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Original Article

Cytoplasmic expression of BAP1 as an independent prognostic biomarker for patients with gliomas

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Abstract: Background: BRCA1-associated protein-1 (BAP1) has been investigated the prognostic value for some carcinomas, including mammary carcinoma, pulmonary carcinoma and mesothelioma and so on. However, the status of BAP1 expression and the relationship of that with overall survival were not still estimated in patients with gliomas. Therefore, it was necessary to investigate the effect of BAP1 expression for the survival of patients with gliomas in this study. Patients and methods: Clinicopathological information of 229 patients with gliomas was used to perform the further analysis. We defined the nucleus expression of BAP1 score of median 0 and cytoplasmic expression of BAP1 score of median 100 as the rational cutoff value for survival analysis, respectively. These patients were categorized into the low cytoplasmic expression of BAP1 and the high expression of BAP1 group, presence of nucleus expression and absence of nucleus expression according to the corresponding cutoff point, respectively. The associations of clinicopathological characteristics with overall survival (OS) were investigated by univariate analysis in patients with gliomas. Multivariate analysis was further performed to find the independent prognostic indicator of OS by Cox regression model. Results: Thirty-nine of 229 patients (17.0%) with gliomas had the nucleus expression of BAP1, 213 of 229 patients (93.0%) had the cytoplasmic expression of BAP1, and 28 patients (12.2%) with both cytoplasmic and nucleus expression, 5 cases (2.2%) without neither cytoplasmic nor nucleus expression. Univariate analysis demonstrated that high cytoplasmic expression of BAP1, tumor location, tumor relapse, advanced clinical stage were significant linkage with worse OS ($P<0.05$). Multivariate analysis revealed that high cytoplasmic expression of BAP1 was a significantly independent biomarker for adverse OS (hazard ratio: 1.516, 95% CI: 1.029-2.234, $P=0.035$). In stratified analysis, we found that the patients with high cytoplasmic expression of BAP1 had the shorter overall survival than these with low cytoplasmic expression of BAP1 in the 190 patients without nucleus expression of BAP1 ($P=0.001$). ROC curve analysis showed that cytoplasmic expression of BAP1 was superior to nucleus expression of BAP1 as a predictive factor in patients with gliomas (AUC=0.583, $P=0.030$ vs. AUC=0.516, $P=0.679$). Conclusions: This study suggested that cytoplasmic expression of BAP1 might be served as a valuable predictive biomarker of the prognosis in gliomas. High cytoplasmic expression of BAP1 might be benefit to identify patients who need to carry out further therapy.

Keywords: BAP1, ROC, OS, gliomas, prognosis, cytoplasmic

Introduction

Gliomas were served as malignant brain tumors. The histological types included astrocytomas, oligodendrogliomas and oligoastrocytomas according to the origin of tumor cells. They were categorized into low grade gliomas and high grade gliomas depending on the following criteria including cell density, cell atypia, mitotic count and presence or absence of necrosis [1]. In recent years, although different therapeutic strategies were applied to clinical practice, such as surgical resection of primary tumors, combining with postoperative radiotherapy and chemotherapy, the median time of survival was still shortened, and the survival rate at 1-year was also less than 30% [2, 3]. A study reported that these treatment strategies were constantly explored and improved, there has not been too many advancements for prognosis of patients with gliomas in the past decades [4], The local progression and relapse

Table 1. Correlation between the expression of BAP1 and clinicopathological features in gliomas

	All cases	BAP1 protein		
		Low cytoplasmic expression	High cytoplasmic expression	*P* value*
Sex				0.347
Female	104	63 (60.6%)	41 (39.4%)	
Male	125	68 (54.4%)	57 (45.6%)	
Age at diagnosis (years)				0.003
<50	172	108 (62.8%)	64 (37.2%)	
≥50	57	23 (40.4%)	34 (59.6%)	
Tumor location				0.055
Above the tentorium	199	109 (54.8%)	90 (45.2%)	
Below the tentorium	30	22 (73.3%)	8 (26.7%)	
Recurrence				0.895
No	125	72 (57.6%)	53 (42.4%)	
Yes	104	59 (56.7%)	45 (43.3%)	
Clinical stage				0.000
I	12	11 (91.7%)	1 (8.3%)	
II	81	64 (79.0%)	17 (21.0%)	
III	72	39 (54.2%)	33 (45.8%)	
IV	64	17 (26.6%)	47 (73.4%)	

*Chi-square test.

were closely associated with the poor prognosis of patients with gliomas [5, 6]. Several clinical factors have been argued broadly with respect to rapid progression of gliomas, however, we still rarely knew about the micro-environmental factors for the progression and relapse of gliomas, including the molecular and genetic factors [7], and biological changes of these factors that occurred during carcinogenesis and progression could facilitate investigation of the signal pathway of tumorigenesis and find valuable prognostic biomarkers to more accurately predict clinical outcome of patients with gliomas, which could be helpful for individual treatments in patients with gliomas. Therefore, it was necessary to explore new prognostic biomarkers and find novel therapeutic strategy for gliomas.

Breast cancer susceptibility protein type 1 (BRCA1)-associated protein-1 (BAP1) had a role of deubiquitinating substrates by interacting with transcriptional regulator host cell factor 1 (HCF-1) [8]. BAP1 played a critical role in tumorigenesis and was identified as a tumor inhibiting factor in various cancers, in addition, BAP1 catalytic activity and nuclear localization represented growth-suppressive properties in the tumor cells [9]. Nevertheless, the molecular mechanisms controlling BAP1 function were still poorly understood, but it was defined as the key regulator during the regulation of cell growth and proliferation [10]. To the best of our knowledge, Wild-type BAP1 protein was located in the nuclear staining and mutant-type BAP1 protein was located in the cytoplasmic staining or negative expression without nuclear staining by immunohistochemistry [11, 12], and the mutant-type BAP1 usually displayed a more pronounced cytoplasmic staining than the wild-type BAP1. Moreover, BAP1 protein was significant nuclear location but appeared to strong cytoplasmic staining interacting with ubiquitin-conjugating enzyme UBE2O [13]. This suggested that the expression of BAP1 protein was mediated by multiple factors. Prior studies also demonstrated that low nuclear expression of BAP1 protein was an indicator of unfavorable prognosis in patients with renal cell carcinoma, uveal melanoma and colorectal cancer [14-16]. There were no relevant studies on the prognostic significance of BAP1 in gliomas. Therefore, we would investigate the status of BAP1 expression in gliomas and normal brain tissues by immunohistochemistry, and the impact of BAP1 expression on overall survival in the patients with gliomas in this study.

Materials and methods

Ethics statement

The research was supported by the Institute Research Medical Ethics Committee of Sun Yat-Sen University. Because several patients were dead in this respective study, we had no writing consents for the patients with gliomas, and all the specimens were anonymous.

Patients

In this study, we collected complete clinical and pathological data. A cohort of 229 samples of gliomas was achieved in Sun Yat-Sen University

Table 2. Univariate and multivariate analyses of different prognostic variables in 229 glioma patients

Variable	Univariate analysis*			Multivariate analysis*	
	All cases	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Sex			0.541		
Female	104	Reference			
Male	125	0.895 (0.628-1.276)			
Age at surgery (years)			0.000	2.487 (1.669-3.706)	0.000
<50	172	Reference			
≥50	57	3.428 (2.350-5.001)			
Tumor location			0.024	0.673 (0.319-1.421)	0.299
Above the tentorium	199	Reference			
Below the tentorium	30	2.184 (1.107-4.312)			
Recurrence			0.000	3.539 (2.364-5.296)	0.000
No	125	Reference			
Yes	104	3.277 (2.269-4.734)			
Clinical stage			0.000	2.832 (1.779-4.508)	0.000
I-II	93	Reference			
III-IV	136	2.967 (1.984-4.436)			
Nucleus expression of BAP1			0.361		
Absence	190	Reference			
Presence	39	1.235 (0.785-1.994)			
Cytoplasmic expression of BAP1			0.000	1.516 (1.029-2.234)	0.035
Low	125	Reference			
High	104	1.943 (1.359-2.778)			

*Cox regression model; CI, confidence interval.

Cancer Center between January 2000 and August 2008. The screening of cases needed to meet the following requirements: the gliomas as pathological diagnosis; detailed clinical data, including overall survival (OS: the interval from the time of diagnosis to the last follow-up time for patients alive or the time died of any causes); without other preoperative malignant tumors; without chemotherapy and radiotherapy history before surgery treatment; consecutively follow-up.

Evaluation and follow-up

In our study, the patients were evaluated four times a year for the 1st year after operation, twice a year for the next 2 years and then once a year starting from the 4th year. The diagnostic physical examinations composed of brain X ray, MRI and CT, were helpful to investigate the local recurrence or distant metastasis of primary gliomas.

Construction of the tissue microarray (TMA)

Tissue microarrays were produced by the common methods [17]. Firstly, we needed to make a mark on the representative tumor areas of the tissue paraffin blocks of 229 specimens by the corresponding H&E stained slides. Secondly, both of tissue cylinders of 2.0 mm diameter were drilled from the marked areas on every tissue block using an instrument to construct the TMA, and put them into the paraffin block of without tissues at an identified position with the same instrument then re-embedded them into the new paraffin blocks to construct the TMA (Beecher Instruments, Silver Spring, MD, USA).

Immunohistochemistry (IHC)

TMA tissue blocks of gliomas were cut into 4 μm thickness and put them into the blank slides. The tissue slides without stained were performed for IHC according to the used methods [18]. Firstly, the TMA slides were deparaffinized in the xylene, and neutralized the xylene by grading alcohol. Secondly, they were submerged in hydrogen peroxide of 3% for 10 minutes to inhibit the activity of peroxidase in tissues, and the slides were cooked for 3 minutes in the citrate buffer (pH=6) to activate the BAP1

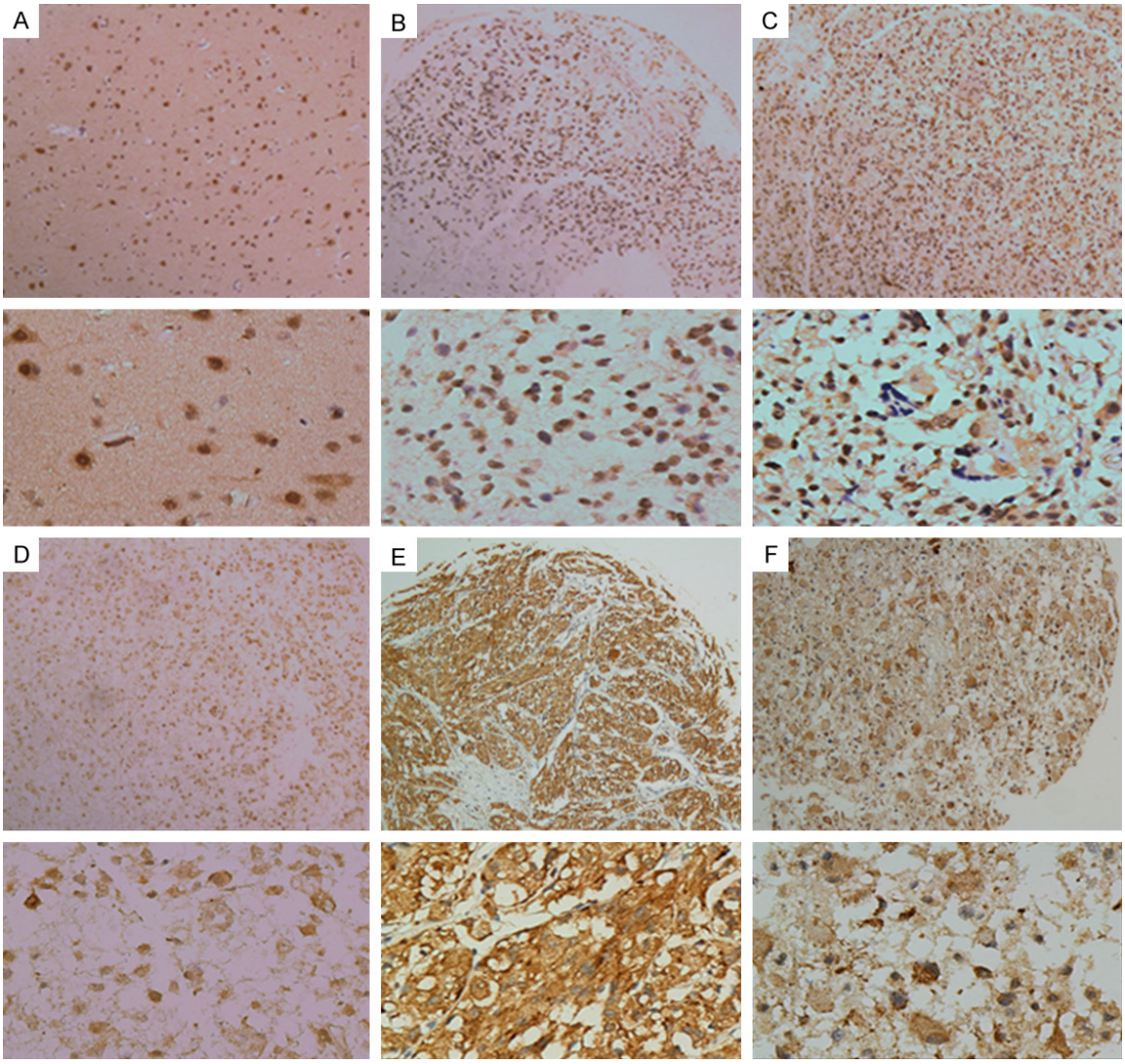

Figure 1. The expression pattern of BAP1 protein in gliomas and normal brain tissues. A. Normal brain tissue showed low cytoplasmic expression of BAP1 protein and high nucleus expression of BAP1 protein (100×). B. Nucleus expression of BAP1 was shown in a glioma case (100×). C. A glioma case demonstrated the nucleus expression scores greater than cytoplasmic expression scores of BAP1 (100×). D. A glioma case displayed the cytoplasmic expression scores greater than nucleus expression scores of BAP1 (100×). E. High cytoplasmic expression of BAP1 was shown in a glioma case (100×). F. Low cytoplasmic expression of BAP1 was shown in a glioma case (100×). The lower panels indicated the higher magnification (400×) from the upper panels.

antigen. Thirdly, we added goat serum of 10% to the TMA slides for 20 minutes to eliminate staining of the background. Then the BAP1 polyclonal antibody (1:100 dilution) was overlaid in the TMA slides, and incubated them in the incubator of 4°C for 12 hours, and then further incubated with the secondary antibody (Envision, Dako, Denmark) for 30 minutes, and colored with DAB (3,3-diaminobenzidine). Finally, the TMA slides were stained with Mayer's hematoxylin and dehydrated. The negative control was performed with the normal rabbit IgG antibody.

IHC evaluation

The status of BAP1 protein expression was assessed using stained TMA slides by microscopy. The presence of both cytoplasmic and nuclear staining was defined as the positive BAP1 expression, and respectively, the cytoplasmic and nuclear staining was briefly evaluated according to the following methods: Each

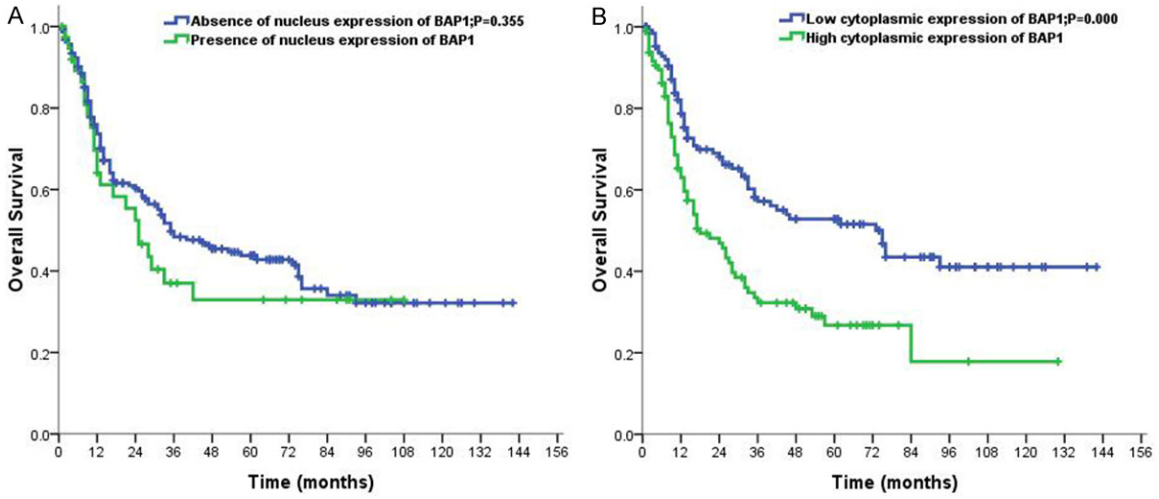

Figure 2. Kaplan-Meier survival analysis of nucleus expression of BAP1 (A) and cytoplasmic expression of BAP1 (B) for overall survival.

spot in TMA included two scores, such as the score of intensity expression from negativity to strong positivity, namely, 0=negativity, 1=weak positivity, 2=moderate positivity, 3=strong positivity and the area score of BAP1 expression was also evaluated by the percentage of stained tumor cells (0=0%-5%, 1=6%-35%, 2=36%-75%, 3=76%-100%). The total score (range from 0 to 300) was retrieved by the multiplication of every intensity score and the corresponding area score (**Figure 1**). The status of BAP1 expression was estimated by two pathologists (X-K Zhang and S-Y Xi) who were blind to the clinicopathological information for the patients with gliomas.

Selection of cutoff score

We select the median of cytoplasmic and nucleus expression scores in BAP1 as the cutoff value, respectively. Low BAP1 expression was identical with the score less than or equal to the cutoff value, and more than the cutoff value was served as high BAP1 expression.

Statistical analysis

Statistical analysis was processed with SPSS, version 16.0 (SPSS, Chicago, USA). The correlation of BAP1 expression with clinicopathological characteristics of patients with gliomas was determined by chi-square test. Survival curve was plotted by the Kaplan-Meier method and the discrepancies between high BAP1 expression and low BAP1 expression of cytoplasmic and nuclear staining was calculated by log-rank test. The Cox regression hazards model was applied to define that the independent prognostic indicators impacted on OS. ROC curves were used to identify the impact of cytoplasmic and nucleus expression in BAP1 on prognosis. $P \leq 0.05$ was considered to be significantly statistical differences in the patients with gliomas.

Results

Patients

The clinicopathological characteristics of patients with gliomas were comparable in **Table 1**. Of 125 (54.6%) men and 104 (45.4%) women were included in the recruited patients with gliomas. The median age was 50 years. Mean time of follow-up was 35.6 months and median survival time was 22.0 months varying from 1.0 to 142.0 months. 93 (40.6%) patients with gliomas of grade I and II were, and the other 136 patients (59.4%) were diagnosed as gliomas of grade III and IV. 199 patients (66.6%) occurred above the tentorium and 30 patients (33.4%) occurred below the tentorium. Importantly, 39 of 229 patients (17.0%) with gliomas had the nucleus expression of BAP1, 213 of 229 patients (93.0%) had the cytoplasmic expression of BAP1, and 28 patients (12.2%) with both cytoplasmic and nucleus expression, 5 cases (2.2%) without neither cytoplasmic nor nucleus expression. 13 cases with normal brain tissues displayed both cytoplasmic and

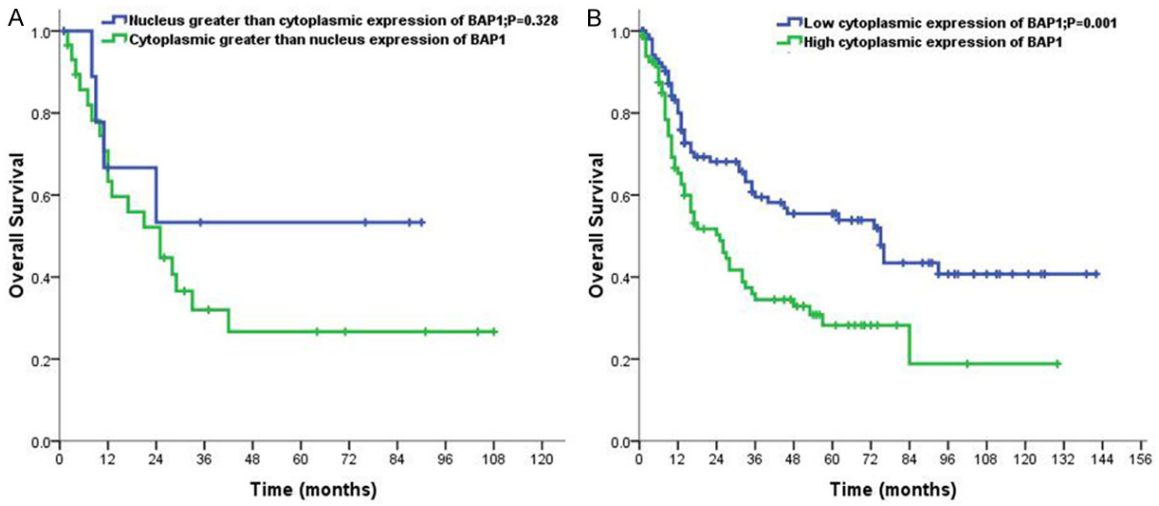

Figure 3. Kaplan-Meier survival analysis of cytoplasmic stronger than nucleus expression of BAP1 (C>N) and nucleus stronger than cytoplasmic expression of BAP1 (N>C) in 39 cases with nucleus expression of BAP1 (A) and cytoplasmic expression of BAP1 in 190 patients without nucleus expression of BAP1 (B) for overall survival.

nucleus expression, and cytoplasmic expression score greater than nucleus expression score.

Selection of the cutoff value for BAP1 expression

We choose a cytoplasmic BAP1 expression score of median 100 as the suitable cutoff value and a nucleus BAP1 expression score of median 0 as the ideal cutoff value for further analysis according to our result.

Relationship of BAP1 expression with the clinicopathological features in 229 patients with gliomas

The relationship between the status of BAP1 expression in patients with gliomas and clinicopathological characteristics were described in **Table 1**. The results demonstrated that high cytoplasmic expression of BAP1 was strong associated with age at diagnosis and clinical stage (P<0.05, **Table 1**), and nucleus expression of BAP1 was not correlated with all the clinicopathological parameters (P>0.05).

Correlation between BAP1 expression and overall survival of 229 patients with gliomas

Univariate analysis revealed that the significant effect was found between these clinicopathological prognostic factors and overall survival, including tumor location, age at diagnosis, tumor relapse and clinical stage (P<0.05, **Table 2**). This study also suggested that high cytoplasmic expression of BAP1 was significantly correlated with adverse overall survival (P<0.001, **Figure 2B**), and nucleus expression of BAP1 was not correlated with overall survival (P>0.05, **Figure 2A**). We found that high cytoplasmic expression in BAP1 was an independent prognostic indicator for overall survival by multivariate analysis including age at diagnosis, tumor location, tumor relapse, clinical stage and cytoplasmic expression of BAP1. In addition, more than 50 years at diagnosis, advanced stage and presence of tumor relapse were also served as independent prognostic factors for overall survival (**Table 2**).

Stratified analysis for the association between BAP1 expression and overall survival of 229 patients with gliomas

We categorized the 229 patients with gliomas into 190 patients without nucleus expression of BAP1 and 39 cases with nucleus expression of BAP1. Univariate analysis showed that the patients with cytoplasmic stronger than nucleus expression of BAP1 (C>N) had a degree of adverse survival tendency towards statistical significance compared to those with nucleus stronger than cytoplasmic expression of BAP1 (N>C) in 39 cases with nucleus expression of BAP1 (P=0.328; **Figure 3A**). Meanwhile, in the 190 patients without nucleus expression of BAP1, a worse survival tendency towards sta-

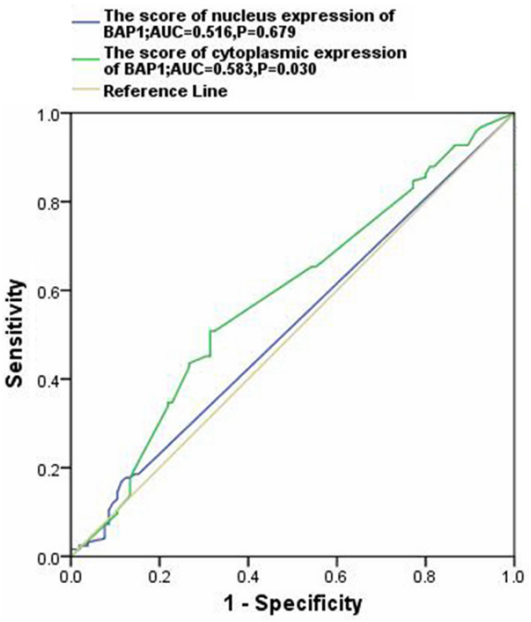

Figure 4. ROC curves of cytoplasmic expression of BAP1 and nucleus expression of BAP1 for prediction of overall survival.

tistical significance was revealed between patients with positive expression of BAP1 and patients with negative expression of BAP1 in cytoplasm by univariate analysis (P=0.160). Importantly, we found that the patients with high cytoplasmic expression of BAP1 had the shorter overall survival than these with low cytoplasmic expression of BAP1 (P=0.001; **Figure 3B**).

Prediction of overall survival by ROC curve

The AUC was 0.516 (95% CI: 0.441 to 0.591, P=0.679) for nucleus expression of BAP1 and 0.583 (95% CI: 0.509 to 0.658, P=0.030) for cytoplasmic expression of BAP1, suggesting that cytoplasmic expression of BAP1 was superior to nucleus expression of BAP1 as a predictive factor in patients with gliomas (**Figure 4**).

Discussion

BAP1 could be served as a suppressive gene by mediating the different pathways when combining with BRCA1 gene in several cancers [9, 19]. There was the evidence that BAP1 was a tumor suppressor. Majority of studies reported that BAP1 was chromatin associated protein and located in the nucleus expression in renal cell carcinoma and malignant pleural mesothelioma by immunohistochemistry [14, 20] Nevertheless, In our study, we revealed that the staining of BAP1 proteins located in both the nuclear and cytoplasm in gliomas, suggesting that BAP1 protein expression had its specificity in gliomas [21]. Moreover, mesotheliomas with germline BAP1 mutation appeared to the weak cytoplasmic expression of BAP1 and the mechanism of varying expression remained poorly defined [12]. In this study, we found that nearly 93.0% of the investigated gliomas harbored a cytoplasmic expression of BAP1 and 46.0% of these patients displayed the strong staining of BAP1, also 17.0% of patients with nucleus expression of BAP1 and 71.8% of these patients with both nucleus and cytoplasmic staining. The feature of the expression was different from that previously mentioned [14, 22]. A recent study showed that the wild-type BAP1 represented a typical nuclear staining, while mutants of BAP1 had negative nuclear expression stronger cytoplasmic staining [23]. However, this theory of BAP1 mutation associated with protein expression could not seem to correctly explain the complexity of BAP1 expression in gliomas. BAP1 was predominant nuclear in the cycle of normal cell growth, and had strong cytoplasmic expression when interacted with UBE2O served as the enzyme of ubiquitination of BAP1, also could translocate to the cytoplasm prior to ubiquitination of UBE2O during the tumorigenesis [13]. These findings might implement the evidence for the status of BAP1 expression in gliomas. The normal brain tissue displayed high expression of UBE2O [24], suggesting that the staining of BAP1 might be located in the nuclear and cytoplasm in the brain, this speculation was in agreement with our study. Moreover, our study demonstrated that nucleus expression of BAP1 was stronger than its cytoplasmic expression in the normal brain tissues. The result of ROC curve suggested that cytoplasmic staining of BAP1 displayed a more significantly impact on the prognosis of patients with gliomas compared with nucleus staining of BAP1. Univariate analysis indicated that nucleus expression of BAP1 was not correlated with favorable overall survival in the patients with gliomas and high cytoplasmic expression of BAP1 was inversely associated with the poor prognosis of these patients, the possibly reason was that downregulation of nucleus BAP1 expression associated with tumor suppressor could exert its cytoplasmic

functions for the progression of gliomas. High cytoplasmic expression of BAP1 was served as an independently poor prognostic indicator by multivariate analysis, which appeared that high cytoplasmic expression of BAP1 might lead to aggressive growth of gliomas and could be used as an important prognostic factor for patients with gliomas. In this present study, we also showed that high cytoplasmic expression of BAP1 was significantly associated with tumor grade and tumor relapse, which indicated that BAP1 could affect the differentiation and proliferation of gliomas.

In stratified survival analysis, cytoplasmic stronger than nucleus expression of BAP1 (C>N) had a degree of adverse survival tendency towards statistical significance compared to these with nucleus stronger than cytoplasmic expression of BAP1 (N>C) in 39 cases with nucleus expression of BAP1, in the 190 patients without nucleus expression of BAP1, we found that the patients with high cytoplasmic expression of BAP1 had the shorter overall survival than these with low cytoplasmic expression of BAP1, further indicating that cytoplasmic expression of BAP1 played a critical role in tumor aggressiveness, and were correlated with the adverse prognosis of patients with gliomas.

On the basis of our report, the role of cytoplasmic expression of BAP1 for the prognosis in patients with gliomas was considered as the most key findings. However, there has not yet been determined the impact of BAP1 protein on the formation of the gliomas. Indeed, a number of factors could form the core of BAP1 complex involved in the broad effect on cellular function [21], which implicated that maybe BAP1 played a more extensive role at the cellular level compared with that prior studies found. In a word, high cytoplasmic expression of BAP1 might be seen as an effective and valuable predictor to define the patients who might appear to the tumor progression by IHC. These findings may help us explore the inhibitor of trafficking pathway of BAP1 nucleus protein in patients with gliomas for a more useful therapeutic method and further investigate the mechanism for the role of BAP1 in gliomas cells by other molecular biology techniques in the future.

In conclusion, our study indicated that the detection of BAP1 expression by IHC might be considered as a valuable tool in determining those patients with gliomas at increased risk of tumor aggressive, and made high cytoplasmic expression of BAP1 as a novel poor independent prognostic indicator in gliomas, which could be of help for us to find the new therapeutic target.

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Disclosure of conflict of interest

None.

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