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RESEARCH ARTICLE

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A-kinase interacting protein 1 (AKIP1) associates with advanced overall disease condition, tumor properties, and unfavorable prognosis in hepatocellular carcinoma patients

Tao Fang[1,2] | **Qi Lu**[1,2]

[1]Department of Hepatobiliary and Pancreatic Surgery, Huangshi Central Hospital of Edong Healthcare Group, Hubei Polytechnic University, Huangshi, China

[2]Hubei Province Key Laboratory of Occupational Hazard Identification and Control, Wuhan University of Scinecne and Technology, Huangshi, China

Correspondence
Qi Lu, Department of Hepatobiliary and Pancreatic Surgery, Huangshi Central Hospital of Edong Healthcare Group, Hubei Polytechnic University, Hubei Province Key Laboratory of Occupational Hazard Identification and Control, Wuhan University of Science and Technology, No. 141, Tianjin Road , Huangshi 435000, Hubei Privince,China.
Email: lanyi888520203@163.com

Abstract

Objective: The presented study aimed to investigate the association of A-kinase interacting protein 1 (AKIP1) expression with tumor properties, liver functions, cancer markers, and overall survival (OS) of hepatocellular carcinoma (HCC) patients.

Methods: A total of 432 HCC patients receiving surgery were retrospectively reviewed in our study. Clinical characteristics of patients were obtained. Tumor tissue specimens of all patients were collected, and AKIP1 expression was evaluated by immunohistochemistry (IHC) assay. OS was assessed, and the median follow-up duration was 35.0 months. AKIP1 high expression was defined as total IHC score more than 3 and was further graded as AKIP1 high+ (IHC 4-6), AKIP1 high++ (IHC 7-9), and AKIP1 high+++ (IHC 10-12).

Results: About 265 (61.3%) patients presented with AKIP1 low expression and 167 (38.7%) patients had AKIP1 high expression. AKIP1 high expression correlated with higher performance status score (P = .006), largest tumor size ≥5.0 cm (P < .001), Barcelona clinic liver cancer (BCLC) stage B (vs stage A; P = .024), increased alpha-fetoprotein level (P = .036), and higher carbohydrate antigen 199 level (P < .001). AKIP1 high expression (P < .001) and increased AKIP1 expression grade (P < .001) both correlated with worse OS, and Cox's regression analyses revealed that AKIP1 high expression (P < .001) was an independent predictive factor for shorter OS. In subgroup analysis, AKIP1 high expression and more advanced AKIP1 expression grade associated with worse OS in both BCLC stage A subgroup patients (both P < .001) and BCLC stage B subgroup patients (both P < .001), respectively.

Conclusion: AKIP1 is a novel and promising biomarker for disease monitoring and prognosis in HCC patients.

KEYWORDS

A-kinase interacting protein 1, biomarker, clinical characteristics, hepatocellular carcinoma, overall survival

1 | INTRODUCTION

Liver cancer, representing as one of the most urgent health problem in the world, mainly comprises of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC).[1] Hepatocellular carcinoma (HCC) roughly takes up 75% ~ 85% of all liver cancers, presenting with an increasing incidence in Eastern Asia mostly due to the high prevalence of hepatitis B virus infection.[2-4] Late diagnosis is still prevalent among HCC patients, resulting in a consequence of majority of the patients could only receive non-potential curative therapies with a require of multidisciplinary team.[1] Thus, overall, the survival of HCC patients is not satisfactory despite promising progress in novel agents, which is also due to a number of the novel agents are reported to be ineffective.[5-8] Therefore, this condition of HCC patients highlights a need for exploration of potential biomarkers facilitating diagnosis, disease monitoring, and prognosis in clinical practice.

A-kinase interacting protein 1 (AKIP1), also known as the breast carcinoma-associated protein 3 (BCA3), is a protein of 23-kDa encoding the alternatively spliced protein that is proline-rich.[9-11] In recent years, AKIP1 has risen as a promising potential biomarker among oncology researches mostly because AKIP1 is aberrantly expressed and can regulate cancer multiple cell functions in multiple carcinomas, such as, promoting angiogenesis and lymphangiogenesis of esophageal squamous cell carcinoma, and advocating angiogenesis as well as tumor growth of cervical cancer.[12,13] Interestingly, a previous report elucidates that AKIP1 (BCA3) participates in the HCC pathogenesis by mediating HCC cell functions via regulating protein kinase B (AKT) and nuclear factor κB (NF-κB) in vitro, which suggests that AKIP1 is probably a regulator of HCC etiology and may have potential to serve as biomarker for diagnosis or prognosis.[14] However, to our best knowledge, no study has been conducted to explore the clinical value of AKIP1 in HCC patients.

Herein, we retrospectively included 432 HCC patients who underwent resection and collected their tumor tissues for AKIP1 quantification by immunohistochemistry (IHC) assay, aiming to investigate the correlation of AKIP1 expression with tumor properties, liver functions, cancer markers, and overall survival (OS) in HCC patients.

2 | MATERIALS AND METHODS

2.1 | Patients

This study retrospectively reviewed 432 HCC patients who underwent resection in our hospital, from January 2014 to December 2015. The inclusion criteria were as follows: (a) newly diagnosed as primary HCC by pathology; (b) Barcelona clinic liver cancer (BCLC) stage A or stage B, and received resection; (c) 18-80 years old; (d) tumor tissue was well preserved and can be used for immunohistochemistry (IHC); and (e) complete clinical data and records of follow-ups. The patients who received neoadjuvant therapy or complicated with other malignancies were excluded. This study was approved by the Ethics Committee of our hospital. All patients or their guardians provided the informed consents before enrollment.

2.2 | Data collection

The clinical characteristics of patients were obtained from medical records, which included age, gender, history of hepatitis B (HB), history of liver cirrhosis, Child-pugh stage, performance status (PS) stage, tumor nodule number (unifocal or multifocal), largest tumor size, BCLC stage, the level of liver function index (such as alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin (TBIL), and the level of tumor marker (such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 199 (CA199)).

2.3 | IHC

The tumor tissue specimens were acquired from the pathology department in our hospital, and all tumor tissue specimens were formalin-fixed and paraffin-embedded. The expression of AKIP1 in tumor tissue specimens was detected by IHC, and the procedures were carried out in accordance with the instruction. Firstly, the tumor tissue specimens were cut into 4 μm sections. Then, the tissue sections were deparaffinized using xylene followed by rehydration in graded alcohol. The antigen retrieval was performed using microwave heating, and the peroxidase activity of tissue sections was blocked by incubating with 0.3% H_2O_2 for 15 minutes. Subsequently, the tissue sections were incubated with 10% normal goat serum (Sigma-Aldrich) for 2 hours at 37°C to prevent nonspecific binding. After that, the tissue sections were incubated overnight at 4°C with the rabbit anti-AKIP1 antibody (1:50, Abcam). Next day, the tissue sections were washed in tris-buffered saline tween (TBST) for 10 minutes and incubated with a horseradish peroxidase-conjugated goat anti-rabbit IgG H&L (1:2000, Abcam) at 37°C for 60 minutes. Last, the tissue sections were stained through diaminobenzidine (DAB; Dako) and counterstained with the use of hematoxylin (Sigma-Aldrich), then sealed with neutral resin (Sango Biotech).

2.4 | Assessment of AKIP1 expression

The immunostaining results were observed using the Nikon ECLIPSE E200 microscope (Nikon Instruments) and assessed by a semi-quantitative scoring method based on the intensity of staining and proportion of positively stained tumor cells, as previously described.[15] The staining intensity was graded as follows: 0, no staining; 1, weak staining; 2, moderate staining; and 3, strong staining. The proportion of positive tumor cells was scored as follows: 0, no positive tumor cells; 1, <25%; 2, 25%–50%; 3, 51%–75%; and 4, >75%. The total IHC score was calculated by multiplying the

staining intensity score and the proportion of positive tumor cells score. AKIP1 low expression was defined as total IHC score ≤3, and AKIP1 high expression was defined as total IHC score more than 3. AKIP1 high expression was further classified as AKIP1 high+ (total IHC score 4-6), AKIP1 high++ (total IHC score 7-9), and AKIP1 high+++ (total IHC score 10-12).[15]

2.5 | Treatment and follow-up

After resection, all HCC patients received adjuvant therapy (such as fluoropyrimidine chemoradiation, fluoropyrimidine-based chemotherapy, or gemcitabine-based chemotherapy) according to NCCN clinical practice guidelines in Oncology: Hepatobiliary Cancers.[16] The survival data were collected from follow-up records, and the last follow-up date was December 31, 2018. The median follow-up duration was 35.0 months, and min-max follow-up duration was 4-59 months. According to the survival data, OS was calculated from the date of resection to the date of death.

2.6 | Statistical analysis

All the statistical analyses were conducted by using SPSS 22.0 software (IBM), and figures were plotted using GraphPad Prism 7.00 (GraphPad Software). The normality of continuous variables was checked by the Kolmogorov-Smirnov test. And the normally distributed continuous variables were presented as mean ± standard deviation (SD), and the non-normal distributed continuous variables were presented as median (interquartile range, IQR). Categorical variables were presented as count (percentage). Comparison of clinical characteristics between AKIP1 high and low expression patients was determined by Student's *t* test, chi-square test, or Wilcoxon rank sum test. The OS was illustrated by Kaplan-Meier curve, and the difference of OS between/among groups was analyzed by log-rank test. Univariate and multivariate Cox's proportional hazard regression model were used for analysis of factors predicting OS *P* value < .05 was considered as significant.

3 | RESULTS

3.1 | Characteristics in patients with HCC

Totally, 432 HCC patients in our study presented with a mean age of 58.9 ± 10.2 years with 84 (19.4%) females and 348 (80.6%) males (Table 1). History of HB and history of liver cirrhosis were presented in 374 (86.6%) patients and 300 (69.4%) patients, respectively. About 352 (81.5%) patients had Child-pugh stage A, and 80 (18.5%) patients had Child-pugh stage B. The numbers of patients assessed to have PS Score of 0 and 1 were 349 (80.8%) and 83 (19.2%), respectively. In addition, the numbers of patients with unifocal disease and multifocal disease were 249 (57.6%) and 183 (42.4%), and the numbers of patients with largest nodule size <5.0 cm and ≥5.0 cm were 247 (57.2%) and 185 (42.8%), respectively. Besides, the numbers of patients in BCLC stage A and BCLC stage B were 208 (48.1%) and 224 (51.9%), respectively. The other information on laboratory indexes levels was displayed in Table 1.

3.2 | AKIP1 expression in HCC patients

The AKIP1 low expression (IHC score 0-3) was presented in 265 (61.3%) HCC patients, and AKIP1 high expression was presented in

TABLE 1 Clinical characteristics of HCC patients

Items	HCC patients (N = 432)
Age (y), mean ± SD	58.9 ± 10.2
Gender, No. (%)	
Female	84 (19.4)
Male	348 (80.6)
History of HB, No. (%)	374 (86.6)
History of liver cirrhosis, No. (%)	300 (69.4)
Child-pugh stage, No. (%)	
A	352 (81.5)
B	80 (18.5)
PS Score, No. (%)	
0	349 (80.8)
1	83 (19.2)
Tumor nodule number, No. (%)	
Unifocal	249 (57.6)
Multifocal	183 (42.4)
Largest tumor size, No. (%)	
<5.0 cm	247 (57.2)
≥5.0 cm	185 (42.8)
BCLC stage, No. (%)	
A	208 (48.1)
B	224 (51.9)
Liver function index, median (IQR)	
ALT (U/L)	27.1 (20.7-38.1)
AST (U/L)	35.2 (26.2-47.3)
ALP (U/L)	102.5 (80.8-141.8)
TBIL (μmol/L)	15.9 (10.8-25.2)
Tumor marker, median (IQR)	
AFP (ng/mL)	33.5 (5.1-1116.4)
CEA (μg/L)	2.5 (1.9-4.1)
CA199 (U/mL)	11.8 (4.8-29.3)

Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; HB, hepatitis B; HCC, hepatocellular carcinoma; IQR, interquartile range; PS, performance status; SD, standard deviation; TBIL, total bilirubin.

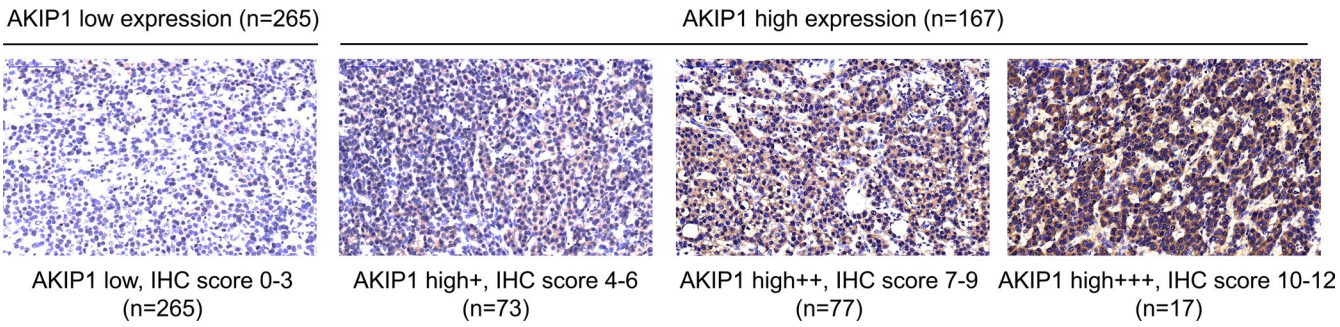

FIGURE 1 Number of patients with AKIP1 high/low expression. AKIP1, A-kinase interacting protein 1; IHC, immunohistochemistry

167 (38.7%) HCC patients (Figure 1). In detail, the numbers of patients with AKIP1 high+ expression (IHC score 4-6), AKIP1 high++ expression (IHC score 7-9), and AKIP1 high+++ expression (IHC score 10-12) were 73 (16.9%), 77 (17.8%), and 17 (3.9%), respectively.

3.3 | Association of AKIP1 expression with clinical characteristics

AKIP1 high expression correlated with higher PS score ($P = .006$), largest tumor size ≥5.0 cm ($P < .001$), BCLC stage B ($P = .024$), increased AFP level ($P = .036$), and higher CA199 level ($P < .001$; Table 2). These data suggested that AKIP1 high expression associated with worse overall disease condition and elevated cancer markers of HCC patients.

3.4 | Association of AKIP1 expression with OS

In total HCC patients, the OS of patients with AKIP1 high expression was shorter compared with that in patients with AKIP1 low expression ($P < .001$; Figure 2A). When patients were divided according to the AKIP1 expression grade, the OS was the worst in patients with AKIP1 high+++ expression, which was followed by that in patients with high++ patients and patients with AKIP1 high+ expression, and it was the best in patients with AKIP1 low expression ($P < .001$; Figure 2B). Subsequently, the univariate Cox's regression illuminated that AKIP1 high expression ($P < .001$) could predict worse OS in HCC patients, and age ≥60 ($P = .001$), history of HB ($P < .001$), history of liver cirrhosis ($P < .001$), higher Child-pugh stage ($P < .001$), largest tumor size ≥5.0 cm ($P < .001$), higher BCLC stage ($P < .001$), increased AST level ($P = .019$) as well as elevated TBIL level ($P = .023$) were also predictors for worse OS (Table 3). Then, the multivariate Cox's regression analysis showed that AKIP1 high expression ($P < .001$) independently predicted less prolonged OS, and other independent predictive factors for worse OS were age ≥60 ($P < .001$), history of HB ($P < .001$), history of liver cirrhosis ($P < .001$), higher Child-pugh stage ($P < .001$), largest tumor size ≥5.0 cm ($P < .001$), and higher BCLC stage ($P < .001$).

3.5 | Association of AKIP1 expression with OS in subgroups divided by BCLC stage

Subsequently, the subgroup analyses of OS were conducted in BCLC stage A HCC patients and BCLC stage B patients. In BCLC stage A patients, the OS was worse in patients with AKIP1 high expression compared with patients with AKIP1 low expression ($P < .001$; Figure 3A). In addition, the OS was the shortest in patients with AKIP1 high+++ expression followed by patients with AKIP1 high++ patients and patients with AKIP1 high+ patients and was the longest in patients with AKIP1 low expression ($P < .001$; Figure 3B). Additionally, in patients who were in BCLC stage B, the correlation of AKIP1 high/low expression with OS ($P < .001$; Figure 3C) and the association of AKIP1 expression grade with OS ($P < .001$; Figure 3D) were similar to those in the BCLC stage A patients.

4 | DISCUSSION

The disease burden caused by HCC continues to be a predominant issue in the world considering the rising death rate caused by multiple shortages in HCC management, such as lack of proper disease surveillance, insufficient evidence of novel therapies' efficacy, and so on.[17] In clinical practice, not many biomarkers are available to assist in the disease monitoring and prognosis prediction in HCC patients, and the existed biomarkers often have limited sensitivity or specificity, such as AFP.[18] Therefore, it is urgent to explore more ancillary biomarkers for improving the management, and subsequently the prognosis of HCC patients. In the present study, we hypothesized that AKIP1 expression could serve as a biomarker for disease monitoring and prognosis in HCC patients and discovered that (a) AKIP1 high expression correlated with increased PS score, largest tumor size ≥5.0 cm, BCLC stage B, higher AFP and CA199 levels; (b) both AKIP1 high expression and increased AKIP1 expression grade correlated with worse OS; and (c) AKIP1 high expression independently predicted worse OS in HCC patients.

AKIP1 has been demonstrated as an oncogenic protein in multiple cancers. For instance, a previous in vitro experiment illustrates that AKIP1 promotes the cancer cell proliferation, invasion, migration, and activates the slug induced epithelial-mesenchymal transition

TABLE 2 Comparison of clinical characteristics between AKIP1 high and low expression patients

Items	AKIP1 expression		*P* value
	Low (n = 265)	High (n = 167)	
Age (y), mean ± SD	59.4 ± 9.8	58.2 ± 9.4	.196
Gender, No. (%)			.537
Female	54 (20.4)	30 (18.0)	
Male	211 (79.6)	137 (82.0)	
History of HB, No. (%)	235 (88.7)	139 (83.2)	.106
History of liver cirrhosis, No. (%)	185 (69.8)	115 (68.9)	.835
Child-pugh stage, No. (%)			.814
A	215 (81.1)	137 (82.0)	
B	50 (18.9)	30 (18.0)	
PS Score, No. (%)			.006
0	225 (84.9)	124 (74.3)	
1	40 (15.1)	43 (25.7)	
Tumor nodule number, No. (%)			.099
Unifocal	161 (60.8)	88 (52.7)	
Multifocal	104 (39.2)	79 (47.3)	
Largest tumor size, No. (%)			<.001
<5.0 cm	185 (69.8)	62 (37.1)	
≥5.0 cm	80 (30.2)	105 (62.9)	
BCLC stage, No. (%)			.024
A	139 (52.5)	69 (41.3)	
B	126 (47.5)	98 (58.7)	
Liver function index, median (IQR)			
ALT (U/L)	27.3 (19.4-38.1)	26.8 (22.6-38.2)	.521
AST (U/L)	33.9 (26.2-46.1)	37.9 (26.1-67.9)	.067
ALP (U/L)	102.1 (82.2-144.8)	103.0 (75.6-140.2)	.299
TBIL (μmol/L)	16.9 (10.1-25.2)	14.7 (11.1-25.2)	.677
Tumor marker, median (IQR)			
AFP (ng/mL)	29.3 (10.9-1356.2)	44.5 (7.5-1045.6)	.036
CEA (μg/L)	2.4 (1.8-4.1)	2.6 (1.9-4.2)	.475
CA199 (U/mL)	10.6 (3.8-26.5)	15.8 (6.2-44.0)	<.001

Note: Comparison was determined by Student's *t* test, chi-square test, or Wilcoxon rank sum test.

Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; HB, hepatitis B; HCC, hepatocellular carcinoma; IQR, interquartile range; PS, performance status; SD, standard deviation; TBIL, total bilirubin.

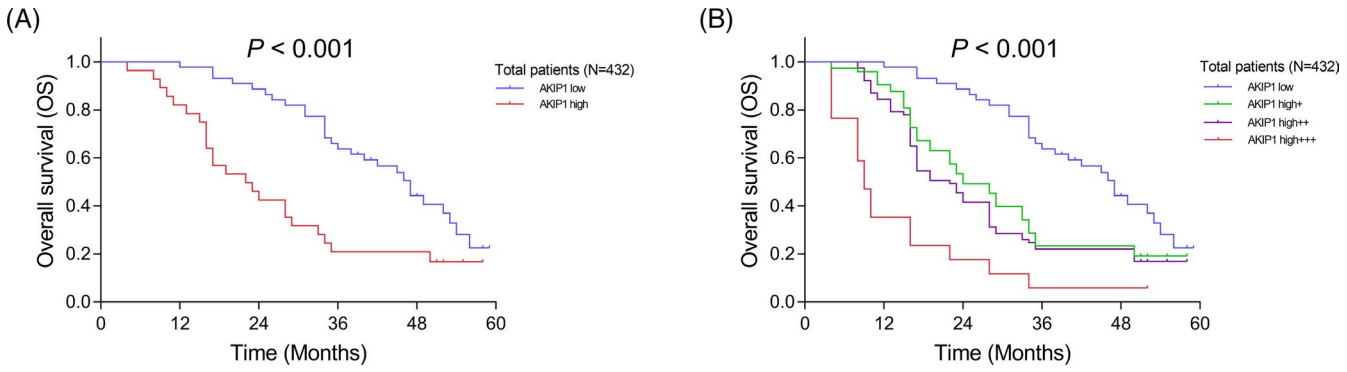

FIGURE 2 The OS in patients with different AKIP1 expressions. The OS in patients with AKIP1 high expression and patients with AKIP1 low expression (A), the OS in patients with AKIP1 low, high+, high++, and high+++ expressions (B). AKIP1, A-kinase interacting protein 1OS, overall survival

TABLE 3 Analysis of factors predicting OS

	Cox's proportional hazard regression model			
			95%CI	
Items	*P* value	HR	Lower	Higher
Univariate Cox's regression				
AKIP1 high expression	<.001	2.377	1.898	2.977
Age (≥60 y)	.001	1.463	1.170	1.830
Gender (male)	.055	1.337	0.994	1.797
History of HB	<.001	2.577	1.725	3.849
History of liver cirrhosis	<.001	1.651	1.281	2.129
Higher Child-pugh stage	<.001	1.958	1.491	2.571
Higher PS Score	.647	1.068	0.806	1.415
Tumor nodule number (multifocal)	.292	1.128	0.902	1.411
Largest tumor size (≥5.0 cm)	<.001	2.225	1.778	2.784
Higher BCLC stage	<.001	2.431	1.914	3.088
ALT (≥40.0 U/L)	.388	0.887	0.675	1.165
AST (≥40.0 U/L)	.019	1.311	1.046	1.645
ALP (≥150.0 U/L)	.297	1.149	0.885	1.492
TBIL (≥19.0 μmol/L)	.023	1.306	1.038	1.644
AFP (≥400.0 ng/mL)	.994	1.001	0.792	1.264
CEA (≥5.0 μg/L)	.394	1.000	1.000	1.001
CA199 (≥37.0 U/mL)	.602	1.072	0.825	1.393
Multivariate Cox's regression				
AKIP1 high expression	<.001	4.022	3.046	5.311
Age (≥60 y)	<.001	3.040	2.355	3.922
History of HB	<.001	3.509	2.207	5.580
History of liver cirrhosis	<.001	2.092	1.522	2.874
Higher Child-pugh stage	<.001	7.248	5.014	10.475
Largest tumor size (≥5.0 cm)	<.001	3.499	2.714	4.512
Higher BCLC stage	<.001	3.491	2.696	4.520
AST (≥40.0 U/L)	.600	1.069	0.833	1.371
TBIL (≥19.0 μmol/L)	.722	0.947	0.699	1.282

Note: Factors predicting OS were analyzed by univariate and multivariate Cox's proportional hazard regression model. The factors with *P* value < .05 in univariate Cox's regression were included in multivariate Cox's regression.

Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; CI, confidence interval; HB, hepatitis B; HR, hazard ratio; OS, overall survival; PS, performance status; TBIL, total bilirubin.

(EMT) in gastric cancer.[19] In addition, another in vitro experiment reports that AKIP1 enhances angiogenesis, cell proliferation, and clone formation by increasing CXCL1, CXCL2, and CXCL8 in cervical cancer cells.[13] And in non-small cell lung cancer (NSCLC), AKIP1 is elucidated to advocate EMT, which is validated by the EMT markers expressions, by transactivating ZEB1 in NSCLC cells.[20] More importantly, AKIP1 could also regulate HCC pathogenesis, a previous study reports that AKIP1 enhances invasion and colony outgrowth of HCC cells and advocates intrahepatic metastasis as well as lung metastasis in xenograft HCC mouse models.[21] These prior findings altogether indicate that AKIP1 act as a protein aggravates tumor progression in several types of cancer. Based on these functions of AKIP1 in cancers revealed by the previous studies, we presumed that AKIP1 might be able to be a biomarker for disease monitor in HCC patients. Therefore, this study was conducted to evaluate the AKIP1 expression with HCC patients' clinical characteristics, which disclosed that AKIP1 high expression associated with elevated PS score, largest tumor size, BCLC stage, AFP level, and CA199 level. And here are some probable interpretations to the results in this study: (a) AKIP1 might promote the progression of HCC tumors via enhancing cell growth, migration, proliferation, and clone formation by regulating tumorigenesis-related proteins, for instance the ZEB1 protein, thus resulted in advanced tumor features and higher clinical stages. Thus, AKIP1 was positively correlated with largest tumor size and BCLC

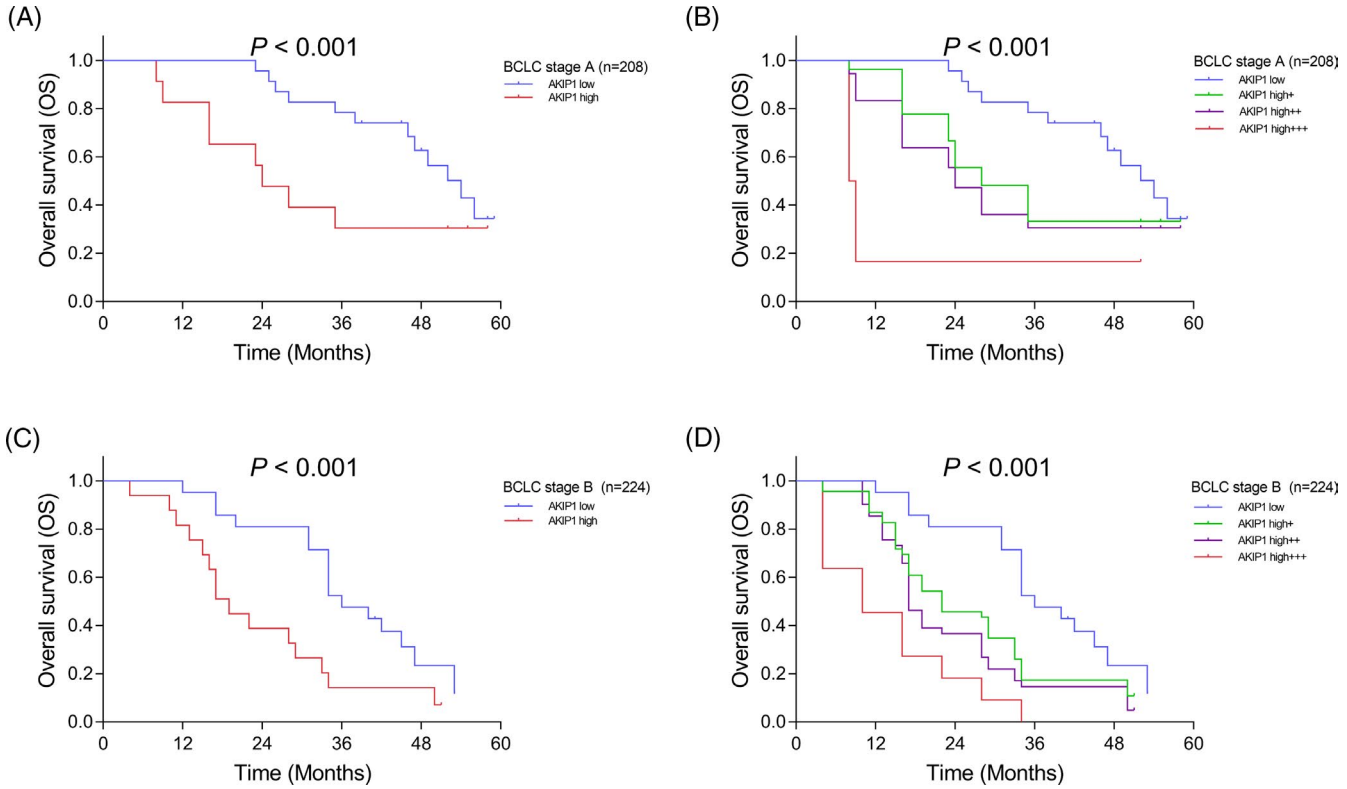

FIGURE 3 The OS in patients with different AKIP1 expression in subgroups. Comparison of OS between BCLC stage A patients with AKIP1 high/low expression (A) and among BCLC stage A patients with AKIP1 low/high+/high++/high+++ expression (B). The difference of OS between BCLC stage B patients with AKIP1 high/low expression (C), and the disparity of OS among BCLC stage B patients with AKIP1 low/high+/high++/high+++ expression (D). AKIP1, A-kinase interacting protein 1; BCLC, Barcelona clinic liver cancer; OS, overall survival

stage; (b) as typical tumor markers of HCC, AFP and CA199 levels indicated the progression of HCC tumor to some extent. Therefore, AKIP1 probably promoted the aggravation of HCC tumor, such as tumor growth and metastasis, which subsequently resulted in increased release of AFP and CA199, which resulted in positive association of AKIP1 with AFP and CA199; (c) due to that AKIP1 aggregates tumor progression in HCC, the patients' physical functions are often decreased, which contributed to a worse PS score.[13,19,20]

Furthermore, AKIP1 is also a potential biomarker for prognosis in various cancers other than HCC as reported by previous studies. For instance, a study reveals that higher AKIP1 expression correlates with increased disease progression of colorectal cancer patients, and AKIP1 also elevates cell migration of colorectal cancer cells in vitro.[22] Besides, a study illuminates that AKIP1 high expression is a predicting factor for poor prognosis of patients with breast cancer, and AKIP1 downregulation represses cancer cell motility and cell invasion of breast cancer.[23] In the present study, we assessed the correlation of AKIP1 expression with OS in HCC patients and found that AKIP1 high expression was associated with unfavorable OS and independently predicted worse OS of patients with HCC, which was partially in accordance with the prognostic role of AKIP1 in other cancers. The possible reasons which might explain these results could be (a) AKIP1 might promote disease progression or the risk of relapse of HCC patients by promoting the malignant behaviors of HCC cells, thus resulted in advanced tumor size, metastasis, etc via regulating multiple pathways, which subsequently contributed to a worse survival of patients; (b) AKIP1 might also decrease the chemosensitivity of HCC patients via mediating EMT, however, which need to be further validated by in vivo and in vitro experiments.[13,20,22]

In addition, there were several advantages and limitations: (a) We included 432 HCC patients in this study, which was a relatively large sample size; (b) the AKIP1 expression was not evaluated in circulating samples in our study, and AKIP1 expression in circulation was more applicable in clinical practice; (c) the follow-up period was not long enough; and (d) the HCC patients who cannot receive surgery were not included in our study, and thus, the value of AKIP1 in disease monitoring and prognosis in unresectable HCC patients was not assessed.

In conclusion, AKIP1 is a novel and promising biomarker for disease monitoring and prognosis in HCC patients.

ORCID

Qi Lu https://orcid.org/0000-0002-9886-782X

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