

RESEARCH ARTICLE

Bolus Arrival Time on Dynamic Contrast-Enhanced Magnetic Resonance Imaging Using the Golden-Angle RADial Sparse Parallel (GRASP) Technique: Characteristics and Clinical Utility in Moyamoya Disease

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Received: 5 March 2025 | **Revised:** 29 May 2025 | **Accepted:** 30 May 2025

Funding: This work was supported by JSPS KAKENHI Grant Numbers JP22K07746, JP24K18796, and The Kyoto University Foundation.

Keywords: bolus arrival time | DCE-MRI | GRASP technique | moyamoya disease | transient ischemic attack

ABSTRACT

Background: Vessel-specific bolus arrival time (BAT) has become calculated with higher spatiotemporal resolution on dynamic contrast-enhanced magnetic resonance imaging using the Golden-angle RADial Sparse Parallel (GRASP) technique. However, its utility in moyamoya disease (MMD) is unclear.

Purpose: To evaluate the relationship between BAT and arterial stenosis/periventricular anastomosis (PA) development, and the utility of BAT in MMD.

Study Type: Retrospective.

Subjects: Sixty-one preoperative MMD patients (mean $\pm$ standard deviation age, 31.0 ± 20.4 years; 46 females; 25 children).

Field Strength/Sequence: 3-T, radial volume interpolated breath-hold examination sequence, and three-dimensional time-of-flight magnetic resonance angiography (3D TOF-MRA).

Assessment: Arterial stenosis, including internal carotid artery, middle cerebral artery (MCA), and posterior cerebral artery, and PA development, including lenticulostriate artery, thalamic perforator, and choroidal channel, were scored on TOF-MRA. Differences in BAT (Δ BATs) between the right and left regions of interest (ROIs), including MCA M2, basal ganglia, thalamus, and choroid plexus, were compared with the right and left arterial stenosis score differences. Δ BATs between the MCA M2 and the ipsilateral basal ganglia, thalamus, and choroid plexus were compared with PA scores. A logistic regression model including Δ BAT was developed to assess the associations with recent transient ischemic attacks (TIAs).

Statistical Tests: Kappa statistic, Friedman test, intraclass correlation coefficient, one-way analysis of variance, Tukey–Kramer test, logistic regression analysis, and receiver operating characteristic analysis. $p < 0.05$ was considered significant.

Results: Δ BATs between the right and left ROIs increased by 0.11–1.76 s depending on arterial stenosis score differences. Δ BATs between the MCA M2 and the ipsilateral ROIs decreased by 0.32–1.46 s with higher PA scores. Models including Δ BAT for recent TIAs showed areas under the curve of 0.81 in children and 0.78 in adults.

Data Conclusion: BAT was indicative of arterial stenosis and PA development, and was associated with recent TIAs in MMD.

Level of Evidence: 3

Technical Efficacy: Stage 2

1 | Introduction

Moyamoya disease (MMD) is a rare cerebrovascular disease characterized by steno-occlusive changes in the circle of Willis, especially in the terminal internal carotid artery (ICA), in which collateral pathways develop to compensate for insufficient blood supply [1, 2]. Although steno-occlusive arterial changes and the development of collateral pathways such as periventricular anastomoses (PAs) do not directly cause symptoms or disabilities, they are associated with risk of ischemic and hemorrhagic events [3–5]. Evaluation of these events using multimodality imaging, including computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), has been a research topic in MMD [4–9], driven by innovations in imaging technology [10–12].

Although multimodality imaging has been used to investigate MMD, the utility of bolus arrival time (BAT) on dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is understudied. BAT, that is, the timing of contrast agent arrival, is an important factor influencing the cerebral circulation [13–15], but its calculation in MMD has been challenging due to the need for higher spatiotemporal resolution [16], and the complexity of cerebral circulation that occurs due to arterial stenosis and collateral development [17]. Furthermore, the inevitable trade-off between temporal resolution and spatial resolution on DCE-MRI is of concern.

Vessel-specific BAT has recently been calculated in these patients with DCE-MRI using the Golden-angle Radial Sparse Parallel (GRASP) technique [18]. In the GRASP technique, data are collected intensively in the center of k-space using radial sampling. By using compressed sensing for image reconstruction with prior knowledge of spatiotemporal redundancy, ultra-fast three-dimensional DCE-MRI can be accomplished with sub-second temporal resolution and iso-voxel spatial resolution of approximately 1 mm [19–21]. The combination of high spatiotemporal resolution and high contrast on DCE-MRI that is possible using this technique enables BAT to be calculated in MMD. Furthermore, DCE-MRI enables calculation of vessel-specific BAT because the intact blood–brain barrier limits enhancement of normal brain parenchyma, resulting in substantially lower signal intensity compared to that of the vessels [22].

Thus the aims of this study were to clarify the characteristics and clinical utility of vessel-specific BAT in MMD by: (1) investigating the optimal reconstruction conditions of the GRASP technique for calculating BAT in MMD; (2) comparing BAT with arterial stenosis and PA development on three-dimensional time-of-flight magnetic resonance angiography (3D TOF-MRA); and (3)

developing a logistic regression model including BAT to identify recent transient ischemic attacks (TIAs) in patients with MMD.

2 | Materials and Methods

2.1 | Ethics Approval and Consent to Participate

Institutional Review Board approval was obtained (No. R4237) and the requirement for written informed consent was waived due to the retrospective nature of the study.

2.2 | Subjects and Data Collection

Seventy consecutive patients of East Asian ethnicity who were clinically diagnosed with MMD [2] and who underwent DCE-MRI using the GRASP technique preoperatively between October 2018 and September 2023 were considered for inclusion in the study. Excluded were: (a) severe motion artifact ($n=1$); (b) no or slight contrast enhancement on DCE-MRI ($n=2$); (c) insufficient data reconstruction ($n=1$) (due to horizontal image orientation); (d) inconstant signal intensity on DCE-MRI ($n=2$) (these cases failed to form a clear slope line in the subsequent time–intensity curve analysis using 13 spokes/frame); and (e) interval > 30 days between DCE-MRI using the GRASP technique and 3D TOF-MRA ($n=3$).

Consequently, 61 preoperative patients with MMD (mean $\pm$ standard deviation age, 31.0 ± 20.4 years; 46 females, 15 males; 25 children, 36 adults; 122 hemispheres) were finally included in the analysis (Figure 1). Demographic and clinical characteristics including age, sex, hypertension, hyperlipidemia, diabetes mellitus, use of antiplatelet drugs, use of antihypertensive drugs, use of antihyperlipidemic drugs, and use of antidiabetic drugs were collected from patients' electronic medical records based on the previous studies in MMD [23–25]. Additionally, recent TIAs were used as an indicator of ischemia in this study. Recent TIA was defined as the occurrence of TIA within the 3 months prior to the MRI. The recent TIA and the corresponding responsible hemisphere were recorded based on clinical assessment. Table 1 lists the patients' demographics. Based on the subjects' age distribution (Figure S1) and the clinical characteristics of MMD [2, 26], the data analyses were conducted separately for all subjects, children (< 18 years of age), and adults.

2.3 | MRI Parameters

All examinations were performed using a 3-T scanner (MAGNETOM Skyra or Prisma; Siemens Healthineers,

Summary

- Plain language summary
 - This study used dynamic contrast-enhanced magnetic resonance imaging with the Golden-angle RAdial Sparse Parallel technique to measure vessel-specific bolus arrival time, which reflects the time it takes for blood to reach specific brain vessels, in moyamoya disease, which is a steno-occlusive cerebrovascular disease.
 - The results demonstrated that differences in bolus arrival time were associated with the arterial stenosis and the development of collateral vessels such as periventricular anastomoses.
 - These differences were also linked to recent transient ischemic attacks.
 - This research highlights the potential of bolus arrival time as a tool for assessing cerebral circulation and ischemia in cerebrovascular diseases.

Erlangen, Germany) with a 64-channel head/neck coil or 32-channel head array coil. Radial volume interpolated breath-hold examination (VIBE) images were acquired as follows: repetition time (TR), 3.25 ms; echo time (TE), 1.53 ms; flip angle (FA), 9°; field of view (FOV), 250 mm × 250 mm; matrix, 256 × 256; slice thickness, 1.0 mm; number of slices, 52; bandwidth, 890 Hz/pixel; acquisition time, 1 min 37 s; total number of spokes, 600. The sequence started approximately 10 s prior to the gadolinium (Gd) contrast agent injection. The Gd contrast agent was administered intravenously at a rate of 1.0 mL/s in adults. In children, the injection was performed manually for safety considerations.

The imaging parameters for 3D TOF-MRA were as follows: TR, 21 ms; TE, 3.7 ms; FA, 20°; echo train length, 68; FOV, 168–187 mm × 220 mm; matrix, 328 × 384; slice thickness, 0.7 mm; number of slices, 156–224; number of slabs, 4–5; and acquisition time, 5 min 50 s to 7 min 18 s.

2.4 | Image Reconstruction and BAT Map

Raw data were anonymized before image reconstruction. Images were reconstructed using dedicated offline software [18, 27]. Temporal resolution was determined by the number of spokes, that is, spokes/frame, which were selected from Fibonacci numbers (i.e., 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, ...). The temporal resolution was calculated as follows:

$$\text{TR} \times \text{number of spokes / frame} \times \text{number of slices}$$

Consequently, the temporal resolutions for 5, 8, 13, 21, 34, 55, and 89 spokes/frame were 0.845, 1.352, 2.197, 3.549, 5.746, 9.295, and 15.041 s, respectively. The acceleration factor was calculated as follows:

$$\frac{\frac{\text{base resolution for read out}}{2} \times \pi}{\text{number of spokes / frame}}$$

Consequently, the acceleration factors for 5, 8, 13, 21, 34, 55, and 89 spokes/frame were 80.4, 50.2, 30.9, 19.1, 11.8, 7.3, and 4.5, respectively.

BAT maps (Figure 2) were generated in a voxel-by-voxel fashion from DCE-MRI (Movie) using an in-house MATLAB (MathWorks, Natick, MA, USA) script. The details of the BAT calculation were as follows. The consecutive frames of the 3D volume (equivalent with initial 20 s before contrast agent arrival) were averaged over time and considered the baseline image. Voxels that showed the top 5% enhancement (defined as the absolute difference between the minimum and the maximum signal intensity throughout the time course) were extracted as candidates for vascular voxels. The time–intensity curve of those voxels was fitted to Tofts' pharmacokinetic model to calculate the maximum slope line [28]. BAT was defined as the time at which the baseline and the maximum slope line intersected (Figure S2). Note that normal brain parenchyma exhibits enhancement after the arrival of the contrast bolus; however, this enhancement is significantly lower than that observed in vascular voxels due to the intact blood–brain barrier [22]. Therefore,

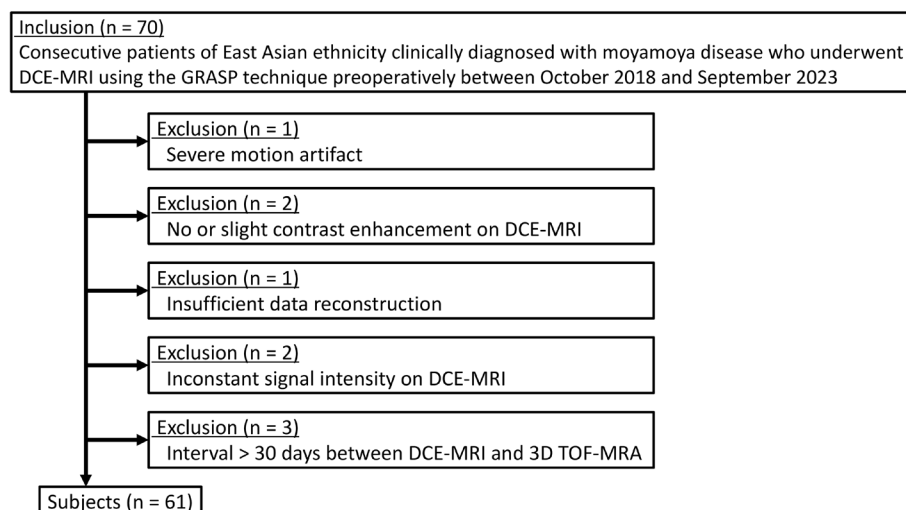


FIGURE 1 | Flowchart of patient enrollment. 3D TOF-MRA, three-dimensional time-of-flight magnetic resonance angiography; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; GRASP, Golden-Angle RAdial Sparse Parallel.

TABLE 1 | Patient demographics.

Characteristic	Overall (n = 61)	Children (n = 25)	Adults (n = 36)
Age (years)*	31.0 ± 20.4	9.4 ± 3.5	46.0 ± 11.8
Sex			
Female	46 (75.4)	17 (68.0)	29 (80.6)
Male	15 (24.6)	8 (32.0)	7 (19.4)
Hypertension	11 (18.0)	0 (0.0)	11 (30.6)
Hyperlipidemia	10 (16.4)	0 (0.0)	10 (27.8)
Diabetes mellitus	1 (1.6)	0 (0.0)	1 (2.8)
Use of antiplatelet drugs	28 (45.9)	16 (64.0)	12 (33.3)
Use of antihypertensive drugs	7 (11.5)	0 (0.0)	7 (19.4)
Use of antihyperlipidemic drugs	5 (8.2)	0 (0.0)	5 (13.9)
Use of antidiabetic drugs	1 (1.6)	0 (0.0)	1 (2.8)
Recent TIA of the right hemisphere	17 (27.9)	8 (32.0)	9 (25.0)
Recent TIA of the left hemisphere	19 (31.1)	11 (44.0)	8 (22.2)
Major medical history			
Developmental venous anomaly	2 (3.3)	1 (4.0)	1 (2.8)
Ophthalmic artery aneurysm	1 (1.6)	0 (0.0)	1 (2.8)
Arteriovenous malformation	1 (1.6)	0 (0.0)	1 (2.8)
Meningioma	1 (1.6)	0 (0.0)	1 (2.8)
Pericallosal lipoma	1 (1.6)	1 (4.0)	0 (0.0)
Metastatic brain tumor	1 (1.6)	0 (0.0)	1 (2.8)

Note: Except where indicated, data are the number of subjects, with percentages in parentheses. Children are defined as subjects < 18 years of age. Recent transient ischemic attack (TIA) is defined as the occurrence of TIA within the 3 months prior to the magnetic resonance imaging.

Abbreviation: TIA, transient ischemic attack.

*Data are presented as the mean ± standard deviation.

BAT calculated by this method is that of vessels, and not of brain parenchyma.

2.5 | ROI

Regions of interest (ROIs) for the right and left middle cerebral artery (MCA) M2 portions, basal ganglia (BG), thalami, and choroid plexuses (CPs) were manually drawn on reconstructed

DCE-MRI and BAT map using ImageJ (NIH, Bethesda, MD, USA) by two board-certified radiologists (S.O. and S.I.: 18 and 10 years of experience in neuroradiology) (Figure S3). To exclude time differences in passing through different slices, all ROIs were drawn on the same slice in each subject. The slice for ROI measurement was selected by the observers to approximate a similar anatomical position across the subjects.

2.6 | Time-Intensity Curve Quality Evaluation to Optimize the Image Reconstruction Condition

An initial check on two patients for several Fibonacci numbers of spokes/frame (Figure S4) showed that 8, 13, and 21 spokes/frame were candidates for the optimal condition. Time-intensity curves for the ROIs were generated on sequentially reconstructed DCE-MRI. The quality of these curves was independently evaluated on all subjects by three board-certified radiologists (S.N., S.O., and S.I.: 20, 18, and 10 years of experience in neuroradiology, respectively) in random order using a 3-point Likert scale as follows: 0, poor; 1, fair; and 2, good.

2.7 | Measurement of BAT

The median BAT value within each ROI was used for subsequent analyses, as extremely high or low values caused by artifacts can affect the mean BAT values. Differences in BAT (ΔBATs) between the right and left MCA M2 portions ($\Delta\text{BAT}_{\text{rtM2-ltM2}}$), BG ($\Delta\text{BAT}_{\text{rtBG-ltBG}}$), and CPs ($\Delta\text{BAT}_{\text{rtCP-ltCP}}$) were calculated for the subsequent comparison. In addition, ΔBATs between the MCA M2 portion and the ipsilateral BG ($\Delta\text{BAT}_{\text{BG-M2}}$), thalamus ($\Delta\text{BAT}_{\text{Tha-M2}}$), and CP ($\Delta\text{BAT}_{\text{CP-M2}}$) were also calculated.

The reason for using ΔBAT for comparisons instead of absolute BAT values was to minimize variations in contrast agent injection timing due to manual initiation, as well as patient-specific differences such as body size and cardiac function [29]. Furthermore, the ICA cavernous portion and other large vessels, particularly those with diameters exceeding 2–3 voxels (voxel size $\sim 1 \text{ mm}^3$), were deemed unsuitable as references for ΔBATs because the inflow effect of large vessels often caused miscalculation of BATs [30]. Accordingly, we employed ΔBAT between the right and left hemispheres, and ΔBAT using the MCA M2 portion as a reference.

2.8 | Scoring for Arterial Stenosis and PA Development on 3D TOF-MRA

Evaluations of arterial stenosis and PA development were conducted on 3D TOF-MRA by the same three board-certified radiologists (S.N., S.O., and S.I.) in random order. MRA scores for arterial stenosis were determined as follows (Figure S5) [31]. For the ICA: 0, normal; 1, stenosis of the ICA C1 portion; 2, discontinuity of the ICA C1 portion; 3, invisible for the ICA. For the MCA: 0, normal; 1, stenosis of the MCA M1 portion; 2, discontinuity of the MCA M1 portion; 3, invisible for the MCA. For the anterior cerebral artery (ACA): 0, the normal ACA A2 portion and its distal; 1, the ACA A2 portion and its

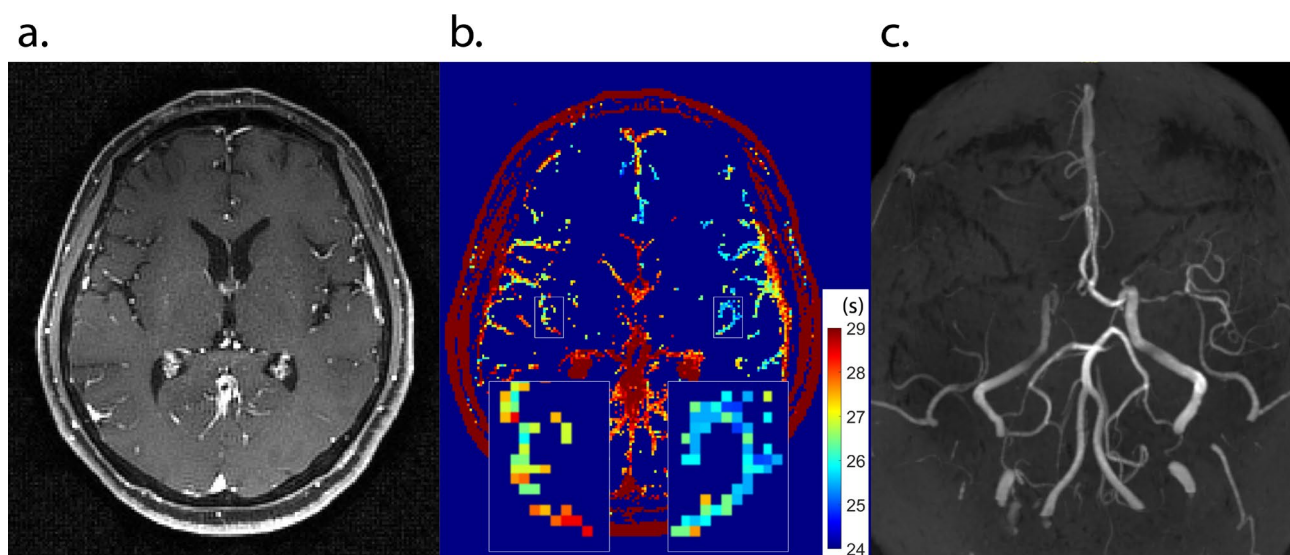


FIGURE 2 | Representative images of a 53-year-old female with right-side dominant moyamoya disease (MMD). (a) Reconstructed dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), (b) bolus arrival time (BAT) map, and (c) corresponding three-dimensional time-of-flight magnetic resonance angiography (3D TOF-MRA) maximum intensity projection (MIP) image. Each colored voxel has its own BAT value (s) (b, color bar). BAT delay is apparent in (b) as yellow to reddish pixels in the right hemisphere (b, left inset) compared with the left hemisphere (b, right inset). In addition, the median BAT value is 26.88 s within the right middle cerebral artery (MCA) M2 portion, and 25.45 s within the left MCA M2 portion. Therefore, the difference in BAT between the right and left MCA M2 portions ($\Delta\text{BAT}_{\text{rtM2-ltM2}}$) is 1.43 s. The MCA MRA score is 3 in the right, and 1 in the left, giving an MCA MRA score difference of 2.

distal signal decrease or loss; 2, invisible for the ACA. For the posterior cerebral artery (PCA): 0, the normal PCA P2 portion and its distal; 1, the PCA P2 portion and its distal signal decrease or loss; 2, invisible for the PCA. The sum of MRA scores for arterial stenosis has been reported to correlate with progression of MMD [31].

MRA scores for PA development were determined as follows (Figure S6) [4, 5]. For the lenticulostriate artery: 0, no dilation or extension; 1, dilation or extension below the level of the pericallosal artery; 2, dilation or extension beyond the level of the pericallosal artery. For the thalamic perforator: 0, no dilation or extension; 1, dilation or extension below the level of the medial posterior choroidal artery; 2, dilation or extension beyond the level of the medial posterior choroidal artery. For the choroidal channel: 0, no dilation or extension; 1, dilation or extension below the level of the lateral ventricle; 2, dilation or extension beyond the level of the lateral ventricle. In a similar manner to arterial stenosis, the sum of MRA scores for PA development is considered an indicator of disease progression [32].

2.9 | Comparison of BAT With Arterial Stenosis and PA Development

$\Delta\text{BAT}_{\text{rtM2-ltM2}}$ and $\Delta\text{BAT}_{\text{rtBG-ltBG}}$ were compared with MRA score differences for the right and left ICA and MCA (Figure S7). $\Delta\text{BAT}_{\text{rtCP-ltCP}}$ were compared with MRA score differences for the right and left PCA. $\Delta\text{BAT}_{\text{BG-M2}}$ were then compared with lenticulostriate artery MRA scores (Figure S7), $\Delta\text{BAT}_{\text{Tha-M2}}$ were compared with thalamic perforator MRA scores, and $\Delta\text{BAT}_{\text{CP-M2}}$ were compared with choroidal channel MRA scores.

2.10 | Statistical Analysis

Interrater reliabilities for time–intensity curve quality evaluation and MRA scores were analyzed using Fleiss' κ statistic. The calculated κ statistic was interpreted as follows: ≤ 0.20 , slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement [33]. Time–intensity curve quality scores were analyzed using a Friedman test followed by pairwise comparisons with Bonferroni correction. ΔBATs measured by the observers were analyzed using intraclass correlation coefficients (ICCs) and visualized with Bland–Altman plots. Comparisons between ΔBATs and MRA score differences/MRA scores were analyzed using one-way analysis of variance (ANOVA) followed by Tukey–Kramer test.

Univariable and multivariable logistic regression analyses were conducted for recent TIAs. Ipsilateral ΔBATs of $\Delta\text{BAT}_{\text{BG-M2}}$, $\Delta\text{BAT}_{\text{Tha-M2}}$, and $\Delta\text{BAT}_{\text{CP-M2}}$, but not bilateral ΔBATs of $\Delta\text{BAT}_{\text{rtM2-ltM2}}$, $\Delta\text{BAT}_{\text{rtBG-ltBG}}$, and $\Delta\text{BAT}_{\text{rtCP-ltCP}}$, were eligible variables because TIA symptoms are hemisphere-specific. The sums of MRA scores for arterial stenosis and PA development were also eligible variables because they are considered an indicator of disease progression [31, 32]. Therefore, clinical information, ipsilateral ΔBATs , and sums of MRA scores were determined as variables. For multivariable analysis, two models were created: (1) a model selecting the three variables with the smallest p values from univariable analyses, and (2) a model including one variable with the smallest p value from each of the following categories in univariable analyses: clinical information, ipsilateral ΔBATs , and sums of MRA scores. The area under the receiver operating

characteristic (ROC) curve (AUC) was analyzed for model assessment. Furthermore, the AUCs of the multivariable models were compared with those of models based on the MRA score alone (MRA-only model), ΔBAT alone (ΔBAT -only model), and the combination of MRA and ΔBAT (MRA + ΔBAT model) to evaluate model performance. A post hoc power analysis was conducted to assess the statistical power of the results from the multivariable models.

All statistical analyses were performed using R version 4.4.1 [34]. A p value < 0.05 indicated statistical significance.

3 | Results

3.1 | Time-Intensity Curve Quality Evaluation to Optimize the Image Reconstruction Condition

Figure S8 summarizes the scores of the three raters. Interrater reliabilities for time-intensity curve quality scores showed substantial to almost perfect agreement ($\kappa = 0.74$ – 0.85) (Table S1). The majority opinion of the raters was designated as the final score. In rare cases where all three raters gave different scores, a consensus was reached through discussion. The majority scores were used for subsequent statistical comparisons. The median [interquartile range] quality scores for 13 spokes/frame (2.0 [2.0–2.0]) and 21 spokes/frame (2.0 [2.0–2.0]) were significantly higher than those for 8 spokes/frame (1.0 [0.5–2.0]) (Table S2). There was no significant difference between 13 and 21 spokes/frame ($p = 0.39$). Considering its higher temporal resolution, 13 spokes/frame with temporal resolution of 2.197s was selected as optimal, and used for BAT calculation.

3.2 | Measurement of BAT

By using 13 spokes/frame, the median BAT values within the ROIs were measured. Subsequently, $\Delta\text{BAT}_{\text{rtM2-ltM2}}$, $\Delta\text{BAT}_{\text{rtBG-ltBG}}$, $\Delta\text{BAT}_{\text{rtCP-ltCP}}$, $\Delta\text{BAT}_{\text{BG-M2}}$, $\Delta\text{BAT}_{\text{Tha-M2}}$, and $\Delta\text{BAT}_{\text{CP-M2}}$ were calculated. The ICCs were 0.88–0.99, suggesting excellent reliability (Table S3). Bland-Altman plots were shown in Figure S9. The mean values of ΔBAT s were used for subsequent comparisons and logistic regression model development.

3.3 | MRA Scores for Arterial Stenosis and PA Development

Figure S10 summarizes the MRA scores of the three raters. Interrater reliabilities were moderate to almost perfect agreement ($\kappa = 0.51$ – 0.93) (Table S1). The majority opinion of the raters was designated as the final score for comparisons with BAT. If the three opinions differed, resolution was obtained by consensus. The final scores are summarized in Table S4. Stenoses in the ICA and MCA were common, whereas PCA stenosis was less likely in both children and adults. Development of the lenticulostriate artery was common in both children and adults, whereas development of the thalamic perforator was more common in children than in adults.

3.4 | Comparison of BAT With Arterial Stenosis and PA Development

Group differences in ΔBAT values according to the right and left arterial stenosis MRA score differences are presented in Table 2 and Figure 3. In all subjects, $\Delta\text{BAT}_{\text{rtM2-ltM2}}$ increased by 0.23–1.39s depending on the combination of the right and left ICA MRA score differences, with 2 out of 6 score difference combinations showing statistically significance. Similarly, $\Delta\text{BAT}_{\text{rtBG-ltBG}}$ increased by 0.11–0.89s depending on the combination of the right and left ICA MRA score differences, with statistical significance observed in 2 of 6 combinations. Regarding the right and left MCA score differences, $\Delta\text{BAT}_{\text{rtM2-ltM2}}$ increased by 0.26–1.40s, with 3 of 6 combinations showing significance, while $\Delta\text{BAT}_{\text{rtBG-ltBG}}$ increased by 0.13–0.85s, with 2 of 6 significant combinations. For the right and left PCA score differences, $\Delta\text{BAT}_{\text{rtCP-ltCP}}$ increased by 0.34–1.76s, with statistical significance noted in 2 out of 3 combinations.

Group differences in ΔBAT values for each group of MRA score related to PA development are presented in Table 3 and Figure 4. In all subjects, $\Delta\text{BAT}_{\text{BG-M2}}$ decreased by 0.69–1.46s depending on the combination of lenticulostriate artery scores, with all 3 score combinations demonstrating statistical significance. $\Delta\text{BAT}_{\text{Tha-M2}}$ decreased by 0.59–1.34s for the combination of thalamic perforator scores, with significance in 2 of 3 combinations. $\Delta\text{BAT}_{\text{CP-M2}}$ decreased by 0.32–0.70s with the combination of choroidal channel scores, and 1 of 3 combinations reached statistical significance.

3.5 | Univariable and Multivariable Logistic Regression Analyses for Recent TIAs

Univariable and multivariable logistic regression analyses for recent TIAs were conducted separately for children and adults based on subjects' age distribution (Figure S1) and the clinical characteristics of MMD [2, 26]. For 50 hemispheres in 25 children, univariable analyses were conducted using the following variables: age, sex, use of antiplatelet drugs, $\Delta\text{BAT}_{\text{BG-M2}}$, $\Delta\text{BAT}_{\text{Tha-M2}}$, $\Delta\text{BAT}_{\text{CP-M2}}$, sum of MRA scores for arterial stenosis, and sum of MRA scores for PA development. Because no pediatric patient had hypertension, hyperlipidemia or diabetes mellitus, these variables and their associated medications were excluded from the analysis. The three variables with the smallest p values in univariable analyses were age (odds ratio (OR), 0.81; 95% confidence interval (CI): 0.65, 0.97), use of antiplatelet drugs (OR, 4.67; 95% CI: 1.23, 23.2), and $\Delta\text{BAT}_{\text{CP-M2}}$ (OR, 0.45; 95% CI: 0.19, 0.93) (Table 4). Child multivariable model [1] that included age (OR, 0.88; 95% CI: 0.70, 1.08; $p = 0.23$), use of antiplatelet drugs (OR, 2.86; 95% CI: 0.66, 15.2; $p = 0.18$), and $\Delta\text{BAT}_{\text{CP-M2}}$ (OR, 0.62; 95% CI: 0.24, 1.41; $p = 0.28$) showed an AUC of 0.77 (Figure 5).

Moreover, one variable with the smallest p value in clinical information, one variable with the smallest p value in ipsilateral ΔBAT s including $\Delta\text{BAT}_{\text{BG-M2}}$, $\Delta\text{BAT}_{\text{Tha-M2}}$, and $\Delta\text{BAT}_{\text{CP-M2}}$, and one variable with the smallest P value in sums of MRA scores in univariable analyses were selected for the child multivariable model [2]. Among the variables included in the child

TABLE 2 | Group differences in difference in bolus arrival time values (s) for each group of the right and left MRA score differences.

	Overall		Children		Adults	
	Mean difference	<i>p</i>	Mean difference	<i>p</i>	Mean difference	<i>p</i>
$\Delta\text{BAT}_{\text{rtM2-ltM2}}$ for the right and left ICA MRA score difference						
Score difference 0–score difference 1	−0.51 (0.29)	0.10	−0.49 (0.34)	0.25	−0.59 (0.49)	0.38
Score difference 0–score difference 2	−0.74 (0.32)	0.016*	−0.80 (0.39)	0.054	−0.71 (0.49)	0.23
Score difference 0–score difference 3	−1.39 (0.45)	<0.001*	−0.96 (0.77)	0.36	−1.49 (0.60)	0.013*
Score difference 1–score difference 2	−0.23 (0.34)	0.82	−0.31 (0.37)	0.69	−0.11 (0.58)	0.99
Score difference 1–score difference 3	−0.88 (0.47)	0.078	−0.46 (0.76)	0.84	−0.89 (0.68)	0.32
Score difference 2–score difference 3	−0.65 (0.49)	0.30	−0.15 (0.78)	0.99	−0.78 (0.68)	0.44
$\Delta\text{BAT}_{\text{rtBG-ltBG}}$ for the right and left ICA MRA score difference						
Score difference 0–score difference 1	−0.11 (0.23)	0.92	0.08 (0.32)	0.99	−0.37 (0.34)	0.47
Score difference 0–score difference 2	−0.29 (0.25)	0.41	−0.14 (0.36)	0.96	−0.43 (0.34)	0.36
Score difference 0–score difference 3	−0.89 (0.36)	0.0091*	−0.39 (0.72)	0.88	−1.01 (0.42)	0.017*
Score difference 1–score difference 2	−0.19 (0.27)	0.80	−0.22 (0.35)	0.84	−0.05 (0.41)	> 0.99
Score difference 1–score difference 3	−0.78 (0.37)	0.036*	−0.47 (0.71)	0.81	−0.63 (0.48)	0.31
Score difference 2–score difference 3	−0.59 (0.38)	0.18	−0.25 (0.73)	0.97	−0.58 (0.48)	0.38
$\Delta\text{BAT}_{\text{rtM2-ltM2}}$ for the right and left MCA MRA score difference						
Score difference 0–score difference 1	−0.66 (0.29)	0.019*	−0.74 (0.30)	0.017*	−0.43 (0.55)	0.72
Score difference 0–score difference 2	−1.14 (0.32)	<0.001*	−0.99 (0.33)	0.0042*	−1.32 (0.55)	0.015*
Score difference 0–score difference 3	−1.40 (0.37)	<0.001*	NA	NA	−1.41 (0.46)	0.0017*
Score difference 1–score difference 2	−0.47 (0.35)	0.28	−0.25 (0.28)	0.55	−0.89 (0.69)	0.33
Score difference 1–score difference 3	−0.74 (0.39)	0.075	NA	NA	−0.97 (0.62)	0.18
Score difference 2–score difference 3	−0.26 (0.42)	0.84	NA	NA	−0.08 (0.62)	> 0.99
$\Delta\text{BAT}_{\text{rtBG-ltBG}}$ for the right and left MCA MRA score difference						
Score difference 0–score difference 1	−0.42 (0.22)	0.059	−0.59 (0.26)	0.034*	−0.55 (0.36)	0.19

(Continues)

TABLE 2 | (Continued)

	Overall		Children		Adults	
	Mean difference	<i>p</i>	Mean difference	<i>p</i>	Mean difference	<i>p</i>
Score difference 0–score difference 2	−0.55 (0.24)	0.019*	−0.53 (0.29)	0.095	−0.85 (0.36)	0.016*
Score difference 0–score difference 3	−0.85 (0.28)	<0.001*	NA	NA	−0.76 (0.30)	0.0097*
Score difference 1–score difference 2	−0.13 (0.26)	0.91	0.06 (0.25)	0.96	−0.30 (0.45)	0.80
Score difference 1–score difference 3	−0.42 (0.29)	0.23	NA	NA	−0.21 (0.40)	0.89
Score difference 2–score difference 3	−0.29 (0.31)	0.60	NA	NA	0.09 (0.40)	0.99
$\Delta\text{BAT}_{\text{rtCP-ltCP}}$ for the right and left PCA MRA score difference						
Score difference 0–score difference 1	−0.34 (0.19)	0.082	−0.34 (0.32)	0.42	−0.33 (0.24)	0.24
Score difference 0–score difference 2	−1.76 (0.39)	<0.001*	−1.84 (0.76)	0.020*	−1.73 (0.46)	<0.001*
Score difference 1–score difference 2	−1.42 (0.41)	<0.001*	−1.51 (0.78)	0.071	−1.40 (0.49)	0.0043*

Note: Data in parentheses are standard errors. NA, not available. * indicates $p < 0.05$.

Abbreviations: $\Delta\text{BAT}_{\text{rtBG-ltBG}}$, difference in bolus arrival time between the right and left basal ganglia; $\Delta\text{BAT}_{\text{rtCP-ltCP}}$, difference in bolus arrival time between the right and left choroid plexuses; $\Delta\text{BAT}_{\text{rtM2-ltM2}}$, difference in bolus arrival time between the right and left middle cerebral artery M2 portions; ICA, internal carotid artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; PCA, posterior cerebral artery.

multivariable model [2], age (OR, 0.72; 95% CI: 0.52, 0.93) and the sum of MRA scores for PA development (OR, 1.95; 95% CI: 1.06, 4.01) were significantly associated with recent TIAs, while $\Delta\text{BAT}_{\text{CP-M2}}$ (OR, 1.15; 95% CI: 0.37, 3.50; $p = 0.80$) was not statistically significant (Table 4). The child multivariable model [2] showed an AUC of 0.81 (Figure 5).

For 72 hemispheres in 36 adults, hypertension, hyperlipidemia, use of antihypertensive drugs, and use of antihyperlipidemic drugs were included as variables in addition to those included in children. Because only one adult patient had diabetes mellitus and used antidiabetic medication, diabetes mellitus and use of diabetic drugs were excluded from the analysis. The three variables with the smallest p values in univariable analyses were hypertension (OR, 3.08; 95% CI: 0.95, 10.2; $p = 0.061$), $\Delta\text{BAT}_{\text{BG-M2}}$ (OR, 1.58; 95% CI: 0.98, 2.95; $p = 0.088$), and sum of MRA scores for arterial stenosis (OR, 1.22; 95% CI: 0.94, 1.62; $p = 0.16$) (Table 5). This variable selection also met the condition of one variable with the smallest p value in clinical information, one variable with the smallest p value in ipsilateral ΔBAT s, and one variable with the smallest P value in sums of MRA scores in univariable analyses. All variables included in the adult multivariable model, hypertension (OR, 4.65; 95% CI: 1.27, 18.8), $\Delta\text{BAT}_{\text{BG-M2}}$ (OR, 2.29; 95% CI: 1.26, 5.61), and sum of MRA scores for arterial stenosis (OR, 1.40; 95% CI: 1.02, 2.03) were significantly associated with recent TIAs (Table 5). The adult multivariable model showed an AUC of 0.78 (Figure 5).

In comparison of AUCs, all multivariable models (child multivariable model (1), child multivariable model (2), and adult multivariable model) outperformed MRA-only model, ΔBAT -only

model, and MRA + ΔBAT model in both children and adults (Table S5).

4 | Discussion

Vessel-specific BAT was calculated on DCE-MRI using the GRASP technique and was found to reflect arterial stenosis and PA development in patients with MMD. Furthermore, ΔBAT was associated with recent TIAs.

On DCE-MRI using the GRASP technique, 13 spokes/frame was determined to be optimal for BAT calculation in MMD. The ability to choose the image reconstruction conditions of DCE-MRI using the GRASP technique allowed flexible adjustment of the temporal resolution and image quality [18], facilitating optimization that enabled observation of BAT changes resulting from arterial stenosis and PA development.

BAT reflected arterial stenosis and PA development, suggesting that the delayed arrival of Gd contrast agents is associated with the stenotic vascular territories [35], whereas faster arrival was linked to the well-developed collateral vessels such as PAs. These observations align with the principle that flow velocity decreases with increasing fluid resistance. Surprisingly, BAT reversal between the MCA M2 portion and the ipsilateral BG/thalamus was observed in accordance with the lenticulostriate artery/thalamic perforator development. This circulatory change with the well-developed PA is consistent with previously reported changes in the medullary artery blood flow direction as MMD progresses [36, 37].

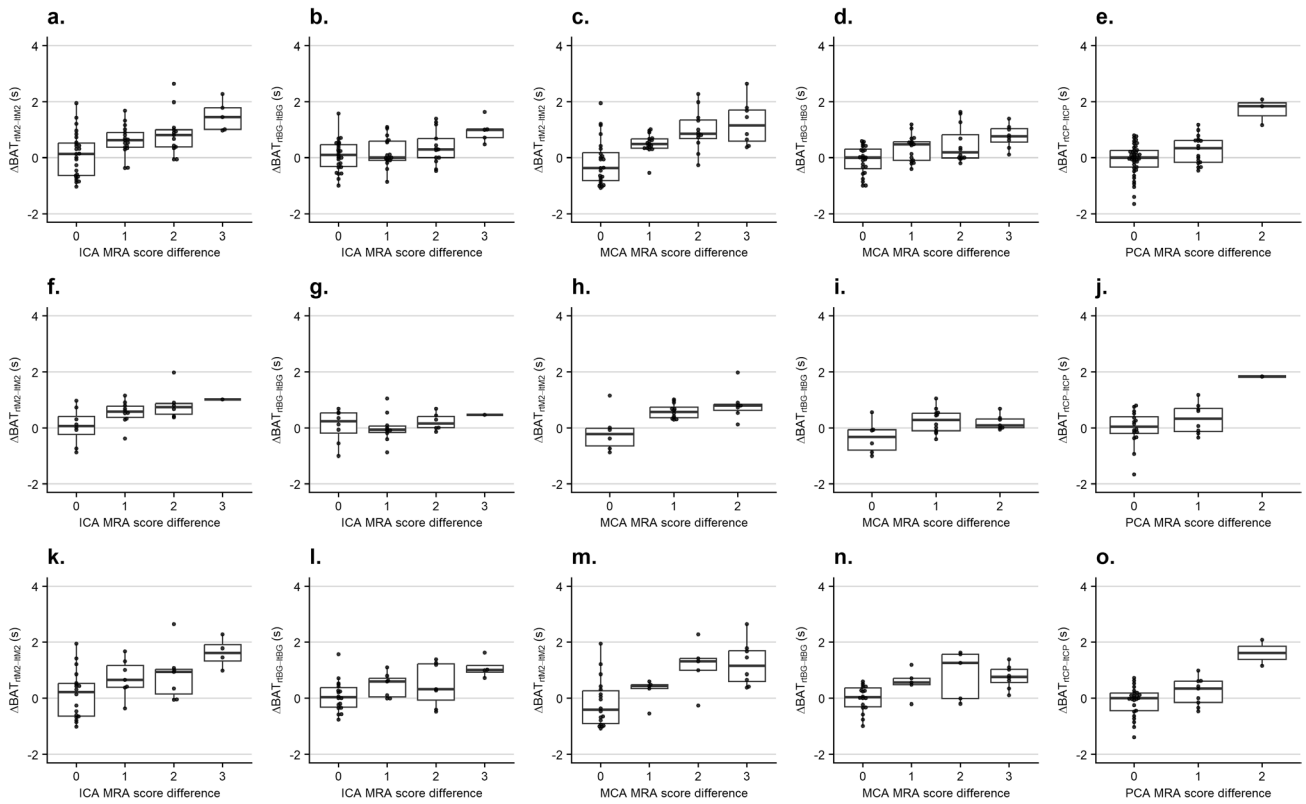


FIGURE 3 | Comparisons of differences in BAT (Δ BATs) with the right and left MRA score differences in all subjects (a–e), children (f–j) and adults (k–o). The comparisons are as follows: Δ BATs between the right and left middle cerebral artery (MCA) M2 portions (Δ BAT_{rtM2–ltM2}) for the right and left internal carotid artery (ICA) MRA score difference (a, f, and k), Δ BATs between the right and left basal ganglia (Δ BAT_{rtBG–ltBG}) for the right and left ICA MRA score difference (b, g, and l), Δ BAT_{rtM2–ltM2} for the right and left MCA MRA score difference (c, h, and m), Δ BAT_{rtBG–ltBG} for the right and left MCA MRA score difference (d, i, and n), and Δ BATs between the right and left choroid plexuses (Δ BAT_{rtCP–ltCP}) for the right and left posterior cerebral artery (PCA) MRA score difference (e, j, and o).

TABLE 3 | Values of difference in bolus arrival time (s) for each MRA score of periventricular anastomosis development.

	Overall		Children		Adults	
	Mean difference	<i>p</i>	Mean difference	<i>p</i>	Mean difference	<i>p</i>
Δ BAT _{BG–M2} for lenticulostriate artery MRA score						
Score 0–score 1	0.77 (0.34)	0.022*	0.20 (0.68)	0.93	0.82 (0.42)	0.056
Score 0–score 2	1.46 (0.37)	<0.001*	1.01 (0.69)	0.19	1.34 (0.48)	0.0041*
Score 1–score 2	0.69 (0.23)	0.0013*	0.82 (0.27)	0.0022*	0.51 (0.36)	0.20
Δ BAT _{Tha–M2} for thalamic perforator MRA score						
Score 0–score 1	0.75 (0.34)	0.026*	0.73 (0.71)	0.44	0.68 (0.43)	0.15
Score 0–score 2	1.34 (0.46)	0.0020*	1.32 (0.82)	0.14	1.25 (0.65)	0.060
Score 1–score 2	0.59 (0.43)	0.24	0.59 (0.59)	0.47	0.57 (0.65)	0.55
Δ BAT _{CP–M2} for choroidal channel MRA score						
Score 0–score 1	0.32 (0.23)	0.23	0.26 (0.33)	0.61	0.44 (0.33)	0.26
Score 0–score 2	0.70 (0.23)	0.0011*	0.97 (0.35)	0.0049*	0.54 (0.30)	0.089
Score 1–score 2	0.38 (0.25)	0.16	0.71 (0.35)	0.048*	0.10 (0.36)	0.93

Note: Data in parentheses are standard errors. * indicates $p < 0.05$.

Abbreviations: Δ BAT_{BG–M2}, difference in bolus arrival time between the middle cerebral artery M2 portion and the ipsilateral basal ganglia; Δ BAT_{CP–M2}, difference in bolus arrival time between the middle cerebral artery M2 portion and the ipsilateral choroid plexus; Δ BAT_{Tha–M2}, difference in bolus arrival time between the middle cerebral artery M2 portion and the ipsilateral thalamus; MRA, magnetic resonance angiography.

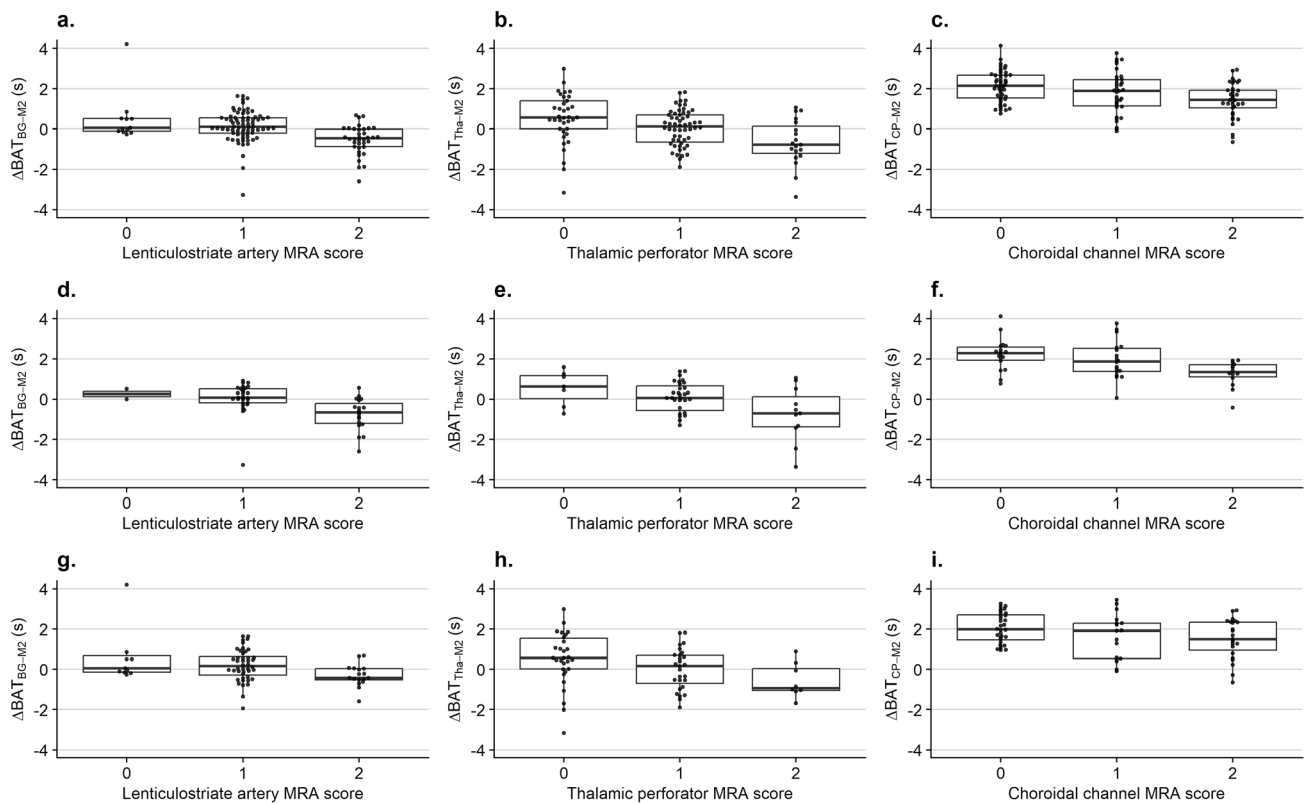


FIGURE 4 | Comparisons of differences in BAT (Δ BATs) with scores of periventricular anastomoses (PAs) in all subjects (a–c), children (d–f) and adults (g–i). The comparisons are as follows: Δ BATs between the middle cerebral artery (MCA) M2 portion and the ipsilateral basal ganglia (Δ BAT_{BG-M2}) for lenticulostriate artery MRA scores (a, d, and g), Δ BAT between the MCA M2 portion and the ipsilateral thalamus (Δ BAT_{Tha-M2}) for thalamic perforator MRA scores (b, e, and h), and Δ BAT between the MCA M2 portion and the ipsilateral choroid plexus (Δ BAT_{CP-M2}) for choroidal channel MRA scores (c, f, and i).

TABLE 4 | Child univariable and multivariable logistic regression analyses for recent transient ischemic attacks (TIAs).

Variable	Univariable analysis		Multivariable model (1)		Multivariable model (2)	
	Odds ratio	<i>p</i>	Odds ratio	<i>p</i>	Odds ratio	<i>p</i>
Age	0.81 (0.65, 0.97)	0.030*	0.88 (0.70, 1.08)	0.23	0.72 (0.52, 0.93)	0.019*
Sex (male)	2.96 (0.87, 10.6)	0.085				
Use of antiplatelet drugs	4.67 (1.23, 23.2)	0.034*	2.86 (0.66, 15.2)	0.18		
Δ BAT _{BG-M2}	1.01 (0.51, 2.07)	0.99				
Δ BAT _{Tha-M2}	1.05 (0.70, 1.66)	0.81				
Δ BAT _{CP-M2}	0.45 (0.19, 0.93)	0.047*	0.62 (0.24, 1.41)	0.28	1.15 (0.37, 3.50)	0.80
Sum of MRA scores for arterial stenosis	1.07 (0.85, 1.35)	0.56				
Sum of MRA scores for PA development	1.40 (0.95, 2.13)	0.10			1.95 (1.06, 4.01)	0.046*

Note: Data in parentheses are 95% confidence intervals. * indicates $p < 0.05$. Recent transient ischemic attack (TIA) is defined as the occurrence of TIA within the 3 months prior to the magnetic resonance imaging.

Abbreviations: Δ BAT_{BG-M2}, difference in bolus arrival time between the middle cerebral artery M2 portion and the ipsilateral basal ganglia; Δ BAT_{CP-M2}, difference in bolus arrival time between the middle cerebral artery M2 portion and the ipsilateral choroid plexus; Δ BAT_{Tha-M2}, difference in bolus arrival time between the middle cerebral artery M2 portion and the ipsilateral thalamus; MRA, magnetic resonance angiography; PA, periventricular anastomosis; TIA, transient ischemic attack.

Unlike other perfusion studies that calculated perfusion parameters for the entire brain [8–10, 17], DCE-MRI using the GRASP technique allows for vessel-specific BAT calculation [18]. This is achieved by visualizing dynamic contrast enhancement of the voxel-sized vessels (~1 mm³) while the

enhancement of normal brain parenchyma is significantly lower due to the intact blood–brain barrier [22]. This capability highlights the important role of the voxel-sized moyamoya vessels, including PAs, in MMD pathophysiology [4, 5]. These findings not only have the potential to provide new insights

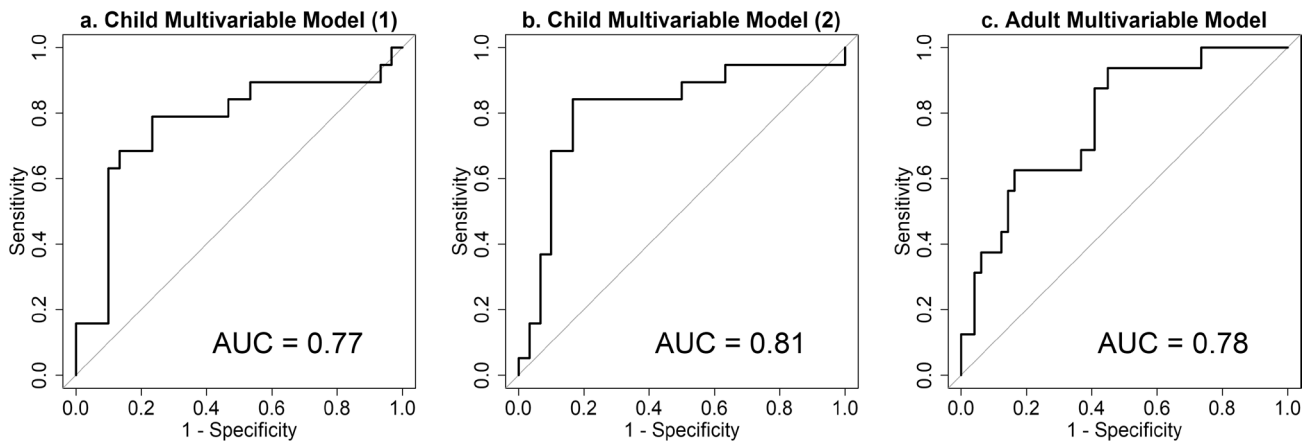


FIGURE 5 | Receiver operating characteristic (ROC) curves for logistic regression models. For recent transient ischemic attacks (TIAs), which is defined as the occurrence of TIAs within the 3 months prior to the magnetic resonance imaging, child multivariable model (1) (a), which includes age, use of antiplatelet drugs, and difference in bolus arrival time (ΔBAT) between the middle cerebral artery (MCA) M2 portion and the ipsilateral choroid plexus ($\Delta\text{BAT}_{\text{CP-M2}}$), shows an area under the curve (AUC) of 0.77. Child multivariable model (2) (b), which includes age, $\Delta\text{BAT}_{\text{CP-M2}}$, and sum of MRA scores for periventricular anastomosis (PA) development, shows an AUC of 0.81. Adult multivariable model (c), which includes hypertension, ΔBAT between the MCA M2 portion and the ipsilateral basal ganglia ($\Delta\text{BAT}_{\text{BG-M2}}$), and sum of MRA scores for arterial stenosis, shows an AUC of 0.78.

TABLE 5 | Adult univariable and multivariable logistic regression analyses for recent transient ischemic attacks (TIAs).

Variable	Univariable analysis		Multivariable model	
	Odds ratio	<i>p</i>	Odds ratio	<i>p</i>
Age	0.99 (0.94, 1.04)	0.64		
Sex (male)	2.00 (0.46, 7.86)	0.33		
Hypertension	3.08 (0.95, 10.2)	0.061	4.65 (1.27, 18.8)	0.023*
Hyperlipidemia	0.76 (0.19, 2.59)	0.67		
Use of antiplatelet drugs	1.50 (0.44, 4.87)	0.50		
Use of antihypertensive drugs	1.71 (0.40, 6.49)	0.44		
Use of antihyperlipidemic drugs	0.73 (0.10, 3.37)	0.71		
$\Delta\text{BAT}_{\text{BG-M2}}$	1.58 (0.98, 2.95)	0.088	2.29 (1.26, 5.61)	0.026*
$\Delta\text{BAT}_{\text{Tha-M2}}$	1.12 (0.74, 1.68)	0.59		
$\Delta\text{BAT}_{\text{CP-M2}}$	0.82 (0.44, 1.52)	0.53		
Sum of MRA scores for arterial stenosis	1.22 (0.94, 1.62)	0.16	1.40 (1.02, 2.03)	0.050*
Sum of MRA scores for PA development	0.87 (0.62, 1.19)	0.39		

Note: Data in parentheses are 95% confidence intervals. * indicates $p < 0.05$. Recent transient ischemic attack (TIA) is defined as the occurrence of TIA within the 3 months prior to the magnetic resonance imaging. Abbreviations: $\Delta\text{BAT}_{\text{BG-M2}}$, difference in bolus arrival time between the middle cerebral artery M2 portion and the ipsilateral basal ganglia; $\Delta\text{BAT}_{\text{CP-M2}}$, difference in bolus arrival time between the middle cerebral artery M2 portion and the ipsilateral choroid plexus; $\Delta\text{BAT}_{\text{Tha-M2}}$, difference in bolus arrival time between the middle cerebral artery M2 portion and the ipsilateral thalamus; MRA, magnetic resonance angiography; PA, periventricular anastomosis; TIA, transient ischemic attack.

into MMD but may also expand our understanding of other cerebrovascular diseases via assessment of vessel-specific perfusion information.

In this study, ΔBAT was associated with recent TIAs in patients with MMD. $\Delta\text{BAT}_{\text{CP-M2}}$ in the child univariable analysis and $\Delta\text{BAT}_{\text{BG-M2}}$ in the adult multivariable analysis were significant. In the child univariable analysis, $\Delta\text{BAT}_{\text{CP-M2}}$ was significantly associated with recent TIAs, but this association was not

significant in the multivariable analysis, suggesting potential confounding effects. Given that $\Delta\text{BAT}_{\text{CP-M2}}$ reflects changes in compensatory blood perfusion in CP [38], it may have a potential relationship with the occurrence of TIA. In adults, $\Delta\text{BAT}_{\text{BG-M2}}$ was adjusted, and steno-occlusive change in the MCA and development of the lenticulostriate artery were common in adult subjects (Table S4). Therefore, $\Delta\text{BAT}_{\text{BG-M2}}$ increase in adult patients with MMD may have potential as a strong predictor for ischemia.

4.1 | Limitations

First, this was a single-center retrospective study with a small sample size. Due to the small sample size, this study has inherent selection bias. The highlighted outliers, which stood out in Figures 3 and 4 due to their noticeably high or low values, raise questions about the accuracy of BAT. For the robustness of BAT calculation, patients with inconstant signal intensity were excluded by reviewing the reconstructed image, BAT map, and time–intensity curve, but a few outliers still remained. In the univariable and multivariable analyses, a few variables showed relatively large odds ratios but did not reach statistical significance, likely due to the limited sample. A multi-center study with a larger sample size is needed. However, the results of a post hoc power analysis for the multivariable models (child multivariable model (1), child multivariable model (2), and adult multivariable model) revealed 0.92–0.98 power at the 0.05 significance level (Table S6). Second, ROIs for BAT analysis were manually drawn on a single slice, introducing potential observer bias and may miss regional heterogeneity. Third, a cranio–caudal volume acquisition with a length of approximately 5 cm cannot cover the entire brain. However, focusing on a specific volume covering clinically important territories, including the MCA M2 portion, basal ganglia, thalamus, and choroid plexus, provided the high spatiotemporal resolution necessary to calculate BAT. Fourth, all subjects were preoperative. As cerebral circulation in MMD changes between the pre- and post-operative states [2, 17, 39, 40], investigating BAT changes between these states would be an important future study.

4.2 | Conclusion

This study using DCE-MRI with the GRASP technique showed the characteristics of vessel-specific BAT in patients with MMD and had the potential to predict ischemia in cerebrovascular diseases.

Acknowledgments

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.