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Performance of Magnetic Resonance Imaging-based Permeability Indices for Preoperative Glioma Grading

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A B S T R A C T

Introduction: Due to the inherent limitations of histopathology as the gold standard method for glioma grading, in recent years, alternative methods, including methods based on imaging data, have been proposed for better glioma grading. This study aimed to determine the performance of permeability parameters (Ktrans, Kep, Ve, and Vp) quantified using the dynamic contrast-enhanced MRI (DCE-MRI) method for preoperative glioma grading.

Materials & Methods: The radiological data of 31 patients with pathologically confirmed gliomas were retrospectively reviewed. The permeability parameters, including Ktrans, Kep, Ve, and Vp, were quantified using DCE-MRI data. The Mann-Whitney U test was used to assess the significance of differences in these parameters between different grades of glioma. The performance of the parameters for glioma grading was evaluated using receiver operating characteristic (ROC) curve analysis.

Results: The mean age of the patients was 39.2 ± 14.1 years, and 18 of the participants were males (58.06%). Ktrans, Kep, and Vp parameters demonstrated a significant difference between different grades of glioma. The results showed that Ktrans yielded the best grading performance compared to other studied parameters (AUC>71%). Vp, Kep, and Ve parameters ranked next.

Conclusion: DCE-MRI provides valuable quantitative parameters that can reliably differentiate between glioma grades. These noninvasive imaging biomarkers can serve as a powerful complement to the standard histopathological grading system, guiding better treatment planning and preventing unnecessary interventions.

Keywords: Glioma, Neoplasm Grading, Dynamic Contrast-Enhanced Magnetic Resonance Imaging, Permeability, Pharmacokinetics

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Introduction

Gliomas are the most common primary neoplasms of the central nervous system, comprising approximately 80% of malignant brain tumors (1, 2). The World Health Organization (WHO) classifies gliomas into four grades, from I to IV, based on their histopathological features such as cellularity, mitotic activity, vascular proliferation, and necrosis (1). This grading is critical, as it dictates the therapeutic approach and prognosis of the tumor. The 5-year survival rate for glioblastoma (Grade IV) is 6.8%, whereas it is significantly higher for lower-grade tumors (3, 4).

The gold standard method for glioma grading is histopathological analysis of tissue samples obtained through stereotactic biopsy or surgical resection (1). However, this method has inherent limitations due to sampling errors, especially in heterogeneous tumors, which can lead to undergrading and, consequently, suboptimal treatment (5, 6).

Advanced magnetic resonance imaging (MRI) techniques offer a noninvasive approach to assess the pathophysiological characteristics of tumors. Conventional MRI methods, while being the diagnostic modality of choice, have limitations in accurately predicting tumor grade, with reported accuracy between 55% and 83% (7). Dynamic contrast-enhanced MRI (DCE-MRI) is an advanced functional imaging technique that provides quantitative information about tumor microvascularity and permeability. The volume transfer constant (Ktrans), the rate constant (Kep), the extravascular extracellular space volume (Ve), and the plasma volume (Vp) would be quantified using this technique. These parameters reflect the neovascularity and breakdown of the blood-brain barrier, which are hallmarks of higher-grade gliomas (8, 9). Given the importance of accurate preoperative grading for patient management, this study aims to evaluate the performance of permeability parameters quantified based on DCE-MRI (Ktrans, Kep, Ve, and Vp) for glioma grading.

Materials and methods

Study Design

This study was a retrospective, cross-sectional, diagnostic accuracy study designed to investigate the classification performance of DCE-MRI permeability parameters for glioma grading.

Setting and Participants

Patients with suspected brain tumors who were referred to the imaging department of a single tertiary referral center between February 2021 and July 2023 were retrospectively reviewed. A total of 31 patients who met the eligibility criteria were included in the study.

The inclusion criteria were: (a) having undergone preoperative DCE-MR imaging before surgery or any other medical intervention, and (b) having a confirmed histopathological diagnosis of the tumor. Patients were excluded if they did not undergo preoperative DCE-MRI, lacked histopathological results, or did not consent to the use of their data for research purposes.

Sample Size

The sample size was determined based on all eligible patients who were referred to our center during the study period and met the inclusion criteria.

Measurements & Validity and Reliability

Demographic tool

Demographic data, including patient age and sex, were collected from the hospital's electronic medical records. The clinical history and final histopathological reports were also extracted from these records.

DCE-MRI Acquisition and Analysis

All MRI examinations were performed using a 1.5T MRI scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). The imaging protocol included conventional sequences as well as

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a DCE-MRI sequence. Standard sequences consisted of T2-weighted, T1-weighted, and fluid-attenuated inversion recovery (FLAIR) imagings. The DCE-MRI was acquired using a T1-weighted gradient-echo sequence with the following parameters: repetition time (TR)/echo time (TE), 4.5/1.7 ms; flip angle, 12°; slice thickness, 5 mm; field of view (FOV), 240×240 mm²; matrix size, 128×128. After initial baseline acquisitions, the bolus of a gadolinium-based contrast agent (Gadovist) was administered intravenously at a dose of 0.1 mmol/kg, followed by a saline flush, both at an injection rate of 3 ml/s.

Image Analysis and Pharmacokinetic Modeling

Parametric maps were generated by analyzing DCE-MRI data. A region of interest (ROI) was manually drawn by a neuroradiologist with 13 years of experience on the most enhancing part of the tumor, avoiding areas of necrosis and large vessels. The arterial input function (AIF) was derived for each patient by placing a region of interest (ROI) over the middle cerebral artery.

To quantify the permeability parameters, the standard Tofts-Kety model, the most widely accepted model for data analysis of DCE-MRI data (10), was fitted to the data. This model assumes a two-compartment system where the contrast agent can move between the blood plasma and the extravascular extracellular space (EES) but does not enter the intracellular space. The model describes the concentration of the contrast agent in the tissue over time based on the following equation:

$$C_{t(t)} = v_p C_{p(t)} + K^{trans} \int_0^t C_{p(\tau)e}^{-k_{\{ep\}(t-\tau)}} d\tau$$

Where $C_{p(t)}$ is the time- concentration of the contrast agent in the arterial plasma. K^{trans} (the volume transfer constant) measures the leakage of the contrast agent from the plasma into the extravascular extracellular space (EES) and K_{ep} (the rate constant) is the rate of transfer from the EES back to the plasma. V_p is the fractional volume of the blood plasma per unit volume of tissue. The fractional volume of the EES, V_e, was calculated as the ratio of the two primary parameters:

$$v_e = \frac{K^{trans}}{k_{ep}}.$$

The mean values of Ktrans, Kep, V_e, and V_p within the ROI were calculated for each patient.

Histopathological Analysis (Gold Standard)

The histopathological results from surgically resected tumor specimens were considered the gold standard for diagnosis and grading. All specimens were analyzed by an expert neuropathologist according to the World Health Organization (WHO) classification of Central Nervous System Tumors (1).

Statistical and Data Analysis

Statistical analysis was performed using SPSS (version 26.0) and MATLAB (version 2016) software. The Shapiro-Wilk test was used to assess the normality of the data distribution. Since the data were not normally distributed, the non-parametric Mann-Whitney U test was used to compare the DCE-MRI parameters between different grades of glioma. A p-value of < 0.05 was considered statistically significant. The grading performance of parameters for differentiating between different grades of glioma was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC), the optimal threshold values, sensitivity, specificity, and accuracy were calculated for each assessment.

Results

Patient characteristics

This retrospective cross-sectional study included 31 patients with a confirmed histopathological diagnosis of glioma who underwent preoperative DCE-MRI. The study population consisted of 18 males (58.06%) and 13 females (41.94%), with a mean age of 39.2 ± 14.1 years. Based on the WHO classification, 14

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patients were diagnosed with Grade II, 8 with Grade III, and 9 with Grade IV glioma.

Image Analysis and Permeability Maps

DCE-MRI data were analyzed using the Tofts-Katy model, and the permeability maps, including Ktrans, Kep, Ve, and Vp indices, were extracted. The exemplary maps achieved for a 67-year-old man with glioblastoma multiforme (GBM) are shown in Figure 1.

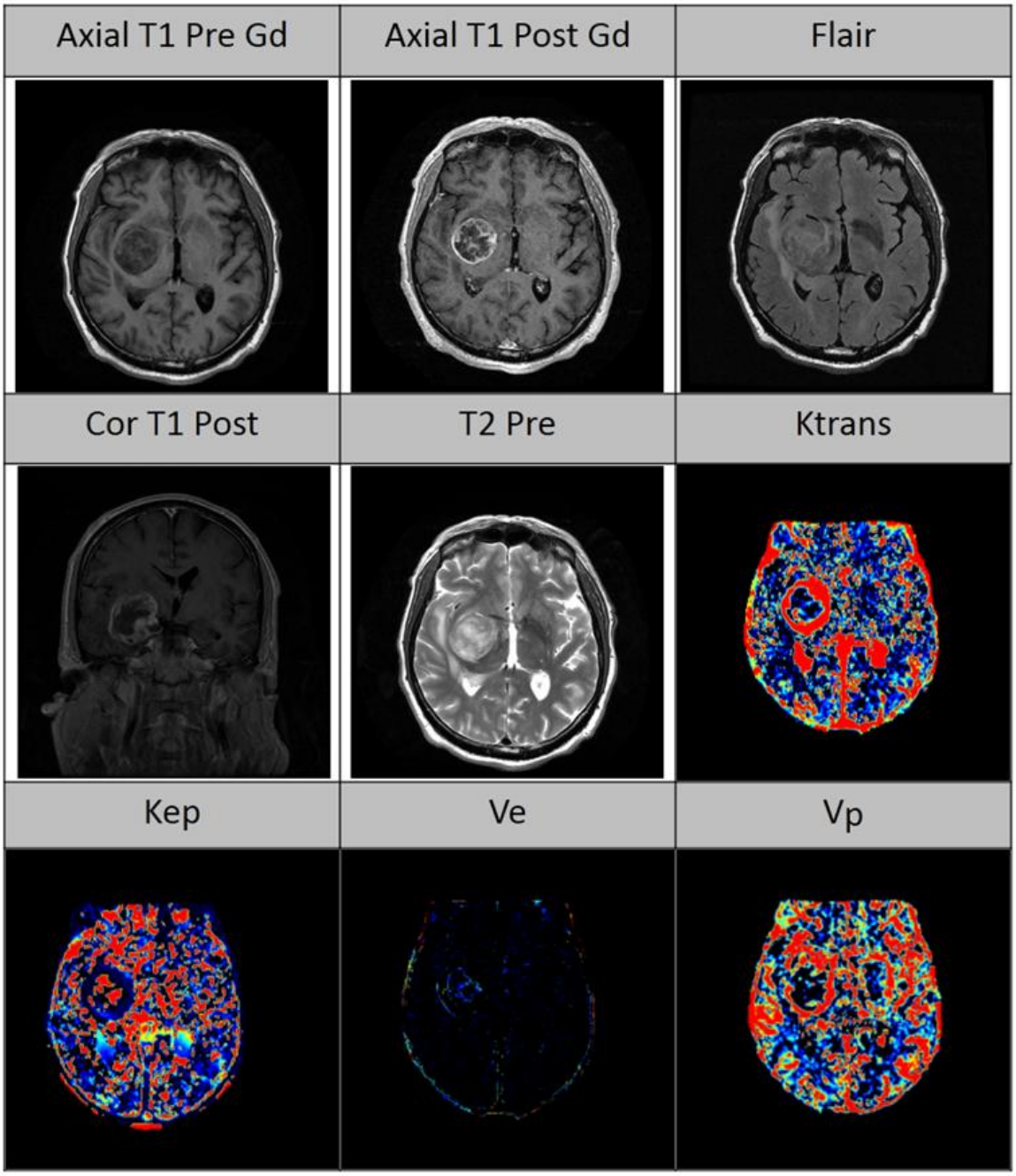

Figure 1. Exemplary maps achieved for a 67-year-old man with left temporal glioblastoma multiforme (GBM). The permeability maps have shown an enhancing lesion in the left temporal lobe.

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Comparison of DCE-MRI parameters in different grades of glioma

Descriptive statistics of permeability parameters for different grades of gliomas are presented in Table 1.

Table 1. Descriptive statistics of permeability parameters for different grades of glioma.

	GII (N=14)	GIII(N=8)	GIV(N=9)
Ktrans(mL/g.min)	0.015±0.012	0.095±0.151	0.598±0.446
Kep(1/min)	0.210±0.174	0.371±0.161	0.749±0.411
Vp(mL/g)	0.044±0.039	0.069±0.053	0.569±0.347
Ve(mL/g)	0.115±0.147	0.299±0.424	0.802±0.283

Data are reported as mean and standard deviation

The results of the non-parametric Mann-Whitney U test for comparison of the permeability indices between different grades of glioma are listed in Table 2. The Mann-Whitney U test revealed that Ktrans, Kep, and Vp values were significantly different between all pairwise comparisons of glioma grades ($p < 0.05$). Ve also showed significant differences between most grades, except for the comparison between Grade II and Grade III gliomas ($p = 0.121$). Generally, all parameters showed an increasing trend with a higher tumor grade.

Table 2. The levels of statistical significance for the permeability indices between different grades of gliomas.

	GII vs. GIII	GII vs. GIV	GIII vs. GIV	LGG vs. HGG
Ktrans(mL/g.min)	0.005	<0.001	0.004	<0.001
Kep(1/min)	0.040	0.002	0.017	0.001
Vp(mL/g)	0.047	<0.001	0.001	<0.001
Ve(mL/g)	0.121	<0.001	0.070	0.001

Classification performance of permeability indices for Glioma Grading

The results of the classification performance of permeability indices to discriminate between different grades of glioma are presented in Table 3. The best thresholds for discriminating between different grades of glioma using the studied parameter are listed in the first column of the table.

Table 3. The accuracy, sensitivity, specificity, PPV, NPV, Kappa coefficient, and area under the ROC curve (AUC) of permeability (Ktrans, Kep, etc.) indices for differentiation between the different grades of gliomas.

		Threshold	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa Coeff	AUC (%)
Ktrans (mL/g.min)	GII vs. GIII	0.028	76.92	70	81.25	70	81.25	0.76	71.06
	GII vs. GIV	0.15	100	100	100	100	100	1	100
	GIII vs. GIV	0.2	84.21	88.89	80	80	88.89	0.83	87.45
	LGG vs. HGG	0.025	82.86	84.21	81.25	84.21	81.25	0.82	82.80
Kep (1/min)	GII vs. GIII	0.23	53.85	70	43.75	43.75	70	0.51	61.42
	GII vs. GIV	0.42	76	77.78	75	63.64	85.71	0.75	86.14
	GIII vs. GIV	0.49	63.16	66.67	60	60	66.67	0.61	74.91

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	LGG vs. HGG	0.29	77.14	78.95	75	78.95	75	0.76	75.93
Vp (mL/g)	GII vs. GIII	0.045	65.38	80	56.25	53.33	81.82	0.63	61.42
	GII vs. GIV	0.16	100	100	100	100	100	1	100
	GIII vs. GIV	0.19	84.21	88.89	80	80	88.89	0.83	100
	LGG vs. HGG	0.065	74.29	73.68	75	77.78	70.59	0.73	75.93
Ve (mL/g)	GII vs. GIII	0.067	57.69	60	56.25	46.15	69.23	0.55	61.42
	GII vs. GIV	0.28	88	88.89	87.5	80	93.33	0.87	90.78
	GIII vs. GIV	0.25	78.95	100	60	69.23	100	0.78	74.91
	LGG vs. HGG	0.15	62.86	68.42	56.25	65	60	0.60	69.05

It must be noted that the results mentioned in Table 3 must be interpreted with caution because the study sample size is small. The ROC curve was plotted for the assessment of the classification performance of each permeability index. The exemplary ROC curves of permeability indices to discriminate high-grade from low-grade glioma are plotted in Figure 2.

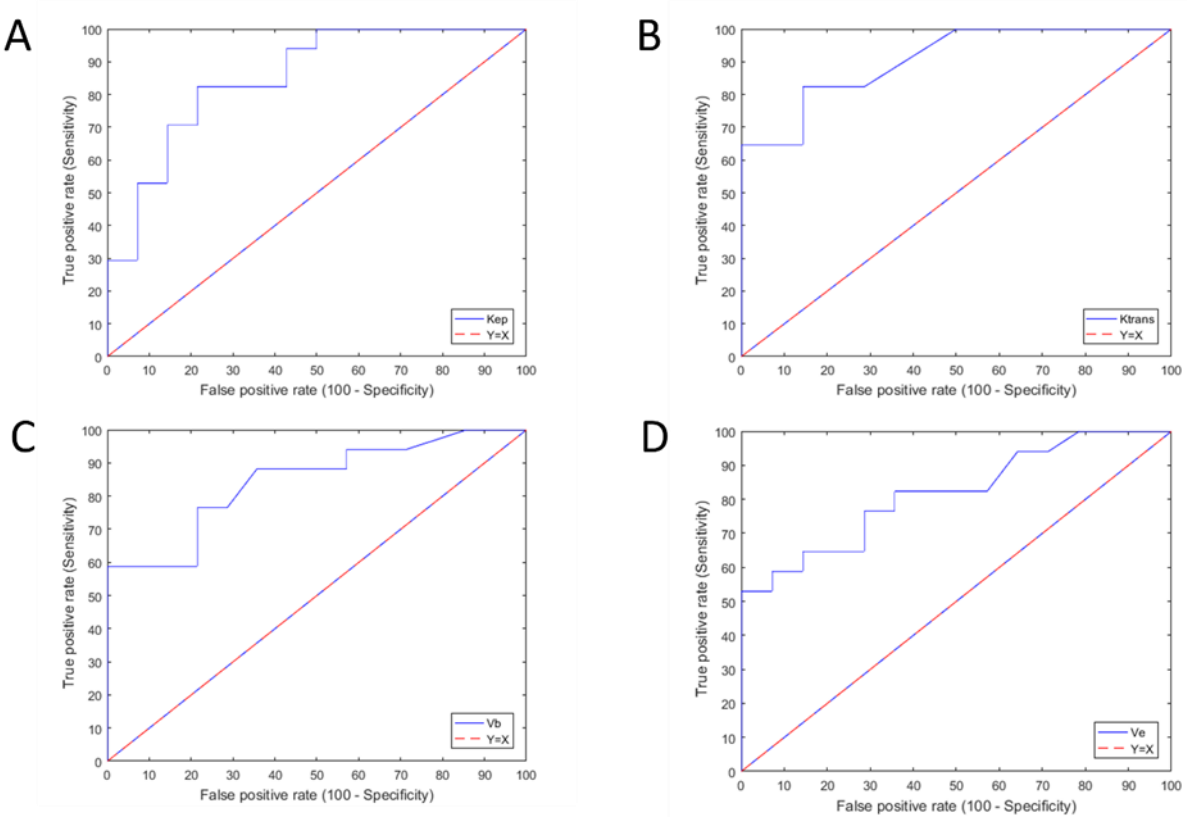

Figure 2. ROC curves of permeability parameters in differentiating high-grade from low-grade glioma. (A) ROC curves of the volume transfer constant (Ktrans), which yielded an area under the curve (AUC) of 0.83; (B) ROC curves of the rate constant (Kep), with an AUC of 0.76; (C) ROC curves of the extravascular extracellular space volume (Ve), with an AUC of 0.69; and (D) ROC curves of the plasma volume (Vp), with an AUC of 0.76. Among the evaluated parameters, Ktrans demonstrated the highest grading performance to discriminate high-grade from low-grade glioma.

Discussion

Grading plays a critical role in the management of cancer patients because the treatment method for tumors is determined based on the tumor grade. Due to the inherent limitations of histopathology as the standard method for glioma grading, in recent years

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alternative methods, including methods based on imaging data, have been proposed for better grading of glioma tumors. In this study, the classification performance of the DCE-MRI method, which is a functional imaging method, is investigated for glioma grading.

The mean values of permeability parameters (Ktrans, Kep, Ve, and Vp) demonstrated an increasing trend with increasing grades of glioma. This increase is due to greater neoangiogenesis in high-grade tumors. Newly formed vessels are immature and have a larger distance between endothelial cells compared to mature vessels, so they have higher permeability to contrast materials. Therefore, permeability parameters increase with increasing tumor grade. There were significant differences for Ktrans, Kep, and Vp indices between different grades of glioma ($P<0.05$). Ve only showed a significant difference between Grade 2 and 4 ($p<0.001$) and LGG and HGG ($p=0.001$). These results showed that permeability parameters can distinguish between different glioma grades.

In the next step, the classification performance of permeability indices was evaluated for glioma grading. The results showed that Ktrans yielded the best grading performance compared to other studied parameters (AUC>0.71). Vp, Kep, and Ve parameters ranked next.

The classification performance of permeability indices for glioma grading was evaluated in previous studies. In the Aydin et al. study (12), the role of perfusion and permeability MRI in glioma grading was investigated. Their study included 38 patients (22 patients with HGG and 16 patients with LGG), and DCE-MRI parameters were assessed. Their results showed that the mean Ktrans value was significantly higher in patients with HGG than in patients with LGG. In their study, a Ktrans threshold of >0.043 yielded a sensitivity of 81.82% and a specificity of 100% for differentiating HGG from LGG.

In another study by Li et al. (13), the utility of DCE-MRI for glioma grading was evaluated in 32 patients. In this study, the patients were scanned using a 3T MRI scanner, and their results showed that Ktrans magnitudes were significantly different between HGG and LGG, as well as across different grades of glioma. A sensitivity of 94.1% and specificity of 93.3% were reported for Ktrans in differentiating HGG from LGG. Our findings were in close agreement with these results. In our study, the optimal Ktrans threshold was 0.025 and resulted in a sensitivity of 82.35% and specificity of 85.71%.

The results showed that there is a strong correlation between tumor microvascular permeability and glioma grade. The gliomas with higher grades have higher permeability indices. This emphasizes the potential of DCE-MRI as a non-invasive biomarker to complement histopathological results as the gold standard method for glioma grading. Integrating the permeability indices into glioma grading leads to guiding treatment decisions for glioma patients and ultimately improving outcomes for these patients.

Limitations and Strengths

This study has several limitations that must be acknowledged. First, the study sample size is small due to the limited number of patients who met the inclusion criteria. Hence, the results must be interpreted with caution. Second, the single-center and retrospective nature of the study limits the external validity and generalizability of the findings. There is a need for multi-site studies with larger sample sizes to validate the results. Third, all ROIs were drawn by a single radiologist, which may lead to variation in results in reanalysis by another observer. ROI selection is an observer-dependent process. While the focus is on DCE-MRI, it is suggested that the performance of this imaging method be compared with other functional imaging methods that provide physiological information (like PET or advanced MRI methods). This will provide us with more information on the performance and

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capabilities of this imaging method for use in clinical situations.

Conclusion

In this study, the performance of permeability parameters quantified based on DCE-MRI (Ktrans, Kep, Ve, and Vp) was evaluated for glioma grading. The permeability parameters show a significant correlation with the histopathological grade of gliomas. These parameters, particularly Ktrans and Vp, demonstrate high diagnostic accuracies for differentiating between different grades of gliomas. Therefore, dynamic contrast-enhanced MRI can serve as a valuable noninvasive tool to complement the current histopathology-based grading system, thereby improving the accuracy of grading results and optimizing treatment strategies for glioma patients.

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Ethical Considerations

This study was approved by the ethical committee of Ilam University of Medical Sciences (IR.MEDILAM.REC.1402.224). The study was conducted in accordance with the principles of the Declaration of Helsinki (11). In this study, the data analyzation was performed retrospectively. Hence, all unique patient identification information was concealed to ensure confidentiality and patient privacy.

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Competing Interests' Disclosure

The authors declare that they have no competing interests.

Authors' contributions

Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Software, Data Curation: SA, Writing–Original Draft Preparation, Writing–Review & Editing, Visualization, Supervision, Project Administration: SSZ.

Writing Disclosure

No AI writing assistance was utilized in the production of this manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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