Addition of Amide Proton Transfer Imaging to FDG-PET/CT Improves Diagnostic Accuracy in Glioma Grading: A Preliminary Study Using the Continuous Net Reclassification Analysis

A. Sakata, T. Okada, Y. Yamamoto, Y. Fushimi, T. Dodo, Y. Arakawa, Y. Mineharu, B. Schmitt, S. Miyamoto and K. Togashi

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ABSTRACT

BACKGROUND AND PURPOSE: Amide proton transfer imaging has been successfully applied to brain tumors, however, the relationships between amide proton transfer and other quantitative imaging values have yet to be investigated. The aim was to examine the additive value of amide proton transfer imaging alongside $^{[18]}$F FDG-PET and DWI for preoperative grading of gliomas.

MATERIALS AND METHODS: Forty-nine patients with newly diagnosed gliomas were included in this retrospective study. All patients had undergone MR imaging, including DWI and amide proton transfer imaging on 3T scanners, and $^{[18]}$F FDG-PET. Logistic regression analyses were conducted to examine the relationship between each imaging parameter and the presence of high-grade (grade III and/or IV) glioma. These parameters included the tumor-to-normal ratio of FDG uptake, minimum ADC, mean amide proton transfer value, and their combinations. In each model, the overall discriminative power for the detection of high-grade glioma was assessed with receiver operating characteristic curve analysis. Additive information from minimum ADC and mean amide proton transfer was also evaluated by continuous net reclassification improvement. $P < .05$ was considered significant.

RESULTS: Tumor-to-normal ratio, minimum ADC, and mean amide proton transfer demonstrated comparable diagnostic accuracy in differentiating high-grade from low-grade gliomas. When mean amide proton transfer was combined with the tumor-to-normal ratio, the continuous net reclassification improvement was 0.64 (95% CI, 0.036–1.24; $P = .04$) for diagnosing high-grade glioma and 0.95 (95% CI, 0.39–1.52; $P = .001$) for diagnosing glioblastoma. When minimum ADC was combined with the tumor-to-normal ratio, the continuous net reclassification improvement was 0.43 (95% CI, −0.17–1.04; $P = .16$) for diagnosing high-grade glioma, and 1.36 (95% CI, 0.79–1.92; $P < .001$) for diagnosing glioblastoma.

CONCLUSIONS: Addition of amide proton transfer imaging to FDG-PET/CT may improve the ability to differentiate high-grade from low-grade gliomas.

ABBREVIATIONS: ADC$_{\text{min}}$ = minimum ADC; APT = amide proton transfer; AUC = area under the curve; NRI = net reclassification improvement; ROC = receiver operating characteristic; 50 image = reference dataset acquired without presaturation; SUV = standard uptake value; T/N = tumor-to-normal

Magnetic resonance imaging has an established role for the localization, characterization, and diagnosis of brain tumors, as well as for assessing the effects of treatment. Several studies have demonstrated the utility of various types of advanced sequences for grading brain tumors through the visualization of water diffusion, tumor metabolites, or perfusion characteristics. $^{1,2}$ For pre- and postoperative assessment of gliomas, DWI has been the most commonly used of these advanced sequences, $^{2}$ and the derived ADC is a quantitative parameter that is inversely correlated with tumor cellularity and hence glioma grade. $^{3,4}$ However, its clinical impact has remained limited because of the substantial overlap in regional ADCs among gliomas of different grades. $^{5}$

PET is another quantitative imaging technique used in neuro-oncology. $^{2}$ The standard uptake value (SUV) obtained with FDG-PET also plays an important role in the grading of brain tumors. $^{2}$ High-grade gliomas generally show a higher level of glucose metabolism than low-grade gliomas and therefore exhibit increased...
SUV. However, physiologic FDG uptake by the brain may obscure tumor uptake. PET also has shortcomings in terms of the cost, exposure to radiation, and relatively low spatial resolution.

In addition to the aforementioned methods, chemical exchange–dependent saturation transfer imaging has recently emerged as a new contrast mechanism for MR imaging in the field of cellular and molecular imaging.6–8 This method of magnetization transfer imaging has several variants, one of which is amide proton transfer (APT) imaging, which focuses on endogenous cytosolic proteins and peptides with amide protons in the peptide bond.9 This technique has been successfully applied to human brain tumors.3,10–16 Some reports have shown that the APT asymmetry value is useful in tumor grading, allowing differentiation of pseudoprogression from recurrence17 and the assessment of treatment response.18,19 However, the relationship between APT and other quantitative imaging values has yet to be investigated.

The purposes of this study were the following: 1) to compare the diagnostic accuracy of APT imaging for preoperative grading of glial tumors with that of DWI and [18F] FDG-PET, and 2) to examine the additive value of APT imaging combined with [18F] FDG-PET and DWI for the preoperative grading of gliomas. To quantify the additive value of APT imaging, we used a statistical method called the net reclassification index (NRI), an index that shows how well a new model reclassifies subjects.20 NRI is calculated as the difference in the proportion of subjects classified correctly as opposed to wrongly classified after application of a new model. This measure can demonstrate the superiority of a new model over a previous one.

MATERIALS AND METHODS

Our institutional review board approved this retrospective study (R0120), and the requirement to obtain informed consent was waived.

Patients

Eighty-three consecutive adult (older than 18 years of age) patients with suspected supratentorial gliomas who were treated at our hospital between December 2012 and April 2015 were reviewed. The inclusion criteria were the following: 1) pathologic diagnosis of grades II–IV diffuse glioma (2007 World Health Organization criteria)21; 2) the availability of results from preoperative MR imaging, including DWI and APT imaging, and FDG-PET obtained within the year before the operation. Twenty-four patients did not meet the inclusion criteria because of no histologic or histology other than glioma (n = 7) or incomplete datasets (n = 17). Ten patients were also excluded because of major therapeutic intervention (such as an operation, radiation therapy, or chemotherapy including steroids) before imaging (n = 5) or severe artifacts (n = 5). Finally, we analyzed data from 49 patients who underwent [18F] FDG-PET/CT and MR imaging, including DWI and APT imaging. Subsets from this patient population (n = 26; 13 each) have been used in previous publications,15,22 though not with the research focus presented in the current study (Fig 1).

Imaging Acquisition

DWI. MR imaging was conducted by using two 3T scanners (Magnetom Trio; Siemens, Erlangen, Germany) with 32-channel head coils. In addition to the conventional FLAIR sequence (TR/TE, 12,000/100 ms; TI, 2760 ms; flip angle, 120°; resolution, 0.69 × 0.69 mm), T2-weighted FSE (TR/TE, 3200/79 ms; flip angle, 120°; resolution, 0.49 × 0.49 mm) and pre- and postcontrast-enhanced T1-weighted imaging were acquired (using gadopentetate dimeglumine [Magnevist; Bayer HealthCare Pharmaceuticals, Wayne, New Jersey] or gadoteridol [ProHance; Bracco Diagnostics, Princeton, New Jersey]). DWI (TR/TE, 5000/77 ms; resolution, 1.4 × 1.4 mm; slice thickness, 3 mm with a 1-mm gap) was performed with motion-probing gradients of b = 1000 s/mm² applied in 3 orthogonal directions. Images without motion-probing gradients were also obtained, and ADC maps were calculated.

APT. APT imaging was conducted using a prototype 3D gradient-echo pulse sequence (TR/TE, 8.3/3.3 ms; flip angle, 12°; 24 slices; resolution, 1.72 × 1.72 × 4 mm). The presaturation pulses consisted of 3 consecutive radiofrequency pulses of 100-ms duration with 100-ms interpulse delays and a time-average amplitude of 2 μT. Eighteen consecutive datasets were acquired with different offset frequencies Δω (0, ±0.6, ±1.2, ±1.8, ±2.4, ±3.0, ±3.6, ±4.2, and ±4.8 ppm) from the bulk water resonance. Saturated images (S[Δω]) were normalized with a reference dataset acquired without presaturation (50 image). The APT effect was calculated as the asymmetry of the magnetization transfer rate using the following equation: $A_{PT_{\text{asym}}} = (S[-3.5\text{ ppm}] - S[+3.5\text{ ppm}]) / S \times 100\%$. The APT_{asym} at 3.5 ppm was obtained from linear interpolation between the originally sampled points using an offset resolution of 0.1 ppm and subsequent correction for inhomogeneity of the static magnetic field, as previously described.23

FIG 1. Flowchart showing the 83 eligible patients who received a histologic diagnosis of primary glioma after MR imaging and PET and subsequently underwent an operation during the 29-month period.
[18F] FDG-PET. PET was performed with a PET/CT scanner (Discovery ST Elite; GE Healthcare, Milwaukee, Wisconsin). Each patient fasted for at least 4 hours before PET. After intravenous administration of FDG at 4 MBq/kg body weight, the patient rested in a waiting room for 30 minutes. After performing low-dose CT for attenuation correction, we performed emission scans of the brain for 15 minutes with a 128 × 128 matrix and 47 slices (resolution, 2.0 × 2.0 × 3.27 mm). The reconstructed PET data were converted to SUV data using the following equation: SUV = Count at a Pixel (kBq/cm³) / Injection Dose (MBq) / Weight (kg).

Imaging Analysis
All image processing was conducted by 2 neuroradiologists (A.S. and T.O., with 4 and 22 years of experience of imaging processing) in consensus to double-check the quality. Images were co-registered using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) implemented in Matlab (MathWorks, Natick, Massachusetts). All postcontrast T1-weighted, ADC, S0, and APT images were co-registered to the corresponding FLAIR images and resliced; S0 images were used for coregistration of APT images to anatomic images. Registrations were visually inspected and manually corrected if necessary. FDG-PET images were not coregistered to MR images because the image resolution and contrast were different.

Minimum ADC
Two board-certified neuroradiologists (A.S. and T.D., each with 7 years of experience in diagnostic neuroradiology) analyzed the ADC maps independently using ImageJ, Version 1.48 (National Institutes of Health, Bethesda, Maryland). All continuous sections that included tumor were evaluated by placing 3 circular ROIs over the low-intensity area corresponding to the solid portion of the tumor.24 The area of the ROIs was predefined as 30 mm², and each ROI was carefully positioned to avoid contamination from adjacent tissues and estimation errors caused by necrosis, hemorrhage, or calcification.

APTmean
For the APT images, board-certified neuroradiologists (A.S. and T.D.) independently placed an ROI over a representative slice of the tumor (1 ROI per patient). In case of tumors with an enhancing portion, ROIs were drawn on the enhanced area (viable tumor core) on the contrast-enhanced T1-weighted images. When such enhancement was absent, ROIs were drawn by selecting abnormal signal areas on the FLAIR images. Foci of necrosis, hemorrhage, or calcification were manually avoided. All ROIs were applied to the resliced APT images, and mean values (APTmean) were calculated.

Tumor-to-Normal Ratio
For SUVmaximum measurement, 2 neuroradiologists with board certification in nuclear medicine (Y.F. and T.O., with 13 and 18 years of experience respectively) independently drew several oval ROIs (diameter = 10 mm) to include the area with the highest SUV. The number of ROIs varied, depending on the size of the tumor (median, 9; range, 1–25). Fifteen ROIs (5 ROIs on each of 3 axial slices) were also placed on the contralateral frontoparietal gray matter. When a tumor occupied the bilateral lobes, the hemisphere with the largest part of the tumor was defined as the side of the tumor. Semiquantitative analysis was performed using the tumor-to-normal (T/N) ratio, defined as the SUVmaximum in the tumor divided by the average SUV of the normal gray matter.25

Pathologic Analysis
Tumors were graded according to the 2007 World Health Organization classification of brain tumors by board-certified neuropathologists with >15 years of experience.21 The grade of glial tumor was determined on the basis of histologic characteristics such as nuclear atypia, mitosis, microvascular proliferation, and the presence of necrosis. Immunohistochemical analyses were used when necessary. Grade III and IV tumors were considered high-grade, and grade II tumors, as low-grade.

Statistical Analysis
To determine the interrater reliability for continuous data (T/N ratio, minimum ADC [ADCmin], and APTmean measurements), the intraclass correlation coefficient was calculated with a 2-way random model with absolute agreement on average measures. Interpretation of the intraclass correlation coefficient followed methods described by Landis and Koch:26 <0, no reproducibility; 0.0–0.20, slight reproducibility; 0.21–0.40, fair reproducibility; 0.41–0.60, moderate reproducibility; 0.61–0.80, substantial reproducibility; and 0.81–1.00, almost perfect reproducibility.

To assess the ability to correctly differentiate high-grade gliomas, we conducted receiver operating characteristic (ROC) curve analysis for APTmean, ADCmin, and the T/N ratio. We compared the areas under the curve (AUCs) using the method described by DeLong et al.27

Clinical models were created for logistic regression analysis, combining 2 of the 3 parameters APTmean, ADCmin, and the T/N ratio. The added value of the additional imaging beyond [18F] FDG-PET (which showed the highest AUC for the primary outcome) was quantified by consecutively extending the basic model and assessing the increase in AUC. Furthermore, the number of patients correctly reclassified after adding these parameters was expressed as the NRI. The continuous NRI generalizes a summary measure proposed for reclassification tables by eliminating risk categories and defining any increase in model-based probability resulting from the addition of a new marker as upward reclassification, and any decrease as downward reclassification. The continuous NRI index is equal to twice the difference in the probabilities of upward reclassification for the events minus the nonevents.20 Internal validation for both logistic regression analysis and NRI was performed with 1000 bootstrapped samples. Furthermore, we conducted additional ROC and NRI analyses to evaluate the additive value of APT to ADC.

Statistical analysis was performed using STATA, Version 13 software (StataCorp, College Station, Texas). P < .05 was considered indicative of a significant difference.

RESULTS
Patient Characteristics
Forty-nine patients (32 men, 17 women) with a new histopathologic diagnosis of glioma and adequate image sets were included in this study. The mean age was 58.3 years (range, 21–90 years).

Grade II glioma was seen in 15 patients (9 diffuse astrocytomas, 4 oligodendrogliomas, 2 oligoastrocytomas); grade III glioma, in 13 patients (9 anaplastic astrocytomas, 1 anaplastic oligodendroglioma, 3 anaplastic oligoastrocytomas); and glioblastoma, in 21 patients. Five patients underwent surgical biopsy, and 44 patients underwent surgical resection. The characteristics of the patients with low- and high-grade gliomas are given in Table 1. Representative cases are shown in Figs 2 and 3.

**Interrater Reliability**

Interrater reliability showed almost perfect reproducibility for the T/N ratio, ADC_{min}, and APT measurements, with intraclass correlation coefficients of 0.89 (95% confidence interval, 0.81–0.94) for T/N ratio, 0.90 (95% CI, 0.82–0.95) for ADC_{min}, and 0.97 (95% CI, 0.95–0.99) for APT. Given the high interrater reliability, the subsequent statistical evaluation of these measurements used the mean of the values measured by both raters for each patient.

**ROC Curve for Each Single Method and Comparison of AUCs**

Table 2 and On-line Fig 1 summarize the results of ROC curve analysis for each parameter. No significant differences were seen among T/N_{ratio}, APT_{mean}, and ADC_{min} in the differentiation of higher grade gliomas from lower grade ones (grades III and IV versus grade II, \( P = .60 \); grade IV versus grades II and III, \( P = .68 \)).

**Logistic Regression Analysis to Evaluate the Added Value of APT Imaging to [18F] FDG-PET for Differentiation of High- from Low-Grade Gliomas**

Table 3 and On-line Fig 2 summarize the results for the AUCs of each combination of the 2 parameters. In comparison with the AUC for the T/N ratio alone, some tendencies toward improvement were seen with either combination of the T/N ratio and APT_{mean}, but the differences did not reach statistical significance.

**Net Reclassification Improvement to Evaluate the Added Value of APT Imaging to [18F] FDG-PET for the Diagnosis of High-Grade Glioma**

Table 4 summarizes the NRI results for each combination of the 2 parameters. When APT_{mean} was combined with the T/N ratio, the continuous NRI was 0.64 (95% CI, 0.036–1.24, \( P = .04 \)) for diagnosis of high-grade glioma and 0.95 (95% CI, 0.39–1.52; \( P = .001 \)) for the diagnosis of glioblastoma.

**Validation**

Results of the internal validation are summarized in Tables 5 and 6.

**Additive Value of APT Imaging to DWI for Glioma Grading**

Table 7 summarizes the results of the AUCs for a combination of ADC_{min} and APT_{mean}. In comparison with the AUC for ADC_{min} alone, some improvement was observed, though the difference did not reach statistical significance (grades III and IV versus grade II, \( P = .36 \); grade IV versus grades II and III, \( P = .42 \)). The continuous NRI was 0.48 (95% CI, −0.13–1.09, \( P = .12 \)) for the diagnosis of high-grade glioma and 1.14 (95% CI, 0.58–1.71; \( P < .001 \)) for diagnosis of glioblastoma when the APT_{mean} was combined with the ADC_{min}.

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**Table 1: Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Low-Grade Gliomas</th>
<th>High-Grade Gliomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (No.)</td>
<td>15</td>
<td>34</td>
</tr>
<tr>
<td>M/F</td>
<td>10/5</td>
<td>22/12</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>51.5 ± 15.9</td>
<td>59.5 ± 15.6</td>
</tr>
<tr>
<td>Median (range) of interval between surgery and MRI (day)</td>
<td>45 (1–168)</td>
<td>13 (8–76)</td>
</tr>
<tr>
<td>Median (range) of interval between surgery and PET (day)</td>
<td>51 (15–306)</td>
<td>13 (1–218)</td>
</tr>
<tr>
<td>T/N</td>
<td>0.75 ± 0.26</td>
<td>1.19 ± 0.43</td>
</tr>
<tr>
<td>ADC_{min} (×10^{-6} mm^2/s)</td>
<td>980 ± 179</td>
<td>757 ± 221</td>
</tr>
<tr>
<td>APT_{mean} [%]</td>
<td>0.87 ± 0.39</td>
<td>1.33 ± 0.46</td>
</tr>
</tbody>
</table>

**FIG 2.** Glioblastoma in a 65-year-old man. A, Axial MR imaging shows a contrast-enhancing lesion in the left thalamus. B, FDG-PET shows less uptake by the lesion compared with gray matter. C, On the ADC map, the medial portion of the tumor demonstrates focal low-to-intermediate ADC values in comparison with normal brain. D, The APT image shows increased signal in both solid and necrotic portions of the tumor.
DISCUSSION

This study has 2 major findings. First, we demonstrated that APT\textsubscript{mean} offered good diagnostic accuracy for high-grade glioma, comparable with that of other single imaging biomarkers such as ADC\textsubscript{min} or the T/N ratio from \[^{18}F\]FDG-PET. Second, our results also indicated that multiparametric analysis including APT and FDG-PET can improve the classification of gliomas of differing aggressiveness.

By focusing on amide protons, APT imaging has been used to visualize endogenous mobile proteins and peptides, and tissue pH, without requiring administration of a contrast agent.\textsuperscript{9,28,29} The method involves a chemical exchange saturation transfer mechanism, with the signal changes observed being the result of a reduction in the bulk water signal intensity caused by chemical exchanges with magnetically labeled backbone amide protons on a resonance of around +3.5 ppm of that of free water.

Prior studies on APT imaging have been successfully applied to the assessment of human brain tumors.\textsuperscript{3,11-18} However, details of the relationships between APT imaging and other clinical imaging parameters of malignancy have yet to be fully elucidated. This study confirmed that APT imaging can be used for grading glial tumors, with a diagnostic accuracy comparable with that of other imaging biomarkers derived from DWI and FDG-PET. Previous studies have shown the diagnostic accuracy of APT imaging to be comparable with DSC-PWI,\textsuperscript{13,16} and better than contrast-enhanced T1-weighted imaging.\textsuperscript{22} As in previous studies, our results also demonstrated excellent interrater reproducibility in the measurement of APT.\textsuperscript{3,11-16} We believe that for the preoperative grading of brain tumors, APT can be considered an alternative approach to PET and other MR imaging methods such as DWI.

Multiparametric analysis including APT has the potential to improve the diagnostic accuracy in glioma grading. Several researchers have argued that multiparametric MR imaging methods have the potential to improve the diagnostic performance of preoperative glioma grading.\textsuperscript{30-32} Furthermore, Yoon et al\textsuperscript{1} reported that adding FDG-PET to multiparametric MR imaging, including DWI, PWI, and MR spectroscopy, can improve the diagnostic accuracy of glioma grading. However, few studies have examined glioma grading with multiparametric imaging that included APT imaging and PWI or DWI.\textsuperscript{10,16} To the best of our knowledge, our investigation represents the first study to show the utility of multiparametric analysis, including APT and PET, in the preoperative grading of gliomas.

To assess discrimination in the multiparametric logistic regression analysis, we applied 2 different statistical methods: ROC curve analysis and NRI. In ROC analysis, the AUC is commonly used to measure the discriminatory ability of a model to correctly classify subjects with or without a disease and has thus been a standard metric used to quantify improvement. However, this metric is known to have various limitations, including a lack of clinical relevance and difficulty in interpreting small-magnitude changes.\textsuperscript{16} We did not observe any significant gains to the AUCs with the addition of either APT\textsubscript{mean} or ADC\textsubscript{min} to the T/N ratio. This was partly due to the relatively high diagnostic accuracy of each single method. As an alternative, NRI allows

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**Table 2: AUCs of each single parameter for predicting glioma grading**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade II vs Grades III and IV</th>
<th>Grades II and III vs Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC 95% CI</td>
<td>Optimal Cutoff</td>
</tr>
<tr>
<td>T/N</td>
<td>0.84 0.72–0.97</td>
<td>0.88</td>
</tr>
<tr>
<td>APT\textsubscript{mean}</td>
<td>0.76 0.66–0.91</td>
<td>1.26%</td>
</tr>
<tr>
<td>ADC\textsubscript{min}</td>
<td>0.78 0.62–0.90</td>
<td>792.5 $\times 10^{-3}$ mm$^2$/s</td>
</tr>
</tbody>
</table>
quantification of the degree of correct reclassification.\(^{33,34}\) This measure is calculated as a change in the proportion of correct classifications minus incorrect ones, resulting from the new model in comparison with the former one.\(^{20}\) Using this approach, we demonstrated that the addition of APT\(_{mean}\) to the first model with a T/N ratio achieved significant improvements, while the addition of APT\(_{min}\) offered no significant improvement in the discrimination of a T/N ratio. We believe that APT is different from a previous study that demonstrated a significant come (ie, the diagnostic accuracy of high-grade glioma). This is because of our observations and prior research. Our findings indicate that APT, DWI, and FDG-PET are useful for predicting the malignant grade of cerebral glioma. In combination with APT imaging, these imaging modalities may provide additional diagnostic information that is helpful for clinical decision making.

CONCLUSIONS

Our findings indicate that APT, DWI, and FDG-PET are useful for predicting the malignant grade of cerebral glioma. In combination with FDG-PET, we found that APT imaging has additive value, even when different scanners of the same type are used. Finally, we did not examine the relationship between the imaging parameters and the molecular profiles of tumors. Several recent studies have clarified the importance of the molecular status of the tumor, including the mutation of genes such as IDH-1, ATRX, and TERT.\(^{37,38}\) We should conduct further studies to investigate the potential associations between imaging parameters and such molecular or genetic profiles of gliomas.

### Table 3: AUCs of each combination of parameters for predicting glioma grading

<table>
<thead>
<tr>
<th>Grade II vs Grades III and IV</th>
<th>Grade II and III vs Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>95% CI</td>
</tr>
<tr>
<td>T/N + APT(_{mean})</td>
<td>0.85</td>
</tr>
<tr>
<td>T/N + APT(_{min})</td>
<td>0.86</td>
</tr>
<tr>
<td>T/N</td>
<td>0.84</td>
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</tbody>
</table>

Note: NA indicates not applicable.

### Table 4: Continuous NRI results with the combination of 2 imaging parameters

<table>
<thead>
<tr>
<th>Grade II vs Grades III and IV</th>
<th>Grade II and III vs Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRI</td>
<td>95% CI</td>
</tr>
<tr>
<td>T/N + APT(_{mean})</td>
<td>0.64</td>
</tr>
<tr>
<td>T/N + APT(_{min})</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Note: NA indicates not applicable.

### Table 5: Validated logistic regression analysis results with the combination of 2 imaging parameters

<table>
<thead>
<tr>
<th>Grade II vs Grades III and IV</th>
<th>Grade IV vs Grades II and III</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>95% CI (Bias-Corrected)</td>
</tr>
<tr>
<td>T/N + APT(_{mean})</td>
<td>0.86</td>
</tr>
<tr>
<td>T/N + APT(_{min})</td>
<td>0.86</td>
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</tbody>
</table>

### Table 6: Validated continuous NRI results with the combination of 2 imaging parameters

<table>
<thead>
<tr>
<th>Grade II vs Grades III and IV</th>
<th>Grade II and III vs Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRI</td>
<td>95% CI (Bias-Corrected)</td>
</tr>
<tr>
<td>T/N + APT(_{mean})</td>
<td>0.64</td>
</tr>
<tr>
<td>T/N + APT(_{min})</td>
<td>0.49</td>
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</tbody>
</table>

### Table 7: AUCs of ADC\(_{min}\) and APT\(_{mean}\), for predicting glioma grading using ROC curve analysis

<table>
<thead>
<tr>
<th>Grade II vs Grades III and IV</th>
<th>Grade II and III vs Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>95% CI</td>
</tr>
<tr>
<td>ADC(<em>{min}) + APT(</em>{mean})</td>
<td>0.82</td>
</tr>
<tr>
<td>APT(_{mean})</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Note: NA indicates not applicable.

Validity in clinical practice requires larger studies and external validation using larger samples.
ACKNOWLEDGMENTS

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