

Synthetic MRI for Evaluation of Brain Gliomas Grade and Tumor Proliferative Activity: A Retrospective Study

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Research Article

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Abstract

PURPOSE

The evaluation of gliomas grade and proliferation contribute to improve prognosis. We explored the clinical value of synthetic MRI in evaluating quantitatively gliomas grade and predicting tumor proliferative activity.

METHODS

Forty-six patients with histopathologically proven gliomas were included in this study and underwent MAGnetic resonance Image Compilation within 1 week before surgery. T1 values pre- and post-contrast agent (T1-pre, T1-Gd) and T2 values pre-contrast agent (T2-pre) were measured in tumor solid parts and normal white matter of contralateral mirror. T1 and T2 values were compared with gliomas grade and expression of proliferation marker Ki-67. Receiver operating characteristic analysis was performed to assess the diagnostic performance of each metric.

RESULTS

The values of T1-pre, $\Delta T1[(T1\text{-pre}) - (T1\text{-Gd})]$ and Ki-67 labeling index (Ki-67 LI) were significantly higher in the group of high-grade gliomas (HGGs, $n = 26$) compared with the group of low-grade gliomas (LGGs, $n = 20$), whereas T1-Gd and the ratio of T1-Gd (rT1-Gd, tumor-to-normal ratio) values were significantly lower in the group of HGGs compared with the group of LGGs. Receiver operating characteristic analysis curves showed that $\Delta T1$ values had the highest diagnostic value (sensitivity: 96.20%, specificity: 60.00%) for gliomas grade, and the optimal cut-off value was 277.88ms. T1-pre ($r_s=0.47$, $P = 0.001$) and $\Delta T1$ ($r_s=0.56$, $P=0.001$) values were positively correlated with Ki-67 LI. T1-Gd ($r_s=-0.42$, $P = 0.004$) and rT1-Gd ($r_s=-0.40$, $P = 0.007$) values were negatively correlated with Ki-67 LI.

CONCLUSIONS

Synthetic MRI is helpful to distinguish HGGs from LGGs and predict the tumor proliferative activity.

Introduction

Gliomas are the most common primary neoplasms of intracranial tumor, which can be divided into grades I, II (low-grade gliomas-LGGs) and grades III, IV (high-grade gliomas-HGGs)[1]. The accurate pre-surgical diagnosis of gliomas grade in the clinical contributed to evaluate the tumor malignancy, to make the individualized treatment program and to improve the prognosis[2].The cellular proliferative activity of tumor led to aggressiveness and progression in gliomas. In addition, the Ki-67 labeling index (Ki-67

LI), as an important marker of proliferation, showed a significant correlation with tumor grading[3, 4]. The Ki-67 level was also correlated with time to recurrence and postoperative survival in brain gliomas[5]. Therefore, it was very essential for the assessment of tumor grading and proliferation in gliomas.

MRI was the most commonly imaging method for brain gliomas. Conventional MRI was helpful to describe the morphology and location of brain gliomas, especially in relation to important functional anatomical structures[6], and the diagnosis of gliomas grading depended on the experience of radiologist but failed to obtain quantitative information. In recent years, some MRI techniques have been used to predict gliomas grade and tumor proliferative activity. Bai et al[7] reported that ADC was significantly lower in HGGs than LGGs with DWI. Some studies[7-9] found that diffusion kurtosis imaging had great advantages for gliomas grade and tumor proliferative activity compared with DWI and DTI. Fudaba et al[10] reported that MR spectroscopy was useful for evaluating gliomas grade and tumor proliferative activity. Choline/Creatine, Lactate/Creatine were positively correlation with Ki-67 LI ($r=0.461, 0.418$). Jain et al[11] found that relative CBV was associated with Ki-67 LI ($r=0.580$) and could distinguish HGGs from LGGs with dynamic contrast-enhanced perfusion MRI. However, these MRI techniques may have some problems such as long scanning time or complex post-processing.

Synthetic MRI as a novel imaging method reduced the scanning time by reconstructing multiple contrasts from a single scan and allowed the measurement of quantitative values such as T1 and T2 values, thus it may provide more information for quantitative diagnosis of diseases[12, 13]. The overall imaging quality of synthetic MRI was comparable to conventional MRI[13]. At present, synthetic MRI has been used to evaluate brain gliomas. For example, some studies revealed that synthetic MRI with the method of measuring quantitatively T1 values of before and after contrast enhancement contributed to detect the enhancement of peritumoral edema which reflected tumor proliferative activity. The enhancement was not usually visible on conventional MRI[14, 15]. However, the prediction of gliomas grade and tumor proliferation by synthetic MRI has not been reported. The purpose of this study is to explore the clinical value of synthetic MRI in evaluating quantitatively the brain gliomas grade and predicting the tumor proliferative activity.

Materials And Methods

Patient

A retrospective study of 46 patients with histopathologically proven brain gliomas (average age: 52.52 ± 11.29 , males 25 and females 21) from October 2018 to December 2020 was performed. The study was approved by the institutional and all cases signed MRI examination informed consent before scanning. Inclusion criteria were: 1) all patients were examined with synthetic MRI before surgery; 2) postoperative pathology confirmed gliomas and immunohistochemical reports were available; 3) the interval between MRI examination and surgery was less than 1 week. Exclusion criteria were as follows: 1) the brain gliomas were recurrent; 2) patients received treatment related to the tumor before MRI examination; 3) obvious artifacts in the imaging influenced the evaluation of result.

MRI acquisition

All patients underwent MRI examinations on a 3-T MRI scanner (Signa Pioneer 3.0T, GE Healthcare, Chicago, IL) with a 21-channel phase array head coil. MAGnetic resonance image compilation (MAGiC) sequence, as a multiple-dynamic, multiple-echo sequence, is an implementation of synthetic MRI image processing on the GE 3.0 T machine[12, 13, 16]. It can reconstruct multiple contrasts from a single scan and quantify both T1 and T2 relaxation time simultaneously.

MAGiC sequence was performed both before and after the application of contrast agent and the main parameters as follows: TR 4000ms, TE 19ms, slice thickness 5mm, FOV 220mm, matrix 416×288, echo length 16, number of excitation 2, the scanning time was 4min32s. Gadoterate meglumine (20ml/dose, 0.5mol/L) with a dose of 0.1mmol/kg was injected intravenously at the rate of 2ml/s. The contrast enhancement scan of MAGiC was acquired after injection of the contrast agent for 8 min.

Data analysis

The imaging post-processing and ROI selection was performed directly on the main scanner console. T1 mapping and T2 mapping was automatically generated by synthetic MRI sequence. Avoiding the areas of necrosis, haemorrhage, calcification and cyst formation, 3-5 ROIs were respectively draw on the solid parts of the tumor and normal white matter of contralateral mirror (**Figure 1**). The solid parts were defined as the region of obvious and uniform enhancement (in the absence of contrast enhancement, a region of equal or high intensity was selected on T2 FLAIR) on contrast-enhanced synthetic T1WI image. In the ROI, the T1 and T2 values were automatically generated from synthetic MRI before (T1-pre, T2-pre) and after (T1-Gd) the contrast enhancement, and the average values were calculated. $\Delta T1 [(T1\text{-pre}) - (T1\text{-Gd})]$ was used to represent the change of T1 values before and after enhancement. The T1 and T2 values were corrected by calculated the tumor-to-normal ratio, which enabled to obtain the ratio of T1-pre (rT1-pre), the ratio of T2-pre (rT2-pre) and the ratio of T1-Gd (rT1-Gd).

Pathological assessment

Tumor grading was determined by the histopathological assessment of surgical specimens and the classification standard was based on the 2007 WHO classification. The Ki-67 LI was measured by immunohistochemical staining. The brown staining particles in the cell nucleus indicated positive staining for Ki-67. At 200 magnification, choosing five fields of view from the highest density of the stained areas calculated the proportion of positive cells. Ki-67 LI was expressed as a percentage, representing the proliferative activity of tumor cells.

Statistical analysis

All data were analyzed by SPSS 20.0 software (IBM Corp, Armonk, NY). The correlation between all MAGiC metrics and Ki-67 LI was performed by Spearman correlation analysis. The different of MAGiC metrics and Ki-67 LI were analyzed by independent sample t test or Mann-Whitney U test in HGGs and LGGs. $P \leq 0.05$ was considered statistically significant. Receiver operating characteristic analysis was used

to evaluate the diagnostic performance of MAGiC metrics and to obtain the optical cut-off value, sensitivity and specificity and area under curve.

Result

Patient Demographics

According to the 2007 WHO classification[1], all included patients consisted in 26 high-grade gliomas (grade III:17, grade IV:9) and 20 low-grade gliomas (grade I:1, grade II:19). In one case with grade II glioma, only pathological grade result was obtained, but Ki-67 immunohistochemical result was not obtained. Therefore, the patient was excluded in the analysis of the correlation between Ki-67 LI and MAGiC metrics (**Table1**).

Assessment of the efficiency of MAGiC metrics and Ki-67 LI in grading gliomas

The values of T1-pre, $\Delta T1$ and Ki-67 LI were significantly higher in the group of HGGs compared with the group of LGGs, whereas the values of T1-Gd and rT1-Gd were significantly lower in the group of HGGs compared with the group of LGGs ($P \leq 0.05$). The values of rT1-pre, T2-pre and rT2-pre were not statistically significant in the group of HGGs and LGGs (**Table2**). The T1WI, T2WI, T1mapping and T2mapping generated by synthetic MRI were shown in the **figure 2**

Receiver operating characteristic curves showed that the areas under curve for T1-pre, T1-Gd, rT1-Gd, $\Delta T1$ and Ki-67 LI were 0.71, 0.76, 0.76, 0.80 and 0.90, respectively (**Table 3**). Of all the MAGiC metrics, the values of $\Delta T1$ showed the highest diagnostic value for gliomas grading, and the optical cut-off value was 277.88ms, sensitivity was 96.20% and specificity was 60.00%.

Correlation of MAGiC metrics with Ki-67 LI

The correlation between MAGiC metrics and tumor proliferation was studied in 45 patients. Ki-67 LI reflected tumor proliferative activity. The values of T1-pre and $\Delta T1$ (T1-pre: $r_s=0.47$, $P=0.001$; $\Delta T1$: $r_s=0.56$, $P \leq 0.001$) were positively correlated with Ki-67 LI. The values of T1-Gd and rT1-Gd (T1-Gd: $r_s=-0.42$, $P=0.004$; rT1-Gd: $r_s=-0.40$, $P=0.007$) were negatively correlated with Ki-67 LI. In addition, the values of rT1-pre, T2-pre, rT2-pre (rT1-pre: $r_s=0.28$, $P=0.06$; T2-pre: $r_s=0.00$, $P=1.00$; rT2-pre: $r_s=0.01$, $P=0.93$) did not show significant correlation with Ki-67 LI ($P \leq 0.05$). The value of $\Delta T1$ had the highest correlation coefficient.

Discussion

Conventional MRI is one of the most important imaging examine for gliomas, and the grade of gliomas is usually evaluated by several aspects such as contrast enhancement, cortical involvement, lesions margin, tumor infiltration, mass effect, necrosis and so on[17-20]. However, conventional MRI offers only anatomical and morphological characteristic through visual comparison, which cannot obtain

quantitative information. Synthetic MRI which is not affected by the scanner settings, inhomogeneity of the B1-field and coil sensitivity profile provided with additional quantitative information about gliomas grading[14]. We retrospectively explored the diagnostic performance of synthetic MRI in evaluating gliomas grading and tumor proliferative activity.

In general, HGGs are more aggressiveness compared with LGGs. The intratumoral histological heterogeneity in gliomas can reflect tumor grading[21]. Histologically, HGGs are different from LGGs in respect of nuclear anaplasia, mitoses, cellularity, neovascularization, and necrosis[22]. Some MRI techniques have been reported to help quantify the features of gliomas. Conventional MRI after contrast enhancement showed that the destruction of BBB was more severe in HGGs than LGGs[19]. DWI reflected the cellularity of gliomas which HGGs show higher cell density[23]. CBV, as an indicator for the tumor neovascularization, reflected the difference of tumor neovascularity between HGGs and LGGs using perfusion MRI[24]. Furthermore, some studies revealed that the concentration of mobile proteins and peptides were higher in HGGs than LGGs[3, 25]. T1 relaxation time, as a basic parameter of MRI, was mainly influenced by interstitial water content[26, 27]. All of these factors may lead to differences in T1 relaxation time between HGGs and LGGs. In our study, the average values of T1-pre were significantly higher in the group of HGGs compared with the group of LGGs, which may be helpful to distinguish HGGs from LGGs. Whereas, the sensitivity (69.2%) and specificity (65.0%) of grading diagnosis based on T1-pre values alone were relatively low.

The injection of contrast agent can better highlight the destruction of BBB. In general, the areas of contrast enhancement on T1-weighted images represent the breakdown of BBB which is usually associated with higher tumor grading[20, 28]. In addition, the degree of malignancy in gliomas is positively associated with massive angiogenesis that provides nutrients for the growth and metabolism of tumor tissues, and promotes tumor cell division and proliferation[29]. These may lead to different changes in T1 relaxation time after enhancement. Our study showed that T1-Gd, rT1-Gd and $\Delta T1$ differed significantly between the group of HGGs and the group of LGGs ($P < 0.05$) and the group of HGGs had lower T1-Gd, rT1-Gd and higher $\Delta T1$ than the group of LGGs. Similar to our study, Su et al [19] scored tumor according to enhancement quality (1=none, 2=mild/minimal, 3=marked/avid) on conventional MRI and found that enhancement quality was significantly different between HGGs and LGGs and the contrast enhancement was more pronounced in HGGs compared with LGGs. In conventional MRI, contrast-enhanced detection was based on subjective comparison of T1-weighted images before and after enhancement[30]. Synthetic MRI can quantitatively measure the T1 relaxation time before and after enhancement and obtain the $\Delta T1$ which more objectively and accurately describes the degree of enhancement. Therefore, synthetic MRI is more advantageous for gliomas grading. $\Delta T1$ values showed the highest diagnostic value (area under curve: 0.804) for gliomas grading, and the optimal cut-off value was 277.88ms, sensitivity was 96.2% and specificity was 60.0%. In other word, when $\Delta T1 \geq 277.88\text{ms}$, the grading diagnosis tended to favor HGGs. In addition, both the values of T1-Gd and rT1-Gd had relatively high sensitivity (T1-Gd: 88.5%; rT1-Gd: 100%).

Ki-67 LI is positively associated with cellular proliferation and malignancy of tumor[16, 31, 32], which is no exception in gliomas[4]. In our study, we found that the Ki-67 LI was positively correlated with tumor grading, and T1 relaxation time was positively correlated with gliomas grading. Therefore, we speculated that there would be certain differences in T1 relaxation time for gliomas with different proliferative activity.

Olsen et al[33] investigated the relationship between proliferation activity and T1,T2 relaxation time in four human melanoma xenograft lines including A-07,D-12,R-18,U-25, and they found that T1 and T2 relaxation time of high proliferative activity tumor were higher than low proliferative activity tumor. In our study, we found that Ki-67 LI was positively correlated with T1-pre. After injecting the contrast agent, Ki-67 LI was negatively correlated with T1-Gd, rT1-Gd and positively correlated with $\Delta T1$, Chang et al[34] explored the correlation between cell density and MR signal intensity in glioblastoma, and they found that the signal intensity of T1-postcontrast subtraction by subtracting coregistration-normalized T1-precontrast volumes from T1-postcontrast volumes was positively correlated with cell density ($r=0.69$). Therefore, T1 relaxation time is expected to be an imaging indicator to express the proliferative activity for gliomas.

Hattingen et al[35] emphasized the important of T2 relaxation time which allowed to detect tumor progression in glioblastoma much earlier compared with conventional MRI. In our study, we failed to find the clinical value of T2 relaxation time in predicting gliomas grade and tumor proliferative activity. Kern et al[36] found that T2 values were higher in grade III gliomas compared with grade II gliomas, whereas the results were not statistically significant. Therefore, the application of T2 relaxation time in gliomas needs further exploration.

Synthetic MRI is a morphologic MRI that can provide quantitative values of T1 and T2. In our study, T1 relaxation time was helpful to differentiate HGGs and LGGs and to predict tumor proliferative activity. The gold standard for gliomas grade and tumor proliferative activity is based on surgical removal or biopsy, however, due to the tumor heterogeneity, the pathological results can only reflect the grading and proliferative activity of the specimens taken, rather than the whole tumor[8, 22].Therefore,T1 relaxation time, which was associated with gliomas grading and Ki-67 LI, may be useful to provide more information for biopsy ,as well as to determine the range of radiation exposure field for radiotherapy.

However, there are still several limitations to this study. Firstly, the number of patients is relatively small and larger samples sizes are needed to confirm these results in the future. Secondly, the selection of ROI cannot accurately correspond to the sampling of pathological specimens, so that the results may be biased to some extent.

Conclusions

In conclusion, synthetic MRI may provide more information for quantitative diagnosis of gliomas. It was helpful to distinguish high-grade gliomas from low-grade gliomas and to predict the tumor proliferative

activity. In particular, the values of $\Delta T1$ showed the highest diagnostic value for gliomas grading and the highest correlation coefficient for the correlation with Ki-67 LI.

Abbreviations

HGGs= high-grade gliomas; LGGs= low-grade gliomas; Ki-67 LI = Ki-67 labeling index; MAGiC= MAGnetic resonance image compilation;

Declarations

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Author contributions

Jiapei Xie: Data curation (Equal); Formal analysis (Lead); Methodology (Equal); Project administration (Lead); Resources (Equal); Software (Equal); Writing-original draft (Lead)

Weidong Zhang: Data curation (Equal); Methodology (Equal); Resources (Equal); Software (Equal)

Liang Xiao: Conceptualization (Lead); Methodology (Supporting); Supervision (Lead); Writing-review & editing (Lead)

Ethics approval: The study was approved by the institutional.

Consent to participate: All patients signed consent.

Consent for publication: All patients consented to publication.

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Tables

Table 1: The clinical information of included patients

	High-grade gliomas n=26	Low-grade gliomas n=20	P
Gender			0.94
Male	14	11	-
Female	12	9	-
Age	56.54±8.19	47.30±12.77	0.008
Gliomas's grades			
I	0	1	-
II	0	19	-
III	17	0	-
IV	9	0	-

Table2: The mean values or median of MAGiC metrics and Ki-67 LI in HGGs and LGGs

	High-grade gliomas	Low-grade gliomas	P
T1-pre (ms)	1418.13±163.71	1302.36±142.06	0.02
rT1-pre	1.89±0.36	1.77±0.27	0.20
T2-pre (ms)	130.21±25.47	134.06±27.44	0.63
rT2-pre	1.56(1.41,1.96)	1.59(1.39,1.88)	0.91 ^b
T1-Gd (ms)	682.96±179.14	952.91±295.19	0.001
rT1-Gd	0.94±0.23	1.37±0.48	0.001
ΔT1 (ms)	763.05(493.50,979.50)	126.53(70.60,746.44)	0.001 ^b
Ki-67 LI (%)	40.00(10.00,60.00)	5.00(2.00,10.00) ^a	0.001 ^b

T1-pre: T1 value before the contrast enhancement; rT1-pre: the tumor-to-normal ratio of T1-pre; T2-pre: T2 value before the contrast enhancement; rT2-pre: the tumor-to-normal ratio of T2-pre; T1-Gd: T1 value after the contrast enhancement; rT1-Gd: the tumor-to-normal ratio of T1-Gd; ΔT1: (T1-pre) – (T1-Gd), represented the change of T1 value before and after enhancement; Ki-67 LI: Ki-67 labeling index

^aOne patient with grade II glioma without the result of tumor proliferative activity

^bThese metrics were analyzed by Mann-Whitney U test in HGGs and LGGs.

Table3: Receiver operating characteristic curve analysis for differentiation of high-grade gliomas and low-grade gliomas

	cut-off values	Sensitivity (%)	Specificity (%)	area under curve
T1-pre(ms)	1336.90	69.20	65.00	0.71
T1-Gd(ms)	892.07	88.50	65.00	0.76
rT1-Gd	1.42	100.00	50.00	0.76
ΔT1(ms)	277.88	96.20	60.00	0.80
Ki-67 LI (%)	35.00	61.50	100.00	0.90

T1-pre: T1 value before the contrast enhancement; T1-Gd: T1 value after the contrast enhancement; rT1-Gd: the tumor-to-normal ratio of T1-Gd; ΔT1: (T1-pre) – (T1-Gd), represented the change of T1 value before and after enhancement; Ki-67 LI: Ki-67 labeling index

Figures

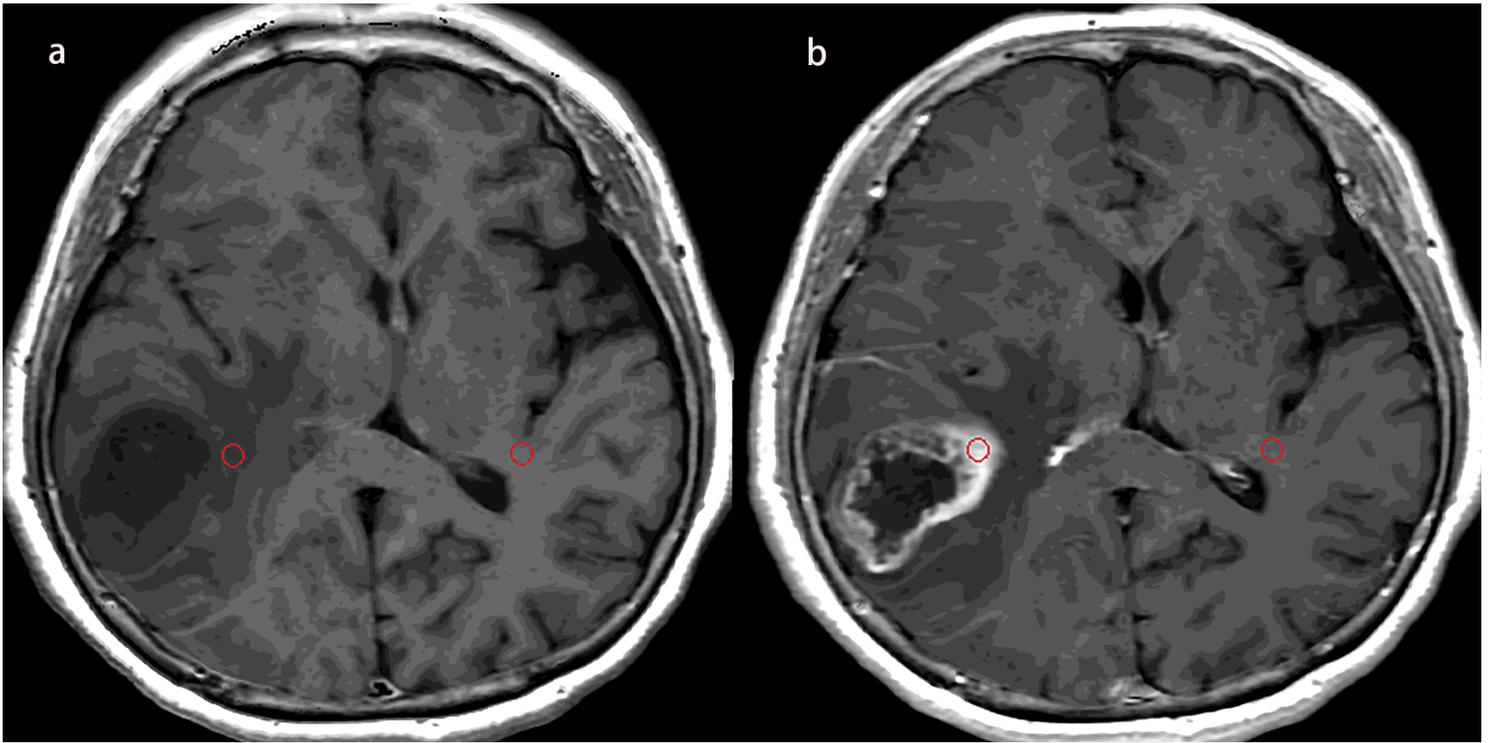


Figure 1

Synthetic MRI in a grade III glioma. A case for ROI was respectively draw on the solid parts of the tumor and normal white matter of the contralateral mirror. a.T1WI; b. T1WI+C

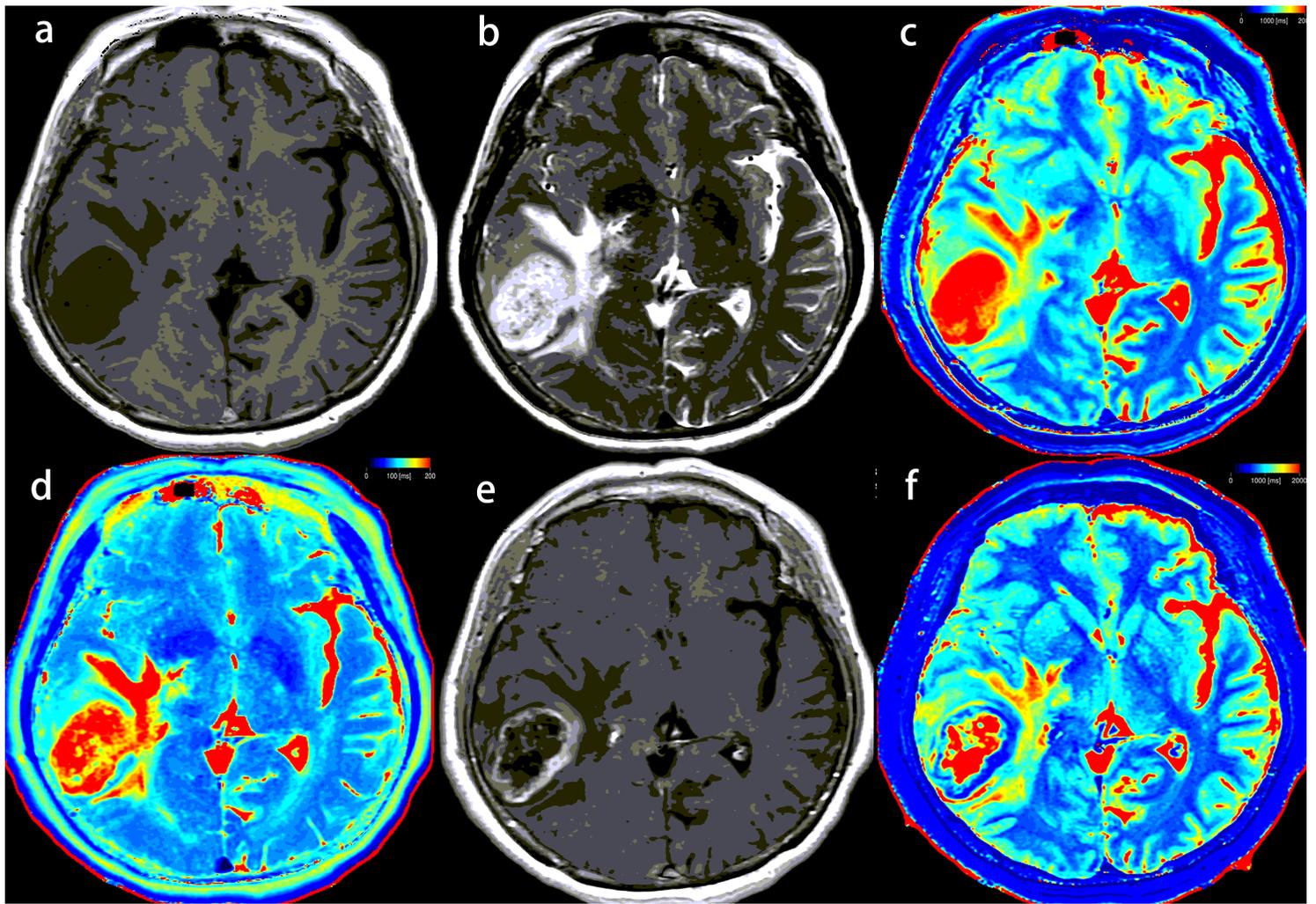


Figure 2

Synthetic MRI in a grade III glioma. a. T1WI; b. T2WI; c. T1 mapping; d. T2 mapping; e. T1WI+C; f. T1 mapping+C

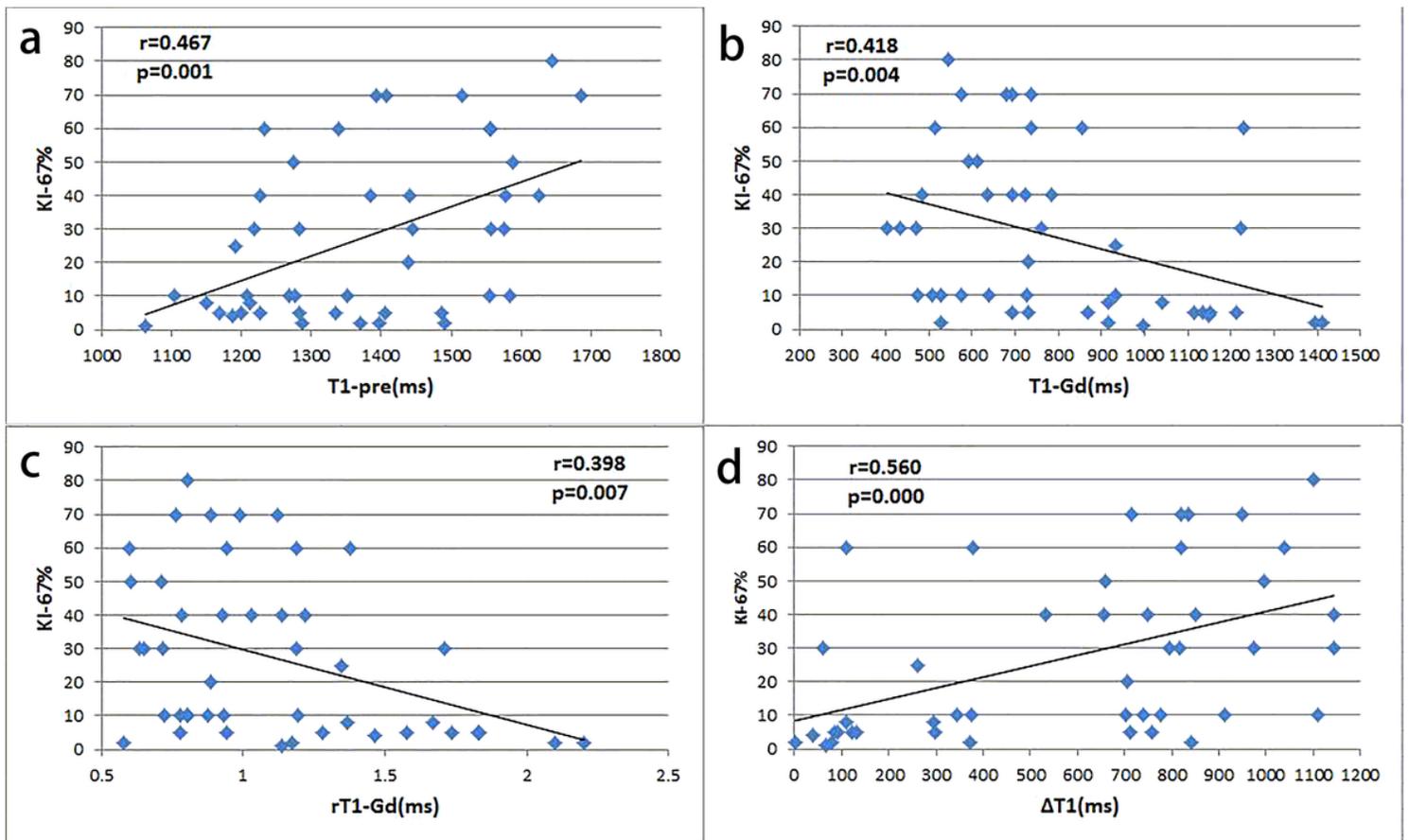


Figure 3

A caption is not available with this version