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Original Article

Identification of histone acetylation-related enzymes as a prognostic indicator in human glioma

Lei Wang[1], Yuelin Liu[2], Yong Gao[3], Chengmin Xuan[4], Yong Liu[1]

[1]Department of Neurosurgery, Brain Hospital, Affiliated Hospital of Xuzhou Medical University, Xuzhou 221002, Jiangsu, P. R. China; [2]Department of Clinical Medicine, Xuzhou Medical University, Xuzhou 221004, Jiangsu, P. R. China; [3]Department of Orthopaedics, Xuzhou Children's Hospital of Xuzhou Medical University, Xuzhou 221006, Jiangsu, P. R. China; [4]Medical Section, Xuzhou Children's Hospital of Xuzhou Medical University, Xuzhou 221006, Jiangsu, P. R. China

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Abstract: Histone acetylation is an important histone post-translational modification that plays a critical role in chromosome structural modification and gene expression regulation. Because histone deacetylase inhibitors (HDACIs) exhibit good anti-tumor effects without obvious side effects, we comprehensively analyzed the role of acetylation-related enzymes (AREs) in 697 glioma patients in the Cancer Genome Atlas (TCGA). AREs are catalysts for histone acetylation modification. We analyzed 49 AREs in the TCGA. We obtained 36 survival-related AREs, and six had a true positive rate of greater than 0.6 and a *p* value of less than 0.05. However, the six genes were not independent prognostic factors. We then used the 36 survival-related AREs to construct a risk model composed of 16 AREs to predict patient prognosis. Survival analysis and ROC analysis found that the model was statistically significant. Multivariate Cox analysis confirmed that the model can be used as an independent prognostic factor for patients with glioma. The risk curve found that patients in the high-risk group had a short survival time and more patients in this group died compared with patients in the low-risk group. This risk model provides a new research direction for histone acetylation modification in glioma.

Keywords: Acetylation, acetylation-related enzymes (AREs), glioma, bioinformatic, genomic, prognosis

Introduction

Despite the availability of comprehensive treatments for glioma, such as surgery, radiotherapy and chemotherapy, the 5-year survival rate of glioma patients is not yet satisfactory [1, 2]. With the continuous emergence of genomic data, big data analysis makes tumor research more effective and reasonable [3-5]. Analyses of genomic data have revealed multiple molecular markers for glioma patients, such as IDH status, MGMT promoter methylation and 1p/19q codeletion [6-8]. Although multiple molecular markers have been discovered, to cure patients with glioma, more prognostic targets for glioma need to be explored.

Histone acetylation modifications regulate gene expression by affecting the ability of histones to bind to DNA [9]. Histone acetylation is regulated by the balance of histone acetyltransferases (HATs) and histone deacetylases (HDACs) activity [10]. Several studies have shown that decreased HAT activity or abnormal HDAC activation is closely involved in tumor occurrence, invasion and metastasis [10, 11]. In gastric cancer and breast cancer, abnormal expression of HDACs leads to abnormal tumor cell proliferation, differentiation and apoptosis [12, 13]. Because of the important role of histone acetylation in tumors, HDAC inhibitors have been used clinically as anti-cancer agents [14]. In addition, several studies have demonstrated the utility of histone acetylation as prognostic indicators in cancer. For example, low levels of H3K9ac or H3K18ac are associated with better prognosis in non-small cell lung cancer, esophageal cancer and glioma [15, 16].

In view of the important role of histone acetylation modification in cancer progression and as

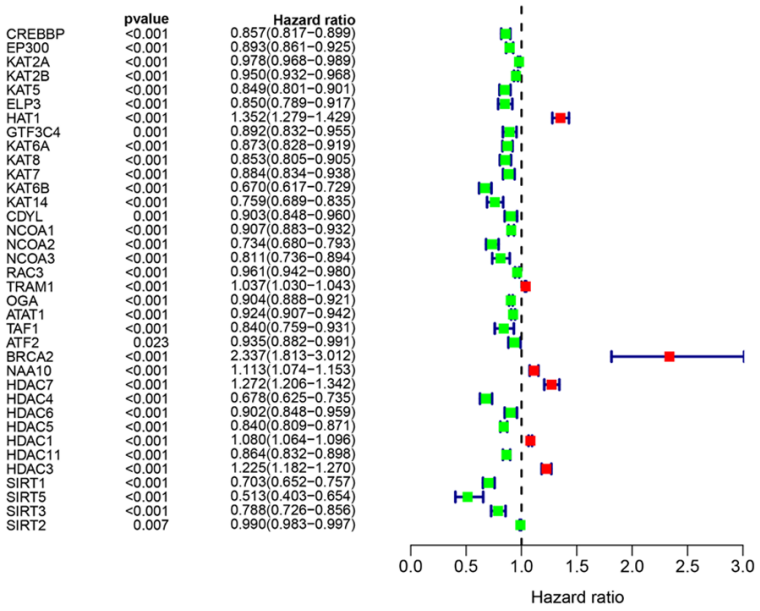

Figure 1. Acquisition of AREs to predict glioma patient prognosis. Among the 47 AREs, we identified 36 AREs that are related to glioma patient survival. In the hazard ratio column, the value in parentheses is the 95% confidence interval of the risk value. The red marker lines indicate high-risk genes, and the green lines indicate low-risk genes.

prognostic indicators, we examined the potential prognostic value of acetylation-related enzymes (AREs) in predicting the prognosis of patients with glioma through bioinformatics analyses. By analyzing a comprehensive list of the 49 AREs in the glioma database, we obtained survival-related AREs and constructed a risk model to predict patient prognosis. Here, we have obtained AREs that are closely related to the prognosis of patients with glioma, which can be used as molecular markers and drug targets for glioma. It provides a new foundation for molecular therapy of glioma.

Materials and methods

Patient samples

The mRNA expression data of patients with glioma were obtained from The Cancer Genome Atlas (TCGA, https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga). The TCGA database contains five cases of non-tumor brain tissue, 221 grade II tumors, 244 grade III tumors, 166 grade IV tumors, and 66 cases with no tumor grade. The World Health Organization (WHO) classification system was used for grading according to our previous descriptions [3].

Identification of survival-related AREs

Through searching the literature, we obtained 49 AREs, including 32 HATs and 17 HDACs [17, 18]. The above two documents summarize HATs and HDACs, and we have taken a collection of the two. The survival package of R software (https://www.r-project.org/) was used to analyze the relationship between the 49 AREs and patient prognosis.

Receiver operating characteristic (ROC) analysis and survival analysis

We used the survival ROC package and survival package to perform ROC analysis and survival analysis, respectively, to determine the accuracy of the survival-related AREs in predicting the prognosis of patients. An AUC value greater than 0.6 and p value less than 0.05 were considered statistically significant.

Construction of the ARE risk model

We used the coxph function of the survival package of R software and 36 survival-related AREs to obtain the optimal ARE risk model for predicting the prognosis of patients.

Univariate and multivariate Cox analysis

The coxph function of the survival package of R software was used for univariate Cox analysis and multivariate Cox analyses to determine the value of various factors in predicting the prognosis of patients. Group information for every factor is based on the previous description [1].

Patient risk display under the ARE risk model

Using the risk formula, we calculated the risk value of each patient and sorted the patients from low to high risk according to the risk value. The patients' survival status and survival time

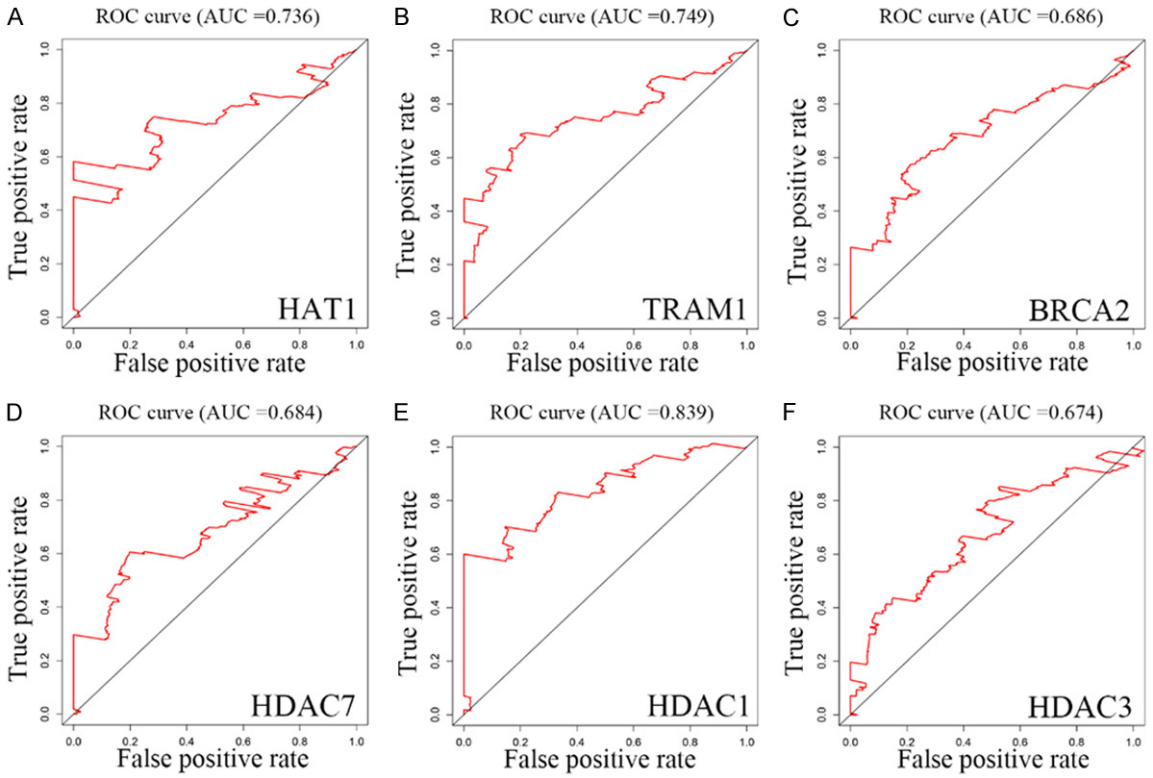

Figure 2. ROC curve analyses of survival-related AREs. ROC curve analysis identified ARE genes that accurately predict the prognosis of glioma patients (AREs with a true positive rate greater than 0.6): HAT1 (A), TRAM1 (B), BRCA2 (C), HDAC7 (D), HDAC1 (E), HDAC3 (F).

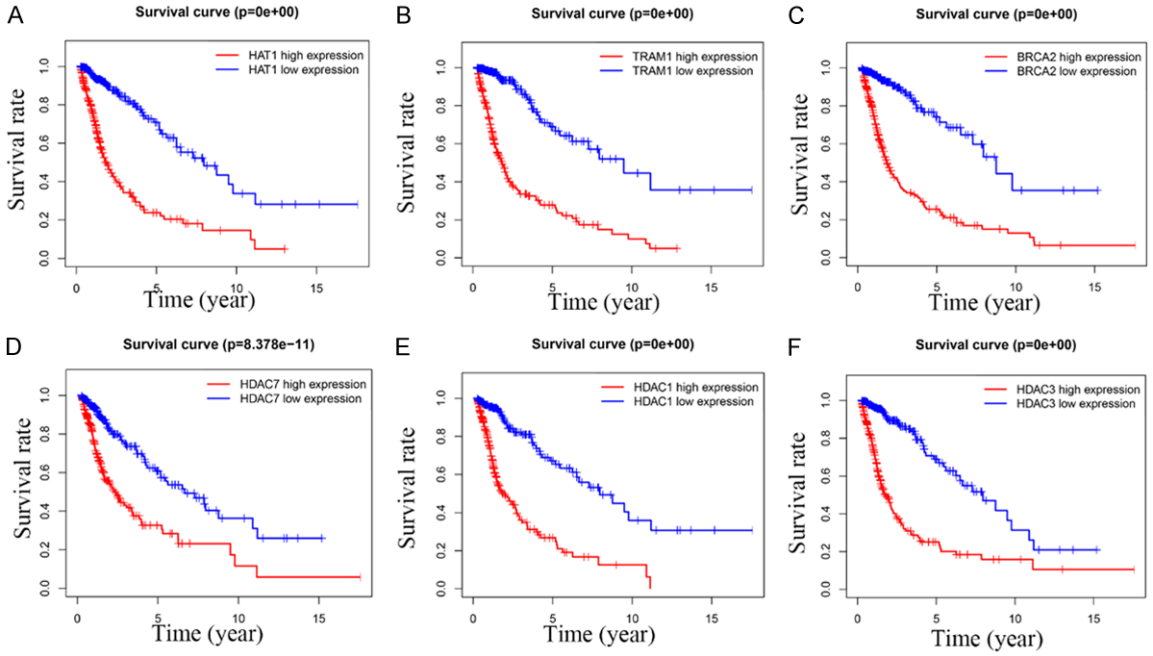

Figure 3. Obtaining the *p* value of survival-related AREs. Six AREs with ROC value greater than 0.6 predict patient prognosis: HAT1 (A), TRAM1 (B), BRCA2 (C), HDAC7 (D), HDAC1 (E), HDAC3 (F).

Table 1. AUC value and *p* value list of 47 AREs

Gene	*P* value	AUC	Gene	*P* value	AUC	Gene	*P* value	AUC
ATAT1	1.84E-12	0.211	***HDAC4***	0	0.171	NAA10	1.32E-11	0.508
ATF2	0.000	0.429	***HDAC5***	0	0.495	NCOA1	1.21E-10	0.319
BRCA2	0	0.686	***HDAC6***	0.004	0.361	NCOA2	2.00E-14	0.396
CDYL	0.000	0.517	***HDAC7***	8.38E-11	0.684	NCOA3	1.35E-06	0.428
CREBBP	8.89E-13	0.378	KAT14	1.82E-07	0.388	OGA	0	0.297
ELP3	1.20E-06	0.409	KAT2A	0.000	0.178	RAC3	1.11E-07	0.393
EP300	4.91E-11	0.392	KAT2B	1.20E-07	0.431	***SIRT1***	0	0.376
GTF3C4	0.041	0.427	KAT5	2.72E-07	0.514	***SIRT2***	1.45E-05	0.442
HAT1	0	0.736	KAT6A	1.67E-08	0.411	***SIRT3***	1.56E-11	0.207
HDAC1	0	0.839	KAT6B	0	0.364	***SIRT5***	1.51E-05	0.172
HDAC11	4.63E-13	0.047	KAT7	4.12E-05	0.355	TAF1	0.002	0.406
HDAC3	0	0.674	KAT8	2.51E-07	0.518	TRAM1	0	0.749

The genes in bold italics are histone deacetylases, and the rest are histone acetyltransferases.

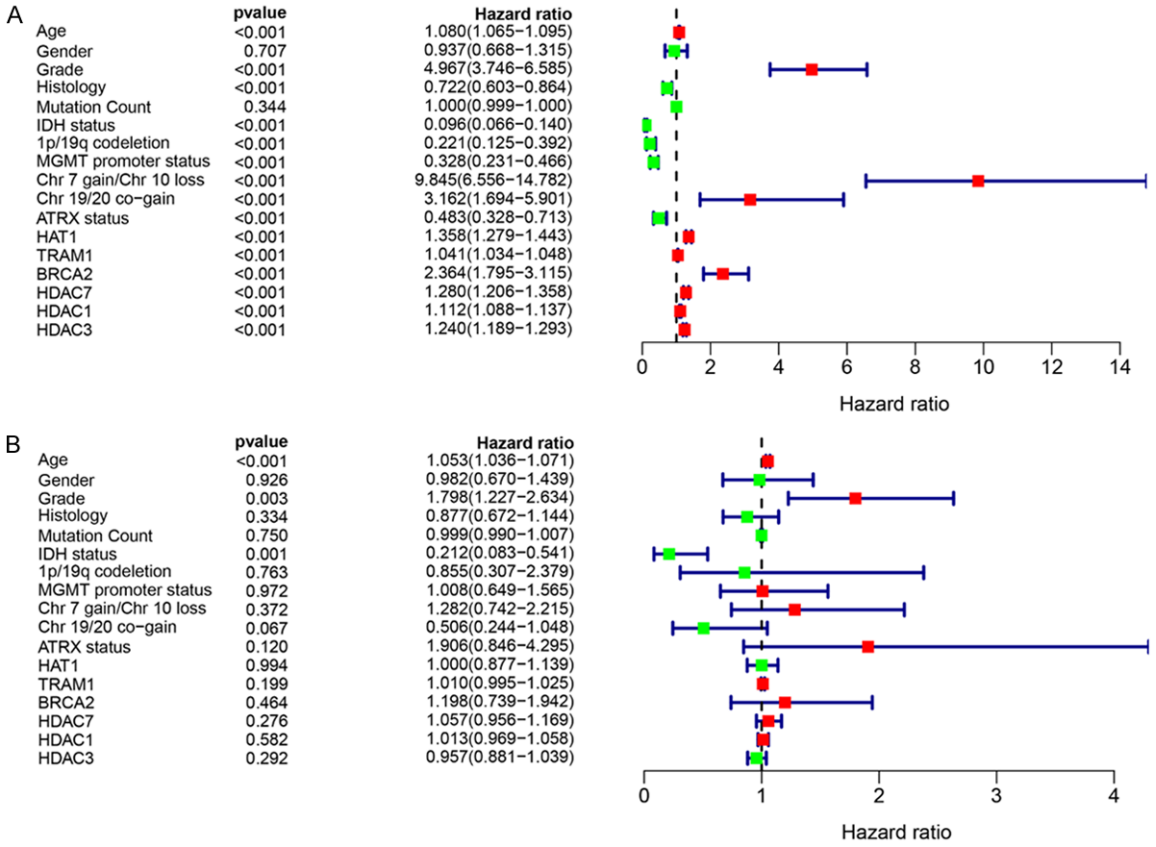

Figure 4. The significance of the six AREs in predicting the prognosis of glioma patients. A. Univariate Cox analysis verified the value of each variable in predicting patient prognosis. B. Multivariate Cox analysis verified the value of each variable in predicting glioma patient prognosis under the influence of multiple factors. Only Age and IDH status are statistically significant. A *p* value of less than 0.05 was considered statistically significant.

were then displayed in the survival status chart. The pheatmap package was used to indicate the expression level of AREs used to construct risk models.

Table 2. Risk model formula for predicting patient prognosis

Gene	coef	HR	HR.95L	HR.95H	*p* value
CREBBP	0.104	1.110	1.009	1.221	0.032
KAT2B	0.021	1.021	1.000	1.042	0.049
KAT5	-0.078	0.925	0.857	0.998	0.044
KAT6A	0.065	1.067	0.988	1.152	0.097
KAT14	0.126	1.134	1.006	1.279	0.040
NCOA3	-0.242	0.785	0.678	0.909	0.001
OGA	-0.063	0.939	0.909	1.969	9.80E-05
ATAT1	-0.025	0.975	0.955	0.995	0.015
ATF2	0.150	1.162	1.074	1.257	0.000
BRCA2	0.631	1.880	1.222	2.893	0.004
HDAC7	0.170	1.186	1.088	1.293	0.000
HDAC4	-0.191	0.825	0.737	0.924	0.001
HDAC1	-0.035	0.966	0.937	0.995	0.023
HDAC3	0.061	1.063	0.999	1.132	0.054
SIRT1	-0.139	0.870	0.769	0.986	0.029
SIRT5	-0.423	0.655	0.496	0.866	0.003

Coef, coefficient; HR, hazard ratio; HR.95L, hazard ratio. 95% low; HR.95H, hazard ratio. 95% high; The genes in bold italics are histone acetyltransferases, and the rest are histone deacetylases.

Statistical analysis

R software was used for statistical analyses. Statistical significance was defined as a two-tailed *P* value <0.05.

Results

Identification of survival-related AREs

By consulting the literature, we obtained 32 HATs and 17 HDACs (Supplementary Table 1). To explore the relationship between AREs and the prognosis of patients with glioma, we conducted a Cox analysis and obtained 36 survival-related AREs (**Figure 1**). We further performed survival analysis and ROC analysis and identified six AREs (HAT1, TRAM1, BRCA2, HDAC7, HDAC1 and HDAC3) with a true positive rate greater than 0.6 and a *P* value greater than 0.05 (**Figures 2**, **3**; **Table 1**). Univariate and multivariate Cox analyses found that while age, grade and IDH status were independent prognostic factors for glioma patients, all six AREs (HAT1, TRAM1, BRCA2, HDAC7, HDAC1 and HDAC3) were not independent prognostic factors for glioma patients (**Figure 4**).

Survival-related AREs for construction of a patient prognosis model

We next used 16 survival-related AREs to build a risk model to predict patient prognosis. These 16 AREs are the most optimal AREs for predicting patient prognosis obtained by Cox analysis of 36 survival-related AREs. The formula is as follows (**Table 2**): [CREBBP expression level × (0.104) + KAT2B expression level × (0.021) + KAT5 expression level × (-0.078) + KAT6A expression level × (0.065) + KAT14 expression level × (0.126) + NCOA3 expression level × (-0.242) + OGA expression level × (0.063) + ATAT1 expression level × (-0.025) + ATF2 expression level × (0.150) + BRCA2 expression level × (0.631) + HDAC7 expression level × (0.170) + HDAC4 expression level × (-0.192) + HDAC1 expression level × (-0.035) + HDAC3 expression level × (0.061) + SIRT1 expression level × (-0.139) + SIRT5 expression level × (-0.423)]. Using the risk model, patients were divided into high- and low-risk groups. Survival analysis showed that the 5-year survival rate of the high-risk group was 17.43%, and the 5-year survival rate of the low-risk group was 79.80% (**Figure 5A**). ROC analysis confirmed that the true positive rate of the model was 86.30% (**Figure 5B**). Univariate and multivariate Cox analyses confirmed that with the risk model we constructed, age, grade, IDH status, and Chr19/20 co-gain were independent prognostic factors (**Figure 6**).

Display of the patient's risk value, survival status and AREs expression

After successfully constructing an independent prognosis model for patients, we calculated the patient's risk value according to the risk formula; we then ranked the patients from high to low risk according to the patient's risk value and divided patients into high and low risk groups (**Figure 7A**). The risk curve showed that in the low-risk group, fewer patients died and the survival time was longer, while in the high-risk group, more patients died and the survival time was shorter (**Figure 7B**). In the high- and low-risk groups, we observed differential expression of multiple AREs from the risk model; among the AREs, HDAC1, HDAC4, SIRT1

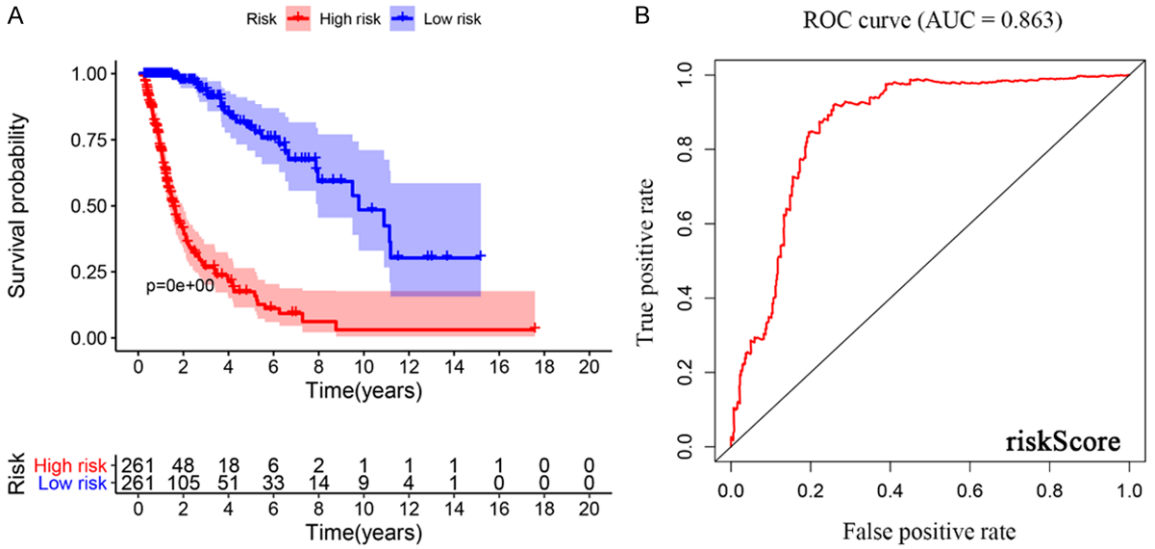

Figure 5. Analysis of the risk model for predicting the prognostic value of glioma patients. A. Survival analysis of glioma patients in the high and low risk groups. Divide the high and low risk groups by the median value. B. ROC analysis verified the false positive rate of the risk model in predicting glioma patient prognosis.

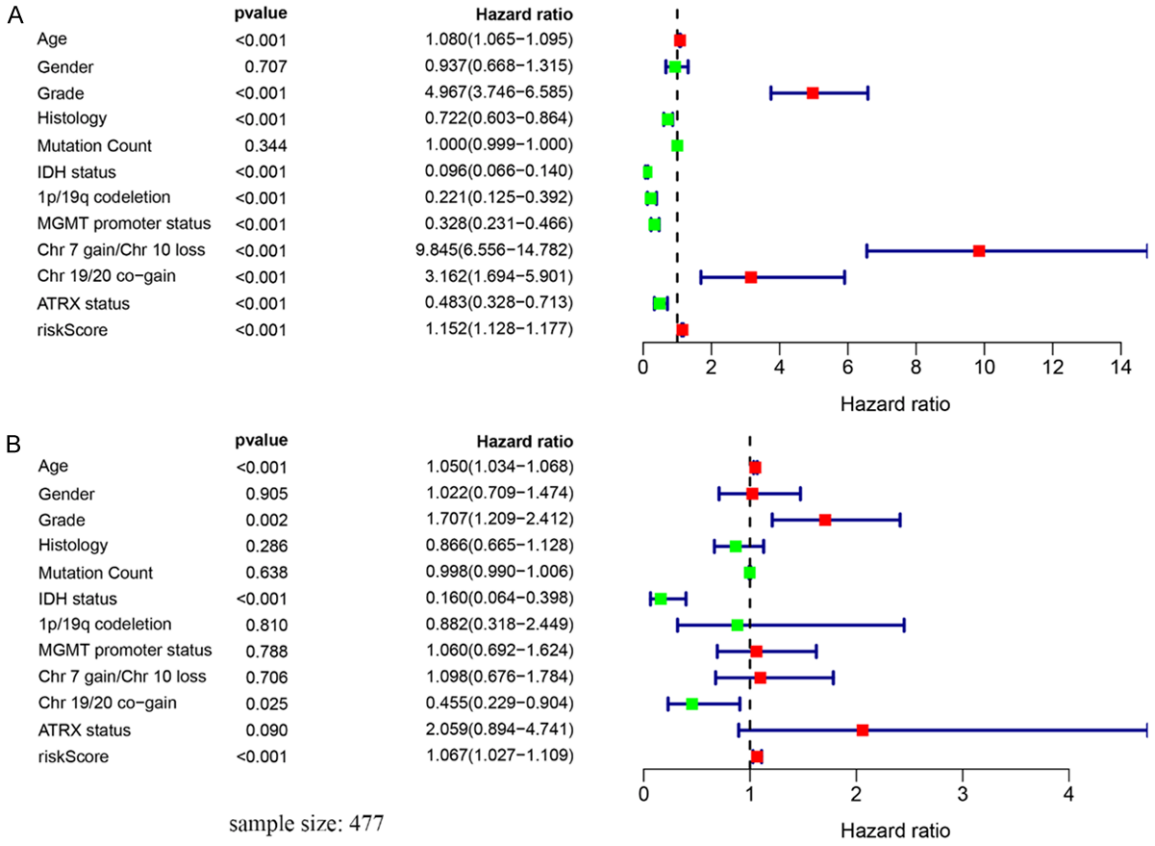

Figure 6. Analysis of the prognostic significance of the risk model predicting the glioma patient prognosis. A. Univariate Cox analysis shows the significance of each factor in predicting glioma patient prognosis. B. Multivariate Cox analysis of the value of various factors to predict the prognosis of glioma patients.

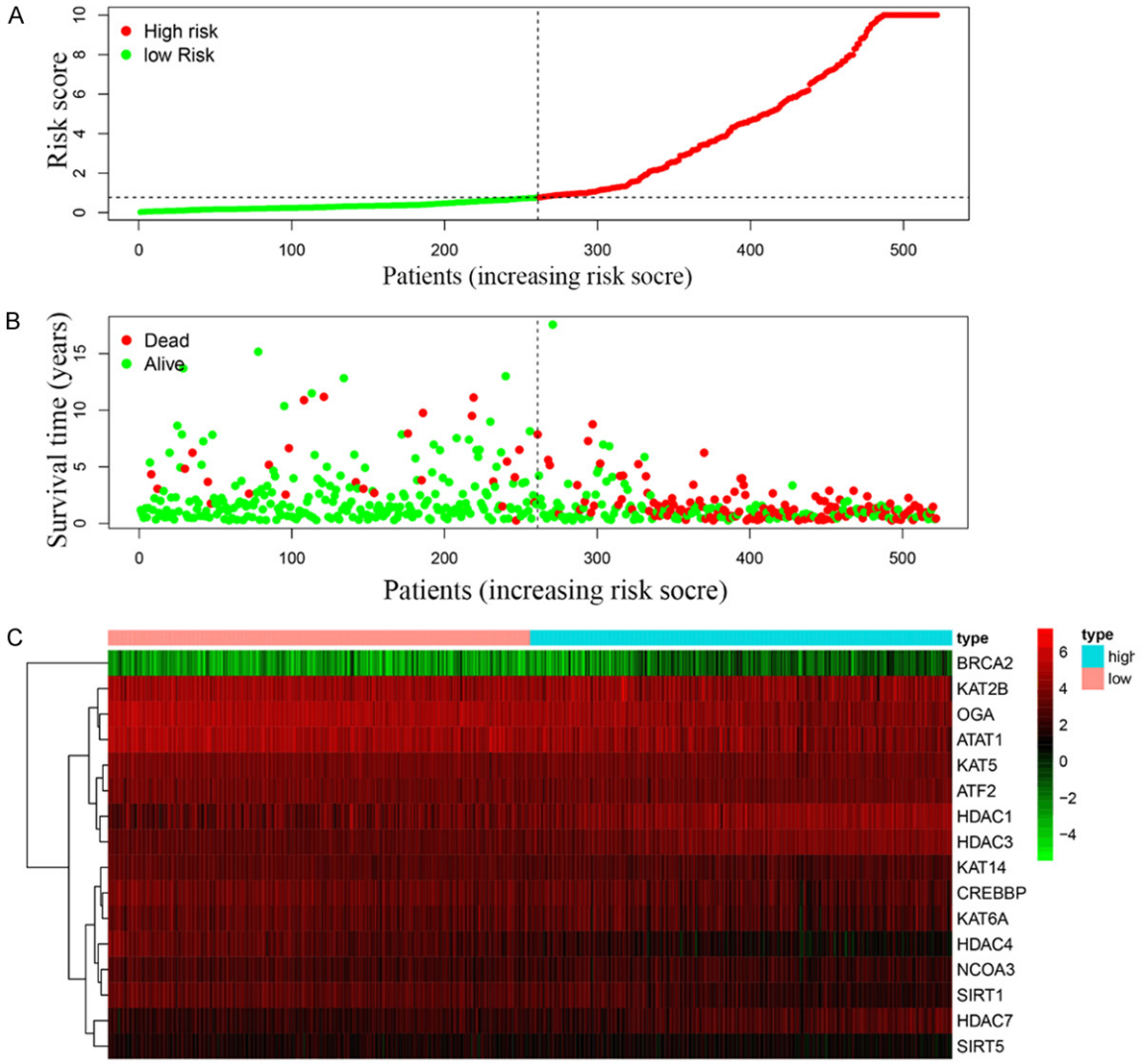

Figure 7. Patients' survival status, survival time and ARE expression under the risk model. A. The risk value of patients in the high and low risk groups is ranked. B. The survival status and time display of patients under grouping. C. The expression of AREs corresponding to the two groups of patients.

and HDAC7 showed immense differences in expression between the groups (**Figure 7C**).

Discussion

By analyzing the relationship between 49 AREs and the prognosis of patients with glioma, we obtained 36 survival-related AREs. After survival analysis combined with ROC analysis, only six AREs (HAT1, TRAM1, BRCA2, HDAC7, HDAC1 and HDAC3) satisfied the AUC value of approximately 0.6 and a *P* value greater than 0.05. However, multivariate Cox analysis revealed that none of the six AREs were independent prognostic factors. We thus combined the 36 survival-related AREs and constructed an optimized risk model containing only 16 AREs through Cox analysis. Survival analysis revealed that the 5-year survival rates of the high and low risk patient groups were 17.43% and 79.80%, respectively. ROC analysis of the model predicted a patient accuracy rate of 86.30%. Risk analysis found that patients in the high-risk group had a short survival time, more deaths and significant differences in the expression of some genes (*HDAC1, HDAC4, SIRT1* and *HDAC7*).

In this study, we identified 16 AREs (**Table 2**) that are closely related to the prognosis of

patients with glioma. A previous study showed that CREBBP is fused with BCOR in infiltrating glioma [19]. KAT2B downregulation inhibits the proliferation and increases apoptosis of medulloblastoma and glioblastoma cells [20]. KAT5 regulates the transcription and invasion of MT1-MMP glioblastoma cells through the NF-κB pathway [21]. KAT6A acetylates lysine 23 of histone H3, which recruits the nuclear receptor binding protein TRIM24 to activate PIK3CA transcription, enhancing PI3K/AKT signaling and tumorigenesis in glioblastoma [22]. A relationship between KAT14 and tumors has not been reported. The remaining 5 HATs (NCOA3, OGA, ATAT1, ATF2, BRCA2) are also closely related to tumor progression [23-28]. The studies of 6 HDACs (HDAC7, HDAC4, HDAC1, HDAC3, SIRT1, SIRT5) also show that they play a vital role in tumor invasion, apoptosis and prognosis [29-36]. The above research shows that AREs play an important role in tumorigenesis and development and also shows the potential value of AREs in the diagnosis and development of new treatment strategies for glioma.

In conclusion, we comprehensively analyzed the relationship between AREs and the prognosis of patients with glioma and constructed a model to predict the independent prognosis of glioma patients. Our research provides a basis for analyzing the mechanism of AREs in glioma and may also provide new molecular targets for the treatment of glioma.

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Disclosure of conflict of interest

None.

Address correspondence to: Chengmin Xuan, Medical Section, Xuzhou Children's Hospital of Xuzhou Medical University, 18 Sudibei Road, Xuzhou 221006, Jiangsu, P. R. China. E-mail: xuanchengmin@126.com; Yong Liu, Department of Neurosurgery, Brain Hospital, Affiliated Hospital of Xuzhou Medical University, 99 West Huaihai Road, Xuzhou 221002, Jiangsu, P. R. China. E-mail: liusui62808@126.com

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Supplementary Table 1. acetylation-related enzymes lists

Histone acetyltransferases (HATs)		Histone deacetylases (HDACs)	
Protein family	Gene	Protein family	Gene
p300_CBP	CREBBP	Class-I	HDAC9
	EP300		HDAC7
GCN5	KAT2A		HDAC4
	NAA40		HDAC6
	KAT2B		HDAC10
	KAT5		HDAC5
ELP3	ELP3		HDAC1
HAT1	HAT1		HDAC8
MYST	KAT6A		HDAC11
	KAT8		HDAC3
	KAT7		HDAC2
	KAT6B	SIR2	SIRT6
GNAT_other family	KAT14		SIRT4
HAT_other family	GTF3C4		SIRT1
	CDY1		SIRT5
	CDY1B		SIRT3
	CDY2A		SIRT2
	CDY2B		
	CDYL		
	NCOA1		
	NCOA2		
	NCOA3		
	RAC3		
	TRAM1		
	OGA		
	ATAT1		
	CLOCK		
	TAF1		
	GTF3C2		
	ATF2		
	BRCA2		
	NAA10		