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A-kinase interacting protein 1 is sufficiently expressed and positively associates with WHO grade, meanwhile predicts unfavorable overall survival independently in glioma patients

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Abstract

The present study aimed to investigate the association of A-kinase interacting protein 1 (AKIP1) with clinical characteristics, and further explore the prognostic value of AKIP1 in glioma patients.

Totally 168 glioma patients who underwent tumor resection were analyzed, and their tumor tissue specimens were acquired for the detection of AKIP1 expression by immunohistochemistry (IHC), which was scored by a semi-quantitative method considering staining intensity and staining density.

According to AKIP1 expression in tumor tissues of glioma patients, there were 65 (38.7%) patients with AKIP1 low expression (IHC score 0–3), 48 (28.6%) patients with AKIP1 high + expression (IHC score 4–6), 42 (25.0%) patients with AKIP1 high++ expression (IHC score 7–9) and 13 (7.7%) patients with AKIP1 high+++ expression (IHC score 10–12), respectively. AKIP1 expression was positively associated with World Health Organization grade. Overall survival (OS) was the lowest in the patients with AKIP1 high+++ expression, followed by those with AKIP1 high++ expression and those with AKIP1 high+ expression, and highest in those with AKIP1 low expression. Further subgroup analysis exhibited that AKIP1 expression was negatively associated with OS especially in high-grade glioma patients. In addition, AKIP1 expression was negatively associated with OS in all subgroups of patients with/without adjuvant radiotherapy, with/without adjuvant chemotherapy. Further multivariate Cox's regression exhibited that AKIP1 high expression was an independent predictive factor for worse OS.

AKIP1 presents with the potential to be a novel biomarker for tumor management and prognosis surveillance in glioma patients.

Abbreviations: AKIP1 = A-kinase interacting protein 1, HCC = hepatocellular carcinoma, IHC = immunohistochemistry, NF-κB = NF-kappaB, OS = overall survival, PKAc = protein kinase A catalytic subunit, WHO = World Health Organization.

Keywords: A-kinase interacting protein 1, glioma, immunohistochemistry, overall survival, World Health Organization grade

1. Introduction

Gliomas are considered as the most common primary intracranial tumor, accounting for approximately 80% malignant brain tumors.[1] According to the population-based studies, overall age-adjusted incidence of glioma is increasing globally.[2,3] Despite great advancement in mainstream therapy approaches for glioma, a cure for glioma has not been discovered, and considering the aggressive nature of glioma and increased drug resistance, the clinical outcomes are undesirable with restricted therapeutic options.[4,5] Therefore, more attention should be paid on the identification of prognostic biomarker and pursuit precision therapy, which would improve the long-term prognosis in glioma patients.

A-kinase interacting protein 1 (AKIP1) serves as a molecular regulator of interaction between protein kinase A catalytic subunit (PKAc) and P65, which subsequently phosphorylating p65 and contributing to NF-kappaB (NF-κB) activation cascade.[6,7] Considering that NF-κB functions as an essential transcriptional factor for the numerous genes, AKIP1 is implicated in biological process of various kinds of diseases such as cancer, leukemia, and inflammatory diseases.[8–11] For example, AKIP1 is upregulated in esophageal squamous cell carcinoma cell lines, and upregulates the expression of vascular endothelial growth factor-C via regulating the downstream genes of NF-κB signaling pathway.[8] Clinically, AKIP1 expression is positively correlated with tumor progression such as increased lymph node metastasis and TNM stage in several tumors, including colorectal cancer, non-small cell lung cancer, gastric

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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cancer.[9,12,13] In addition, NF-κB is associated with autophagic response, tumor initiation, drug resistance and glioma stem cell differentiation in diverse phases of gliomagenesis.[14–16] Therefore, we generated a hypothesis that AKIP1 might be implicated in the development and progression of glioma, however, the role of AKIP1 in glioma has not been explored yet. Here, we conducted the present study to investigate the association of AKIP1 with clinical characteristics, and further explore the potential of AKIP1 as a prognostic biomarker for glioma.

2. Methods

2.1. Patients

Between January 2014 and December 2018, a total of 168 glioma patients admitted to Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University for tumor resection were analyzed in this retrospective study. All patients reviewed in this study were:

(i) first ever diagnosed as primary glioma;
(ii) received tumor resection;
(iii) not complicated with other nervous system cancers (such as ependymomas, meningiomas, leptomeningeal metastases, and so on);
(iv) age above 18 and less than 80 years old at surgery;
(v) no history of other malignancies;
(vi) no history of chemotherapy or radiotherapy;
(vii) tumor tissues resected from surgery were available and suitable for immunohistochemistry (IHC) detection;
(viii) preoperative clinical characteristics and follow-up data were complete.

The Ethics Committee of Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University had approved this study, and the written informed consents were acquired from the patients or their family members.

2.2. Data collection

Demographics (age and gender), World Health Organization (WHO) grade of glioma, adjuvant treatments (radiotherapy and chemotherapy) as well as follow-up data were extracted from the electronic database of Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University. Glioma WHO grade of patients was evaluated according to the 2007 WHO tumors of the central nervous system.[17] According to the WHO grade, the glioma with WHO grade I/II was defined as low-grade glioma, and the glioma with WHO grade III/IV was defined as high-grade glioma. As recorded in the follow-up documents, the last follow-up date was 12/31/2018, and the median follow-up duration was 24.0 months. Besides, for survival analysis, the overall survival (OS) was defined as the duration from resection to the date of death.

2.3. AKIP1 detection by IHC assay

The tumor tissue specimens were acquired from specimen storehouse of Pathology Department in Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, and the expression of AKIP1 in tumor tissue was detected by IHC. In brief, the formalin-fixed and paraffin-embedded tumor tissue specimens were cut into 4 μm sections, then deparaffination, rehydration and antigen retrieval for the sections were performed using xylene, graded ethanol, and microwave heating, respectively. After blocking the peroxidase activity and nonspecific binding, the sections were incubated with AKIP1 Polyclonal Antibody (1:30, Invitrogen, Waltham, MA) at 4°C overnight. Next day, the sections were incubated with Goat anti-Rabbit IgG (H+L) Secondary Antibody, HRP (1:10000, Invitrogen, Waltham, MA) at room temperature for 1 hour. Finally, the staining and counterstaining of the sections were carried out using diaminobenzidine (Sigma-Aldrich, Louis, MO, USA) and hematoxylin (Sigma-Aldrich, Louis, MO). The IHC staining result was assessed by a semi-quantitative scoring method, and total IHC score was calculated using staining intensity score and staining density score.[18] The total IHC score was ranging from 0 to 12, and the expression of AKIP1 was categorized as low expression (IHC score 0–3), high+ expression (IHC score 4–6), high++ expression (IHC score 7–9) and high+++ expression (IHC score 10–12).[18]

2.4. Statistical analysis

Statistical analyses were performed using SPSS 24.0 (IBM, Chicago, IL). Figures were plotted using GraphPad Prism 7.00 (GraphPad Software, La Jolla, CA). Correlation of AKIP1 expression with age, gender, adjuvant radiotherapy, or adjuvant chemotherapy was analyzed by Chi-squared test. Correlation of AKIP1 expression with WHO grade was determined by Spearman rank correlation test. OS was illuminated with the use of Kaplan–Meier curve. Comparison of OS among patients with different AKIP1 expression was determined by Log-rank test. Factors correlated with OS was analyzed by univariate and multivariate Cox's proportional hazard regression model. All tests were 2-side, and P value $< .05$ was considered as significant.

3. Results

3.1. AKIP1 expression in glioma tumor tissue

The AKIP1 expression in glioma tumor tissue was detected by IHC, and all tissues were categorized as low expression (IHC score 0–3), high+ expression (IHC score 4–6), high++ expression (IHC score 7–9) and high+++ expression (IHC score 10–12). Representative IHC images exhibiting AKIP1 low expression, AKIP1 high+ expression, AKIP1 high++ expression and AKIP1 high+++ expression in glioma tumor tissues were shown (Fig. 1A). According to AKIP1 expression in tumor tissues, there were 65 (38.7%) patients with AKIP1 low expression, 48 (28.6%) patients with AKIP1 high + expression, 42 (25.0%) patients with AKIP1 high++ expression, and 13 (7.7%) patients with AKIP1 high+++ expression, respectively (Fig. 1B).

3.2. Correlation of AKIP1 with clinical characteristics in glioma patients

AKIP1 expression was positively associated with WHO grade ($P < .001$), however, there was no association of AKIP1 expression with age ($P = .484$), gender ($P = .671$), adjuvant radiotherapy ($P = .105$) or adjuvant chemotherapy ($P = .328$) in glioma patients (Table 1).

3.3. Correlation of AKIP1 expression with OS in glioma patients

OS was the lowest in the patients with AKIP1 high+++ expression, followed by those with AKIP1 high++ expression

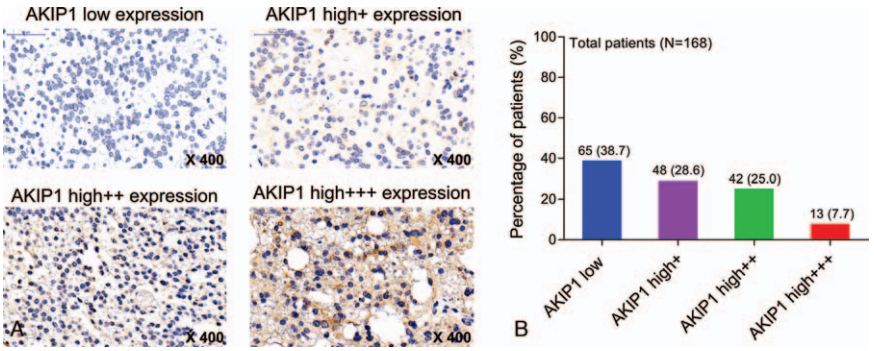

Figure 1. A-kinase interacting protein 1 (AKIP1) expression in glioma. The representative image of AKIP1 low, high+, high++, high+++ expression in glioma tissues (A). The percentage of patients with AKIP1 low, high+, high++, high+++ expression (B). AKIP1 = A-kinase interacting protein 1.

and those with AKIP1 high+ expression, and the highest in patients with AKIP1 low expression ($P < .001$) (Fig. 2). These suggested that AKIP1 expression was negatively associated with OS in glioma patients.

3.4. Correlation of AKIP1 expression with OS in subgroup with low/high grade glioma

According to the WHO grade, all patients was grouped as low-grade glioma patients (WHO grade I/II) and high-grade glioma patients (WHO grade III/IV). In low-grade glioma patients (n = 73), AKIP1 expression was not associated with OS ($P = .270$) (Fig. 3A). However, in high-grade glioma patients (n = 95), OS was the shortest in patients with AKIP1 high+++ expression, and then those with AKIP1 high++ expression and those with AKIP1 high+ expression, and the longest in those with AKIP1 low expression ($P = .001$) (Fig. 3B). These indicated that AKIP1 expression was negatively associated with OS in high-grade glioma patients rather than low-grade glioma patients.

3.5. Correlation of AKIP1 with OS in subgroup with/without adjuvant radiotherapy or chemotherapy

According to the adjuvant therapy that glioma patients received post surgery, all patients were divided into subgroup of patients without adjuvant radiotherapy, subgroup of patients with adjuvant radiotherapy, subgroup of patients without adjuvant chemotherapy, subgroup of patients with adjuvant chemotherapy. In subgroup of patients without adjuvant radiotherapy (n = 63) ($P < .001$) (Fig. 4A), subgroup of patients with adjuvant radiotherapy (n = 105) ($P < .001$) (Fig. 4B), subgroup of patients without adjuvant chemotherapy (n = 102) ($P = .001$) (Fig. 4C) and subgroup of patients with adjuvant chemotherapy (n = 66) ($P < .001$) (Fig. 4D), OS was all the most reduced in patients with AKIP1 high+++ expression, followed by patients with AKIP1 high++ expression and those with AKIP1 high+ expression, and the most increased in patients with AKIP1 low expression. These indicated that AKIP1 expression was negatively associated with OS in glioma patients independent of adjuvant radiotherapy/chemotherapy.

Table 1

Correlation of A-kinase interacting protein 1 expression with clinical characteristics.

Items	N	AKIP1 expression				*P* value
		Low	High+	High++	High+++	
Total patients, No. (%)	168	65 (38.7)	48 (28.6)	42 (25.0)	13 (7.7)	
Age (yr), No. (%)						.484
≤40 yr	82	34 (41.5)	20 (24.4)	23 (28.0)	5 (6.1)	
>40 yr	86	31 (36.0)	28 (32.6)	19 (22.1)	8 (9.3)	
Gender, No. (%)						.671
Female	75	30 (40.0)	18 (24.0)	21 (28.0)	6 (8.0)	
Male	93	35 (37.6)	30 (32.3)	21 (22.6)	7 (7.5)	
WHO grade, No. (%)						<.001
I	9	6 (66.7)	2 (22.2)	1 (11.1)	0 (0.0)	
II	64	33 (51.6)	17 (26.5)	13 (20.3)	1 (1.6)	
III	64	19 (29.7)	22 (34.4)	17 (26.5)	6 (9.4)	
IV	31	7 (22.6)	7 (22.6)	11 (35.5)	6 (19.3)	
Adjuvant radiotherapy, No. (%)						.105
No	63	28 (44.4)	11 (17.5)	18 (28.6)	6 (9.5)	
Yes	105	37 (35.2)	37 (35.2)	24 (22.9)	7 (6.7)	
Adjuvant chemotherapy, No. (%)						.328
No	102	44 (43.1)	25 (24.6)	24 (23.5)	9 (8.8)	
Yes	66	21 (31.8)	23 (34.8)	18 (27.3)	4 (6.1)	

Correlation was determined by Chi-squared test or Spearman rank correlation test. AKIP1 = A-kinase interacting protein 1, WHO = World Health Organization.

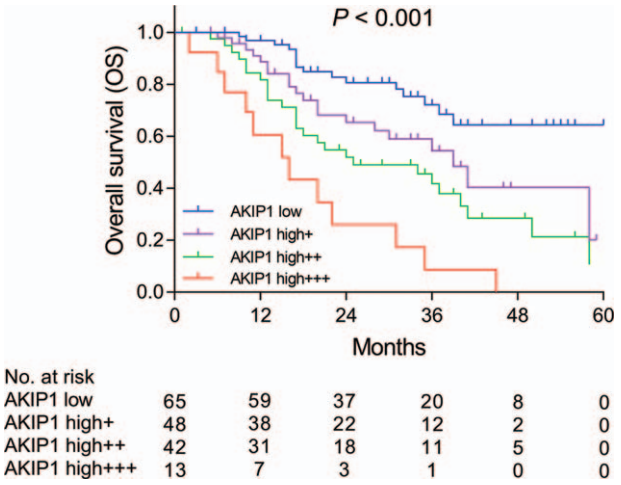

Figure 2. Comparison of OS among glioma patients with different A-kinase interacting protein 1 (AKIP1) expression. Comparison of overall survival among glioma patients with AKIP1 low expression, patients with AKIP1 high+ expression, patients with AKIP1 high++ expression, and patients with AKIP1 high+++ expression. AKIP1 = A-kinase interacting protein 1, OS = overall survival.

3.6. Factors affecting OS in glioma patients

Univariate Cox's regression indicated that higher AKIP1 expression (HR = 1.838, $P < .001$), age (>40 years) (HR = 1.849, $P = .009$), higher WHO grade (HR = 2.444, $P < .001$) were associated with decreased OS in glioma patients (Table 2). Further multivariate Cox's regression exhibited that higher AKIP1 expression (HR = 1.581, $P < .001$), male (HR = 1.853, $P = .018$), higher WHO grade (HR = 2.088, $P < .001$) were independent predictive factors for decreased OS, while adjuvant radiotherapy (HR = 0.595, $P = .040$) was an independent predictive factor for increased OS in glioma patients (Table 2).

3.7. Factors affecting OS in subgroup of low-grade glioma patients

Univariate Cox's regression identified that no factors were correlated with OS in subgroup of low-grade glioma patients (Table 3). Multivariate Cox's regression exhibited that higher AKIP1 expression (HR = 1.820, $P = .031$) and age (>40 years) (HR = 3.758, $P = .016$) were independent predictive factors for decreased OS in subgroup of low-grade glioma patients (Table 3).

3.8. Factors affecting OS in subgroup of high-grade glioma patients

Univariate Cox's regression revealed that higher AKIP1 expression (HR = 1.649, $P = .001$) was associated with decreased OS in subgroup of high-grade glioma patients (Table 4). Further multivariate Cox's regression exhibited that higher AKIP1 expression (HR = 1.648, $P < .001$) was an independent predictive factor for decreased OS, while adjuvant radiotherapy (HR = 0.472, $P = .020$) was an independent predictive factor for increased OS in subgroup of high-grade glioma patients (Table 4).

4. Discussion

In the present study, we found that

(1) AKIP1 was sufficiently expressed, and positively associated with WHO grade in glioma patients.
(2) AKIP1 expression was negative associated with OS in glioma patients independent of glioma grade and post-surgery adjuvant therapies.
(3) AKIP1 expression could serve as a good biomarker for the prognosis of each subgroup glioma patients.

Endogenous AKIP1 is localized as speckles to the nucleus, and interacts with protein kinase A by binding to the amino terminus of PKAc, which contributes to the NF-κB signaling.[6,19] Recent researches reveal that AKIP1 serves as a potential oncogenic regulator, and facilitates growth and metastasis of several tumors via activating oncogenic signaling pathways.[9,10,12,13] For example, AKIP1 expression is reported to be increased in hepatocellular carcinoma (HCC) clinical samples, and further in vitro experiments show that its overexpression promotes invasion and colony outgrowth of HCC via activating Wnt/β-catenin signaling.[10] Another study presents that AKIP1 knockdown inhibits cell proliferation, and even tumor growth

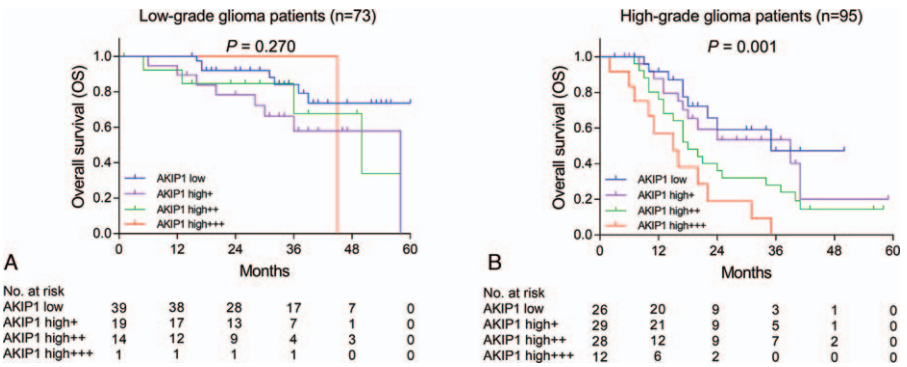

Figure 3. Comparison of overall survival (OS) among low-grade/high-grade glioma patients with different A-kinase interacting protein 1 (AKIP1) expression. In low-grade glioma patients, comparison of OS among patients with AKIP1 low expression, patients with AKIP1 high+ expression, patients with AKIP1 high++ expression, and patients with AKIP1 high+++ expression (A). In high-grade glioma patients, comparison of OS among patients with AKIP1 low expression, patients with AKIP1 high+ expression, patients with AKIP1 high++ expression, and patients with AKIP1 high+++ expression (B). AKIP1 = A-kinase interacting protein 1, OS = overall survival.

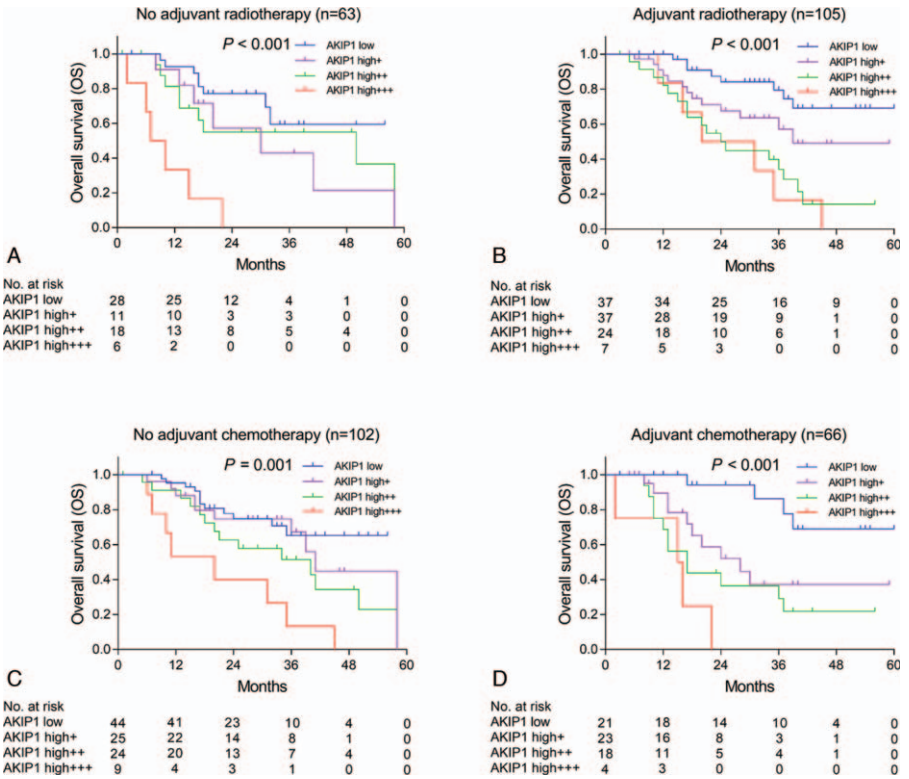

Figure 4. Comparison of overall survival (OS) among glioma patients with different A-kinase interacting protein 1 (AKIP1) expression in subgroups characterized by adjuvant therapies. In glioma patients without adjuvant radiotherapy (A) and glioma patients with adjuvant radiotherapy (B), comparison of OS among patients with AKIP1 low expression, patients with AKIP1 high+ expression, patients with AKIP1 high++ expression, and patients with AKIP1 high+++ expression. In glioma patients without adjuvant chemotherapy (C) and glioma patients with adjuvant chemotherapy (D), comparison of OS among patients with AKIP1 low expression, patients with AKIP1 high+ expression, patients with AKIP1 high++ expression, and patients with AKIP1 high+++ expression. AKIP1 = A-kinase interacting protein 1, OS = overall survival.

as well as angiogenesis via inactivating NF-κB-dependent chemokines CXC motif ligand (CXCL) 1, CXCL2, and CXCL8 in cervical cancer.[20] Clinically, AKIP1 is positively associated with advanced TNM stage and lymph node metastasis in patients with several tumors, including HCC, colorectal cancer and.[10,12,21] Although AKIP1 has been regarded to be a critical regulator of progression and development in tumors, the consensus knowledge of AKIP1 clinical significance in glioma has not been investigated yet. In the present study, we conducted the clinical association analysis in glioma patients, which exhibits that AKIP1 was positively correlated with WHO grade in glioma patients. The possible reason might include that

(1) According to the previous study, increased AKIP1 level might promote the interaction between P65 and PKAc, further enhancing and methylating NF-κB signaling, which led to promotion of cell proliferation and persistence of self-renewal in glioma.[15]

Therefore, AKIP1 high expression is positively associated with advanced WHO grade in glioma patients.

(2) Considering the positive association between chemokine CXCL with glioma susceptibility, AKIP1 might promote chemokine CXCL expressions, which enhanced the sphere-forming ability of glioma stem cell and contributed to glioma onset, growth as well as recurrence.

Table 2

Analysis of factors correlated with overall survival.

	Univariate Cox's regression		Multivariate Cox's regression	
Items	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**
Higher AKIP1 expression*	<.001	1.838 (1.458–2.318)	<.001	1.581 (1.240–2.017)
Age (>40 yr)	.009	1.849 (1.164–2.937)	.054	1.626 (0.992–2.667)
Male	.197	1.361 (0.852–2.173)	.018	1.853 (1.111–3.093)
Higher WHO grade*	<.001	2.444 (1.796–3.325)	<.001	2.088 (1.465–2.976)
Adjuvant radiotherapy	.236	0.754 (0.472–1.203)	.040	0.595 (0.363–0.975)
Adjuvant chemotherapy	.350	1.248 (0.784–1.987)	.323	1.274 (0.788–2.059)

Factors correlated with overall survival were analyzed by univariate and multivariate Cox's proportional hazard regression model.

* A-kinase interacting protein 1 expression in the Cox's regression analysis in the form of ordered categorical variable, which were encoded as: low = 0, high+ = 1, high++ = 2, high+++ = 3; World Health Organization grade in the Cox's regression was encoded as: grade I = 1, grade II = 2, grade III = 3, grade IV = 4. AKIP1 = A-kinase interacting protein 1, CI = confidence, HR = hazard ratio, OS = overall survival, WHO = World Health Organization.

Table 3

Analysis of factors correlated with overall survival in low-grade glioma patients.

	Univariate Cox's regression		Multivariate Cox's regression	
Items	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**
Higher AKIP1 expression*	.083	1.500 (0.949–2.372)	.031	1.820 (1.056–3.136)
Age (>40 yr)	.135	1.997 (0.806–4.949)	.016	3.758 (1.285–10.986)
Male	.351	1.519 (0.631–3.656)	.183	1.875 (0.744–4.730)
Adjuvant radiotherapy	.270	0.610 (0.254–1.469)	.234	0.544 (0.199–1.482)
Adjuvant chemotherapy	.414	1.446 (0.597–3.505)	.090	2.313 (0.878–6.094)

Factors correlated with overall survival were analyzed by univariate and multivariate Cox's proportional hazard regression model.
* A-kinase interacting protein 1 expression in the Cox's regression analysis in the form of ordered categorical variable, which were encoded as: low = 0, high+ = 1, high++ = 2, high+++ = 3. AKIP1 = A-kinase interacting protein 1, CI = confidence, HR = hazard ratio, OS = overall survival.

Table 4

Analysis of factors correlated with overall survival in high-grade glioma patients.

	Univariate Cox's regression		Multivariate Cox's regression	
Items	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**
Higher AKIP1 expression*	.001	1.649 (1.239–2.194)	<.001	1.648 (1.246–2.181)
Age (>40 yr)	.238	1.398 (0.801–2.440)	.404	1.284 (0.714–2.307)
Male	.441	1.240 (0.717–2.147)	.116	1.622 (0.888–2.964)
Adjuvant radiotherapy	.053	0.572 (0.325–1.008)	.020	0.472 (0.251–0.887)
Adjuvant chemotherapy	.674	0.889 (0.514–1.538)	.828	1.064 (0.607–1.868)

Factors correlated with overall survival were analyzed by univariate and multivariate Cox's proportional hazard regression model.
* A-kinase interacting protein 1 expression in the Cox's regression analysis in the form of ordered categorical variable, which were encoded as: low = 0, high+ = 1, high++ = 2, high+++ = 3. AKIP1 = A-kinase interacting protein 1, CI = confidence, HR = hazard ratio, OS = overall survival.

Hence, high expression of AKIP1 was correlated with advanced WHO grade in glioma patients. however, the exact underlying regulatory role of AKIP1 in glioma needs further exploration.

AKIP1 is reported to present association with unfavorable prognosis in diverse kinds of cancers by existing studies.[12,13,21] For example, AKIP1 high expression is associated with worse disease-free survival and OS, and further multivariate Cox's regression exhibits that AKIP1 high expression independently predicts poor survival profile in patients with non-small cell lung cancer.[21] Furthermore, in colorectal cancer, Kaplan–Meier survival analysis demonstrates that patients with elevated AKIP1 expression have worse OS compared with those with decreased AKIP1 expression.[12] As for the potential of AKIP1 in predicting survival profiles in glioma, it is still unknown. We detected the association of AKIP1 expression with OS in glioma patients and found that AKIP1 expression was negatively associated with OS in glioma patients. Notably, further subgroup analysis found that AKIP1 expression was negatively associated with OS especially in high-grade glioma patients, and in all glioma patients received radiotherapy/chemotherapy or not. The possible reasons might include that

(1) Based on our previous finding, AKIP1 high expression was associated with advanced WHO grade in glioma patients, which inferred worse prognosis.[1]
(2) AKIP1 high expression might protect tumor cells against chemotherapy cytotoxicity (temozolomide) and enhance the self-renew ability of glioma stem-like cells via regulating NF-kB signaling pathway, which increased the tumor recurrence rate and reinforced the drug resistance in glioma patients, hence, patients with AKIP1 high expression presented poor prognosis compared with those with those with AKIP1 low expression.[14,15]

However, there exist some limitations in our present study.

(1) As the present study was a single-center study, therefore a larger sample size from multiple regions were essential for further validation in the future.
(2) Our present study did not explore the underlying molecular mechanism of AKIP1 in the pathological process of glioma, further cellular experiments were needed.
(3) Considering that our present study was a retrospective study, therefore, some selection bias might exist, further prospective study with longer follow-up was needed for validating the clinical role of AKIP1 in glioma management.

In conclusion, AKIP1 is sufficiently expressed and positively associated with tumor grade, meanwhile it predicts poor survival profile independent of tumor grade and post-surgery adjuvant therapies, which suggests the role of AKIP1 as a biomarker in glioma management and prognosis surveillance.

Author contributions

Conceptualization: Yiqun Yao.
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Formal analysis: Songbo Shen.
Investigation: Songbo Shen.
Methodology: Songbo Shen.
Resources: Yiqun Yao.
Supervision: Yiqun Yao.
Writing – original draft: Songbo Shen.
Writing – review & editing: Yiqun Yao.

References

[1] Ostrom QT, Bauchet L, Davis FG, et al. The epidemiology of glioma in adults: a "state of the science" review. Neuro Oncol 2014;16:896–913.

[2] Larjavaara S, Mantyla R, Salminen T, et al. Incidence of gliomas by anatomic location. Neuro Oncol 2007;9:319–25.
[3] Ostrom QT, Gittleman H, Farah P, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. Neuro Oncol 2013;15(Suppl 2):ii1–56.
[4] Bush NA, Chang SM, Berger MS. Current and future strategies for treatment of glioma. Neurosurg Rev 2017;40:1–4.
[5] Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
[6] Gao N, Hibi Y, Cueno M, et al. A-kinase-interacting protein 1 (AKIP1) acts as a molecular determinant of PKA in NF-kappaB signaling. J Biol Chem 2010;285:28097–104.
[7] Gao N, Asamitsu K, Hibi Y, et al. AKIP1 enhances NF-kappaB-dependent gene expression by promoting the nuclear retention and phosphorylation of p65. J Biol Chem 2008;283:7834–43.
[8] Lin C, Song L, Liu A, et al. Overexpression of AKIP1 promotes angiogenesis and lymphangiogenesis in human esophageal squamous cell carcinoma. Oncogene 2015;34:384–93.
[9] Chen D, Cao G, Liu Q. A-kinase-interacting protein 1 facilitates growth and metastasis of gastric cancer cells via slug-induced epithelial-mesenchymal transition. J Cell Mol Med 2019;23:4434–42.
[10] Cui Y, Wu X, Lin C, et al. AKIP1 promotes early recurrence of hepatocellular carcinoma through activating the Wnt/beta-catenin/CBP signaling pathway. Oncogene 2019;38:5516–29.
[11] Tian ZQ, Jiang H, Lu ZB. MiR-320 regulates cardiomyocyte apoptosis induced by ischemia-reperfusion injury by targeting AKIP1. Cell Mol Biol Lett 2018;23:41.
[12] Jiang W, Yang W, Yuan L, et al. Upregulation of AKIP1 contributes to metastasis and progression and predicts poor prognosis of patients with colorectal cancer. Onco Targets Ther 2018;11:6795–801.
[13] Liu Y, Tian J, Qin D, et al. AKIP1 expression in tumor tissue as a new biomarker for disease monitoring and prognosis in non-small cell lung cancer: results of a retrospective study. J Clin Lab Anal 2020;34:e23128.
[14] Feng F, Zhang M, Yang C, et al. The dual roles of autophagy in gliomagenesis and clinical therapy strategies based on autophagic regulation mechanisms. Biomed Pharmacother 2019;120:109441.
[15] Liu H, Sun Y, Qi X, et al. EZH2 phosphorylation promotes self-renewal of glioma stem-like cells through NF-kappaB methylation. Front Oncol 2019;9:641.
[16] Chen J, McKay RM, Parada LF. Malignant glioma: lessons from genomics, mouse models, and stem cells. Cell 2012;149:36–47.
[17] Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97–109.
[18] Fu H, Jin C, Zhu Q, et al. Dysregulated expressions of PTEN, NF-kappaB, WWP2, p53 and c-Myc in different subtypes of B cell lymphoma and reactive follicular hyperplasia. Am J Transl Res 2019;11:1092–101.
[19] Sastri M, Barraclough DM, Carmichael PT, et al. A-kinase-interacting protein localizes protein kinase A in the nucleus. Proc Natl Acad Sci U S A 2005;102:349–54.
[20] Zhang W, Wu Q, Wang C, et al. AKIP1 promotes angiogenesis and tumor growth by upregulating CXC-chemokines in cervical cancer cells. Mol Cell Biochem 2018;448:311–20.
[21] Mo D, Li X, Li C, et al. Overexpression of AKIP1 predicts poor prognosis of patients with breast carcinoma and promotes cancer metastasis through Akt/GSK-3beta/Snail pathway. Am J Transl Res 2016;8:4951–9.