis confirmed that patients with high DHX15 expression had a shorter overall postoperative survival time than did those with low DHX15 expression (*P* = .004, Fig. 3A). To further investigate the prognostic value of DHX15 in different subgroups, patients were stratified according to BCLC stage (Fig. 3B). The high expression of DHX15 maintained its prognostic value in predicting shorter OS in all of these subgroups. Moreover, the Cox proportional hazards regression model showed that high expression of DHX15 was an independent risk factor associated with the prognosis of patients with HCC (hazard ratio, = 3.012; 95% confidence

Table 4 Cox regression analysis of prognostic factors for HCC patients

Variables	*P*	HR	95% CI	
			Lower	Upper
Age	.455	1.365	0.603	3.087
Sex	.644	1.281	0.449	3.652
Tumor size	.278	1.702	0.652	4.446
Differentiation	.726	0.829	0.290	2.367
Tumor number	.125	1.833	0.844	3.978
Intrahepatic and external hepatic metastases	.025 *	5.838	1.254	27.180
Serum HBV level	.321	1.593	0.635	3.993
Serum AFP level	.871	1.071	0.467	2.457
DHX15 expression level	.036 *	3.012	1.075	8.435

Abbreviations: CI, Confidence interval; HR, hazard ratio.
* Statistically significant, $P < .05$.

interval, 1.075-8.435; $P = .036$; Table 4). Thus, DHX15 predicted the outcomes of HCC patients and can be used as a biomarker to predict patient prognosis.

4. Discussion

DHX15 is overexpressed in acute myeloid leukemia patients and associated with poor overall survival and relapse-free survival [15]. However, there are few studies examining DHX15 expression in HCC, especially in the Asian population. Therefore, the aim of the present study was to comprehensively evaluate the clinical relevance and expression patterns of DHX15 in HCC among Chinese patients. To the best of our knowledge, the present study is the first to demonstrate that DHX15 expression in HCC is associated with poor survival. As in acute myeloid leukemia, high DHX15 expression was correlated with decreased overall survival, and DHX15 expression was an independent prognostic predictor of postoperative survival time in patients with HCC. These results not only suggested that DHX15 plays a critical role in human HCC development but also that additional studies may help develop DHX15 as a potential biomarker for predicting the prognosis of HCC patients; namely, patients with high DHX15 expression may have a worse prognosis. The present data add to the growing body of evidence that DHX15 maybe play a critical role in the carcinogenesis of HCC.

DHX15 is upregulated in prostate cancer specimens, and its expression is correlated with Gleason scores and prostate-specific antigen recurrence [17]. Pan et al [15] reported that DHX15 expression is significantly higher in acute myeloid leukemia samples than in normal tissues. Consistent with these findings, the present study demonstrated that DHX15 protein expression was significantly increased in HCC cancer tissues. However, Ito et al [18] reported the opposite results, suggesting that DHX15 expression is lower in human glioma cell lines than in normal neural stem cells. Such discrepancies regarding the expression levels of DHX15 may be attributed to the different tumor tissues used in different studies. Hence, organ specificity and cell heterogeneity should be taken into consideration in the evaluation of DHX15 expression. It seems that the biology of DHX15 is rather complex with its partners and acting as part of multiple protein complexes sometimes cooperating with oncoprotein and sometimes with tumor suppressors, depending on the context of an individual malignancy. In addition, these apparent discrepancies between DHX15 expression patterns in different tumors suggest that DHX15 acts differentially in various carcinomas and microenvironment.

Previous studies reported that DHX15 upregulation is associated with aggressive pathologic characteristics and poor prognosis in acute myeloid leukemia and prostate cancer patients. Consistent with these findings, we found that DHX15 expression in HCC was associated with poor differentiation, metastasis, recurrence, and other malignant phenotypes. However, further work is required to investigate the expression level of DHX15 via IHC in a large clinical cohort collected prospectively and to explore whether DHX15 has translational relevance as a prognostic marker in clinical practice. In addition, these results were obtained in a local cohort and should be confirmed in other populations of HCC patients in future studies. Another limitation of this study was that the follow-up time was relatively short. To strengthen our current study, a longer follow-up and questionnaires are warranted to provide more objective data.

DHX15 promotes the nuclear translocation and activation of P65, which activates leukemia cell proliferation and inhibits cell apoptosis and G1-phase arrest [15]. Jing et al [17] reported that DHX15 knockdown inhibits the growth of C4-2 prostate tumor xenografts in vivo. In contrast to these studies, several reports showed that DHX15 overexpression suppresses glioma cell proliferation in vitro and tumor formation in vivo [18]. Xiao et al [19] reported that DHX15 mediates the inhibition of gastric cancer cell migration and proliferation by cerium oxide nanoparticles. Although DHX15 expression is associated with a variety of malignant biological characteristics, the precise function of neoplastic DHX15 expression in HCC remains to be elucidated. Whether this overexpression is an ending or initiating event in the malignant transformation of HCC, and whether it is essential for ongoing tumor progression or contributes to adjuvant therapy response remains to be determined.

In summary, to the best of our knowledge, the present study is the first to demonstrate the significant overexpression of DHX15 in human primary HCC, which indicates that overexpression of DHX15 may play a pivotal role in the carcinogenesis of HCC. We showed that high DHX15 expression was associated with recurrence and worse overall survival, suggesting that DHX15 expression is an independent predictor of prognosis. Our findings suggest that DHX15 may serve as a biomarker for determining the level of malignancy of this disease, a prognostic marker, and a potential candidate for future HCC therapies after additional studies. The roles of DHX15 in HCC need to be further examined in large-scale prospective studies and additional basic research.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2018.10.006.

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