Application of histogram analysis for the evaluation of vascular permeability in glioma by the K2 parameter obtained with the dynamic susceptibility contrast method: Comparisons with Ktrans obtained with the dynamic contrast enhance method and cerebral blood volume

Toshiaki Taoka MD PhD[1], Hisashi Kawai MD PhD[1], Toshiki Nakane MD PhD[1], Saeka Hori MD[2], Tomoko Ochi MD PhD[2], Toshiteru Miyasaka MD PhD[2], Masahiko Sakamoto MD PhD[2], Kimihiko Kichikawa MD PhD[2], Shinji Naganawa MD PhD[1]

[1]Department of Radiology, Nagoya University, Aichi, Japan

[2]Department of Radiology, Nara Medical University, Nara, Japan

Corresponding Author:

Toshiaki Taoka

Department of Radiology,

Nagoya University Hospital,

65 Tsurumai-cho, Showa-ku, Nagoya, Aichi

466-8550, Japan

Tel: +81-52-744-2327, Fax: +81-52-744-2335

E-mail:ttaoka@med.nagoya-u.ac.jp

Abstract

Purpose: The “K2” value is a factor that represents the vascular permeability of tumors and can be calculated from datasets obtained with the dynamic susceptibility contrast (DSC) method. The purpose of the current study was to correlate K2 with Ktrans, which is a well-established permeability parameter obtained with the dynamic contrast enhance (DCE) method, and determine the usefulness of K2 for glioma grading with histogram analysis.

Methods: The subjects were 22 glioma patients (Grade II: 5, III: 6, IV: 11) who underwent DSC studies, including eight patients in which both DSC and DCE studies were performed on separate days within 10 days. We performed histogram analysis of regions of interest of the tumors and acquired 20th percentile values for leakage-corrected cerebral blood volume ($rCBV_{20\%ile}$), K2 ($K2_{20\%ile}$), and for patients who underwent a DCE study, Ktrans ($Ktrans_{20\%ile}$). We evaluated the correlation between $K2_{20\%ile}$ and $Ktrans_{20\%ile}$ and the statistical difference between $rCBV_{20\%ile}$ and $K2_{20\%ile}$.

Results: We found a statistically significant correlation between $K2_{20\%ile}$ and $Ktrans_{20\%ile}$ ($r = 0.717$, $p < 0.05$). $rCBV_{20\%ile}$ showed a significant difference between Grades II and III and between Grades II and IV, whereas $K2_{20\%ile}$ showed a statistically significant ($p < 0.05$) difference between Grades II and IV and between Grades III and IV.

Conclusions: The K2 value calculated from the DSC dataset, which can be obtained with a short acquisition time, showed a correlation with Ktrans obtained with the DCE method and may be useful for glioma grading when analyzed with histogram analysis.

Key words

Permeability imaging; K2; Perfusion imaging; MRI; Glioma

1. Introduction

Advanced magnetic resonance (MR) imaging techniques including perfusion imaging can provide important in vivo physiological or metabolic information for histopathological grading of gliomas. MR methods have been developed for evaluating the local cerebral circulation, which is useful for characterizing gliomas because tumor aggressiveness is associated with endothelial hyperplasia and neovascularization [1]. The dynamic susceptibility contrast (DSC) method, in which gadolinium-based contrast medium is used as a nondiffusible tracer, provides information about cerebral perfusion including regional cerebral blood volume (rCBV) and regional cerebral blood flow. For this DSC method, contrast medium is injected as a bolus, and a time intensity curve in the tissue is acquired for each voxel for 1 or 2 minutes including the first pass of the contrast medium. In addition to information about tissue perfusion, vascular permeability in the tissue is also correlated with the glioma grade [2, 3]. The standard method for evaluating tissue permeability is the dynamic contrast enhancement (DCE) method, which can provide Ktrans using kinetic analysis with a bidirectional two-compartment model. Although several models have been proposed to analyze the data obtained with DCE measurement [4], the model by Tofts et al. is widely used to evaluate tissue permeability with DCE measurement [5]. However, DCE methods require long imaging times of up to 5 to 10 minutes for dynamic acquisitions.

Tissue permeability can also be calculated using the DSC method, which can be performed in the first pass time window. K2 is an index that represents permeability and can be calculated from the dataset obtained with the DSC method. To measure rCBV with higher accuracy, a mathematical leakage-correction model has been proposed to process the DSC perfusion data. This model allows simultaneous assessment of tumor vascularity and permeability by calculating leakage-corrected rCBV and the leakage coefficient, which is defined as K2, a byproduct of the mathematical correction process that weighs the relative contributions of T1-weighted effects and T2-weighted effects to the signal change observed during rapid passage of MR contrast material [3, 6, 7]. Several studies have applied the K2 value for grading or differential diagnosis of a tumor. Although most of these studies evaluated the mean value within the region of interest (ROI), histogram analysis within the ROI is effective for investigating the correlation with the glioma grade [8].

The purpose of the current study was to evaluate the usefulness of K2 obtained with the DSC method for grading of gliomas, as well as rCBV from the same datasets. We also

performed DCE measurement to calculate Ktrans and evaluated the correlation with K2. For this purpose, we applied histogram analysis in the current study.

2. Materials and Methods

2.1. Subjects

Twenty-two patients with glioma (age range 16 to 82 years old, average: 56 years old, males: 9, females: 13) underwent DSC studies. The number of Grade II gliomas was five (age range 16 to 66 years old, average: 46 years old, males: 1, females: 4), Grade III was six (age range 33 to 82 years old, average: 52 years old, males: 3, females: 3), and Grade IV was 11 (age range 45 to 72 years old, average: 63 years old, males: 5, females: 6). Within this population, eight patients (Grade II: 2 cases, Grade III: 1 case, Grade IV: 5 cases) underwent both DSC and DCE studies, which were performed on separate days within 10 days. Informed consent for the imaging study was obtained from all patients or their families after the nature of the procedures had been fully explained.

2.2. Imaging and post-processing

Imaging was performed with 3-T magnetic resonance imaging (MRI) (Siemens MAGNETOM Verio with a 32-channel head coil). DSC perfusion datasets were acquired using the EPI sequence (TR/TE = 1370/35 ms, field of view (FOV): 240 mm, matrix of 128 × 128, section thickness of 5 mm) during 1-s intervals for 90 s. Gadolinium-based contrast medium (gadopentetate dimeglumine: Magnevist; Bayer Yakuhin, Osaka, Japan, 0.1 mmol/kg body weight) was administered intravenously through a peripheral vein as a bolus, at a rate of 3 mL/s, followed by a flush with 20 mL saline using a power injector.

For the eight cases in which the DCE permeability study was performed on another day, datasets were acquired using the gradient echo sequence (3D VIBE: TR/TE = 3.88/1.31 ms, FA = 12 deg, FOV: 240 mm, matrix of 224 × 224, section thickness of 1 mm) during 10-s intervals for 7 minutes. Gadolinium-based contrast medium was administered at a rate of 1 mL/s, followed by a flush with 20 mL saline using a power injector.

For every examination, usual MRI examination including T2-weighted spin-echo imaging (T2WI; TR/TE 3000/105 ms, 5-mm thickness, 256 × 256 matrix, and 230-mm FOV), FLAIR (TR/TE/TI = 10000/124/2400 ms, 5-mm thickness, 256 × 256 matrix, and 230-mm FOV), and contrast-enhanced T1-weighted spin-echo imaging (T1WI; TR/TE 492/9.50 ms, 5-mm thickness, 256 × 256 matrix, and 230-mm FOV) was

performed.
Images from DSC and DCE studies were transferred to a PC workstation, and K2, rCBV, and Ktrans were calculated using post-processing software Olea Sphere v2.3 (Olea Medical, La Ciotat, France). rCBV computations were made by using the block circulant singular value decomposition with leakage correction. Ktrans computations were made with the Extended Tofts method [5]. K2 computations were made with the method reported by Boxerman et al. [6].

2.3. Histogram analysis

We placed ROIs on the tumor based on Response Assessment in Neuro-Oncology WG (RANO) criteria [9]. Thus, for a "measurable tumor" with contrast enhancing lesions with clearly defined margins, we placed the ROI on contrast-enhanced T1WI and for a "non-measurable tumor" without clearly defined margins on contrast MRI, we placed the ROI on T2WI or FLAIR (Fig. 1). We performed histogram analysis of ROIs of the tumors and acquired 5, 10, 15, 20, and 30%ile values, as well as the mean percentile values for leakage-corrected rCBV, K2, and, for cases with a DCE study, Ktrans (Fig. 2).
We analyzed (1) the correlation between $K2_{20\%ile}$ and $Ktrans_{20\%ile}$ by using simple linear regression and (2) the statistical difference in $rCBV_{20\%ile}$ and $K2_{20\%ile}$ values as well as mean values among glioma grades (II, III, and IV). (3) We also performed the same post-processing for the 5%ile, 10%ile, 15%ile, 30%ile, and the mean values of the same ROIs and performed receiver-operating characteristic (ROC) analysis for grading gliomas (II vs. III and III vs. IV) according to rCBV and K2.

3. Results

(1) We found a statistically significant correlation between $K2_{20\%ile}$ and $Ktrans_{20\%ile}$ ($r = 0.717$, $p < 0.05$, Fig. 3) when analyzing K2 obtained with the DSC method and Ktrans obtained with the DCE method.
(2) For the assessment to discriminate tumor grades at the 20%ile value, rCBV was significantly different between Grades II and III and between Grades II and IV. On the other hand, K2 was significantly different ($p < 0.05$) between Grades II and IV and between Grades III and IV (Fig. 4a, b). For the comparison according to the mean value, rCBV was significantly different between Grades II and III ($p < 0.05$) and between Grades II and IV ($p < 0.05$). However, the mean values of K2 were not significantly different (Fig. 4c, d).
(3) ROC analysis (Fig. 5) indicated a large (>0.8) area under the curve (AUC) for

discrimination between Grades II and III by rCBV for the 5%ile, 15%ile, 20%ile, 30%ile, and mean value. For K2, a large (>0.8) AUC was not obtained. Similarly, for discrimination between Grades III and IV by rCBV, a large (>0.8) AUC was not obtained. For K2, a large (>0.8) AUC was obtained for the 5%ile, 10%ile, 15%ile, 20%ile, and 30%ile.

4. Discussion

To determine the malignancy grade of tumors in the central nervous system, evaluation of rCBV with the DSC method is a standard procedure in clinical practice and is used for post-treatment follow-up. These days, although post-processing involves complex and technical difficulties, Ktrans obtained with the DCE method is also used to evaluate the malignancy of tumors in clinical practice. For example, regarding evaluation of the malignancy of gliomas, rCBV and Ktrans can be used in a complementary manner. Although a significant difference exists between Grade III or higher gliomas and Grade II gliomas with rCBV, Ktrans is significantly different between Grade III and Grade IV [10]. On the other hand, the ability to differentiate the malignancy of gliomas with rCBV and vascular permeability is comparable [11]. Another study indicated that vascular permeability is significantly lower in metastatic brain tumors compared to gliomas [12]. Although typical and atypical meningiomas show no significant difference in rCBV values, Ktrans is significantly higher in atypical meningiomas. Thus, measurement of Ktrans is useful for distinguishing atypical from typical meningiomas [13]. Evaluation of vascular permeability with the DCE method is increasing in popularity for understanding tissue characterization.

Permeability studies with the DCE method can be performed to follow the time course of a post-contrast agent administered in units of "minutes". Because of the recent increase in the number of MRI examinations in clinical practice, time-consuming techniques such as the DCE method have become difficult to perform. Because images for the DSC method can be obtained in a short time, new attempts to acquire information about permeability using the DSC method are increasing in popularity. One method is to calculate the Ktrans from the time signal curve of the DSC method. In addition to calculating the Ktrans value from the data obtained with the usual DSC method, several approaches such as a method using a dual-echo EPI method [14] and a method using the EPI method that combines the spin echo and gradient echo method [15] have been reported. A Ktrans calculation algorithm using the datasets obtained with the DSC method has also been implemented in several commercial software packages.

Another approach is a method that uses the factor of K2, which is used during the leakage correction for rCBV calculations from DSC datasets [3, 6, 16]. K2 is a byproduct of the mathematical leakage correction process and refers to the leakage rate detected in the DSC method. Although quantitative interpretation of K2 is complex, K2 is proportional to the vascular permeability [6].

Many studies on perfusion or permeability of tumors in the central nervous system or other parts of the body have reported development of these methods. In many previous studies, only the mean value of the tumor mass was used as an indicator or predictor of tumor characteristics. However, heterogeneity of the tumor blood supply and other factors within the tumor are well-described phenomena in malignant tumors, and the mean enhancement value does not account for the variable degree of perfusion or other histological factors throughout the tumor [17]. In malignant tumors in particular, the central core of the tumor regions has a poor blood supply, and oxygenation is believed to be heterogeneously distributed throughout the tumor. Therefore, if a mean perfusion or permeability value is used, important information may be lost regarding the quantification of critically low perfusion regions within the tumor [17]. Pixel-by-pixel histogram analysis of perfusion or permeability can now assess these regional variations in tumor microcirculation and allow better assessment of heterogeneity within tumors. Also regarding the problems of interobserver variability, Law et al. indicated that histogram analysis of DSC perfusion imaging data allows prediction of the glioma grade and may be useful for obtaining comparable perfusion metrics by operators compared with ROI-based techniques [8].

In the current study, we performed histogram analysis for the perfusion and permeability metrics including rCBV and K2 obtained with the DSC method and Ktrans obtained with the DCE method. In our histogram analysis of the 20%ile value, Ktrans obtained with the DCE method and K2 obtained with the DSC method correlated well. A recent report that compared the K2 value and Ktrans value of malignant glioma cases indicated that a voxel-wise comparison of K2 obtained with the DSC method and Ktrans calculated with the DSC method revealed nonsignificant linear correlations that may be attributed to competing T1 and T2* leakage effects and the effect of TE on K2 [18]. However, the current study compared these metrics as a group of voxels using histogram analysis and statistically significant linear correlations. Our results indicate the feasibility of using K2 obtained with the DSC method as a substitute for Ktrans obtained with the DCE method. We made comparison across all tumor grades for K2

and Ktrans, since grades of gliomas are classified by histopathological spectrum and sharing the pathological characters. In addition, the small sample size of the cases in which both Trans and K2 were measured is another reason for this comparison. Also in the current study, the rCBV value obtained with the DSC method showed a statistically significant difference between Grades II and III, both in the mean value and with histogram analysis. In contrast, the K2 value obtained with the DSC method showed a statistically significant difference between Grades III and IV only in histogram analysis. Thus, the K2 value obtained with the DSC method can be used as a substitute for Ktrans obtained with the DCE method when histogram analysis (~30%ile) is performed. ROC analysis of the current study also showed that histogram analysis is important for evaluating malignancy of tumor tissues. Comparison of the mean value did not show a statistically significant difference in glioma tissue grades, and application of the histogram analysis might be helpful for evaluation of tumor grades. As shown in a report by Cha et al. [10], a significant difference is present between Grade III or higher gliomas and Grade II gliomas with rCBV, and permeability as measured with the K2 value also showed a significant difference between Grade III and Grade IV in this study.

Our study has several limitations. First of all, the sample size is rather small for making statistical evaluations. So the detailed result may differ by cohorts. However, our result made us believe that usage of K2 with histogram analysis will be helpful for the discrimination between grade III and IV gliomas. Second, because of the clinical environment, we could not compare the value of Ktrans obtained with the DCE method and K2 obtained with the DSC method in all cases. We did not obtain DSC and DCE measurements on the same day to avoid a pre-load effect in the permeability measurement, which makes performing both DSC and DCE studies on different days necessary. Third, our study has lack of direct correlations between perfusion or permeability parameters and histologic findings besides tumor grade. In addition, the K2 value obtained in the DSC study reflects the summation effect of all these factors on vascular leakiness including the vascular surface area, vascular permeability, blood flow, and hydrostatic, interstitial, and osmotic gradients across the endothelium [16]. Thus, the K2 value is not a truly quantitative parameter for measuring tissue permeability, but rather a semi-quantitative or qualitative parameter. Fourth, in order to avoid complexity, we presented result for the evaluation of correlation between K2 and Ktrans and the statistical difference in rCBV and K2 values among glioma grades only result on 20%ile value and mean value without presenting on all percentile value. Instead, we presented ROC curve of every cut off percentile value to show the trend for difference among

cutoff percentile values. We selected 20%ile value for presentation in this report representing 5 to 30%ile values because the area under curve value of ROC analysis showed high value both in rCBV and K2.

5. Conclusion

The K2 value calculated from the DSC dataset, which can be obtained with a short acquisition time, was correlated with Ktrans obtained with the DCE method and seems useful for glioma grading, especially for discrimination between Grades III and IV when evaluated using histogram analysis.

Conflicts of interest: none

References

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Figure Legends

Figure 1

Conventional images for placement of ROI, rCBV images, and K2 images.

a, b, c: Diffuse astrocytoma (Grade II)

d, e, f: Anaplastic astrocytoma (Grade III)

g, h, i: Glioblastoma multiforme (Grade IV)

Conventional images (a: FLAIR, d: T2WI, g: contrast-enhanced T1WI), rCBV images (b, e, h), and K2 images (c, f, i) are shown. ROIs for histogram analysis were placed according to the RANO criteria. For a "measurable tumor" including a contrast enhancing lesion with clearly defined margins, we placed the ROI on contrast-enhanced T1WI (g), and for a "non-measurable tumor" without clearly defined margins on contrast MRI, we placed the ROI on T2WI (e) or FLAIR (b).

Figure 2

Example of a histogram.

The distribution of the number of pixels for the K2 value of an anaplastic astrocytoma (Figure 1 e) is shown. We calculated the 20%ile value of the histogram, as well as the 5, 10, 15, and 30%ile values and the mean value.

Figure 3

Correlation between K2 obtained with the DSC method and Ktrans obtained with the DCE method.

We found a statistically significant correlation between $K2_{20\%ile}$ and $Ktrans_{20\%ile}$ ($r = 0.717$, $p < 0.05$).

Figure 4

Statistically significant differences among grades (II, III, and IV) of gliomas for rCBV and K2 values.

a: Comparison according to the 20%ile rCBV

b: Comparison according to the 20%ile K2

c: Comparison according to the mean rCBV

d: Comparison according to the mean K2

The rCBV value obtained with the DSC method showed a statistically significant difference between Grades II and III, both in the 20%ile value on histogram analysis (a: $p < 0.05$) and the mean value (c: $p < 0.05$). The difference was also statistically

significant between Grades II and IV, both in the 20%ile value on histogram analysis (a: $p < 0.01$) and the mean value (c: $p < 0.05$).
The K2 value obtained with the DSC method showed a statistically significant difference between Grades III and IV only in the 20%ile value on histogram analysis (b: $p < 0.01$). A difference between Grades II and IV was also seen only with the 20%ile value on histogram analysis (b: $p < 0.05$).

Figure 5

ROC analysis for grading gliomas (II vs. III and III vs. IV) by rCBV and K2.

a: ROC for discriminating Grades II and III by rCBV
b: ROC for discriminating Grades II and III by K2
c: ROC for discriminating Grades III and IV by rCBV
d: ROC for discriminating Grades III and IV by K2
Areas under the curve (AUC) for discrimination between Grades II and III by rCBV (a) were: 5%ile: 0.83, 10%ile: 0.77, 15%ile: 0.87, 20%ile: 0.87, 30%ile: 0.87, mean value: 0.87 (Underlined values are larger than 0.8). The same analysis by K2 (b) showed: 5%ile: 0.53, 10%ile: 0.60, 15%ile: 0.67, 20%ile: 0.70, 30%ile: 0.78, mean value: 0.73. Similarly, discrimination between Grades III and IV by rCBV (c) were: 5%ile: 0.67, 10%ile: 0.59, 15%ile: 0.59, 20%ile: 0.53, 30%ile: 0.58, mean value: 0.53. The same analysis by K2 (d) showed: 5%ile: 0.89, 10%ile: 0.91, 15%ile: 0.94, 20%ile: 0.91, 30% ile: 0.86, mean value: 0.32.

Figure 1

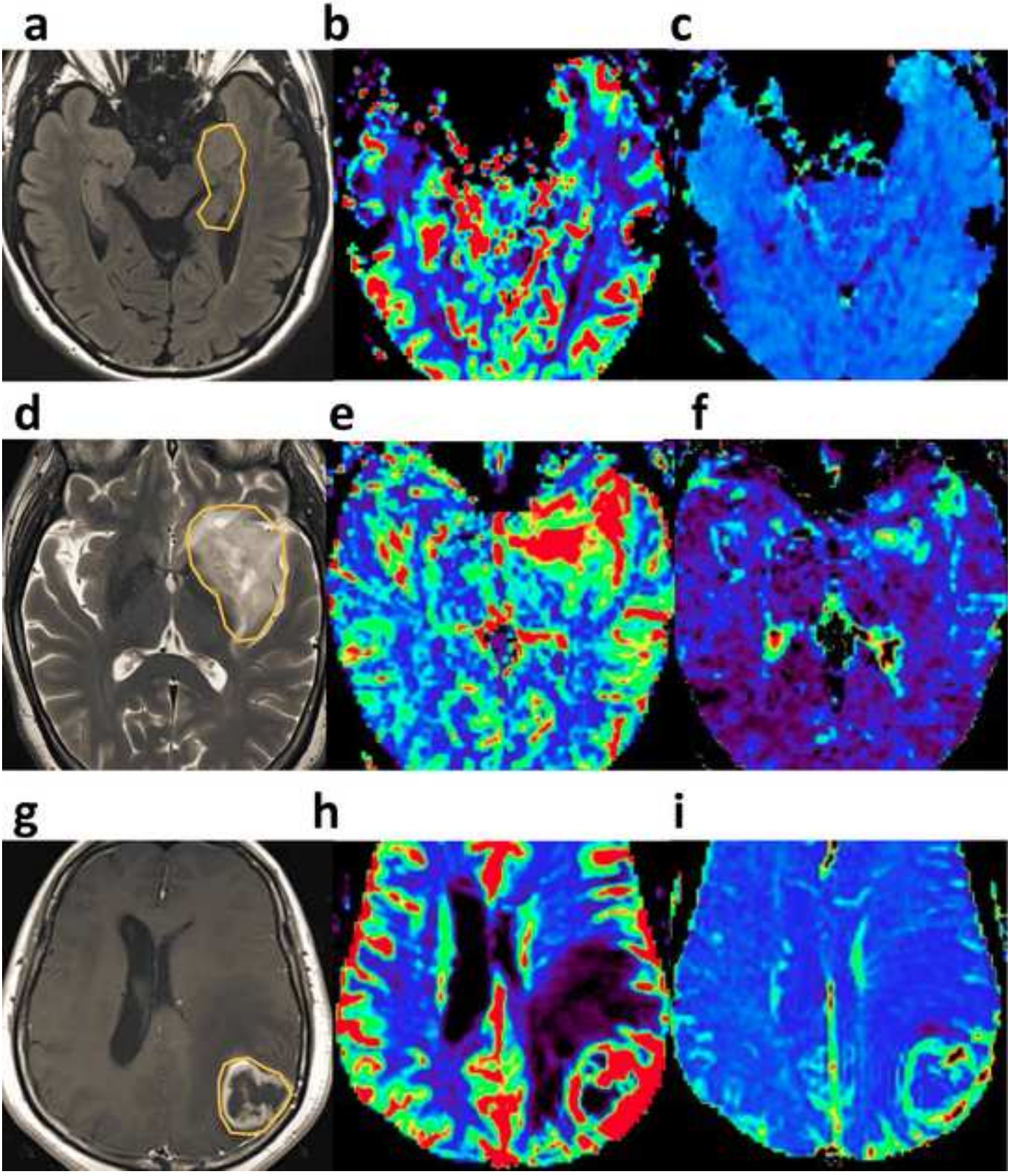


Figure 2

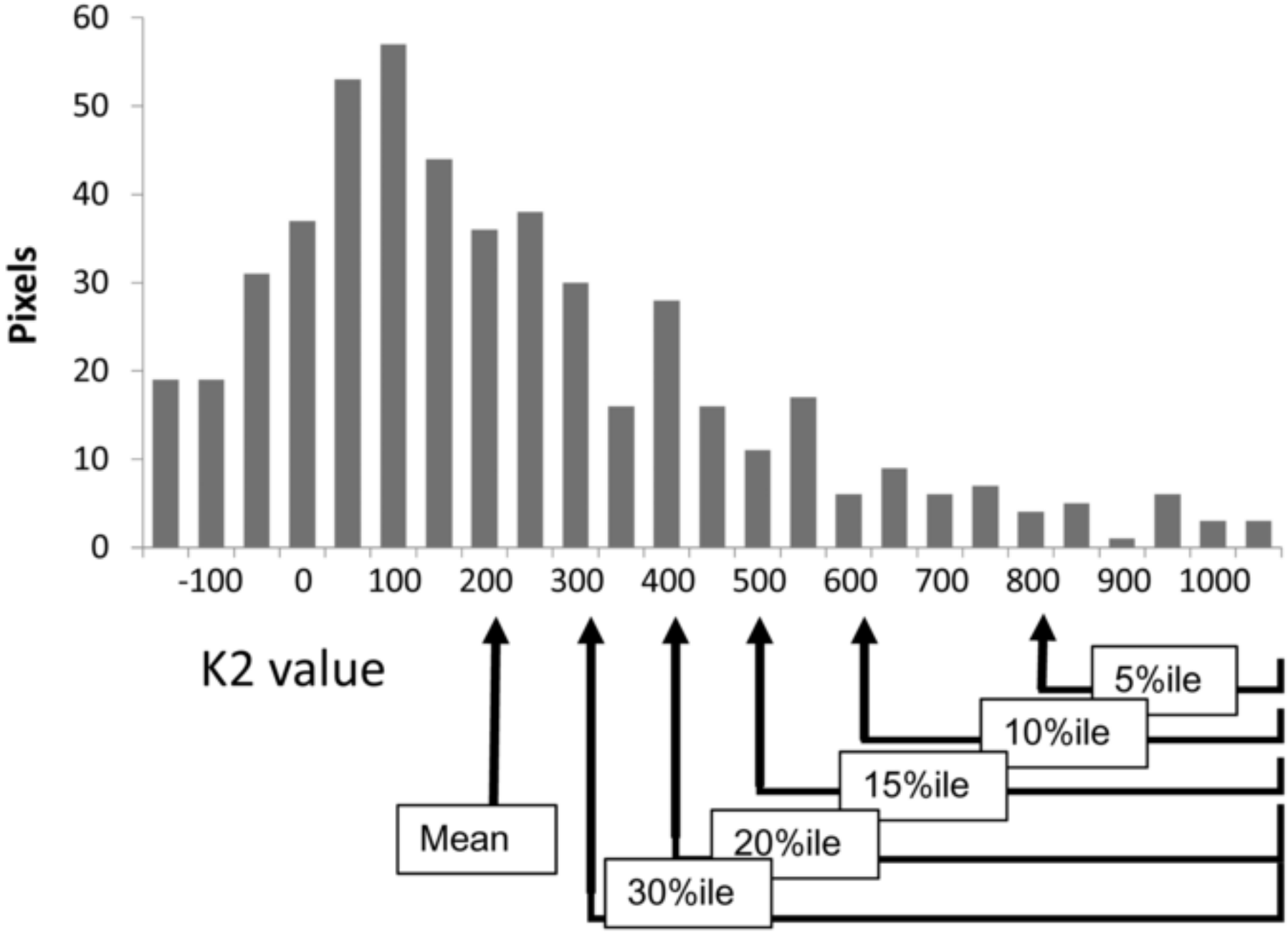

Pixels
60
50
40
30
20
10
0
-100
0
100
200
300
400
500
600
700
800
900
1000
K2 value
Mean
30%ile
20%ile
15%ile
10%ile
5%ile

Figure 3

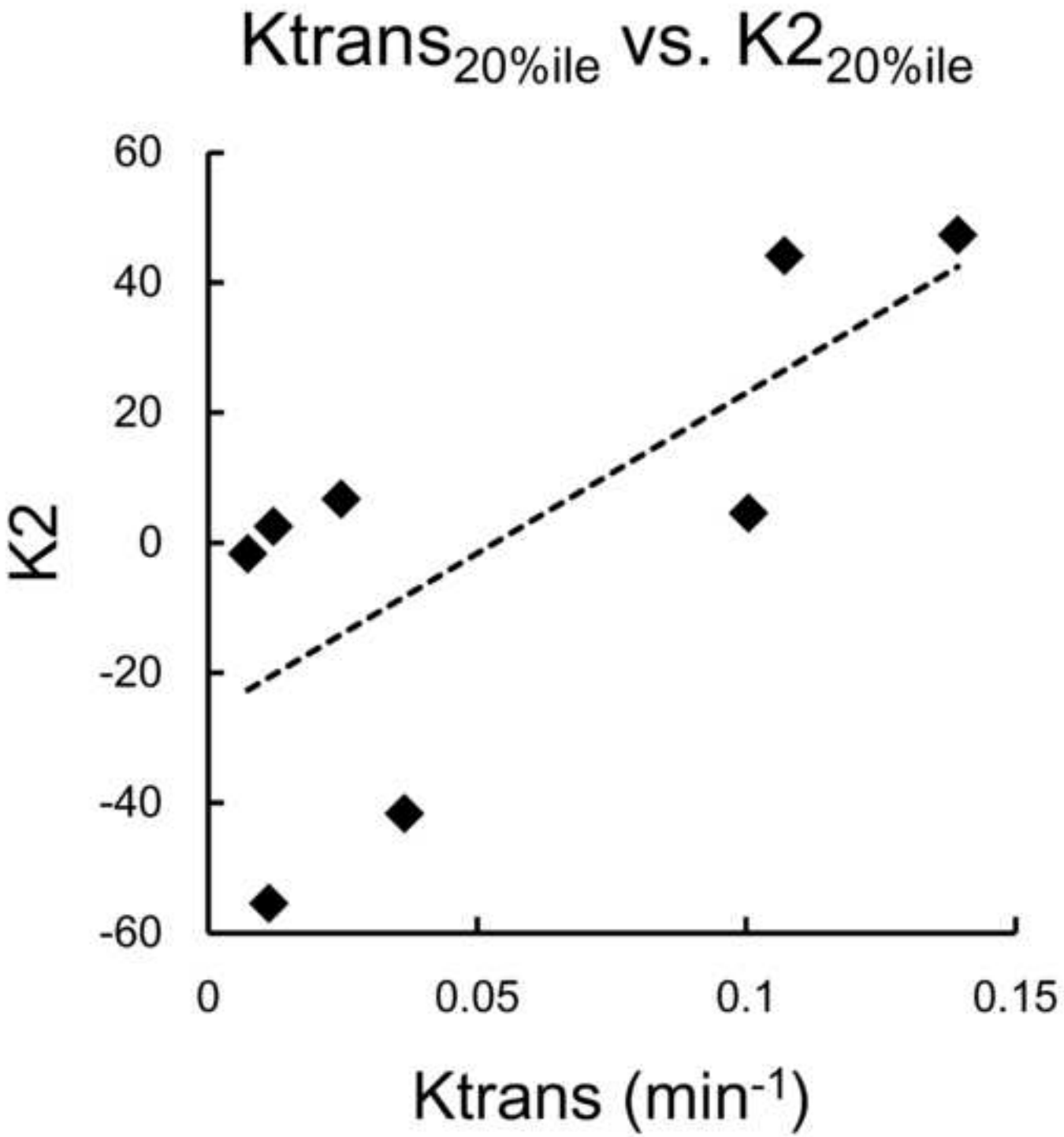

Ktrans20%ile vs. K220%ile
60
40
20
0
-20
-40
-60
K2
0
0.05
0.1
0.15
Ktrans (min-1)

Figure 4

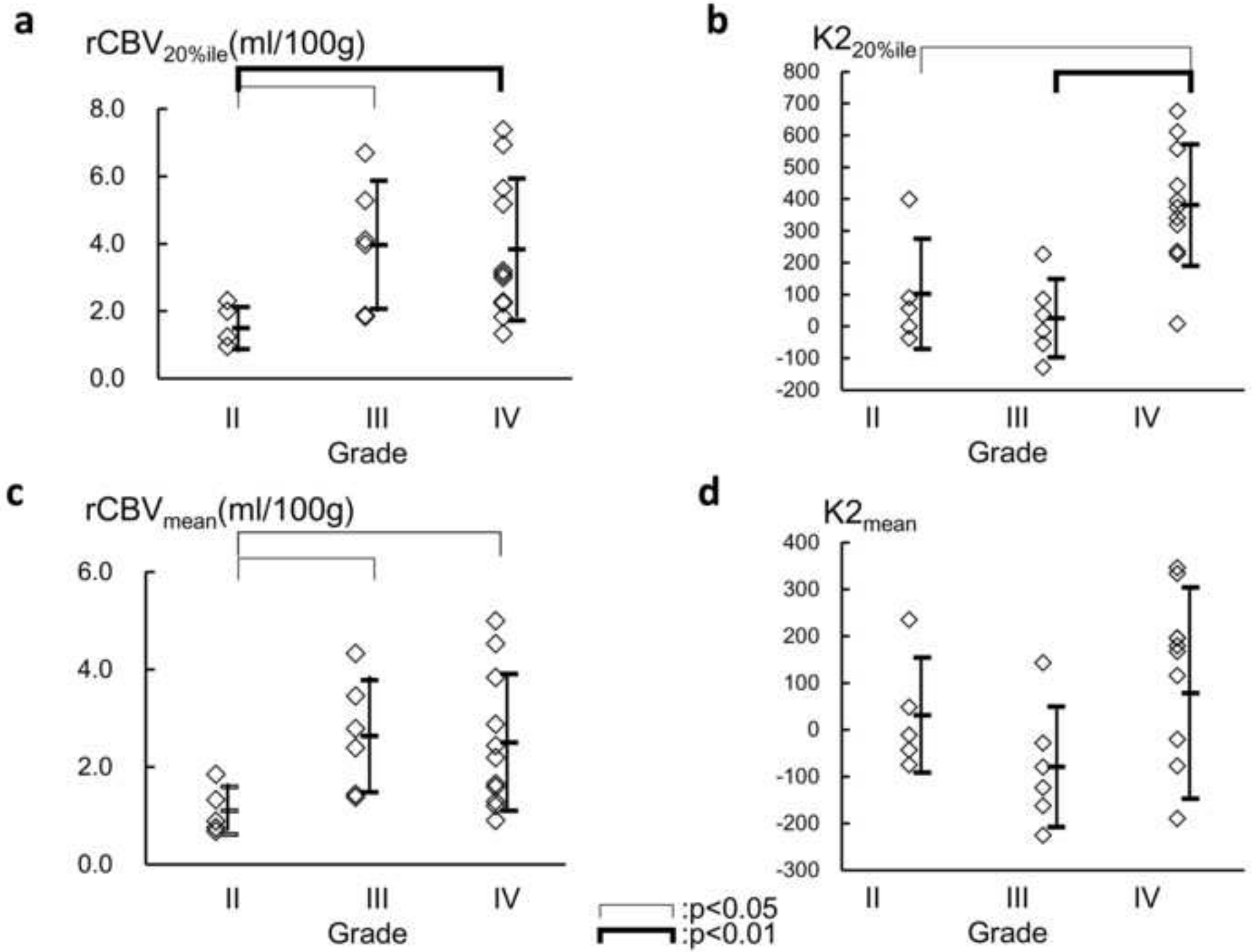
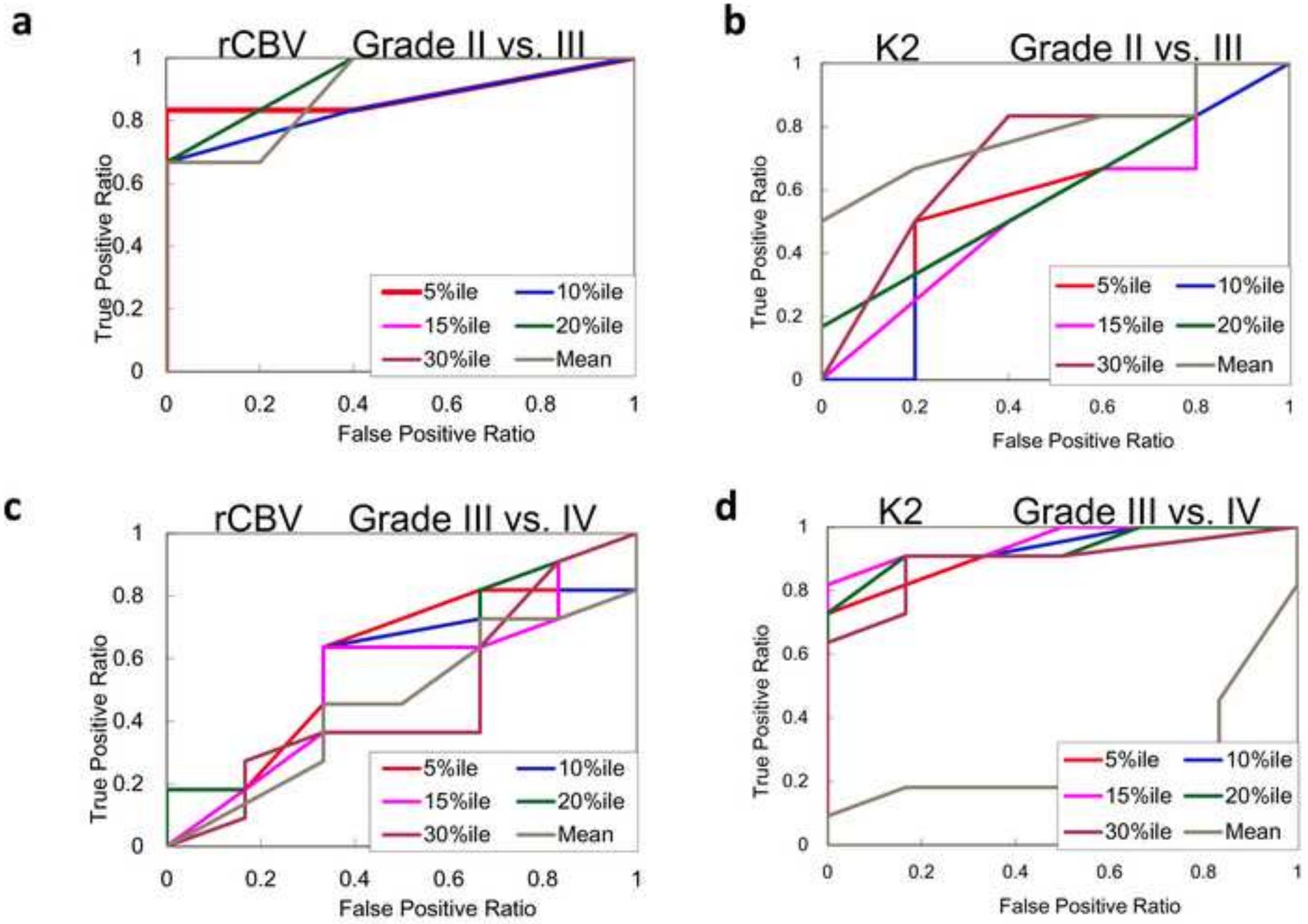

a
rCBV20%ile(ml/100g)
8.0
6.0
4.0
2.0
0.0
II
III
IV
Grade
b
K220%ile
800
700
600
500
400
300
200
100
0
-100
-200
II
III
IV
Grade
c
rCBVmean(ml/100g)
6.0
4.0
2.0
0.0
II
III
IV
Grade
:p<0.05
:p<0.01
d
K2mean
400
300
200
100
0
-100
-200
-300
II
III
IV
Grade

Figure 5


a
rCBV Grade II vs. III
True Positive Ratio
False Positive Ratio
5%ile
10%ile
15%ile
20%ile
30%ile
Mean
b
K2 Grade II vs. III
True Positive Ratio
False Positive Ratio
5%ile
10%ile
15%ile
20%ile
30%ile
Mean
c
rCBV Grade III vs. IV
True Positive Ratio
False Positive Ratio
5%ile
10%ile
15%ile
20%ile
30%ile
Mean
d
K2 Grade III vs. IV
True Positive Ratio
False Positive Ratio
5%ile
10%ile
15%ile
20%ile
30%ile
Mean