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Can Dynamic Susceptibility Contrast Perfusion Imaging be Utilized to Detect Isocitrate Dehydrogenase Gene Mutation in Gliomas?

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ABSTRACT

AIM: To explore the ability of dynamic susceptibility contrast perfusion imaging (DSC-PI) to detect isocitrate dehydrogenase (IDH) gene mutation in gliomas.

MATERIAL and METHODS: Preoperative DSC-PI data on histopathologically proven gliomas obtained between January 2015 and December 2019 were reviewed retrospectively. All magnetic resonance imaging (MRI) examinations were performed using a 1.5-T scanner. The maximum relative cerebral blood volume (rCBVmax), percentage signal recovery (PSR), and normalized PSR of tumor cores were calculated. Differences in these values between IDH-mutant and wild-type gliomas were compared, and receiver operating characteristic curves were generated.

RESULTS: The patients (32 females, 47 males) were aged 21–76 years (mean 50.7 ± 15 years). The rCBVmax and all PSR values differed significantly between patients with IDH-mutant and those with wild-type tumors ($p<0.01$ for all comparisons).

CONCLUSION: The rCBVmax and PSR values obtained by DSC-PI may facilitate noninvasive detection of the IDH mutation status of gliomas. PSR provided more reliable values for differentiation of IDH-mutant gliomas from wild-type gliomas.

KEYWORDS: Perfusion, Magnetic resonance imaging, Glioma, Isocitrate dehydrogenase, Mutation

ABBREVIATIONS: AUC: Area under the curve, **CBV:** Cerebral blood volume, **DSC-PI:** Dynamic susceptibility contrast perfusion imaging, **IDH:** Isocitrate dehydrogenase, **MRI:** Magnetic resonance imaging, **PCR:** Polymerase chain reaction, **PMRI:** Perfusion magnetic resonance imaging, **PSR:** Percentage signal recovery, **rCBVmax:** Relative maximum cerebral blood volume, **ROCs:** Receiver operating characteristics, **WHO:** World Health Organization

INTRODUCTION

Gliomas are the most common primary brain neoplasms in adults (4). In 2007, the World Health Organization (WHO) classified infiltrative gliomas into low-grade (grade II) and high-grade (grades III and IV) tumors. Glioma grading is performed by the histopathological evaluation of tissues obtained via biopsy or surgical excision. Tumor differentiation, cellularity, mitotic activity, nuclear atypia, and the

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extent of microvascular proliferation affect the tumor grade. However, the molecular characteristics of brain tumors are important in terms of both prognosis and therapeutic decision-making (3,18). The WHO updated the classification of brain tumors in 2016 based on the finding that isocitrate dehydrogenase (IDH)-mutant gliomas are associated with a good prognosis, whereas patients with IDH-wild-type tumors have a poor prognosis (10). Currently, the IDH mutation status is usually analyzed immunohistochemically via biopsy or surgical resection. Nonimmunoreactive cases could be studied by polymerase chain reaction (PCR) following recommendations of the 2016 WHO guidelines. Most intracranial masses can be biopsied rather safely. IDH mutations can also be detected preoperatively using noninvasive perfusion magnetic resonance imaging (PMRI) (20). Over the past few years, noninvasive imaging detection of IDH mutations has been reported (6,9,13,16,18). PMRI has been used extensively to determine the subtypes, aggressiveness, and early malignant transformation of gliomas (9). Dynamic susceptibility contrast perfusion imaging (DSC-PI) is frequently used in clinical practice to evaluate blood delivery to tissues by monitoring a bolus of contrast agent as it passes through the vasculature. DSC-PI yields the relative cerebral blood volume (rCBV), a useful biomarker. High-grade tumors exhibit a rCBV greater than low-grade tumors, and the rCBV is strongly correlated with glioma vascularity (2,9). Percentage signal recovery (PSR) denotes the percentage of signal intensity that is received at the end of the first pass of the contrast agent relative to baseline. This signal recovery depends on many factors, including contrast leakage, the size of the extravascular space, and the blood flow rate (11). We evaluated whether noninvasively derived PSR, rPSR, and rCBV values can predict the IDH mutation status of gliomas.

MATERIAL and METHODS

Patients and Groups

This retrospective study was authorized by our institutional review board and informed consent was waived. Pretreatment magnetic resonance imaging (MRI) scans of all adult patients with newly diagnosed, histopathologically confirmed diffuse gliomas treated from January 2015 to December 2019 were reviewed retrospectively. The inclusion criteria were 1) histologically diagnosed WHO grade II, III, or IV astrocytoma, glioblastoma, or oligodendroglioma; 2) performance of both conventional cranial MRI and DSC-PI at the time of the initial diagnosis, before treatment; and 3) a known IDH mutation status. Mutations were evaluated by immunohistochemistry. Exclusion criteria were patients younger than 18 years and DSC-PI examinations with poor diagnostic quality.

In the analyses of tumor groups, all gliomas in the study cohort were compared in terms of mutant and wild-type gliomas. The classification of gliomas was based on WHO 2021 guidelines (17). Further, among all gliomas, a high-grade glioma group was created and the same statistical analyses were applied to this group.

Imaging Protocol

All MRI examinations were performed in patients with glioma using a 1.5-T platform (Aera; Siemens Healthcare, Erlangen, Germany) with an 18-channel head array receiving coil. Our imaging protocol includes non-enhanced conventional sequences, DSC-PI, and enhanced T1-weighted axial and coronal sequences following the administration of 0.1 mmol/kg gadolinium-based contrast material with an injection rate of 3–5 ml/s. T2*-weighted gradient-echo EPI sequence was used for DSC-PI.

Post-Processing and Image Analyses

All MRI examinations were evaluated by consensus of two neuroradiologists with 15 and 6 years of experienced. For DSC-PI data processing, perfusion data were transferred to a dedicated workstation (Siemens, Syngo via, Version VB30A) running MRI neurology software. Contrast enhancement was noted in conventional sequences. Lesions were grouped by enhancement status (yes or no). After evaluation of conventional sequences, cerebral blood volume (CBV) maps were created. T1 correction was not performed. After evaluating all slices, three round regions of interest with an area of 10–30 mm^2 were manually drawn on the most vascular tumoral regions, avoiding areas of necrosis and hemorrhage, and the maximum values were enrolled. The CBV of the tumor was normalized to that of the white matter of the unaffected contralateral hemisphere and termed the rCBV. PSR values were calculated using the time-to-signal intensity curves. PSR^1 refers to the signal recovery after the first pass of the contrast bolus and PSR^2 at about the 90th second of the sequence (Figure 1). The relative PSR (rPSR) was obtained by normalizing the PSR of the tumor core to that of the white matter of the unaffected contralateral hemisphere.

Statistical Analyses

The Shapiro–Wilk test was used to evaluate if the age and perfusion imaging parameters of the two groups were normally distributed. IDH-mutant and wild-type gliomas were compared using the independent samples t-test. Receiver operating characteristic (ROC) curves were created for perfusion parameters exhibiting significant differences and were used to set cutoff values for the determination of the IDH mutation status. The X^2 test was used to compare gender differences in the two groups. SPSS v. 23.0 was utilized for statistical analyses. A P value of <0.05 was used to determine statistical significance.

RESULTS

The study cohort included 79 patients, aged 21–76 years (mean age: 50.7 ± 1 5 years), with histologically proven gliomas. The histological diagnoses were glioblastoma (n=55), grade 4 astrocytoma (n=4), grade 3 astrocytoma (n=6), grade 2 astrocytoma (n=7), grade 2 oligodendroglioma (n=5), and grade 3 oligodendroglioma (n=2) (Figure 2). The sex ratio did not differ between mutant and wild-type IDH groups (p=0.17). The mean age of the patients with IDH-mutant gliomas was significantly lower than that of patients with wild-type gliomas ($p<0.001$).

In conventional sequences, significantly greater contrast enhancement was seen in wild-type gliomas than in mutant gliomas. Contrast enhancement was seen in 89.1% of IDH wild-type gliomas; whereas this ratio was 25% in IDH-mutant gliomas All the DSC-PI parameters differed significantly between the two groups. Patient baseline characteristics and quantitative perfusion imaging parameters are listed in Table I. The rCBV was higher in wild-type than in IDH-mutant gliomas ($p<0.001$), whereas PSR^1, $rPSR^1$, PSR^2, and $rPSR^2$ values were significantly lower ($p<0.01$ for all comparisons). ROC analyses depicting sensitivity, specificity, cutoff, and area under the curve (AUC) values are shown in Table II. PSR^1 was the best parameter for discriminating two groups in diffuse gliomas (AUC was 0.846). The ROC curves for perfusion parameters are demonstrated in Figure 3. Magnetic resonance images of IDH-mutant and wild-type gliomas are shown in Figures 4 and 5.

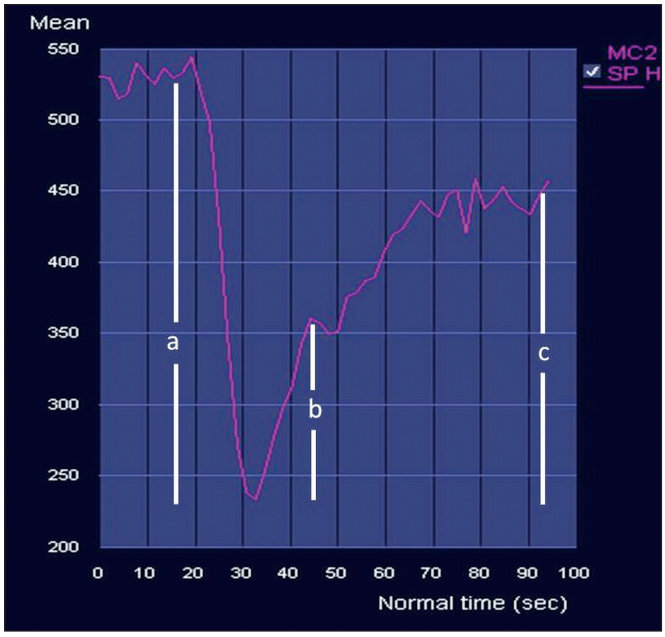

Figure 1: A time-to-signal intensity curve. PSR^1 = b/a, and PSR^2 = c/a.

The high-grade glioma subgroup consisted of 67 lesions (55 were wild-type and 12 were IDH-mutant). DSC-PI parameters of high-grade gliomas according to the IDH gene status are presented in Table III. ROC analyses depicting cutoff and AUC values for high-grade gliomas are shown in Table IV. PSR^1 was the best parameter for discriminating two groups in high-grade astrocytomas (the AUC was 0.842). ROC curves for high-grade gliomas are presented in Figure 6. Box-plot graphics of DCS-PI parameters in discriminating IDH mutations are revealed in Figure 7.

DISCUSSION

We investigated the role of various DSC-PI parameters in determining the IDH gene status noninvasively. To evaluate the signal recovery percentages, PSR^1 and PSR^2 are described as novel diagnostic approaches.

The clinical prognosis of gliomas depends on the histopathological grade. Recently, various mutations that affect prognosis and survival have been identified. IDH mutations in high-grade gliomas are associated with longer overall survival and better prognosis than gliomas with wild-type IDH, independent of the histological grade (12,19,20). We found that wild-type gliomas exhibited higher rCBV and lower PSR values than those of IDH-mutant gliomas, suggesting that the PSR and rCBV derived from DSC-PI can aid in the noninvasive detection of the IDH mutation status.

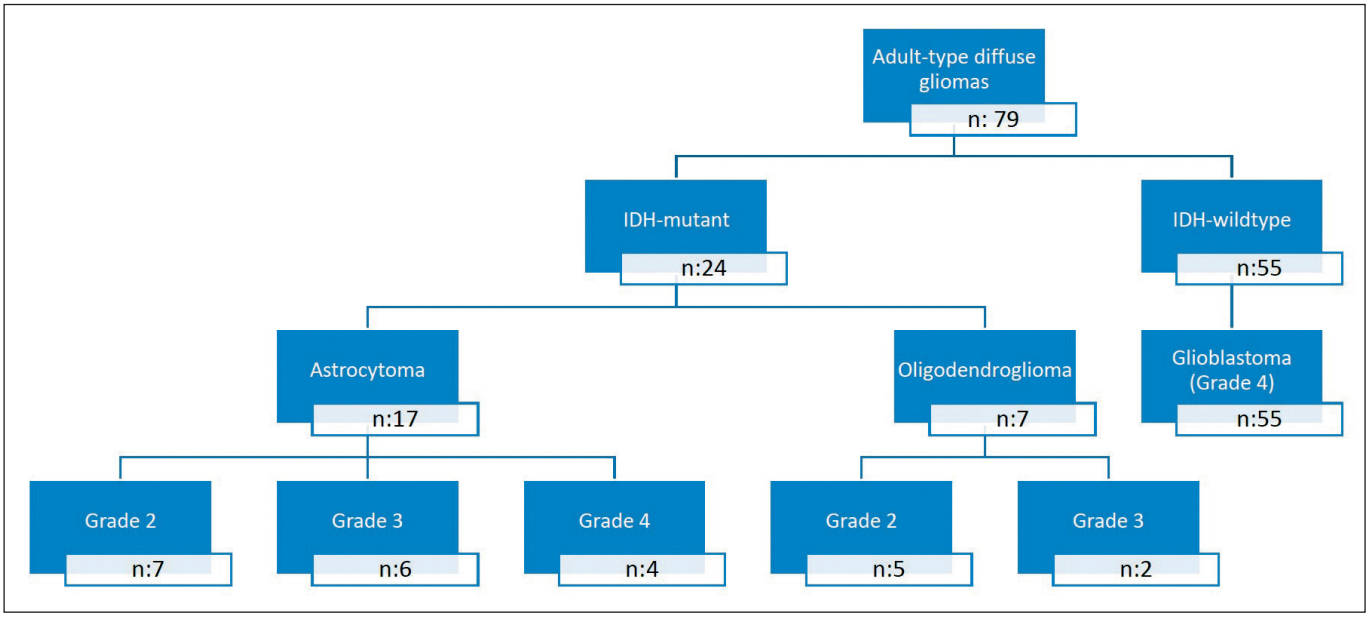

Figure 2: Flow chart depicting the types and IDH mutation status of gliomas according to the WHO 2021 classification.

Table I: Patient Demographics, Contrast Enhancement, and Perfusion Parameters according to IDH Mutation Status

	IDH-mutant (n=24)	Wild-type (n=55)	p
Age	39±10.8	55.8 ± 13.7	**<0.001**
Sex (F:M)	7:17	25:30	0.17
Contrast enhancement	6 (25%)	49 (89.1%)	**<0.001**
rCBVmax	2.41 ± 1.25	4.11 ± 1.71	**<0.001**
PSR^1	0.84 ± 0.14	0.64 ± 0.15	**<0.001**
PSR^2	0.91 ± 0.12	0.75 ± 0.17	**<0.001**
rPSR^1	1 ± 0.17	0.77 ± 0.19	**<0.001**
rPSR^2	1 ± 0.13	0.88 ± 0.21	**<0.01**

Table II: Receiver Operating Characteristic Curve Analysis for Discrimination IDH Gene Mutation Status in Adult Type Gliomas

	Cutoff	Sensitivity %	Specificity %	Area under the curve
rCBVmax	2.56	76.4	70.8	0.814
PSR^1	0.75	83.3	80	0.846
PSR^2	0.83	83.3	74.5	0.793
rPSR^1	0.91	87.5	78.2	0.820
rPSR^2	0.94	79.2	65.5	0.702

Table III: Patient Demographics, Contrast Enhancement, and Perfusion Parameters According to IDH Mutation Status in the High-Grade Glioma Subgroup

	IDH-mutant (n=12)	Wild-type (n=55)	p
Age	34.2 ± 8.3	55.8 ± 13.7	**<0.001**
Sex (F:M)	2:10	25:30	0.065
Contrast enhancement	5 (40%)	49 (92.5%)	**<0.01**
rCBVmax	3 ± 1.43	4.11 ± 1.71	**0.041**
PSR^1	0.86 ± 0.17	0.64 ± 0.16	**<0.001**
PSR^2	0.92 ± 0.14	0.75 ± 0.17	**<0.01**
rPSR^1	1 ± 0.19	0.77 ± 0.19	**0.001**
rPSR^2	1 ± 0.16	0.88 ± 0.21	**0.058**

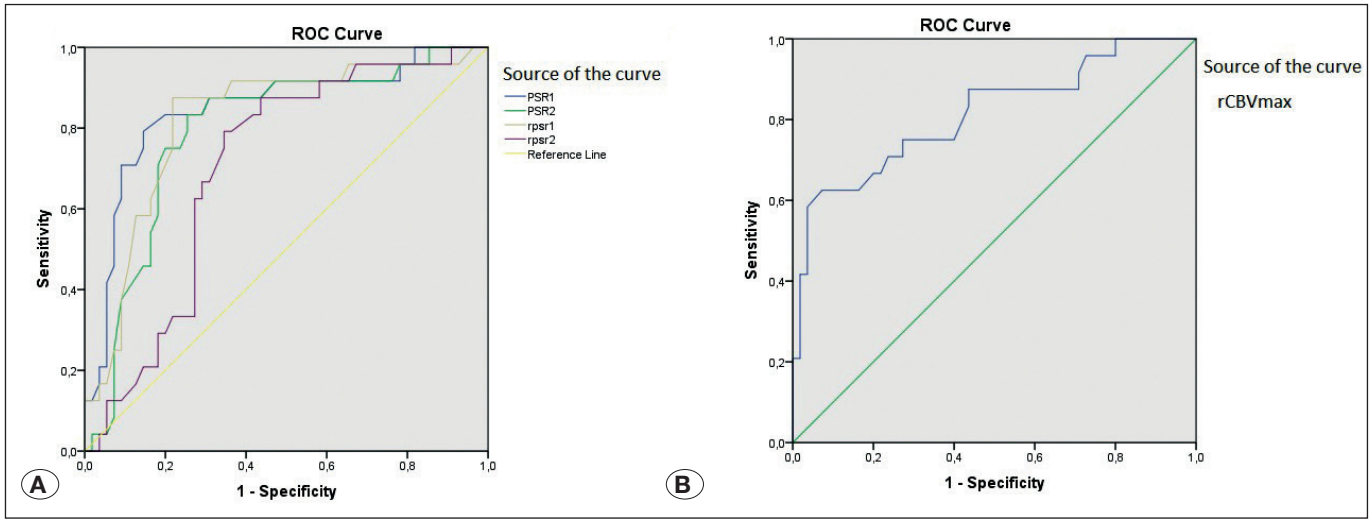

Figure 3A, B: ROC curves for DSC-PI parameters.

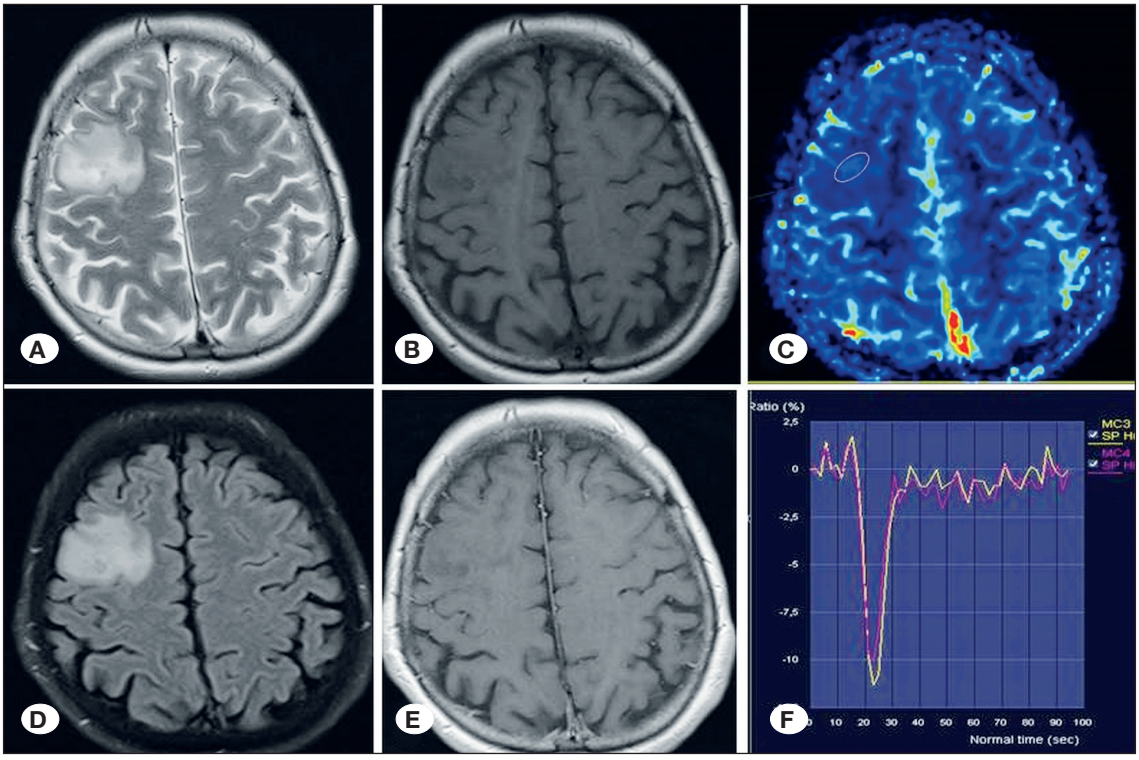

Figure 4: A 48-year-old male patient. T2-weighted **(A)**, FLAIR **(B)**, T1-weighted **(C)**, and contrast-enhanced T1-weighted **(D)** images reveal a tumor in the right frontal lobe. The CBV map **(E)** and time-to-signal intensity curve **(F)** are shown. The rCBVmax is 1.96 and the PSR[1] is 0.98. The pathological diagnosis was grade 2 astrocytoma with an IDH mutation.

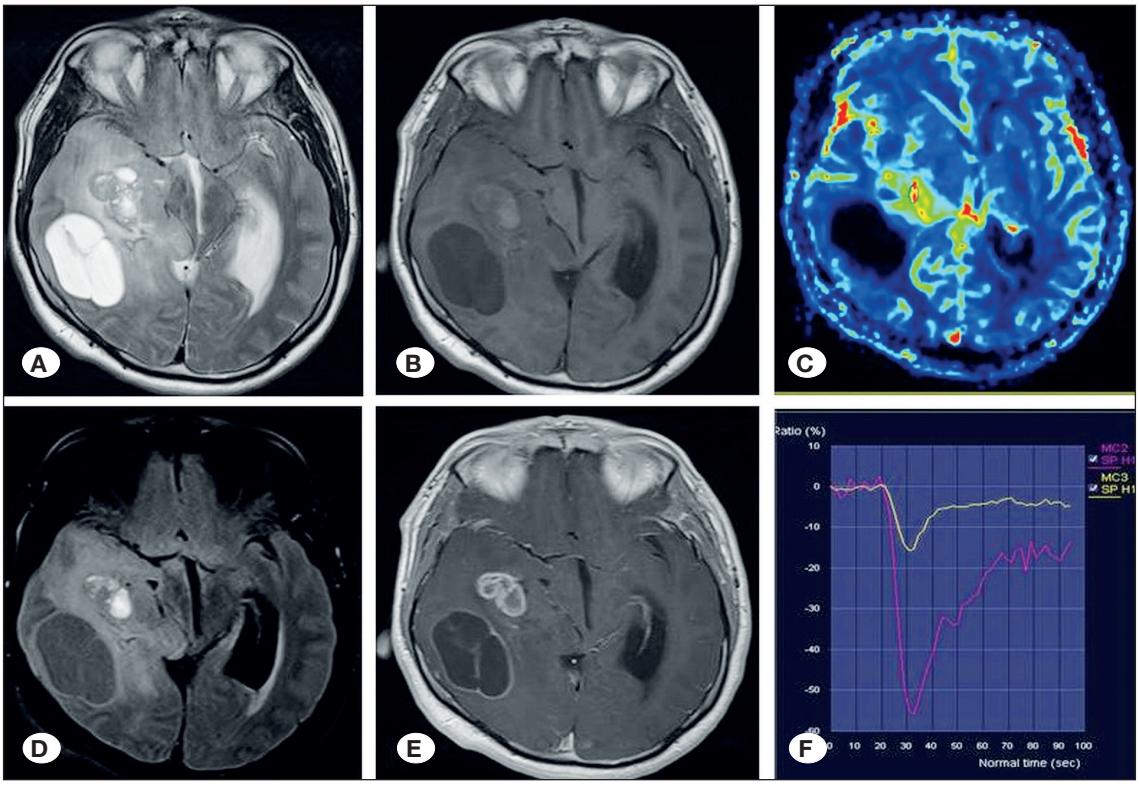

Figure 5: A 40-year-old male patient. Axial T2-weighted **(A)**, FLAIR **(B)**, T1-weighted **(C)**, and contrast-enhanced T1-weighted **(D)** images reveal a tumor with cystic and solid components in the right parietal and temporal lobes. The CBV map **(E)** and time-to-signal intensity curve **(F)** are shown. The rCBVmax is 5.05 and the PSR[1] is 0.49. The pathological diagnosis was IDH-wild-type glioblastoma.

Table IV: Receiver Operating Characteristic Curve Analysis for Discrimination IDH Gene Mutation Status in High-Grade Glioma Subgroup

	Cutoff	Sensitivity %	Specificity %	Area under the curve
rCBVmax	3.42	75	56.4	0.682
PSR[1]	0.77	83.3	85.5	0.842
PSR[2]	0.90	83.3	81.8	0.794
rPSR[1]	0.92	83.3	78.2	0.807

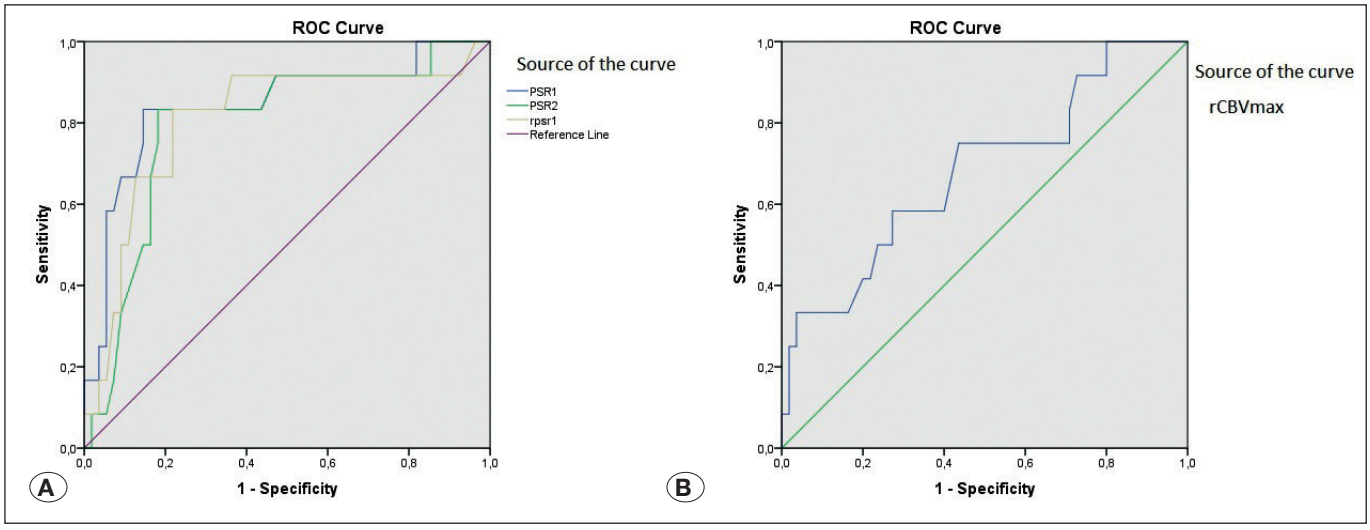

Figure 6:A, B) ROC curves for DSC-PI parameters in the high-grade glioma subgroup.

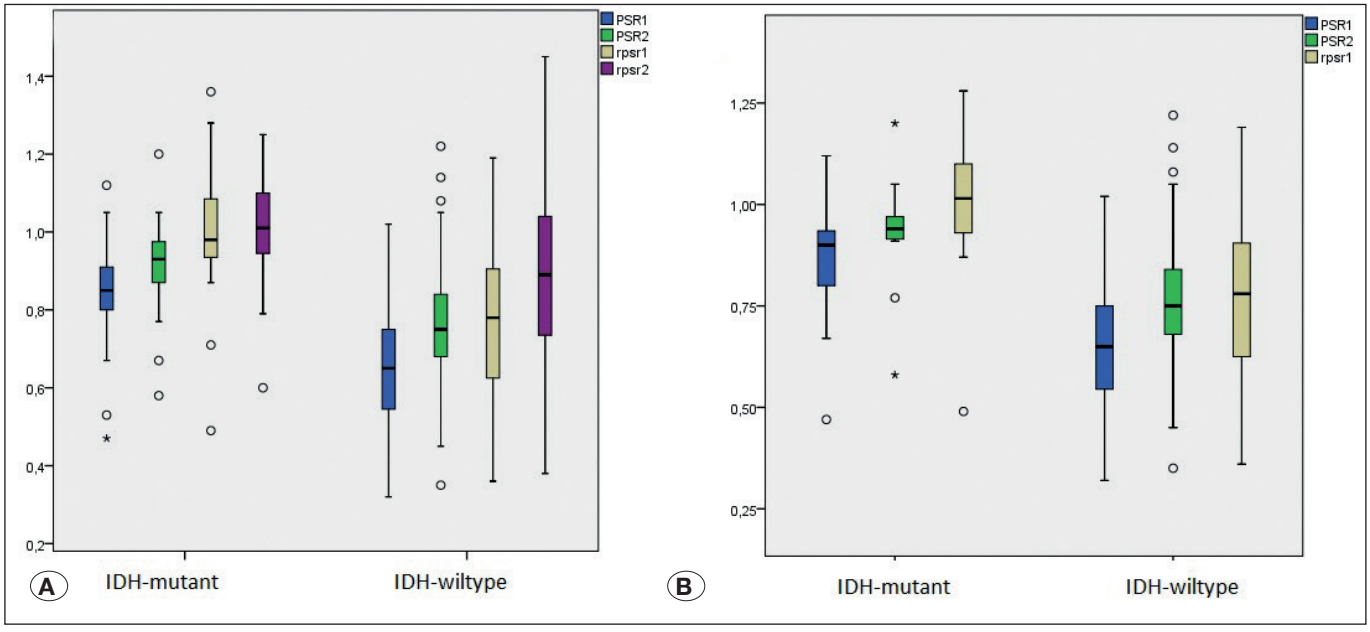

Figure 7: Box-plot graphics of DSC-PI parameters in IDH-mutant and wild-type gliomas. **A)** All gliomas. **B)** High-grade glioma subgroup.

The role of MRI in the noninvasive assessment of IDH gene mutations was examined by several authors. In a recent meta-analysis of 18 MRI studies, the summary sensitivity was 86% and the summary specificity was 87% in predicting IDH mutations (15). Different MRI techniques were analyzed in this meta-analysis, such as conventional MRI, diffusion-weighted imaging, magnetic resonance spectroscopy, susceptibility-weighted imaging, and sodium MRI. Only a few articles focused on the diagnostic success of DSC-PI in determining IDH gene mutations (8,9,16,18). In a recent study conducted by Tan et al. (17), the authors concluded that the rCBV distinguished mutants from wild-type astrocytomas with high sensitivity and specificity. The rCBV cutoff values were 2.20, 3.14, and 5.63 and AUC values were 0.83, 0.86, and 0.94 for grades 2, 3, and 4 astrocytomas, respectively. Given the differences between oligodendrogliomas and astrocytomas in terms of vascular density and rCBV, Tan et al. focused exclusively on astrocytomas. Furthermore, they compared their patients according to the astrocytoma grade (2, 3, or 4), with no intergrade comparisons. Our results were not consistent with the results of Tan et al. (16); in our study cohort, rCBV did not reveal high diagnostic accuracy in differentiating the IDH gene status in high-grade gliomas. The sensitivity was 75% and the specificity was 56.4%, with a cutoff value of 3.42 (AUC: 0.682).

In this present study, all diffuse gliomas, including astrocytomas and oligodendrogliomas with different histopathological grades, were analyzed. Comparing a heterogeneous IDH-mutant glioma group (which includes low-grade glioma cases) with high-grade wild-type glioblastomas can be slightly controversial. That is why we performed subgroup analysis excluding low-grade gliomas. In the analysis of all study cohorts, PSR^1 yielded higher sensitivity, specificity, and AUC values than the rCBVmax. Moreover, when a subgroup containing high-grade gliomas was created, the diagnostic accuracy of PSR^1 increased. In this group, PSR^1 revealed 83.3% sensitivity and 85.5% specificity for determining the IDH gene mutation status, with a cutoff of 0.77. Previous studies regarding DSC-PI in brain tumors reported that rCBV is the most reliable and valuable parameter in determining tumor grade and type (5,7). In this study, we also investigated a relatively less used parameter, PSR. Several studies have explored the role of the PSR in brain tumors. Mangla et al. (11) concluded that the PSR can distinguish malignant intracerebral lesions including glioblastoma, metastases, and lymphomas. They reported that mean PSR values of lymphoma, glioblastoma, and metastases are 1.13 ± 0.41, 0.78 ± 0.14, and 0.53 ± 0.12, respectively. In another study conducted in 2014, the authors concluded that the PSR proved better than the CBV for determining the grade of the brain and is, therefore, a useful tool to be considered in the magnetic resonance evaluation of gliomas (1). A more recent study also reported that the rPSR was inversely correlated with the glial tumor grade and that the overall diagnostic performance of the rPSR was better than those of the rCBV and relative cerebral blood flow in differentiating low- and high-grade gliomas (14). This study did not mention the relationship between the glioma grade and PSR; however, our results revealed high diagnostic performance with PSR in comparison to rCBV for discriminating the IDH mutation in gliomas. Previous studies regarding PSR defined this term as the ratio of signal recovery at the end of first pass of the contrast bolus, whereas this study grouped the PSR as PSR^1 and PSR^2.

There were six IDH wild-type glioblastoma cases without contrast enhancement in our study cohort. Their mean ± SD rCBVmax value was 2.75 ± 0.91, which is closer to the high-grade IDH-mutant glioma group (mean ± SD rCBVmax 3 ± 1.4) rather than the wild-type glioblastoma group (mean ± SD rCBVmax 4.11 ± 1.71). The mean ± SD rCBVmax values were 1.82 ± 0.68, 2.84 ± 1.41, and 3.3 ± 1.62 for grade 2, 3, and 4 IDH-mutant gliomas, respectively. One can infer that the mean rCBVmax value of wild-type glioblastoma cases without contrast enhancement is similar to those of grade 3 IDH-mutant gliomas.

The latest WHO 2021 guidelines have altered the grading of adult-type gliomas, especially via molecular features. Hence, previously reported rCBV and PSR values can be different from our study results, which are based on the latest classification.

Our work had certain limitations. First, as a major limitation, PCR was not performed for the detection of IDH mutations in nonimmunoreactive cases. This study is retrospective, and the number of patients is small. Astrocytomas may exhibit multiple genetic alterations (in the vascular endothelial growth factor and epidermal growth factor receptor genes and altered promoter methylation of oxygen-6-methylguanine-DNA methyltransferase), but we focused only on IDH mutations. As a result of consensus reading, interobserver agreement analysis was not performed. The major strength of this study is that we performed an analysis with diffuse gliomas of various types and grades, including both astrocytomas and oligodendrogliomas.

CONCLUSION

The relative CBV and PSR values derived from DSC-PI are promising in their ability to distinguish gliomas based on the IDH mutation status. IDH-mutant gliomas are associated with lower rCBV and higher PSR^1 values. PSR is a more reliable parameter than rCBV for discrimination between IDH-mutant and wild-type gliomas. Further studies involving more patients are needed.

AUTHORSHIP CONTRIBUTION

Study conception and design: HC, AK, YP

Data collection: HC, NS, AK, MS, EK, HK, PK

Analysis and interpretation of results: AK, HC, EU

Draft manuscript preparation: AK, HC, MSD

Critical revision of the article: HC, YP, AK, EU, MSD

Other (study supervision, fundings, materials, etc...): AK, MS, EK, HK, PK

All authors (AK, HC, NS, MSD, EU, MS, EK, HK, PK, YP) reviewed the results and approved the final version of the manuscript.

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