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Diffusion kurtosis imaging combined with molecular markers as a comprehensive approach to predict overall survival in patients with gliomas

Xuan Wang[a], Fuyan Li[b], Dawei Wang[a], Qingshi Zeng[a,*]

[a] Department of Radiology, Qilu Hospital of Shandong University, Jinan, China
[b] Department of Radiology, Shandong Medical Imaging Research Institute, Jinan, China

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ABSTRACT

Purpose: The purpose of this study was to explore the usefulness of diffusion kurtosis imaging (DKI) and molecular markers in predicting the prognosis of glioma patients.

Method: Fifty-one patients with gliomas were examined by conventional MRI and DKI at 3.0 T before operation. The mean kurtosis (MK), mean diffusivity (MD), axial kurtosis (AK), and radial kurtosis (RK) values of tumors were measured and normalized to the contralateral normal-appearing white matter. The molecular markers of gliomas, including isocitrate dehydrogenase-1 (IDH1), α thalassemia/mental retardation syndrome x-linked (ATRX) and O6-methylguanine-DNA methyltransferase (MGMT), were immunohistochemically stained on the resected tumor tissues. Statistical methods, including the chi-square test, independent sample *t*-test, receiver operating characteristic curve analysis, Kaplan-Meier curve analysis, and Cox regression analysis were performed.

Results: The patients with lower MK, AK, RK, and higher MD values showed significantly better prognosis ($P < 0.001$). Survival time was better in glioma patients with IDH1 mutation ($P < 0.01$), ATRX loss of expression ($P < 0.05$), and MGMT negative expression ($P < 0.05$). However, among the groups of gliomas with IDH1 wild type, ATRX retention and those with MGMT positive expression, the patients with lower MK showed better outcome ($P < 0.01$). Cox multivariate regression analysis demonstrated that MK, RK values and ATRX retention could be used as independent prognostic risk factors, and high MK values had the highest risk for prognosis (HR = 65.288).

Conclusions: Molecular markers and DKI parameters, especially MK values, can be used to effectively evaluate the prognosis of glioma patients.

1. Introduction

Gliomas are the most common intracranial malignant tumors of the central nervous system, and are characterized by high incidence and poor prognosis [1]. A previous study showed that the survival time of patients with high-grade gliomas (HGGs) is significantly shorter than that of patients with low-grade gliomas (LGGs) [2]. In recent years, however, clinical studies have proven that simple pathology classification has limited effects for the direction of glioma treatment and the judgment of prognosis [1,3]. Molecular classification seems to be more accurate in terms of prognosis determination; therefore, the investigation of molecular markers associated with prognosis has recently become a popular research topic.The recently updated World Health Organization classification of tumors of the central nervous system (2016 CNS WHO) have joined genotyping on the basis of traditional histology [4]. The current common molecular markers of gliomas associated with prognosis include isocitrate dehydrogenase-1 (IDH1), O6-methylguanine-DNA methyltransferase (MGMT), and alpha thalassemia /mental retardation syndrome x-linked(ATRX) [5–7], etc.

However, the determination of the pathological grade and molecular classification are invasive for patients, and are unsuitable for post-treatment monitoring of potential tumor recurrence, for follow-up of patients with suspected low-grade glioma or those not being eligible for surgery. The non-invasive analysis of gliomas may therefore contribute to the evaluation of patient prognosis.

Diffusion kurtosis imaging (DKI), an advanced MR diffusion imaging method, can non-invasively reveal the microstructural characteristics and microscopic dynamics of the tumor via its parameter changes [8]; the parameters include mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK). Additionally, diffusion tensor parameters such as

* Corresponding author at: Department of Radiology, Qilu Hospital of Shandong University, 107 Wenhuaxi Road, Jinan, 250012, Shandong Province, China.
E-mail address: zengqingshi@sina.com (Q. Zeng).

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Table 1
Some population information based on the grade of the tumors.

Grade	Age (Years)	Survival time (Months)	Sex (M/F)
LGGs	40 ± 17	25 ± 19	11/8
HGGs	53 ± 11	12 ± 9	20/12

LGGs, low grade gliomas; HGGs, high grade gliomas.

mean diffusion (MD) and fractional anisotropy (FA) can be obtained simultaneously. Compared with traditional diffusion imaging, DKI extends the DTI model and enables to evaluate how much the distribution of the diffusion displacements of water molecules deviates from a Gaussian function [9], and has fairly higher sensitivity and specificity in the evaluation of the heterogeneity of tumors [10]. However, DKI in combination with molecular markers as a comprehensive approach to predict survival in patients with gliomas has been rarely reported [5]. Thus, the purposes of this study were to (1) explore the relationship between DKI parameters and different molecular subtypes of gliomas; (2) further evaluate the feasibility of molecular markers combined with DKI parameters in predicting the prognosis of glioma patients.

2. Materials and methods

2.1. Patients

A total of 54 patients with gliomas (34 males and 20 females, aged 10–69 years with an average age of 47 years old) were enrolled in this study from June 2014 to December 2018. Three patients who withdrew at the time of follow-up were excluded.

After MR examinations, surgical removal was undertaken in all patients. According to the WHO classification of gliomas, 19 cases were LGGs and 32 cases were HGGs. The population characteristics base on the tumor grade was shown in Table 1. All patients were followed up to investigate the overall survival time from the date of surgery to the date of death or the end of follow-up. The overall survival time was between 3 and 53.5 months (the mean time ± standard deviation, 16.7 ± 14.7 months), and the shortest follow-up time for the patients who were still alive was 6.5 months. This study was approved by the ethics committee of our hospital.

2.2. MR imaging methods

All patients were examined with a 3.0-T MR imager (MagnetomVerio, Siemens, Germany). DKI data was acquired in an ep2d_diff ; sequence by the following protocol: an axial plane with six *b* values (0, 500, 1000, 1500, 2000, and 2500s/mm^2), with every *b* value encoded with 30 diffusion directions; field of view = 256 × 256 mm; matrix = 128 × 128; section number = 15; section thickness = 4 mm; TE = 109 ms; TR = 3000 ms. All patients also received routine MR imaging including transverse T2-weighted turbo spin-echo imaging (T2WI) (TR/TE = 4000/93; field of view = 220 × 184 mm; matrix = 256 × 256; 20 sections; section thickness = 5 mm) and contrast-enhanced T1WI (CE–T1WI) sequences (TR/TE = 19/4.92; field of view = 250 × 170 mm; matrix = 256 × 256; 20 sections; slice thickness = 5 mm). The total acquisition time for this protocol was 15 min and 17 s.

2.3. Image processing and data analysis

Diffusional Kurtosis Estimator software (http://www.ninc.org/projects/dke) was used to post-process the DKI images to obtain the maps of MK, AK, RK, MD, and FA [11]. Before drawing the regions of interest (ROIs), the contrast-enhanced 3D T1-FLASH and T2-FSE images were co-registered and resliced to the DKI metric maps by running modules developed in-house in SPM 8 software (http://www.fil.ion.ucl.ac.uk/spm/software/) and MATLAB 8.2 ((Mathworks, Natick, MA, USA, Natick, MA, USA) [12,13]. This ensured that the locations of the images were the same after the ROIs were copied from the CE-T1WI or T2WI to all DKI parameter maps. Then, MRIcro software (http://www.nitric.org/projects/mricron) was applied to draw the ROIs at the tumor centers. For the HGGs, the CE-T1WI was used as a reference, and regions with obvious enhancement of tumors were selected. For the LGGs that were not enhanced, the ROIs were defined in areas with an increased T2-signal on T2WI. Necrosis, hemorrhage, and calcification should be avoided during the course of drawing. The ROIs were copied from the CE-T1WI or T2WI to all DKI parameter maps. For the contralateral normal-appearing white matter (NAWMc), the ROIs were located in the white matter of the contralateral cerebral hemisphere that was symmetric with the lesion location. Finally, MRIcro software was used to measure the MD, MK, AK, RK, and FA values of the ROIs. To reduce the differences caused by the ages and sexes of patients [8,10], all DKI parameters were standardized as the final research metrics as follows: normalized MK = MK (tumor center)/MK (NAWMc). The other normalized metrics (normalized MD, AK, RK, and FA) were calculated in the same manner, and are herein abbreviated as N-MK, N-MD, N-AK, N-RK, and N-FA. An example of plotting the ROIs in gliomas is presented in Fig. 1.

2.4. Pathology and immunohistochemistry

All specimens were fixed with 10 % formaldehyde, embedded with paraffin tissue, sliced continuously into 3-μm thickness, and were

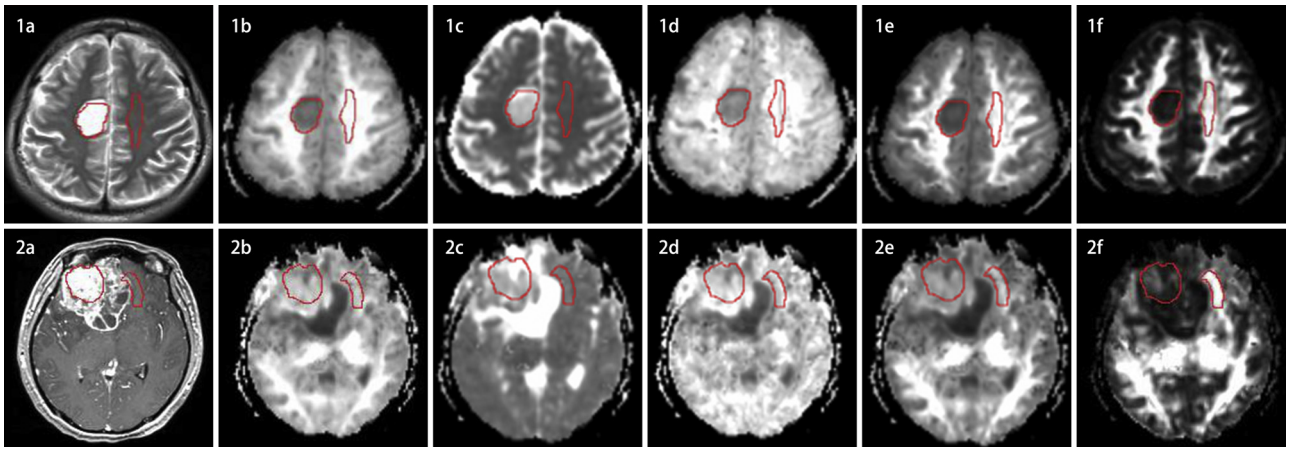

Fig. 1. ROIs on MR images in patients with grade II gliomas and grade IV gliomas. The ROIs were copied from the T2WI (1a) or CE-T1WI (2a) to mean diffusivity map (b), mean kurtosis map (c), axial kurtosis map (d), radial kurtosis map (e) and fractional anisotropy map (f).

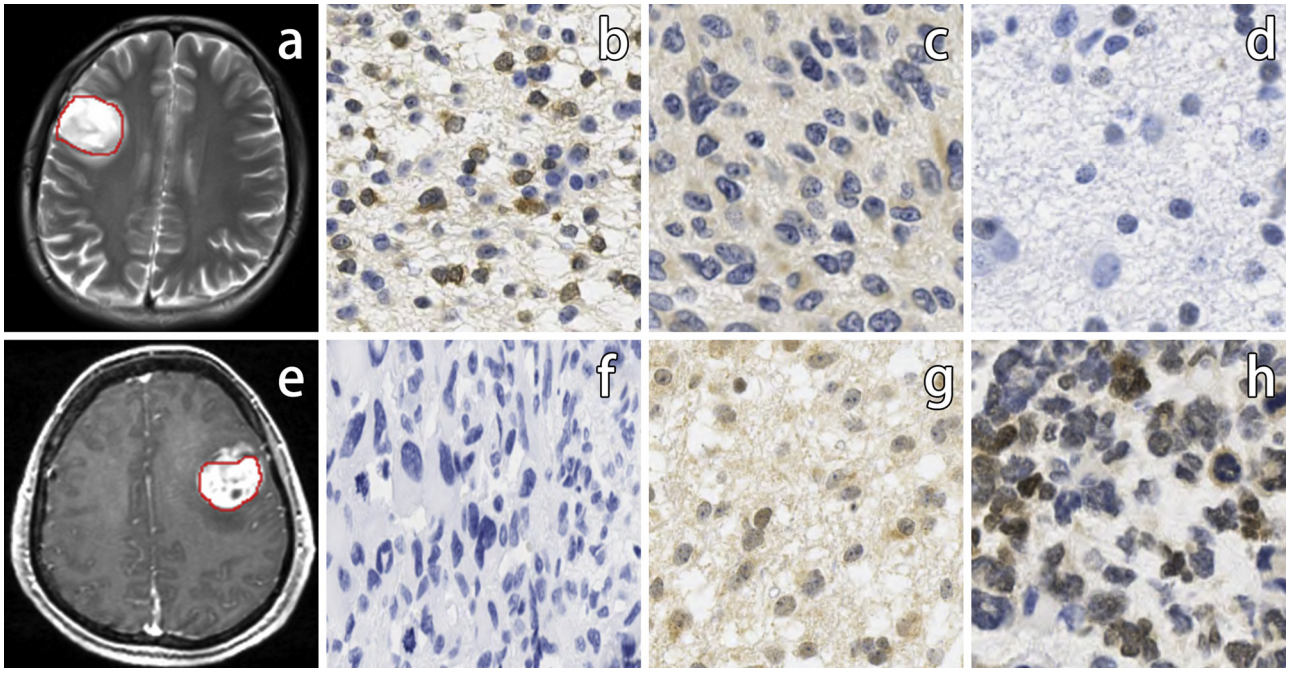

Fig. 2. ROIs and results of immunohistochemistry from two patients with grade II gliomas (a-d) and grade IV gliomas (e-h), respectively. Immunohistochemistry indicators from left to right were IDH-1 mutation (b)/wild type (f); ATRX loss(c)/expression (g); MGMT negative expression (d)/positive expression (h).

Table 2
Relationship between DKI parameters and different expression status of molecular markers (The significant differences between groups were corrected by False Discovery Rate (FDR)).

Variable	N-MK	N-MD	N-AK	N-RK	N-FA
IDH-1					
IDH1 wild type (n = 34)	0.68 ± 0.16	1.53 ± 0.27	0.8 ± 0.16	0.57 ± 0.13	0.39 ± 0.08
IDH1 mutation (n = 17)	0.55 ± 0.09	1.69 ± 0.13	0.67 ± 0.08	0.50 ± 0.07	0.4 ± 0.07
adjusted P	0.000**	0.033*	0.000**	0.075*	0.968
ATRX					
ATRX loss (n = 19)	0.60 ± 0.14	1.58 ± 0.21	0.73 ± 0.12	0.52 ± 0.11	0.38 ± 0.07
ATRX retention (n = 32)	0.66 ± 0.15	1.56 ± 0.26	0.77 ± 0.13	0.57 ± 0.13	0.40 ± 0.08
adjusted P	0.420	0.850	0.520	0.390	0.520
MGMT					
negative (n = 29)	0.63 ± 0.15	1.60 ± 0.28	0.76 ± 0.16	0.54 ± 0.12	0.39 ± 0.08
positive (n = 22)	0.65 ± 0.15	1.52 ± 0.17	0.75 ± 0.15	0.56 ± 0.13	0.40 ± 0.07
adjusted P	0.693	0.520	0.968	0.693	0.850

IDH-1, isocitrate dehy-drogenase-1; ATRX, alpha-thalassemia/mental retardation syndrome X-linked; MGMT, O6-methylguanine-DNA methyltransferase; MK, mean kurtosis; MD, mean diffusivity; AK, axial kurtosis; RK, radial kurtosis; FA, fractional anisotropy.
* $P < 0.05$.
** $P < 0.01$.

Table 3
The normalized DKI Parameter Values to evaluate the prognosis of gliomas.

Diffusion Parameter	AUC	P value	Optimal Threshold	Sensitivity (%)	Specificity (%)
N-MK	0.826	0.000**	0.585	0.955	0.724
N-MD	0.730	0.006**	1.591	0.586	0.864
N-RK	0.715	0.009**	0.579	0.591	0.759
N-AK	0.713	0.010*	0.850	0.455	0.897
N-FA	0.560	0.464	0.405	0.591	0.586

AUC, the area under receiver operating characteristic curve.
* $P < 0.05$.
** $P < 0.01$.

immunohistochemically stained with streptomycin antibiotic protein-peroxidase (S-P) method. An Olympus Microfire Camera was used to detect the tumor-intensive areas and observe three visual fields at 400 magnification, as shown in Fig. 2. The positive expression rate was then analyzed with Image-Pro Plus 5.0 analysis software. The IDH1 mutation expressed as brown granules in the cytoplasm and more than 10 % positive cells. ATRX retention expressed as brown granules in the nucleus and more than 10 % positive cells [14]. The positive staining of MGMT was expressed as brown granules in the nucleus and more than 10 % positive cells.

2.5. Statistical analysis

All data were analyzed with SPSS statistical software (version 20.0, IBM Corp, Armonk, NY, USA). The differences between DKI parameters of the LGGs and HGGs were compared by the independent sample *t*-test. The chi-square test was used to compare the different expression status of IDH1, ATRX, and MGMT between LGGs and HGGs. The independent sample *t*-test was also used to analyze the relationship between the DKI

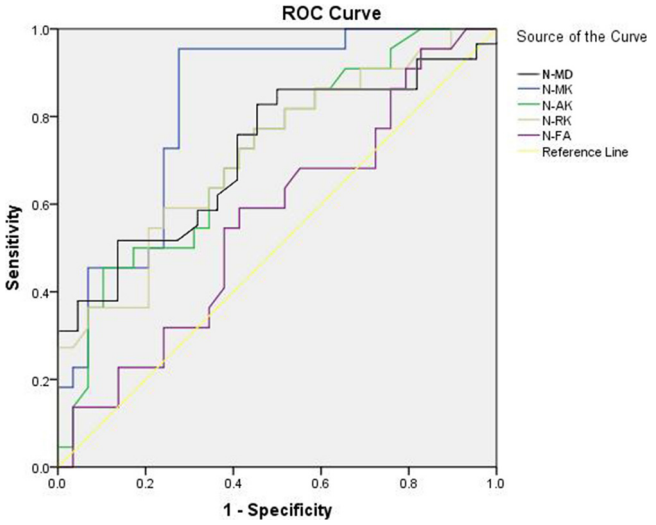

Fig. 3. Receiver operating characteristic curves for normalized mean diffusivity (MD), mean kurtosis (MK), axial kurtosis (AK), radial kurtosis (RK), fractional anisotropy (FA) to evaluate the glioma prognosis. Normalized MK exhibited the biggest area under the curve (0.826) in predicting the prognosis.

parameters and molecular subtypes of gliomas. The receiver operating characteristic curve (ROC) and the area under the ROC (AUC) were used to explore the usefulness of the DKI parameters in evaluating the prognosis of gliomas. The Kaplan-Meier survival curves were obtained with the optimal diagnostic threshold as a demarcation point. Univariate and multivariate Cox proportional hazards models were used to analyze the impact of the investigated factors on prognosis, and the hazard ratio (HR) were obtained. The results of the multiple testing were corrected by the false discovery rate (FDR), and $P < 0.05$ was considered to be statistically significant in all the tests.

3. Results

3.1. DKI parameters and the expression of molecular markers in high-grade and low-grade gliomas

The values of the DKI parameters in the HGGs and LGGs were exhibited in Table 1 in Supplementary files. Compared with LGGs, N-MK, N-AK and N-RK values in HGGs were significantly higher ($P < 0.001$), whereas the N-MD values were lower ($P < 0.001$). However, there were no significant differences between the N-FA values in HGGs and LGGs ($P > 0.05$).

The expression status of molecular markers in the gliomas of different grades were expressed in Table 2 in Supplementary files. The rate of IDH1 mutation in LGGs was higher than that in HGGs ($P < 0.01$). There were no significant differences in the expression status of ATRX

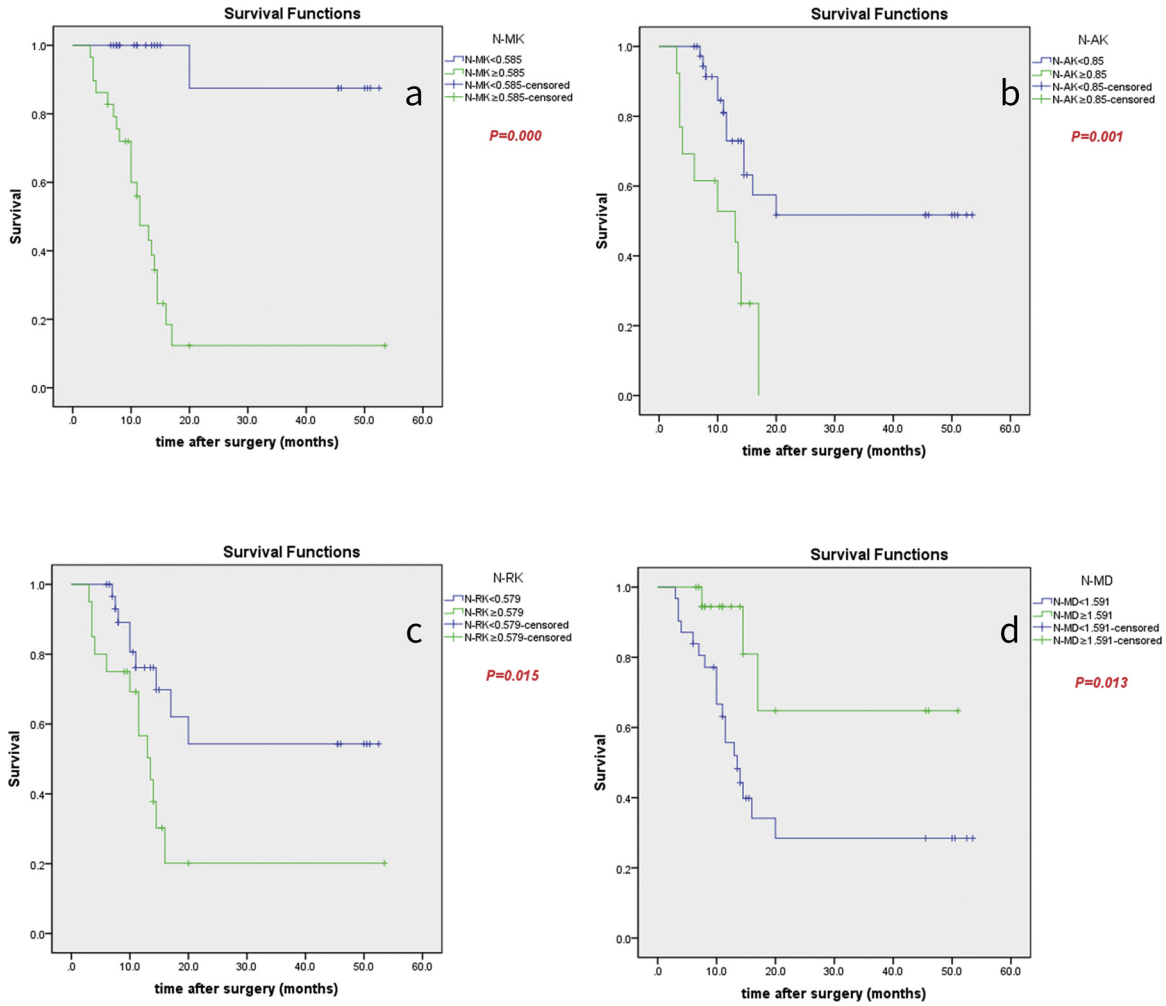

Fig. 4. Kaplan-Meier survival curves for normalized mean kurtosis (MK) (a), axial kurtosis (AK) (b), radial kurtosis (RK) (c) and mean diffusivity (MD) (d) to predict the glioma prognosis. As shown in the figures (a-d), patients with higher N-MK, N-AK, N-RK values and lower N-MD values had poor prognosis.

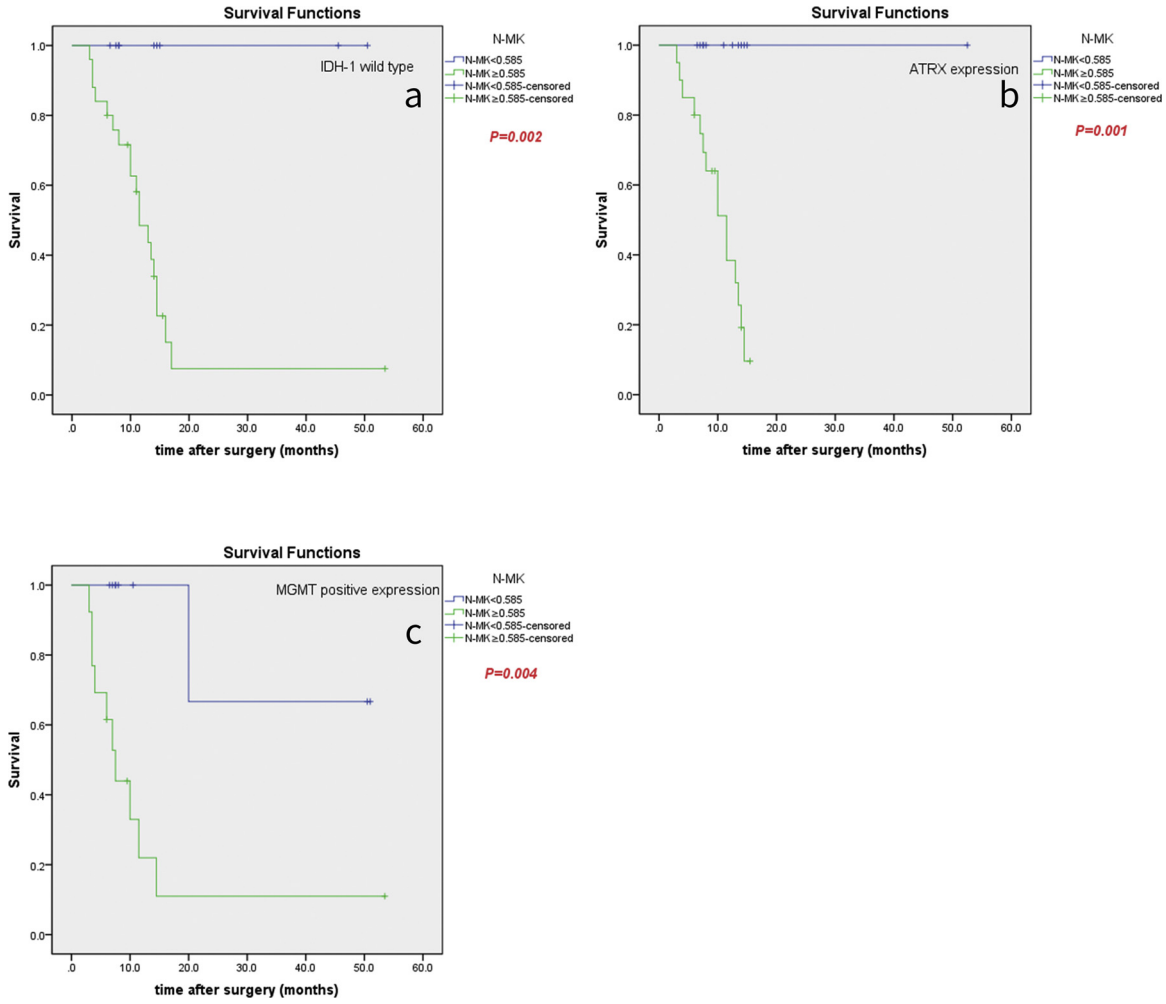

Fig. 5. Kaplan-Meier survival curves for DKI parameters and molecular markers to predict the glioma prognosis. Fig. 5a–c illustrated the patients with lower MK values showed significantly better survival time among the groups of gliomas with IDH1 wild type (a), ATRX expression (b) and MGMT positive expression (c) gliomas.

and MGMT between HGGs and LGGs. In addition, the rate of IDH1 mutation and the ATRX loss of expression in grade II/III gliomas were higher than those in grade I/IV gliomas ($P < 0.01$).

Furthermore, the relationship between DKI parameters and different molecular subtypes of gliomas was shown in Table 2. The N-MK, N-AK valuesc were significantly lower in tumors with IDH1 mutation than in those with IDH1wild type ($P < 0.05$), while the N-MD values were lower in tumors with IDH1 wild type than in those with IDH1mutation ($P < 0.05$). However, no significant relationship was found in the DKI parameters among gliomas with different ATRX and MGMT expression status.

3.2. DKI parameters and molecular markers for the evaluation of glioma prognosis

The optimal diagnostic threshold, sensitivity and specificity of the DKI parameters for evaluating the prognosis of gliomas were exhibited in Table 3, and the corresponding ROC curves were presented in Fig. 3. The Kaplan-Meier survival curves with the optimal threshold as a demarcation point were presented in Fig. 4. The N-MK values had the largest AUC (AUC = 0.826, $P < 0.001$), indicating that the N-MK values had the highest efficiency in evaluating the prognosis of gliomas. The sensitivity and specificity of the N-MK values were 0.955 and 0.724, respectively ($P < 0.001$). The Kaplan-Meier survival curves revealed that patients with high N-MK, N-AK, N-RK values and low N-MD values had poor prognoses ($P < 0.05$ for all).

Gliomas were grouped into two groups via negative or positive immunohistochemistry results, and the Kaplan-Meier survival curves were obtained, as shown in Fig. 1 in Supplementary files. The results revealed that the glioma patients with IDH-1 wild type, ATRX retained expression and MGMT positive expression had poor prognosis (IDH1, $P < 0.01$; ATRX and MGMT, $P < 0.05$). According to the expression status of IDH-1 and ATRX, we further divided the patients into three groups (IDH-1 mutation and ATRX loss of expression; only IDH-1 mutation or only ATRX loss of expression; IDH-1 wild type and ATRX retained expression). The Kaplan-Meier survival curves indicated that the patients with both IDH1 mutation and ATRX loss of expression had the best survival, followed by patients with only IDH1 mutation or only ATRX loss of expression, and the glioma patients with both IDH-1 wild type and ATRX retained expression had the worst prognosis ($P < 0.01$).

As shown in Fig. 5, the Kaplan-Meier survival curves indicated that among the groups of gliomas with IDH1 wild type, ATRX retention and those with MGMT positive expression, the patients with lower MK values showed better outcome ($P < 0.01$).

The Cox regression model was used to analyze the influences of all the factors, mentioned above as well as the age and grade, on the overall survival time of glioma patients. As presented in Table 4, Cox univariate analysis revealed that the DKI parameters (N-MK, N-MD, N-AK, N-RK), the molecular markers (IDH1 and ATRX), and the clinical

Table 4
Univariate Cox proportional hazards model for overall survival in gliomas.

Variable	P value	HR	Hazard Ratio (95 % CI)
Age			
< 46	0.017**	1.0	1.270 – 11.153
≥46		3.764	
WHO grade			
LGGs	0.003**	1.0	2.973 – 171.079
HGGs		22.552	
IDH-1			
IDH1 wild type	0.017*	1.0	0.064 – 0.760
IDH1 mutation		0.220	
MGMT			
negative expression	0.050	1.0	1.001 – 5.471
Positive expression		2.341	
ATRX			
ATRX loss	0.030*	1.0	1.111 – 8.006
ATRX retention		2.982	
MD			
< 1.591	0.024*	4.086	1.208 – 13.825
≥1.591		1.0	
MK			
< 0.585	0.002**	1.0	3.421 – 194.448
≥0.585		25.791	
AK			
< 0.850	0.002**	1.0	1.627 – 9.275
≥0.850		3.884	
RK			
< 0.579	0.020*	1.0	1.172 – 6.550
≥0.579		2.771	

Isocitrate-dehydrogenase1gene-1 (IDH1) mutation status; alpha-thalassemia/mental retardation syndrome X-linked (ATRX) loss of expression; O6-methylguanine -DNA -methyltransferase (MGMT) negative expression; MK, mean kurtosis; MD, mean diffusivity; AK, axial kurtosis; RK, radial kurtosis; FA, fractional anisotropy; LGGs, low grade gliomas; HGGs, high grade gliomas.
* P < 0.05.
** P < 0.01.

Table 5
Multivariate Cox proportional hazards model for overall survival in gliomas.

Variable	P value	HR	Hazard Ratio (95 % CI)
N-RK	0.027*	0.312	0.111 – 0.875
ATRX	0.012*	4.756	1.414 – 15.999
N-MK	0.000**	65.288	7.178 – 593.813

MK, mean kurtosis; RK, radial kurtosis; ATRX, alpha-thalassemia/mental retardation syndrome X-linked; HR, hazard ratio.
* P < 0.05.
** P < 0.01.

indicators (age and grade) all influenced the prognosis ($P < 0.05$). As presented in Table 5, Cox multivariate regression analysis was then used to analyze the factors with statistical differences in univariate analysis, and indicated that high MK values ($P < 0.001$, HR = 65.288), high RK values ($P = 0.027$, HR = 0.312) and ATRX retained expression ($P = 0.012$, HR = 4.756) were significantly correlated with shortened overall survival time, and they could be used as independent prognostic risk factors for gliomas. Furthermore, high MK values were found to have the worst effect on prognosis.

4. Discussion

In the past two decades, large-scale genomic and epigenetic studies have greatly deepened the acknowledgement of the molecular typing of gliomas, making it possible to use molecular markers to evaluate prognosis [1,4,15,16]. In addition, DKI, a new MR imaging method that can reflect the complexity and inhomogeneity of microenvironment of the tissue [8–10], can also be used to non-invasively assess prognosis. Consequently, in this study, the expression status of molecular markers were detected in combination with DKI parameters to provide a new idea for comprehensively evaluating the prognosis of gliomas. Our results revealed that the glioma patients with high MK, AK, RK values and low MD values, as well as the glioma patients with IDH1 wild type, ATRX loss of expression, and MGMT negative expression, had poor prognosis. Furthermore, MK, RK values and ATRX retention could be used as independent prognostic risk factors for gliomas. More importantly, high MK values were found to have the worst effect on prognosis (HR = 65.288).

IDH-1 is one of the key enzymes in the tricarboxylic acid cycle of eukaryotic organisms. It provides nicotinamide adenine dinucleotide phosphate (NADPH) and alpha-ketoglutarate (α-KG) [17]. ATRX is a very important helicase in chromosome remodeling. To improve the abilities of cell proliferation and survival, glioma cells maintain the alternative lengthening of telomeres (ALT) phenotype [18] by ATRX. We found that IDH-1 mutation and ATRX loss of expression mainly occurred in grade II/III diffuse astrocytomas, whereas they rarely occurred in primary glioblastomas, which was consistent with previous study results [19]. Furthermore, the rate of IDH1 mutation in LGGs was higher than that in HGGs. According to the Kaplan-Meier survival curves, it was found that IDH1 mutant glioma patients had better prognosis than those with IDH1 wild-type gliomas, which was consistent with the results of an existing study [19]. The reasons for this may be because there are two important modes of energy supply in glioma cells; one is the NAHPT pathway, and the other is the IDH1 pathway. After the mutation of IDH1, one of the energy-supplying pathways is blocked; this can result in the inertia of cells in a low-energy state, and their growth is relatively inactive. In addition, after IDH-1 mutation, NADPH decreases and makes cells more susceptible to external oxidative erosion, which improves the sensitivity of patients to radiotherapy and chemotherapy, and therefore prolongs the overall survival time of patients [20]. According to the Kaplan-Meier survival curves, ATRX loss of expression was also found to be a favorable prognostic factor for gliomas in the present study. The reason for this may be that ATRX loss of expression can lead to ALT disruption, which eventually leads to chromosome rupture and tumor cell death [21].

Almost all diffuse gliomas with IDH-1 mutation also have ATRX mutation. In other words, ATRX protein loss occurs mostly in IDH1 mutant gliomas, and rarely in IDH1 wild-type gliomas. Additionally, in IDH-1 mutant gliomas, ATRX loss of expression can support the diagnosis of astrocytoma [14]. Therefore, in this study, IDH1 and ATRX protein expression were further divided into three subgroups. The results showed that the glioma patients with both IDH-1 mutation and ATRX loss of expression had better prognosis [3] than those only with IDH-1 mutation or only with ATRX loss of expression. The prognosis of glioma patients with both IDH1 wild type and ATRX retention was the worst. These results suggested that IDH1 combined with ATRX could be used to more accurately evaluate the prognosis of glioma patients. To find a relatively better prognosis, the molecular markers was combined with MK values to be studied. The results demonstrated that patients with lower MK showed significantly better overall survival time among the groups of gliomas with IDH1 wild type and ATRX expression, which was partially consistent with the results of Hempel et al. [5]. MGMT is a ubiquitous DNA repair protein that can transfer the alkyl of O6-alkylguanine at the O6 site, which is also the main site of alkylating agents. Therefore, MGMT can repair DNA damage, mutagenicity, and cytotoxicity caused by alkylating agents, which is the main reason for drug resistance of tumor cells to chemotherapeutic drugs, especially alkylating agents. A previous study found that the expression of the MGMT protein in gliomas was related to the overall survival time of patients,

and gliomas with negative expressions of MGMT were sensitive to chemotherapeutic drugs [22]. Therefore, MGMT could be used as an efficient molecular marker to evaluate chemotherapeutic sensitivity and prognosis. Our results showed that the patients had significantly longer survival time among gliomas with MGMT negative expression.

The data in our study demonstrated that the DKI parameters and molecular marker subtypes had important significances in predicting prognosis of glioma patients. We found that the overall survival time of patients with low MK values and high MD values was significantly improved; the result was consistent with previous studies [5,8]. And our study further revealed that patients with low N-AK and N-RK values had better prognosis, and that N-MK values had the highest diagnostic efficiency in evaluating the prognosis of glioma patients. The prognostic values of DKI parameters reveal that the overall survival may be related to the complexity and heterogeneity of the tumor microenvironment [5]. It was also found that the N-MK, N-AK values were lower in tumors with IDH1 mutation than in those with IDH1wild type ($P < 0.05$), while the N-MD values were lower in tumors with IDH1 wild type than in those with IDH1 mutation ($P < 0.05$). These results suggested that IDH-1 wild-type gliomas exhibit the active proliferation of tumor cells, obvious cell heterogeneity, extensive vascular proliferation, and more hemorrhage and necrosis, which results in water molecules a higher degree of deviation from the Gaussian distribution and a slower diffusion rate. On the contrary, IDH-1 mutant gliomas have lower cell density and more uniform cell structure [6,23,24].

Furthermore, to explore the comprehensive influences of all factors on the prognosis of gliomas, the DKI parameters, molecular markers, and clinical indicators were all included in the Cox regression analysis. Univariate regression analysis revealed that the grade, age, N-MK, N-AK, N-RK, and N-MD values, IDH1, and ATRX were all important factors that affect prognosis. Multivariate regression demonstrated that N-MK, N-RK, and ATRX could independently predict the prognosis. Moreover, the Cox model can quantify the death risk, and it was found that MK had the highest hazard ratio (HR = 65.288). Previous studies have found that IDH-1 mutation and pathological grading are independent prognostic factors in gliomas [25,26]; however, in the present study, the gliomas with high MK values had the worst prognosis. This can be explained from a few aspects. First, as a non-Gaussian diffusion imaging technique, DKI is better than conventional DWI and DTI in providing information about changes in the glioma microstructure [11,12], and high MK values reflect more complex cell structure and higher cell density [9,10,27]. In addition, the N-MK values are closely related to the IDH-1 expression status and pathological grading [5,6,8]. Additionally, there are currently some limitations of molecular markers in the evaluation of prognosis. First, it is impossible for inspectors to take tissue samples frequently, and thus the biopsy method cannot be used to monitor the changes of the primary tumor over time. Secondly, different antibodies, different detection methods, and different detection personnel can impact the results of molecular markers [1]. Therefore, the MK values, as a quantitative imaging biomarker, may be a clinically practical parameter for predicting prognosis of glioma patients.

5. Conclusion

Molecular markers and DKI parameters were found to be important for the evaluation of the prognosis of gliomas. The N-MK, N-RK values and ATRX expression status can also be used as independent prognostic factors of gliomas. More importantly, the glioma patients with high MK values had the worst prognosis.

CRediT authorship contribution statement

Xuan Wang: Writing - original draft, Data curation. **Fuyan Li:** Formal analysis, Methodology. **Dawei Wang:** Software. **Qingshi Zeng:** Funding acquisition, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2020.108985.

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