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RESEARCH ARTICLE

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A-kinase interacting protein 1 as a potential biomarker of advanced tumor features and increased recurrence risk in papillary thyroid carcinoma patients

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Abstract

Background: This study aimed to detect the expression of A-kinase interacting protein 1 (AKIP1) and explore its correlation with clinicopathological features and clinical outcomes in papillary thyroid carcinoma (PTC) patients.

Methods: A total of 245 PTC patients treated by lobectomy or thyroidectomy were analyzed in this retrospective study. AKIP1 expression in tumor and adjacent tissue (from Specimen Room of our hospital) was detected by immunohistochemical (IHC) assay and then categorized as four grades: AKIP1 low (IHC score ≤3), high+ (IHC score 4-6), high++ (IHC score 7-9), and high+++ (IHC score 10-12).

Results: A-kinase interacting protein 1 low, high+, high++, and high+++ expression was 101 (41.2%), 101 (41.2%), 32 (13.1%), and 11 (4.5%) in tumor tissues, while was 173 (70.6%), 61 (24.9%), 9 (3.7%), and 2 (0.8%) in adjacent tissues. Further comparison analysis showed increased grade of AKIP1 expression in tumor tissues compared to adjacent tissue. Meanwhile, increased grade of tumor AKIP1 expression was correlated with larger tumor size, extrathyroidal invasion, increased pT stage, and higher pTNM stage. For prognosis, increased grade of tumor AKIP1 expression was correlated with shorter disease-free survival (DFS), while was not correlated with overall survival (OS). Forward stepwise multivariate Cox's regression revealed that higher tumor AKIP1 was an independent factor predicting worse DFS, but not OS.

Conclusion: AKIP1 is upregulated in tumor tissue, and increased tumor AKIP1 expression correlates with advanced tumor features and increased recurrence risk in PTC patients, which suggest that AKIP1 severs as a potential marker for effective supervision of PTC progression.

KEYWORDS

A-kinase interacting protein 1, clinicopathological features, disease-free survival, overall survival, papillary thyroid carcinoma

1 | INTRODUCTION

Thyroid cancer, one of the most common endocrine malignancies, has aroused more and more attentions owning to its fastest increase in incidence among all cancer types globally.[1] As the predominant histologic type of thyroid cancer, papillary thyroid carcinoma (PTC), occupies approximately 80% of thyroid cancer.[2] Surgical resection along with adjuvant therapies (including radioiodine therapy and thyroid hormone therapy; monotherapy with levothyroxine [LT4]) is recommended as appropriate treatments for most PTC patients.[2] Despite an indolent clinical course and a favorable prognosis with the 10-year overall survival (OS) rate of 93%, parts of PTC patients still suffer from early-stage extradural invasion, lymph node metastasis, and even distant metastasis, which seriously caused poor prognosis and decreased quality of life (QoL) of them.[3,4] Therefore, an in-depth study exploring the potential biomarkers monitoring disease progression of PTC may increase important theoretical significance and potentially valuable clinical implications.

A-kinase interacting protein 1 (AKIP1) is initially reported as a novel breast cancer-associated protein 3 (BCA3) and has six exons with the translational start in exon two, which is able to encode an alternatively spliced proline-rich protein and promote the nuclear translocation of catalytic subunit of protein kinase A (PKAc).[5] Recently, AKIP1 has been identified as an oncogene to promote tumorigenesis and invasiveness in several carcinomas, for instance, breast cancer, non-small cell lung cancer (NSCLC), and esophageal squamous cell carcinoma (ESCC).[6-8] Clinically, AKIP1 is related to advanced disease conditions and prognosis in patients with many carcinomas, such as non-small cell lung cancer (NSCLC) and breast cancer.[6,9] Hence, it seems reasonable to believe that AKIP1 acts as a potential biomarker for the diagnosis and prognosis for several cancers, whereas a consensus knowledge of its clinical significance in PTC patients has not yet been reached. In this study, in order to research the clinical value of AKIP1 in PTC, the expression of AKIP1 was detected and its correlation with clinicopathological features and clinical outcomes in PTC patients was investigated. We envisaged that our findings might provide useful information for the effective surveillance for PTC.

2 | MATERIALS AND METHODS

2.1 | Patients

Two hundred and forty-five PTC patients treated by lobectomy or thyroidectomy in our hospital from January 2015 to December 2019 were screened out and analyzed in this retrospective study. Patients were eligible for analysis if they met following criteria: (a) confirmed as primary PTC by pathological diagnosis according to the World Health Organization (WHO) Classification Criteria[10]; (b) older than 18 years; (c) underwent lobectomy or thyroidectomy; (d) formalin-fixed paraffin-embedded (FFPE) tumor and adjacent tissue specimens were available; (e) tumor feature data were complete; and (f) follow-up data (disease relapse, progression, and survival status) were documented in detail. While following patients were excluded: (a) other histological thyroid cancers (eg, follicular thyroid carcinoma, medullary thyroid carcinoma, etc); (b) distant metastases at diagnosis; (c) history of thyroid surgery before thyroidectomy; and (d) history of other malignances. This study was approved by the Research Ethics Committee of our hospital, and written informed consents were collected from all patients or their family members.

2.2 | Data extraction

Following patients' characteristics were extracted from medical records: age, gender, tumor size, extrathyroidal invasion status, pathological T stage (pT) stage, pathological N (pN) stage, and pathological TNM (pTNM) stage. The pTNM stage was assessed according to the American Joint Committee on Cancer (AJCC) 7th Edition Cancer Staging Manual.[11]

2.3 | AKIP1 detection

FFPE tumor and adjacent tissue specimens were collected from Specimen Room of our hospital. And the AKIP1 expression in the tumor and adjacent tissue was detected by immunohistochemical (IHC) assay. The Rabbit Anti-C11orf17 antibody (1:100 dilution; Abcam) was used as primary antibody. The Goat Anti-Rabbit IgG H&L (HRP) (1:10 000 dilution; Abcam) was served as secondary antibody. The IHC procedures were performed as described in the previous study.[9] The IHC staining result was evaluated by a clinical pathologist without awareness of clinical data of patients using a semi-quantitative scoring method based on staining intensity and density (percentage of positively stained tumor cells). Details of IHC scoring procedures were described in a previous study[12]; briefly, the staining intensity was scored as follows: 0 (no staining), 1 (weak staining), 2 (moderate staining), and 3 (strong staining); and the staining density was reflected by the percentage of positively stained tumor cells, which was scored as follows: 0 (0%), 1 (<25%), 2 (26%~50%), 3 (51%~75%), and 4 (75%~100%). Multiplying the intensity score by density score, a total IHC score was obtained, which was ranging from 0 to 12. IHC score ≤3 was defined as AKIP1 low expression; correspondingly, IHC score within 4~12 was defined as AKIP1 high expression. Moreover, the AKIP1 high expression was further classified as high + expression (IHC score 4-6), high++ expression (IHC score 7-9), and high+++ expression (IHC score 10-12).[12]

2.4 | Postoperative treatment and follow-up

After lobectomy or thyroidectomy, patients were treated with ^{131}I remnant ablation administration and thyroid-stimulating hormone (TSH) suppression therapy according to the risk stratification system recommended by American Thyroid Association Guidelines

Taskforce.[13] In the current study, 71 patients received 30~150 mCi ^{131}I administration and TSH-suppression therapy, and remaining patients only received TSH-suppression therapy postthyroidectomy. Periodic follow-up including thyroid function test, serum thyroglobulin (Tg) test, TSH measurement, neck ultrasound, and whole-body scan was performed for patients according to the risk stratification for recurrence. The total follow-up duration was ranging from 1.0 to 60.0 months. Disease-free survival (DFS) was defined as the duration from lobectomy or thyroidectomy to disease recurrence or patient' death. OS was defined as the duration from lobectomy or thyroidectomy to patient' death. Patients who lost follow-up were censored on the date of their last visit in the analysis.

2.4.1 | Sample size calculation

According to a previous study,[9] the adjusted hazard ratio (related to DFS) for AKIP1 high vs low was 1.7. Based on which, a two-sided log-rank test with an overall sample size of 204 subjects achieved 90.1% power at a 0.050 significance level to detect a hazard ratio of 1.70. Considering that PTC had an indolent clinical course and a low recurrence, the sample size was increased to 245 to ensure a favorable statistical power.

2.5 | Statistical analysis

SPSS 24.0 statistical software (IBM) was used for statistical data processing, and GraphPad Prism 7.02 (GraphPad Software Inc) was applied for plotting figures. Data were described as mean and standard deviation (SD) or number (percentage). Comparison for independent samples was determined by chi-square test or Spearman's rank correlation test. Comparison for paired samples was determined by McNemar's test. DFS and OS curves were plotted using Kaplan-Meier method, and the comparison for curve was determined by log-rank test. Univariable and forward stepwise multivariable Cox's proportional hazard regression model analyses were performed to screen the factors predicting DFS or OS P value <.05 was considered as statistically significant.

3 | RESULTS

3.1 | Clinical features

The mean age of PTC patients was 43.7 ± 12.1 years (including 187 [76.3%] females and 58 [23.7%] males) (Table 1). Regarding tumor features, the mean value of tumor size was 3.0 ± 1.6 cm. There were 100 (40.8%) patients suffering form extrathyroidal invasion. As to pT stage, 67 (27.4%), 51 (20.8%), 48 (19.6%), and 79 (32.2%) patients were at T1 stage, T2 stage, T3 stage, and T4 stage, respectively. For pN stage, 84 (34.3%) patients were at N0 stage, while 161 (65.7%) patients were at N1 stage. As for pTNM stage, 169 (69.0%), 38 (15.5%), 25 (10.2%), and 13 (5.3%) patients were at I stage, II stage, III stage, and IV stage, respectively. After surgery, there were 71 (29.0%) patients who received radioiodine. The details of clinical characteristics are shown in Table 1.

TABLE 1 Clinical characteristics of PTC patients

Items	PTC patients (N = 245)
Age (y), mean ± SD	43.7 ± 12.1
<45 y, N (%)	133 (54.3)
≥45 y, N (%)	112 (45.7)
Gender, N (%)	
Female	187 (76.3)
Male	58 (23.7)
Tumor size (cm), mean ± SD	3.0 ± 1.6
<4 cm, N (%)	176 (71.8)
≥4 cm, N (%)	69 (28.2)
Extrathyroidal invasion, N (%)	
No	145 (59.2)
Yes	100 (40.8)
pT stage, N (%)	
T1	67 (27.4)
T2	51 (20.8)
T3	48 (19.6)
T4	79 (32.2)
pN stage, N (%)	
N0	84 (34.3)
N1	161 (65.7)
pTNM stage, N (%)	
I	169 (69.0)
II	38 (15.5)
III	25 (10.2)
IV	13 (5.3)
Radioiodine, N (%)	
No	174 (71.0)
Yes	71 (29.0)

Abbreviations: PTC, papillary thyroid carcinoma; SD, standard deviation.

3.2 | AKIP1 expression

The examples of AKIP1 high/low expression in the tumor or adjacent tissue by IHC assay were shown in Figure 1A. In tumor tissue, the AIKP1 high expression and low expression was presented in 144 (58.8%) and 101 (41.2%) cases; while in adjacent tissue, the AIKP1 high expression and low expression was presented in 72 (29.4%) and 173 (70.6%) cases. Meanwhile, the percentage of AKIP1 high expression was increased in tumor tissue compared to

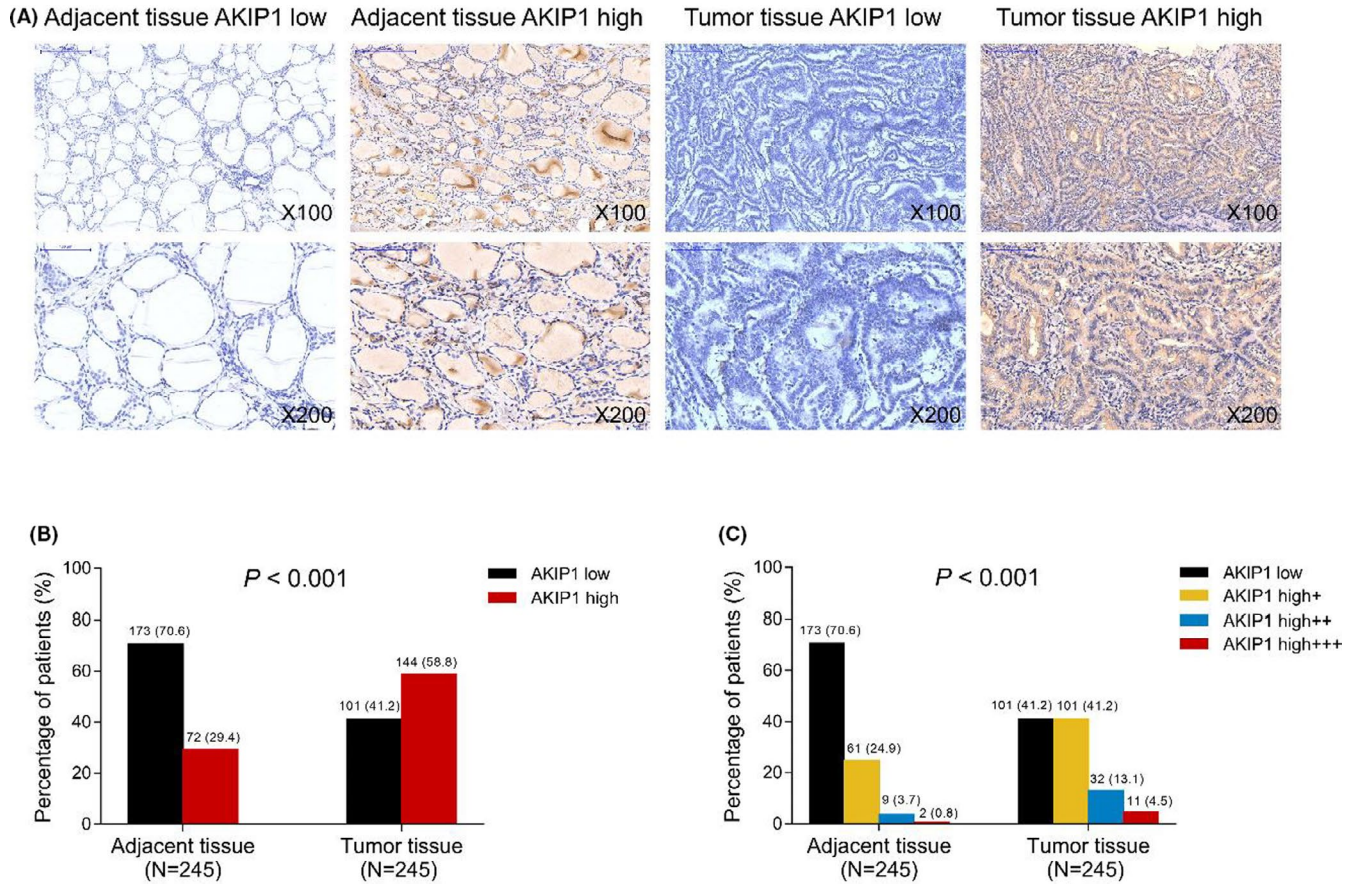

FIGURE 1 Different AKIP1 expression in tumor tissue and adjacent tissue. The examples of AKIP1 expression in the tumor and adjacent tissue by IHC assay (A). Comparison of percentage of patients with AKIP1 high/low expression (B) and with AKIP1 low/high+/high++/high+++ expression in tumor tissue and adjacent tissue (C). AKIP1, A-kinase interacting protein 1; IHC, immunohistochemical; PTC, papillary thyroid carcinoma

adjacent tissue ($P < .001$) (Figure 1B). Furthermore, 101 (41.2%), 101 (41.2%), 32 (13.1%), and 11 (4.5%) tumor tissues were with AKIP1 low, high+, high++, and high+++ expressions, respectively, while 173 (70.6%), 61 (24.9%), 9 (3.7%), and 2 (0.8%) adjacent tissues were with AKIP1 low, high+, high++, and high+++ expressions, respectively. Further comparison analysis showed grade of AKIP1 expression was increased in tumor tissues compared to adjacent tissue ($P < .001$) (Figure 1C).

3.3 | Association of tumor AKIP1 expression with clinical features

In order to verify the correlation of tumor AKIP1 expression with clinical features, we divided tumor AKIP1 expression into low/high expression, meanwhile classified it as low/high+/high++/high+++ expression (based on semi-quantitative scoring system) and then assessed their association of clinical features, respectively. According to classification of AKIP1 high/low expression, tumor AKIP1 high expression was correlated with larger tumor size ($P = .006$), extrathyroidal invasion ($P < .001$), increased pT stage ($P < .001$), raised pN stage ($P = .022$), and its high expression was numerically correlated with increased pTNM stage (but without statistical significance, $P = .096$), while it was not correlated with age ($P = .277$) or gender ($P = .560$) (Table 2). According to classification of AKIP1 low/high+/high++/high+++ expression, increased grade of AKIP1 expression was correlated with larger tumor size ($P = .003$), extrathyroidal invasion ($P < .001$), higher pT stage ($P < .001$), and it showed a trend to be positively correlated with pN stage ($P = .091$) as well as pTNM stage ($P = .060$) (but without statistical significance), while it was not correlated with age ($P = .437$) or gender ($P = .492$).

3.4 | Association of tumor AKIP1 expression with accumulating DFS and OS

According to the classification of AKIP1 high/low expression, tumor AKIP1 high expression was correlated with poor DFS ($P = .037$) (Figure 2A), while it was not correlated with OS ($P = .297$) (Figure 2B). According to the classification of AKIP1 low/high+/high++/high+++ expression, increased grade of AKIP1 expression was correlated with shorter DFS ($P = .007$) (Figure 3A), while it was not correlated with poor OS ($P = .583$) (Figure 3B).

TABLE 2 Correlation of tumor AKIP1 expression with clinical characteristics

Items	AKIP1 expression							
	Low (n = 101)	High (n = 144)	*P* value	Low (n = 101)	High+ (n = 101)	High++ (n = 32)	High+++ (n = 11)	*P* value
Age, N (%)								
<45 y	59 (58.4)	74 (51.4)	.277	59 (58.4)	50 (49.5)	19 (59.4)	5 (45.5)	.437
≥45 y	42 (41.6)	70 (48.6)		42 (41.6)	51 (50.5)	13 (40.6)	6 (54.5)	
Gender, N (%)								
Female	79 (78.2)	108 (75.0)	.560	79 (78.2)	77 (76.2)	22 (68.8)	9 (81.8)	.492
Male	22 (21.8)	36 (25.0)		22 (21.8)	24 (23.8)	10 (31.2)	2 (18.2)	
Tumor size, N (%)								
<4 cm	82 (81.2)	94 (65.3)	.006	82 (81.2)	69 (68.3)	19 (59.4)	6 (54.5)	.003
≥4 cm	19 (18.8)	50 (34.7)		19 (18.8)	32 (31.7)	13 (40.6)	5 (45.5)	
Extrathyroidal invasion, N (%)								
No	74 (73.3)	71 (49.3)	<.001	74 (73.3)	51 (50.5)	18 (56.2)	2 (18.2)	<.001
Yes	27 (26.7)	73 (50.7)		27 (26.7)	50 (49.5)	14 (43.8)	9 (81.8)	
pT stage, N (%)								
T1	38 (37.6)	29 (20.1)	<.001	38 (37.6)	22 (21.8)	7 (21.9)	0 (0.0)	<.001
T2	27 (26.8)	24 (16.7)		27 (26.8)	15 (14.8)	8 (25.0)	1 (9.1)	
T3	18 (17.8)	30 (20.8)		18 (17.8)	22 (21.8)	4 (12.5)	4 (36.4)	
T4	18 (17.8)	61 (42.4)		18 (17.8)	42 (41.6)	13 (40.6)	6 (54.5)	
pN stage, N (%)								
N0	43 (42.6)	41 (28.5)	.022	43 (42.6)	26 (25.7)	11 (34.4)	4 (36.4)	.091
N1	58 (57.4)	103 (71.5)		58 (57.4)	75 (74.3)	21 (65.6)	7 (63.6)	
pTNM stage, N (%)								
I	74 (73.3)	95 (66.0)	.096	74 (73.3)	63 (62.4)	25 (78.0)	7 (63.6)	.060
II	17 (16.8)	21 (14.6)		17 (16.8)	17 (16.8)	3 (9.4)	1 (9.1)	
III	7 (6.9)	18 (12.5)		7 (6.9)	14 (13.9)	2 (6.3)	2 (18.2)	
IV	3 (3.0)	10 (6.9)		3 (3.0)	7 (6.9)	2 (6.3)	1 (9.1)	

Note: Comparison was determined by Chi-square test or Spearman's rank correlation test.
Abbreviation: AKIP1, A-kinase interacting protein 1.

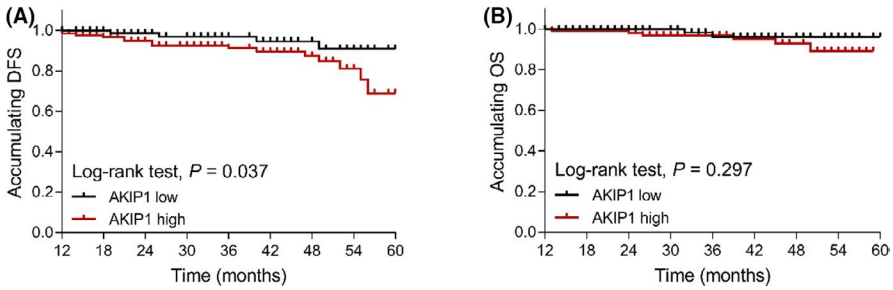

FIGURE 2 Accumulating DFS and OS in PTC patients with AKIP1 high/low expression. Comparison of DFS (A) and OS (B) between PTC patients with AKIP1 high/low expression. AKIP1, A-kinase interacting protein 1; DFS, disease-free survival; OS, overall survival; PTC, papillary thyroid carcinoma

3.5 | Assessment of factors affecting DFS

Based on univariate Cox's regression analysis, higher tumor AKIP1 expression ($P = .004$) was correlated with worse DFS in PTC patients; meanwhile, age (≥45 years) ($P = .005$), tumor size (>4 cm) ($P = .014$), extrathyroidal invasion ($P = .036$), pT stage ($P = .013$), pN stage ($P = .040$), and pTNM stage ($P < .001$) were correlated with shorter DFS in PTC patients (Table 3). Forward stepwise multivariate Cox's regression revealed that higher tumor AKIP1 expression ($P = .002$) was an independent factor predicting worse DFS; meanwhile, pTNM stage ($P < .001$) independently predicted shorter DFS in PTC patients as well. In addition, assessing factors predicting DFS by using Enter method multivariate Cox's analysis, Backward stepwise method multivariate Cox's analysis as well as univariate and Enter method multivariate Cox's proportional hazard regression model (only factors with *P* value <0.05 in the univariate Cox's proportional

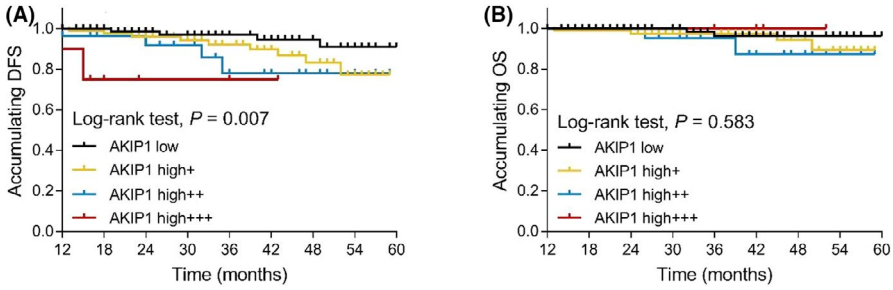

FIGURE 3 Accumulating DFS and OS in PTC patients with AKIP1 low/high+/high++/high+++ expression. Comparison of DFS (A) and OS (B) between PTC patients with AKIP1 low/high+/high++/high+++ expression. AKIP1, A-kinase interacting protein 1; DFS, disease-free survival; OS, overall survival; PTC, papillary thyroid carcinoma

TABLE 3 Analysis of factors predicting DFS

	Cox's proportional hazard regression model			
			95% CI	
Items	*P* value	HR	Lower	Higher
Univariate Cox's regression				
Higher AKIP1[a]	.004	2.149	1.279	3.612
Age ≥ 45 y	.005	5.835	1.697	20.066
Male	.237	1.756	0.691	4.463
Tumor size > 4 cm	.014	3.091	1.254	7.619
Extrathyroidal invasion	.036	2.723	1.068	6.944
pT stage	.013	1.757	1.127	2.739
pN stage	.040	4.633	1.070	20.059
pTNM stage	<.001	2.735	1.859	4.026
Radioiodine	.345	1.551	0.623	3.864
Forward stepwise multivariate Cox's regression				
Higher AKIP1[a]	.002	2.709	1.458	5.034
pTNM stage	<.001	2.903	1.943	4.339

Note: Factors predicting DFS were analyzed by univariate and forward stepwise multivariate Cox's proportional hazard regression model. All factors in the univariate Cox's proportional hazard regression model were further included in multivariate Cox's proportional hazard regression model.

Abbreviations: AKIP1, A-kinase interacting protein 1; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio.

[a]The level of AKIP1 was categorized as low expression = 0, high + expression = 1, higher++ expression = 2 and high+++expression = 3; pT stage was scored as T1 = 1, T2 = 2, T3 = 3, T4 = 4; pTNM stage was scored as stage I = 1, stage II = 2, stage III = 3, stage IV = 4.

hazard regression model were further included in multivariate Cox's proportional hazard regression model) are shown in Tables S1-S3.

3.6 | Assessment of factors affecting OS

According to univariate Cox's regression analysis, higher AKIP1 expression was not correlated with poor OS in PTC patients ($P = .366$), while tumor size (>4 cm) ($P = .011$), pT stage ($P = .035$), and pTNM stage ($P < .001$) were correlated with shorter OS in PTC patients (Table 4). Forward stepwise multivariate Cox's regression displayed that higher AKIP1 expression was not an independent factor predicting poor OS in PTC patients, whereas pTNM stage ($P = .001$) was an independent factor predicting shorter OS in PTC patients. In addition, assessing factors predicting OS by using Enter method multivariate Cox's analysis, Backward stepwise method multivariate Cox's analysis as well as univariate and Enter method multivariate Cox's proportional hazard regression model (only factors with *P* value <0.05 in the univariate Cox's proportional hazard regression model were further included in multivariate Cox's proportional hazard regression model) are shown in Tables S4-S6.

4 | DISCUSSION

As A-kinase interacting protein, AKIP1, has been reported to be a differentially expressed gene in many human malignancies, and frequently interacts with several cell signaling factors (such as NF-kappaB [NF-κB] and protein kinase A [PKA]) to participant in tumorigenesis and invasiveness.[5,6,14] For example, AKIP1 promotes NSCLC tumorigenicity through accelerating cell migration, facilitating cell invasion, and activating epithelial-mesenchymal transition (EMT).[7] In another study, AKIP1 enhances gastric cancer cells proliferation, migration, and invasion through the activation of Slug-induced EMT.[15] Meanwhile, AKIP1 facilitates cellular motility and invasion via promoting threonine kinase 1 (Akt)/glycogen synthase kinase 3 beta (GSK-3β)/Snail pathway in breast cancer.[6] Furthermore, AKIP1 via upregulates the NF-κB-dependent chemokines CXCL1, CXCL2, and CXCL8 to promote angiogenesis and cell proliferation, but suppress cell apoptosis in cervical cancer.[16] In brief, AKIP1 may play a critical role in the pathological processes of various cancer.

Apart from the mechanism of AKIP1 underlying carcinomas, the role of AKIP1 in cancer patients also has become a hot topic. For instance, AKIP1 is highly expressed in CRC tissue compared with that of noncancerous colorectal mucosa, and its tumor high expression (tumor tissue) is associated with tumor diameter, TNM stage, and lymph node metastasis in CRC patients.[5] In addition, AKIP1 expression is elevated in tumor tissue compared with paired adjacent tissue,

TABLE 4 Analysis of factors predicting OS

	Cox's proportional hazard regression model			
			95% CI	
Items	***P* value**	**HR**	**Lower**	**Higher**
Univariate Cox's regression				
Higher AKIP1[a]	.366	1.447	0.649	3.226
Age ≥ 45 y	.152	64.083	0.216	18 975.521
Male	.478	1.681	0.401	7.055
Tumor size > 4 cm	.011	7.960	1.603	39.518
Extrathyroidal invasion	.061	4.633	0.932	23.035
pT stage	.035	2.749	1.074	7.042
pN stage	.221	3.706	0.456	30.136
pTNM stage	<.001	3.623	1.861	7.055
Radioiodine	.795	1.210	0.289	5.068
Forward stepwise multivariate Cox's regression				
pTNM stage	.001	3.306	1.613	6.774

Note: Factors predicting OS were analyzed by univariate and forward stepwise multivariate Cox's proportional hazard regression model. All factors in the univariate Cox's proportional hazard regression model were further included in multivariate Cox's proportional hazard regression model.

Abbreviations: AKIP1, A-kinase interacting protein 1; CI, confidence interval; HR, hazard ratio; OS, overall survival.

[a]The level of AKIP1 was categorized as low expression = 0, high + expression = 1, higher++ expression = 2 and high+++expression = 3; pT stage was scored as T1 = 1, T2 = 2, T3 = 3, T4 = 4; pTNM stage was scored as stage I = 1, stage II = 2, stage III = 3, stage IV = 4.

and tumor AKIP1 expression is positively correlated with pathological differentiation, tumor size, lymph node metastasis, TNM stages, and abnormal CEA level in NSCLC patients.[9] Furthermore, tumor AKIP1 high expression has been illustrated to be correlated with higher performance status score, larger tumor size, barcelona clinic liver cancer (BCLC) stage B (vs stage A), increased alpha-fetoprotein level and higher carbohydrate antigen 199 level in hepatocellular carcinoma patients.[17] However, to the best of our knowledge, the clinical value of AKIP1 in PTC patients has not yet been elucidated. Herein, we discovered that AKIP1 expression was increased in tumor tissue compared to adjacent tissue. Interesting, its tumor expression was positively associated with tumor size, extrathyroidal invasion, pT stage, and pN stage in PTC patients. The probable explanations were as follows: (a) AKIP1 might activate multiple oncogenic signaling pathways (including Wnt/β-catenin signaling) to promoting the tumorigenicity of PTC; hence, tumor tissue of PTC was characterized by increased AKIP1 expression compared to adjacent tissue.[18] (b) Upregulated ARIP1 (as its role in gastric cancer) could induce Slug-induced EMT to promote cell proliferation, cell invasion and cell migration to facilitate tumor growth and metastasis, which further accelerated tumor progression and extrathyroidal invasion in PTC patients.[15] (c) ARIP1 (as its role in breast cancer) could active Akt/GSK-3β/Snail pathway to induce cellular motility and invasion, subsequently contributed to tumor metastasis, thereby increasing extrathyroidal invasion in PTC patients.[6]

Recent studies have confirmed AKIP1 as a potential prognostic marker in several solid cancers.[9,17,19] For instance, CRC patients with positive tumor AKIP1 expression obviously have poorer OS rates when compare with those with negative tumor AKIP1 expression.[19] In NSCLC, tumor AKIP1 high expression has been identified to be an independent predictive factor for worse DFS and OS.[9] In breast cancer, overexpression of tumor AKIP1 is related to shorter OS and recurrence-free survival in those patients.[6] In hepatocellular carcinoma, tumor AKIP1 high expression is related to worse OS, and it also is an independent predictive factor for shorter OS.[17] In line with these published studies, we found that according to classification of AKIP1 high/low expression, tumor AKIP1 high expression was correlated with poor DFS; according to classification of AKIP1 low/high+/high++/high+++ expression, increased grade of AKIP1 expression was also correlated with worse DFS, interestingly, higher tumor AKIP1 expression could predict independently poor DFS in PTC patients, which might be explained that: (a) AKIP1 could accelerate various cell signaling factors (such as CXCL1, NF-κB and PKA) and multiple carcinogenic pathways (such as Slug-induced EMT and Wnt/β-catenin signaling pathway) to facilitate cell growth and metastasis, thereby participated in tumor development and led to worse prognosis in PTC patients.[6,14-16] (b) AKIP1 might interact with some pathways (such as Wnt/β-catenin/cyclic adenosine monophosphate [AMP] response element-binding protein [CBP] signaling pathway) to subsequently increase drug resistance and cause poor treatment outcomes, hence, AKIP1 was related to shorter DFS, and acted as a potential prognostic factor in PTC patients.[20] Whereas the detailed mechanism of AIPK1 underlying PTC still needs further exploration via cellular experiments. Interestingly, we also discovered

no correlation of AKIP1 with OS in PTC patients, which might be caused by the good prognosis of PTC, thus, there were few death events occurred during the follow-up, thereby resulted in decreased statistical power.

However, there were still some limitations in our present study: (a) Owning to relatively small sample size in this study, extra studies with a larger sample size are necessary to verify the role of AKIP1 in PTC patients. (b) The follow-up duration was relatively short. Hence, the occurrence of relapse and death events was relatively small, which might cause the low statistical efficacy. (c) There was no validation cohort study, further cohort study is needed.

Taken together, AKIP1 is upregulated in tumor tissue, and increased tumor AKIP1 expression correlates with advanced tumor features and unfavorable survival data in PTC patients. Thus, our findings suggest that AKIP1 severs as a potential marker for effective supervision of PTC progression.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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