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Combination of three-dimensional arterial spin labeling and stretched-exponential model in grading of gliomas

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Abstract

To evaluate the diagnostic value of combining 3D arterial spin labeling (ASL) and stretched-exponential diffusion model in grading of gliomas.

A total of 72 patients with histo-pathology proved gliomas (34 low-grade, 38 high-grade) were included in this study. 3D ASL and multi-*b* diffusion weighted imaging (DWI) images were retrospectively analyzed. The ASL and DWI parameters—tumor blood flow (TBF), distributed diffusion coefficient (DDC), and diffusion heterogeneity α were compared between high-grade and low-grade groups and $P < .05$ was regarded as statistically significant. TBF was also normalized to the corresponding values in contralateral mirror regions of interest (ROI) (M-TBF), normal grey matter (G-TBF), and white matter (W-TBF) and were compared between high and low-grade tumors.

TBF values were significantly higher in high-grade gliomas ($P < .001$). In stretched-exponential model, the α value of low-grade gliomas showed significant higher than high-grade gliomas group ($P < .001$), but there was no difference of DDC ($P > .05$). When TBF values were normalized to contralateral mirror ROI, normal grey matter and white matter, G-TBF showed the highest sensitivity and specificity for differentiation high-grade and low-grade gliomas. The area under area under curve (AUC) of G-TBF and α for glioma grading were 0.926 and 0.892, respectively. The area under AUC of the G-TBF combination with α was 0.960 and corresponding sensitivity and specificity were 94.1% and 98.7%.

The combination of 3D ASL and stretched-exponential model parameters can be used to differentiate high-grade and low-grade gliomas. Combination G-TBF and α value can obtain best diagnostic performance.

Abbreviations: ADC = apparent diffusion coefficient, ASL = arterial spin labeling, AUC = area under curve, CASL = continuous ASL, CBF = cerebral blood flow, DDC = distributed diffusion coefficient, DWI = diffusion weighted imaging, Gd-CEMRI = gadolinium-contrast-enhanced magnetic resonance imaging, PASL = pulsed ASL, pCASL = pseudo-continuous ASL, PLD = post label delay, ROC = receiver operating characteristic, ROI = regions of interest, TBF = tumor blood flow.

Keywords: arterial spin labeling, glioma, stretched-exponential model

1. Introduction

Gliomas are the most common primary tumors of the brain in adults and can be classified into 4 grades according to the criteria from World Health Organization.[1] Accurate grading of gliomas is of great importance both for treatment optimization and prognosis evaluation. Conventional gadolinium-contrast-enhanced magnetic resonance imaging (Gd-CEMRI) is usually used for gliomas grading. However, the nature of Gd-CEMRI, which only highlights the breakdown area of blood brain barrier rather than complete tumor vascular area, has been found to limit the accuracy of Gd-CEMRI in grading gliomas.[2]

Perfusion imaging provides functional information that can be used to measure the blood flow of tissues, making it capable of grading the tumor by evaluating the abundance of local angiogenesis. Nowadays, there are 2 major MRI perfusion methods used in routine clinical: one is called dynamic susceptibility weighted contrast (DSC), which measures dynamic signal variation induced by injected exogenous endovascular agent; the other one is arterial spin labeling (ASL), which utilizes magnetically labeled water protons as an endogenous tracer. The fact that no need for contrast medium injection and absolute quantification of cerebral blood flow (CBF) has been making ASL a promising tool in clinical usage. In terms of spin labeling technique in ASL, there are 3 approaches: pulsed ASL (PASL), continuous ASL (CASL), and pseudo-continuous ASL (pCASL). Combining the advantages of pASL and CASL, pCASL is now recommended as golden practice for clinical application.[3] Diffusion weighted imaging (DWI) can measure apparent diffusion coefficient (ADC) and have proven to be useful in the characterization of cancerous tissues.[4] The ADC value can reflect tissue cellularity which is often higher in malignant tumors. In the past, ADC is derived using a mono-exponential model. However, with physiological evidences, more and more studies

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found that microvascular perfusion also contributes to DWI signals and should not be neglected.[5] Thus, bi-exponential model was considered to be better in describing the diffusion signal decay.[6] Nevertheless, in brain and brain tumors, DWI signal attenuation is consistent with a multicompartmental of water diffusion, bi-exponential curve fit may oversimplification the complex reality. Bennett et al[7] introduced the stretched-exponential model, in which making assumption that each voxel is composed of a continuous distribution of diffusion rate based on stretched-exponential function.

To date, pCASL and stretched-exponential model alone have proved to be useful in grading gliomas.[8,9] However, each technique still has some misdiagnose in differentiating high-grade and low-grade gliomas. By comparing the sensitivity and specificity for tumor grading, the aim of this study is to investigate if combination these 2 techniques can achieve better diagnostic value than each technique alone.

2. Materials and methods

2.1. Patient population

This retrospective study was approved by the local institutional review board and written informed consents were obtained from all participants. From September 2015 to April 2018, a total number of 72 patients in our hospital (40 men, 32 women; age range, 37–76 years; mean age, 56.3 years) with pathologically (biopsy or tumor resection) proven gliomas (grade II, astrocytoma, n = 28, oligodendroglioma, n = 6; grade III, anaplastic astrocytoma, n = 16; grade IV, glioblastoma multiforme, n = 22) were included in this study. All the subjects had undergone multi-*b* values DWI imaging and 3D pCASL before any treatment. Exclusion criteria contain general contraindications to MR imaging, such as implanted pacemaker and claustrophobia.

2.2. Imaging protocol

All MRI measurements were performed on a 1.5T MRI scanner (HDxt, GE Healthcare, Milwaukee, WI) using an 8 channel phase array head coil. Conventional MR sequences were acquired as follows, axial 2D T2 fast spine echo (FSE), field of view (FOV) = 24 cm, repetition time (TR) = 4900, echo time (TE) = 124 ms, slice thickness = 4 mm, no slice gap, matrix = 320×320, number of excitation (NEX) = 2; axial 3D isotropic post-contrast T1 BRAVO, FOV = 25.6×25.6 cm, flip angle = 12°, TR/TE = 8.3/3.2 ms, inversion time (TI) = 400 ms, slice thickness = 1 mm, matrix = 256×256 mm.

Axial three-dimensional (3D) pCASL was acquired using 3D spiral fast spin echo with the following parameters:

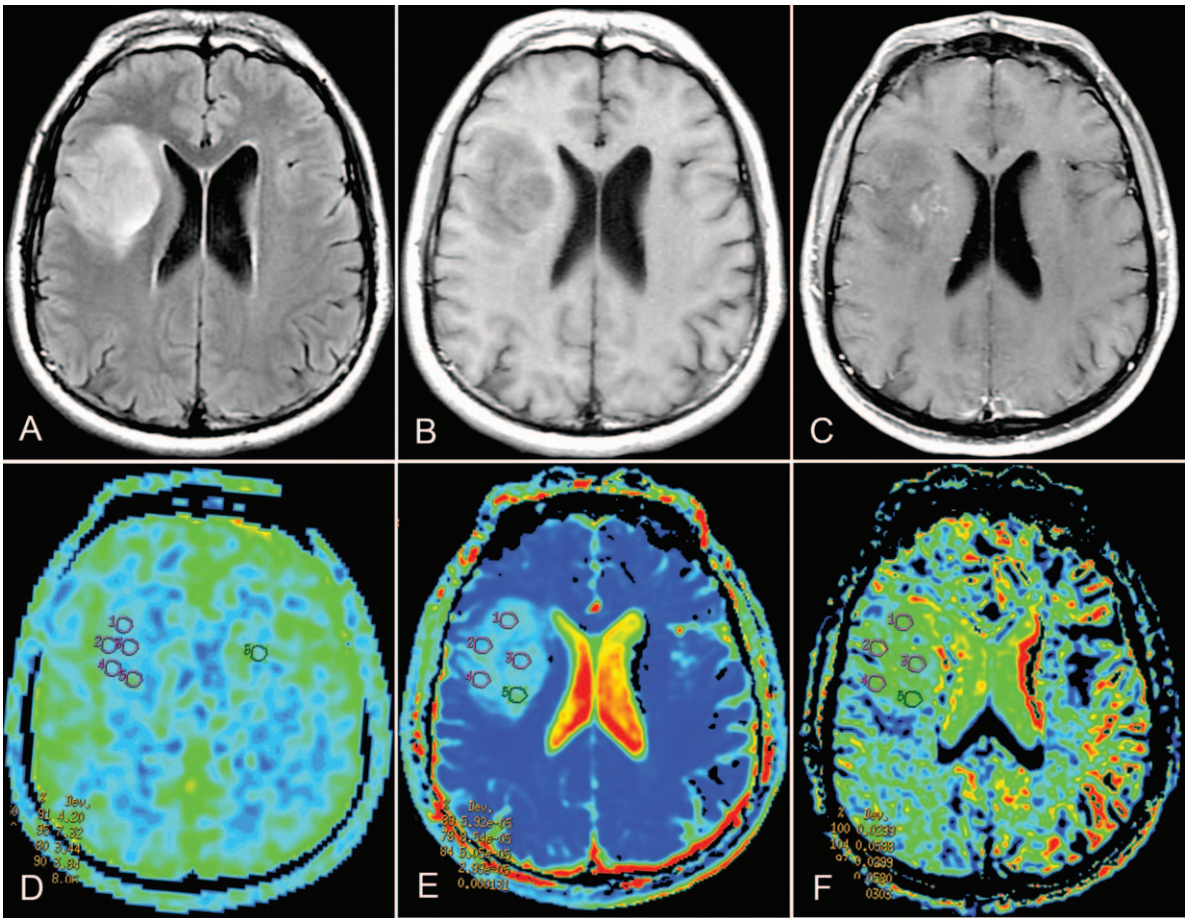

Figure 1. Images A–F correspond to the patients with astrocytoma (WHO grade II) in the right hemisphere. (A) T2Flair showed homogeneous hyperintensity of the tumor. (B) T1WI showed homogeneous hypointensity. (C) Post-gadolinium T1-weighted image showed slight enhancement in the tumor. (D) The TBF map showed hypoperfusion in the whole tumor area. (E) The DDC maps demonstrated slight higher values compared with normal cerebral parenchyma. (F) The α map showed heterogeneous signal intensity in tumor area. DDC = distributed diffusion coefficient, TBF = tumor blood flow.

TR/TE = 4625/10.5 ms, FOV = 24 × 24 cm, post label delay (PLD) = 1525 ms, labeling duration = 1500 ms, slice thickness = 4 mm, number of the slice = 36, 512 sampling points on 8 spirals, NEX = 3; besides perfusion weighted images, 3D pCASL sequence also produces spatially matched PD images by turning off background suppression pulses and labeling pulses. Axial multi-*b* value DWI was performed by using a single shot echo-planar sequence (SE-EPI), FOV = 24 × 24 cm, TR/TE = 5000/84 ms, matrix = 128 × 128, slice thickness = 4 mm, no slice gap, 10 *b* values (0, 50, 100, 200, 400, 800, 1000, 1500, 2000, 3000 s/mm^2), copy the localizer of 3D pCASL.

2.3. Data processing

After data acquisition was done, perfusion weighted images as well as PD images were transferred to a GE Advanced Workstation 4.6 (AW4.6 Healthcare) for CBF quantification using below established model:

$$\mathrm{CBF} = 6000 \times \lambda \frac{\{-\exp[-\mathrm{ST}/\mathrm{T1}_t]\}\exp[\mathrm{PLD}/\mathrm{T1}_b]}{2T1_b\{1-\exp[-\mathrm{LT}/\mathrm{T1}_b]\}\varepsilon \times \mathrm{NEX}_{pw}} \left(\frac{\mathrm{PW}}{\mathrm{SF}_{pw}\mathrm{PD}}\right)$$

In this equation, $T1_b$ is T1 of blood and is assumed to be 1.4 seconds at 1.5 T. The partial saturation of the reference image (PD) is corrected for by using a T1t of 1.2 seconds. ST is saturation time and is set to 2 seconds. It is used to correct the grey/white matter signal intensity changes on labeling image caused by labeling radiofrequency pulses. The partition coefficient λ, is set to 0.9. The efficiency, ε, is a combination of both inversion efficiency (0.8) and background suppression efficiency (0.75) resulting in an overall efficiency of 0.6. LT is the labeling duration and is set to 1.5 seconds for the current study. PW is the perfusion weighted or the raw difference image. SF_{pw} is the scaling factor of PW sequence. NEX_{pw} is the number of excitation for PW images. The CBF is reported in mL/100 g/min units. Considering that CBF value was affected by age and sex, this study also measured contralateral mirror ROI, normal grey matter and white matter with the same size ROI and calculated the ratio between tumor and control: M-TBF = TBF/(Mirror ROI CBF); G-TBF = TBF/(Grey matter CBF); W-TBF = TBF/(White matter CBF).

The stretch-exponential model was expressed by the following equation:

$$\frac{S_b}{S_0} = \exp([-b\cdot\mathrm{DDC}]^a),$$

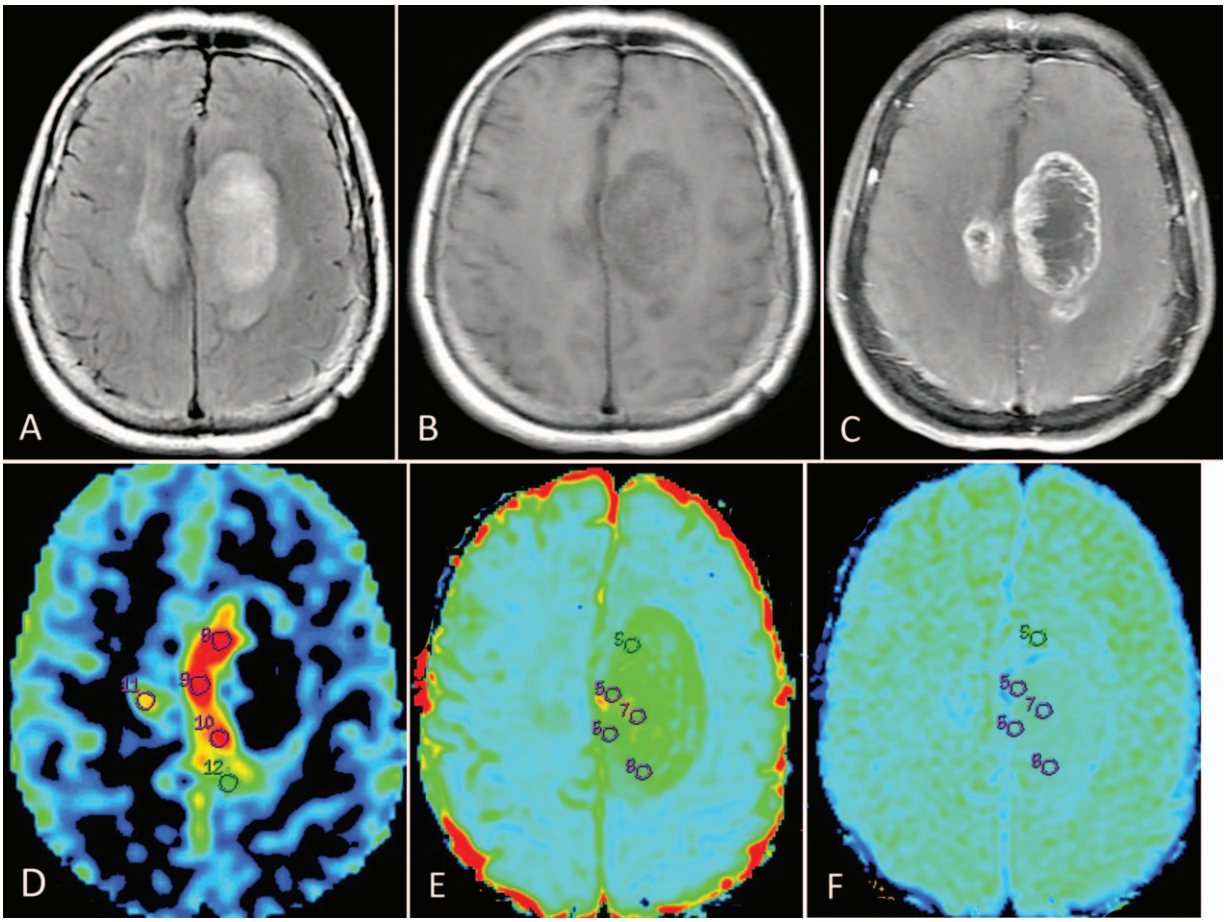

Figure 2. Images A–F correspond to the patients with anaplastic astrocytoma (WHO grade III) in the left hemisphere. (A) T2Flair showed inhomogeneous hyperintensity in the tumor. (B) T1WI showed hypointensity. (C) Post-gadolinium T1-weighted image showed peripheral enhancement of the tumor. (D) The TBF map showed hyperperfusion in part of the tumor area. (E) The DDC maps demonstrated moderate higher values compared with normal cerebral parenchyma. (F) The α map showed heterogeneous signal intensity in tumor area. DDC = distributed diffusion coefficient, TBF = tumor blood flow.

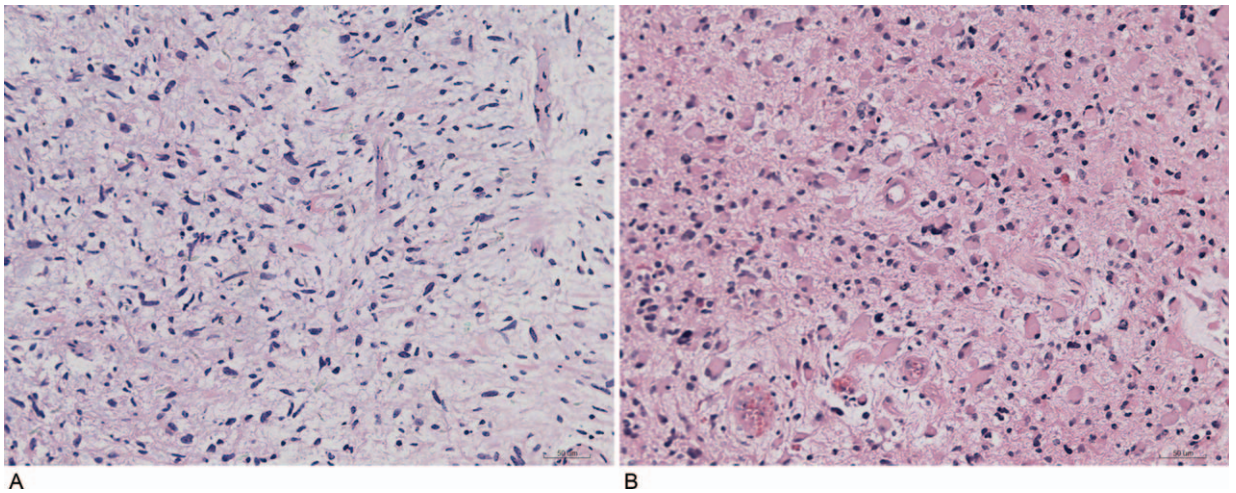

Figure 3. Histologic images of astrocytoma (A) and anaplastic astrocytoma (B) (HE 200×).

Where S_b is the signal intensity in the voxel with diffusion gradient, S_0 is the signal intensity in the voxel without diffusion gradient, DDC is the distributed diffusion coefficient, representing mean intravoxel diffusion rate, α is related to intravoxel water diffusion heterogeneity, vary between 0 and 1. A numerically low α value represents high intravoxel diffusion heterogeneity.

2.4. Statistical analysis

All images analysis and parameters calculation were performed with a manufacturer-supplied software on Advantage Workstation (AW4.6 MADC, GE Healthcare). Tumor blood flow (TBF), DDC, and α map were created for measurement. Six regions of interest (ROIs) of 10 to 15 mm^2 were manually drawn by 2 experienced radiologists on solid tumors compartments to calculate tumor blood flow (TBF), DDC, and α values. Necrosis, hemorrhage, large vessel, and tumor margins were avoided. All results were expressed as mean ± SD. Normal data distribution was verified via Kolmogorov–Smirnov test. Two-tailed, independent Student *t* test was used to compare the quantitative imaging parameters between the high-grade and the low-grade gliomas. Receiver operating characteristic (ROC) curves were generated for each parameter to assess the area under the receiver operating characteristic curve (AUC) and to determine which parameter was optimal for the grading of gliomas. All statistics were performed using SPSS (SPSS 19.0, Chicago, IL). Tests were considered statistically significant when *P* value <.05.

3. Results

In conventional MR images, 26 of 38 high-grade gliomas and 7 of 34 low-grade gliomas demonstrated hyperintense contrast enhancement. The sensitivity and specificity of grading by Gd-CEMRI were 78.7% and 68.2%, respectively. DDC, α, and ASL-CBF map were generated and all parameters were measured successfully. Representative MR findings and histological images of a low-grade and a high glioma are shown in Figs. 1–3, respectively.

The TBF, M-TBF, G-TBF, W-TBF, DDC, and α values of high-grade and low-grade gliomas were summarized in Table 1 and Fig. 4. In all these parameters, TBF, M-TBF, G-TBF, and W-TBF values were significantly higher for high-grade gliomas ($P < .001$), α value was significantly lower in high-grade gliomas and DDC values showed no significantly difference between 2 groups.

ROC curve analysis results in differentiating high-grade gliomas from low-grade gliomas were summarized in Table 2 and Fig. 5. AUC values were 0.861 for TBF, 0.892 for M-TBF, 0.926 for G-TBF, 0.877 for W-TBF, 0.892 for α value, and 0.960

Table 1

Comparison of TBF and stretch exponential model parameters between low-grade and high-grade gliomas.

Parameters	HGG (n = 38)	LGG (n = 34)	*P* value
TBF, mL/100 g min	86.5 ± 19.1	62.7 ± 11.3	<.001
M-TBF	1.82 ± 0.28	1.43 ± 0.19	<.001
G-TBF	1.59 ± 0.28	1.10 ± 0.17	<.001
W-TBF	2.75 ± 0.71	1.83 ± 0.43	<.001
DDC, $\times 10^{-3}$ mm^2/s	0.66 ± 0.18	0.77 ± 0.22	>.05
α	0.57 ± 0.11	0.74 ± 0.09	<.001

The *P*-values were compared between the high-grade and low-grade gliomas.
DDC = distributed diffusion coefficient, HGG = high-grade glioma, LGG = low-grade glioma, M-TBF, G-TBF, W-TBF values correspond to the values of TBF normalized by contralateral mirror ROI, grey matter and white matter normalization, respectively. TBF = tumor blood flow.

Table 2

Diagnostic performance of TBF and stretch exponential model parameters for discrimination of low-grade and high-grade gliomas.

Parameters	AUC	Sensitivity (%)	Specificity (%)	Cutoff value
TBF, mL/100 g min	0.861	76.5	85.7	>75.1
M-TBF	0.892	82.4	85.7	>1.62
G-TBF	0.926	94.1	83.1	>1.21
W-TBF	0.877	73.5	92.9	>2.33
DDC, $\times 10^{-3}$ mm^2/s	0.636	64.3	61.8	<0.68
A	0.892	82.1	85.3	<0.67
G-TBF and α	0.960	94.1	98.7	>1.55

Combination G-TBF and α showed the highest AUC in differentiating high-grade from low-grade gliomas. DDC = distributed diffusion coefficient, TBF = tumor blood flow, M-TBF, G-TBF, W-TBF values correspond to the values of TBF normalized by contralateral mirror ROI, grey matter, and white matter normalization, respectively.

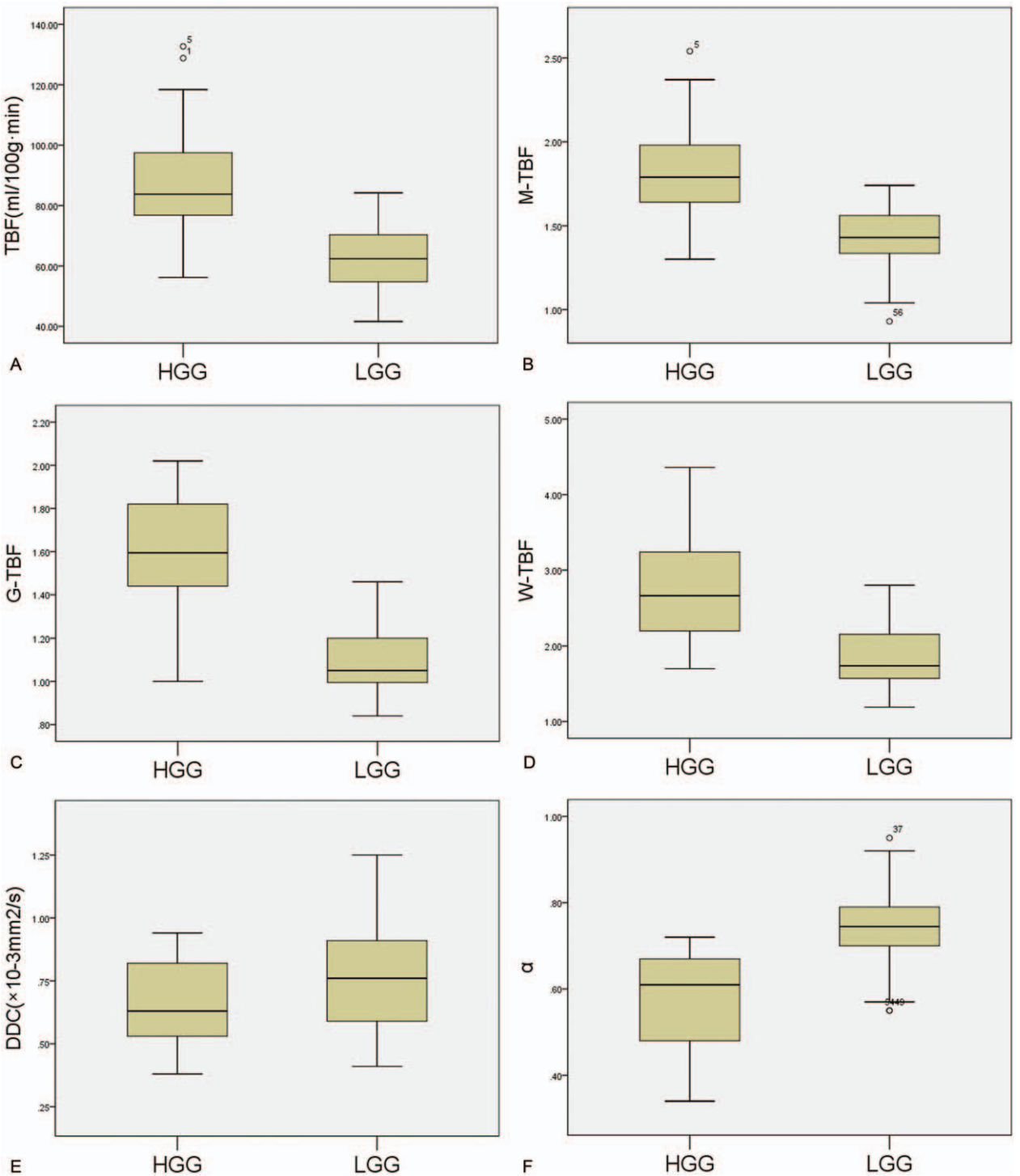

Figure 4. Box plots for TBF (A), M-TBF (B), G-TBF (C), W-TBF (D), DDC (E), and α (F) values in high-grade and low-grade gliomas. DDC = distributed diffusion coefficient, TBF = tumor blood flow.

for combining G-TBF and α. When the cutoff value of TBF was 75.1 mL/100 g min, the sensitivity was 76.5% and the specificity was 85.7%. When the cutoff value of α was 0.67, the sensitivity was 82.1% and the specificity was 85.3%. The sensitivity and specificity of the combined G-TBF and α values were 94.1% and 98.7%, respectively. The parameters derived from pCASL and stretch-exponential model showed higher sensitivity and specificity of glioma grading than Gd-CEMRI.

4. Discussion

In general, Gd-CEMRI could provide morphological information to help determine the solid part of the tumor. However, the accuracy of Gd-CEMRI in glioma grading is limited because the enhancement after contrast agent reflects blood brain barrier disruption rather than a true assessment of tumor vascularity.[10,11] Our findings confirmed those of previous studies showing the sensitivity and specificity of glioma grading

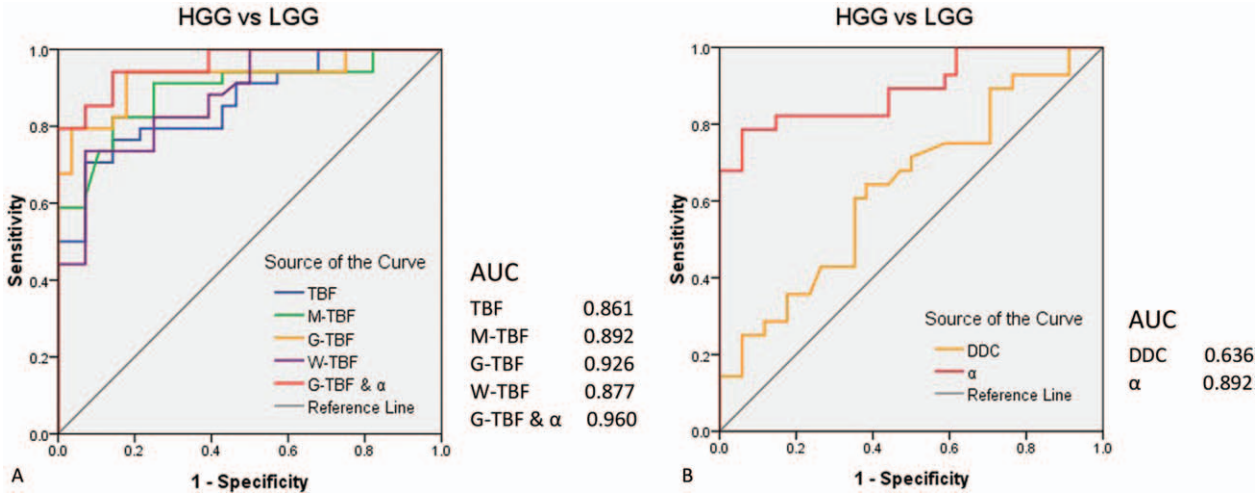

Figure 5. (A) Receiver operating characteristic curves for TBF, M-TBF, G-TBF, W-TBF, and combination of G-TBF and α in distinguishing high- from low-grade gliomas. (B) Receiver operating characteristic curves for DDC and α in distinguishing high- from low-grade gliomas. DDC = distributed diffusion coefficient, TBF = tumor blood flow.

by Gd-CEMRI were significantly lower than pCASL and stretched-exponential model techniques. Several studies have demonstrated ASL perfusion have comparable results with DSC perfusion and could provide useful information in tumor grading.[12] Owing to low signal-noise ratio (SNR) and long scan time, ASL technique has not been widely used in clinical practice yet. In our study, perfusion was measured by 3D pCASL commercially available from GE Healthcare. This sequence uses pseudo-continuous labeling technique and 3D spiral fast spin echo readout. According to recommendation from authorities,[13,14] this approach has superior performance in terms of SNR, magnetization transfer effect control as well as reduction of negative impact from tissue's susceptibility. The reliability of CBF measurements obtained by pCASL has been evaluated.[15,16]

Our findings showed that the TBF values in high-grade gliomas were significantly higher than low-grade gliomas, which confirmed previous results.[17–19] Meanwhile, to eliminate the influence of each patient's own physiological condition on the CBF quantification, this current study also measured the CBF values for the same size ROI on contralateral mirror position, normal gray matter, and white matter. The ratio was calculated to correct individual bias. The results demonstrated that in these 4 parameters, G-TBF showed the highest sensitivity and specificity in differentiating high-grade and low-grade gliomas, followed by M-TBF, W-TBF, and original TBF. One possible explanation of this finding is that ASL quantification is affected by PLD time. Considering enough SNR for measurement and scan time, the PLD time in this study was set to 1525ms. For this delay time, labeled bolus should be delivered to most grey matter tissues. However, for white matter, which has a relative longer transit time, will suffer from signal loss.[20] Meanwhile, because of the variability of tumor location, measured values from mirror ROI may be affected by partial volume effects. Our study suggested that elevated G-TBF value has the strongest positive correlation with glioma grade.

Previous study reported that tumor cellularity was higher in high-grade gliomas than low-grade.[4] Therefore, it can be speculated that ADC values from diffusion-weighted imaging can be used in differentiating high-grade and low-grade gliomas. However, more and more studies found that there were overlap of mono-exponential model-based ADC values between different grade of gliomas.[21] In this work, stretched-exponential model was adopted for analyzing the diffusion signal. DDC can be considered as the composite of diffusion values weighted on the volume fraction of different tissues. Theoretically DDC and α values may more accurately reveal the complex composition of gliomas. The results of this study showed that α values of high-grade gliomas were significantly lower than low-grade gliomas. This finding was consistent with previous reports.[22] It can be explained by the fact that high-grade gliomas are associated with conspicuous histologic heterogeneity. Pleomorphism of tumor cells, lesions within the cystic degeneration, necrosis and calcification can all contribute to the final diffusion signal. The DDC value, however, was not found to have obvious difference between high-grade and low-grade gliomas, which was different from the previous study,[23] in which the DDC value was significantly lower in high-grade gliomas. We speculate this discordance arises from the different b value used in scan. In present study, due to scan time and SNR consideration on 1.5 T, the number and distribution of b value were different from Bai study. In addition, the composition of different grades of gliomas may also affect the statistical results.

Tissue perfusion information can reflect tumor vascularity, while stretched-exponential diffusion parameters are related with tumor microstructural heterogeneity. Therefore, the combination of these 2 techniques parameter is expected to further reveal tumor pathological features. The results of this study also showed that combination G-TBF and α values has both higher sensitivity and specificity for grading glioma higher each parameter alone.

There are some limitations in this study. First, relatively small number of the patients were included in the current study, because lacking of pathological results. Second, in ASL study, we followed recommendation and set PLD time to 1525 ms for all patients to avoid sequence bias. However, the twisted tumor vascular structure could lead to delayed arrival of the labeled bolus for some subjects, resulting an underestimated perfusion.[24] In addition, patients with different age would have different cardiovascular status, so one fixed PLD time may not be

optimal for all subjects. Recent studies reported that the coupling between CBF fluctuations and resting-state Blood Oxygenation Level (BOLD) signal is highly variable across the brain and is sensible to hemodynamic changes during aging.[25] The dynamic coupling between BOLD and CBF fluctuations could be measured concurrent from a single dual-echo pCASL sequence.[26] The combination of BOLD and ASL data may helpful to correct the age differences in CBF calculation and improve the diagnostic accuracy in glioma grading. This enhanced pCASL will imply in our future study. Third, to match the ROIs selection for these 2 techniques, only solid elements of tumor on parameter maps were selected by drawing ROIs based on high perfusion or enhancement area, while avoiding the necrosis, this selection may underestimate the overall heterogeneity of the lesion.

5. Conclusion

In conclusion, both 3D pCASL and stretched-exponential model can differentiate high-grade and low-grade gliomas, and combination of normalized G-TBF and α have higher sensitivity and specificity in glioma grading, therefore, it can be used as a noninvasive preoperative grading and follow-up.

Author contributions

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Resources: Jie Jiang.
Software: Guangnan Quan.
Supervision: Jie Jiang.
Validation: Guangnan Quan.
Writing – original draft: Yuan Qu.
Writing – review & editing: Xiaocheng Wei.

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