Application of T1 Map Information Based on Synthetic MRI for Dynamic Contrast-Enhanced Imaging: A Comparison Study with the Fixed Baseline T1 Value Method

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Objective: For an accurate dynamic contrast-enhanced (DCE) MRI analysis, exact baseline T1 mapping is critical. The purpose of this study was to compare the pharmacokinetic parameters of DCE MRI using synthetic MRI with those using fixed baseline T1 values.

Materials and Methods: This retrospective study included 102 patients who underwent both DCE and synthetic brain MRI. Two methods were set for the baseline T1: one using the fixed value and the other using the T1 map from synthetic MRI. The volume transfer constant (Ktrans), volume of the vascular plasma space (vp), and the volume of the extravascular extracellular space (ve) were compared between the two methods. The interclass correlation coefficients and the Bland-Altman method were used to assess the reliability.

Results: In normal-appearing frontal white matter (WM), the mean values of Ktrans, ve, and vp were significantly higher in the fixed value method than in the T1 map method. In the normal-appearing occipital WM, the mean values of ve and vp were significantly higher in the fixed value method. In the putamen and head of the caudate nucleus, the mean values of Ktrans, ve, and vp were significantly lower in the fixed value method. In addition, the T1 map method showed comparable interobserver agreements with the fixed baseline T1 value method.

Conclusion: The T1 map method using synthetic MRI may be useful for reflecting individual differences and reliable measurements in clinical applications of DCE MRI.

Keywords: Magnetic resonance imaging; Perfusion imaging; Synthetic imaging; Dynamic contrast-enhanced MRI

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INTRODUCTION

Dynamic contrast-enhanced (DCE) MRI is a noninvasive imaging technique for assessing microcirculation physiology and is relevant when studying a wide range of diseases and conditions. DCE MRI uses rapid T1-weighted image (T1WI) to measure the relaxation changes that result from gadolinium leakage into and out of the extravascular extracellular space and allows for the assessment of hemodynamic information, representing the vessel permeability, perfusion, and blood volume [1,2]. DCE MRI can be used to analyze the quantitative pharmacokinetic parameters that reflect the microcirculatory environment in imaged tissues. volume transfer constant (Ktrans) is the volume transfer constant between the blood plasma and the extravascular extracellular space, volume of extravascular extracellular space (ve) is the volume of extravascular extracellular space per unit volume of tissue and is also called the leakage space, and volume of vascular plasma space (vp) is the volume of vascular plasma space per unit volume of tissue [3]. For an accurate DCE MRI analysis, it is important to obtain exact pharmacokinetic parameters, and in order to obtain these exact parametric values, accurate baseline T1 mapping is critical. Various imaging techniques for T1 mapping have been described in the literature, such as the variable flip angle technique, inversion recovery technique, and the look-locker technique [4-6]. However, these techniques are not robust, so recently, a fixed T1 value has been more widely used [7,8]. Nonetheless, the fixed T1 method has limitations in terms of accurately measuring the DCE parameters because every tissue is set at the same value [9].

Synthetic MRI is a technique based on the quantification of physical tissue properties. This technique uses a multi-echo and multi-delay acquisition method that quantifies the longitudinal T1 and transverse T2 relaxation times and proton density. By manipulating the acquisition parameters, including the repetition time (TR), echo time (TE), and inversion time, a single acquisition can generate multiple sequences and obtain a precise T1 value for each pixel [10-12]. Synthetic MRIs have already been used for relaxation measurements [13,14], and their accuracy and reproducibility have been demonstrated in repeated phantom measurements [15]. The previously proposed T1 measurement methods are known to have limitations, including low reproducibility and long scan time [16]. Our proposed T1 map method based on synthetic MRI could overcome these limitations, which have a reasonable scan time and reproducible measurement.

To the best of our knowledge, there have been no previous reports regarding the application of baseline T1 mapping from synthetic MRI for DCE MRI analysis. The purpose of the present study was to compare the pharmacokinetic parameters of DCE MRI using synthetic MRI with those using the fixed baseline T1 values and the interobserver agreements in the DCE parameters between these two methods.

MATERIALS AND METHODS

The Institutional Review Board of Seoul National University Hospital approved this retrospective study and waived the informed consent requirement (IRB No. H-1803-137-933).

Patients

We retrospectively enrolled 102 consecutive patients who had undergone both DCE and synthetic MRI from September 2016 to June 2017 (32 male, 70 female; mean age, 62.65 years; age range, 22–87 years) for the further evaluation of clinically suspected white matter (WM) disease or neurological disorders. Final diagnoses included migraine (33%), small vessel disease (19%), other headaches (10%), infarctions (8%), dementia (5%), and other diagnoses (26%).

Image Acquisition

All brain imaging was performed on a 3T MRI system (Discovery MR 750; GE Healthcare) using a 32-channel phased array head coil. All patients underwent a synthetic MR sequence (multi-dynamic multi-echo sequence; MDME sequence) and a DCE MR sequence in addition to conventional MR sequences.

The MDME sequence data were acquired before injection of the contrast agent. The data include four automatically calculated saturation delays and two TEs (21.4 msec and 85.4 msec), and a TR of 4000 msec. The MDME data were reconstructed using a vendor-provided program (SyMRI 7.2; Synthetic MR), and quantitative T1 maps were generated. The parameters used for the quantitative T1 map were: field of view, 240 x 240 mm; matrix, 320 x 256; echo-train length, 12; bandwidth, 22.73 kHz; slice thickness/gap, 4.0 mm/1.0 mm; number of slices, 20; and a total acquisition time of 5 minutes and 8 seconds.
DCE MRI was performed using a 3D gradient-echo T1WI after intravenous administration of gadobutrol (Gadovist, Bayer Schering Pharma) (0.1 mmol/kg body weight) using a power injector (Spectris, MedRad) at a rate of 4 mL/s. A 30 mL bolus injection of saline followed the gadobutrol treatment at the same injection rate. For each section, 40 slices per patient were acquired at intervals equal to the TR. The following MR parameters were used: TR, 2.8 msec; TE, 1.0 msec; flip angle, 10°; and matrix, 128 x 128 with a section thickness of 3 mm, a field of view of 249 x 249 mm, a voxel size of 1.25 x 1.25 x 3 mm³, a pixel bandwidth of 789 Hz, and a total acquisition time of 5 minutes and 25 seconds.

Image Analysis
In all 102 patients, the DCE parameters were measured in the normal-appearing frontal and occipital WM, putamen, and head of caudate nucleus. We then measured the DCE parameters of the high signal intensity areas on fluid attenuated inversion recovery (FLAIR) imaging in the frontal and occipital WM in 78 and 66 patients, respectively, which did not show any visual contrast enhancement on the contrast-enhanced T1WI. DCE MRI analysis was performed using a dedicated software package (NordicICE 4.1.1, NordicNeuroLab). In the DCE analysis, we used two methods for setting the baseline T1: one using the fixed value and the other using the T1 map from the synthetic MRI. The

Fig. 1. Pharmacokinetic parametric maps.
A. Fluid attenuated inversion recovery. B. Precontrast. C. Post T1-weighted images. D. \(K_{\text{trans}}\). E. \(v_e\). F. \(v_p\) maps obtained by the fixed value method. G. \(K_{\text{trans}}\). H. \(v_e\). I. \(v_p\) maps obtained by the T1 map method using synthetic MRI. \(K_{\text{trans}}\) = volume transfer constant, \(v_e\) = volume of extravascular extracellular space, \(v_p\) = volume of vascular plasma space
fixed baseline T1 values were determined by averaging the results of the T1 relaxation time reported in several studies [17-20]. The averaging results of each region are as follows: frontal WM, 795 ms; occipital WM, 795 ms; putamen, 1257 ms; and head of caudate nucleus, 1379 ms. In the T1 map, the quantitative T1 map obtained from the synthetic MRI was used. Coregistration between the DCE MRI and the quantitative T1 map was performed automatically using the dedicated software package. For the arterial input function (AIF), a population-based AIF was determined using NordicICE. On the basis of the extended Tofts model, the perfusion analysis method was used to calculate pharmacokinetic parameters, including $K^{\text{trans}}$, $v_e$, and $v_p$ (Fig. 1). Owing to the differences in the slice number and thickness between the FLAIR images and parametric maps, the FLAIR images were resampled automatically based on the pharmacokinetic maps. One neuroradiologist (observer 1) (with 8 years of brain MRI experience) drew regions of interest (ROIs) in both the normal-appearing and high signal intensity areas in the occipital and frontal WM on the resampled FLAIR images in each patient. ROIs were also drawn in the putamen, and the head of caudate nucleus, where no abnormal signal changes were observed (Fig. 2). The average size of all ROIs was approximately 0.7 cm$^2$. Finally, in each ROI, the mean parametric values from the DCE MRI were obtained using both the fixed value method and the T1 map method (Fig. 3). The other neuroradiologist (observer 2) measured the parametric values in an identical way to evaluate the interobserver agreement (with 16 years of experience in brain MRI).

Statistical Analysis
All statistical analyses were performed using SPSS, version 19 (IBM Corp.) or MedCalc statistical software, version 18 (MedCalc). $p$ values less than 0.05 were considered statistically significant.

We compared the mean values of the pharmacokinetic parameters, including $K^{\text{trans}}$, $v_e$, and $v_p$, from the DCE MRI between the fixed value method and the T1 map method using paired $t$ tests (SPSS). To compare the differences in the pharmacokinetic parameters between normal-appearing WM and high signal intensity areas in WM on FLAIR imaging, paired $t$ tests were also used (MedCalc). We assessed the interobserver reproducibility by using the interclass correlation coefficient (ICC) and the Bland-Altman plot (MedCalc). The interobserver assessment was defined as a comparison between the measurements from observers 1 and 2. All values of the pharmacokinetic parameters were assessed. The ICC values were categorized as follows: $< 0.40$, poor; $0.40$–$0.59$, fair; $0.60$–$0.74$, good; and $> 0.74$, excellent. We also correlated the T1 and pharmacokinetic values based on the T1 map method with age and sex, which are given in the online appendix (SPSS).

RESULTS

Comparison of the T1 Values and the Pharmacokinetic Parameters between the Fixed Value and T1 Map Method

The comparison results between the mean T1 values in the literature and mean T1 values from the synthetic MRI are shown in Table 1. In the normal-appearing occipital

![Fig. 2. Resampled fluid attenuated inversion recovery images based on the parametric maps.](image)
WM, putamen, and head of caudate nucleus, the mean T1 values from the synthetic MRI were significantly lower than the mean T1 values in the literature.

The comparison results between the mean parametric values using a fixed baseline T1 value and a T1 map using synthetic MRI are shown in Table 2. In the normal-

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**Fig. 3. Flowchart of the study.** The fixed T1 values were used according to the brain areas where the ROIs were drawn, which is available by using the dedicated software package. For example, when a ROI was drawn on the frontal WM and putamen, we used a fixed T1 value of 795 and 1257 msec, respectively, for the measurement of the permeability values. DCE = dynamic contrast-enhanced, FLAIR = fluid attenuated inversion recovery, $K^{\text{trans}}$ = volume transfer constant, ROI = region of interest, $v_e$ = volume of extravascular extracellular space, $v_p$ = volume of vascular plasma space, WM = white matter.
appearing frontal WM, the mean values of \( K_{\text{trans}} \), \( v_e \), and \( v_p \) were significantly higher in the fixed value method than in the T1 map method. In the normal-appearing occipital WM, the mean values of \( v_e \) and \( v_p \) were significantly higher in the fixed value method than in the T1 map method. In the putamen and head of caudate nucleus, the mean values of \( K_{\text{trans}} \), \( v_e \), and \( v_p \) were significantly lower in the fixed value method than in the T1 map method. In the high signal intensity areas of the frontal WM on FLAIR images, the mean values of \( K_{\text{trans}} \) and \( v_p \) were significantly higher in the fixed value method than in the T1 map method. In the high signal intensity areas of the occipital WM on FLAIR images, the mean values of \( K_{\text{trans}} \), \( v_e \), and \( v_p \) were significantly higher in the fixed value method than in the T1 map method. In terms of the comparison of the pharmacokinetic parameters between the fixed value and T1 map method, the box-and-whisker graphs and dot-and-line diagrams for the pharmacokinetic parameters are shown in Figure 4, and the Bland-Altman plots are shown in Figure 5.
Fig. 4. Box-whisker plots and dot-and-line diagrams showing the pharmacokinetic parametric values of the two methods in the normal-appearing areas (A) and high SI areas (B). Lines in boxes = median values. Boundaries of boxes = 25th and 75th percentiles, with whiskers extending from the median to ±1.5 x interquartile ranges and outliers beyond the whiskers denoted by points. Statistically significant results are marked with asterisks. $K_{\text{trans}}$ = volume transfer constant, SI = signal intensity, $v_e$ = volume of extravascular extracellular space, $v_p$ = volume of vascular plasma space, WM = white matter.
Comparison of the Pharmacokinetic Parameters between the Normal Appearing WM and High Signal Intensity Areas in the WM on FLAIR Imaging

The comparison results of the mean parametric values between the normal-appearing WM and high signal intensity areas in the WM on FLAIR imaging are shown in Table 3. In the frontal WM, the mean value of ve was significantly higher in the high signal intensity area than in the normal-appearing area when only based on the fixed value methods. In addition, the mean values of vp were significantly lower in the high signal intensity area than in the normal-appearing area when based on both fixed value and T1 map methods. In the occipital WM, the mean value of Ktrans was significantly lower in the high signal intensity area than in the normal-appearing area when only based on the fixed value method. The mean values of vp were significantly lower in the high signal intensity area than in the normal-appearing area when based on both fixed value
Fig. 5. Bland-Altman plots showing the comparison of the pharmacokinetic values between fixed value method and T1 map method in normal-appearing areas (A) and high signal intensity areas (B). Fixed = fixed value method, $K^{\text{trans}}$ = volume transfer constant, SD = standard deviation, T1 map = T1 map method, $v_e$ = volume of extravascular extracellular space, $v_p$ = volume of vascular plasma space, WM = white matter.
and T1 map methods. In all WM, the mean value of \( v_p \) was significantly lower in the high signal intensity area than in the normal-appearing area when only based on the T1 map method.

### Interobserver Reproducibility of the Fixed Value and T1 Map Method

Interobserver reproducibility revealed an ICC that showed similar reproducibility between the two methods (Table 4).

![Bland-Altman plots](image)

**Fig. 5.** Bland-Altman plots showing the comparison of the pharmacokinetic values between fixed value method and T1 map method in normal-appearing areas (A) and high signal intensity areas (B). Fixed = fixed value method, \( K^{\text{trans}} \) = volume transfer constant, SD = standard deviation, T1 map = T1 map method, \( v_e \) = volume of extravascular extracellular space, \( v_p \) = volume of vascular plasma space, WM = white matter
Excellent interobserver agreements were achieved in areas with high signal intensity of the normal-appearing occipital WM and high signal intensity areas in the occipital WM and head of the caudate nucleus. Except for the $K_{\text{trans}}$ value in the high signal intensity areas in frontal WM, fair to excellent interobserver agreements were noted in areas of normal-appearing frontal WM, high signal intensity areas in frontal WM, and putamen. The results of the Bland-Altman plot revealed good agreement in both the fixed value and the T1 map methods for measuring the pharmacokinetic parameters, which are presented in Figure 6.

Correlations of the T1 Values based on T1 Map Method with Age and Sex

The comparison results between the T1 values based on the T1 map method and age are shown in Figure 7. The comparison results between the T1 values based on the T1 map method and sex are shown in Table 5.

**DISCUSSION**

This study compared the pharmacokinetic parameters of DCE MRI between the fixed value and T1 map methods. There were significant differences between the two methods. For WM, the DCE parameters tend to be lower in the T1 map method than in the fixed value methods, and vice versa for the head of caudate nucleus and putamen. In addition, the two methods showed similar interobserver agreements for the measurement.

The T1 relaxation time varies depending on the

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**Table 3. Comparison of the Pharmacokinetic Parameters between the Normal-Appearing WM and the High Signal Intensity Areas in the WM**

| Pharmacokinetic Parameters | Normal-Appearing Areas | High Signal Intensity Areas | Difference* | Mean Difference (%)† | $P$ |
|-----------------------------|------------------------|-----------------------------|-------------|----------------------|-----|
| **Frontal WM**              |                        |                             |             |                      |     |
| Fixed value method          |                        |                             |             |                      |     |
| $K_{\text{trans}}$          | 0.0152                 | 0.0173                      | -0.0021     | -13.82               | 0.431 |
| $v_e$                       | 4.4484                 | 8.3140                      | -3.8656     | -86.90               | 0.048 |
| $v_p$                       | 0.2391                 | 0.1653                      | 0.0738      | 30.87                | 0.005 |
| T1 map method               |                        |                             |             |                      |     |
| $K_{\text{trans}}$          | 0.0118                 | 0.0133                      | -0.0015     | -12.71               | 0.586 |
| $v_e$                       | 3.6670                 | 9.3860                      | -5.7190     | -155.96              | 0.129 |
| $v_p$                       | 0.1800                 | 0.1220                      | 0.0580      | 32.22                | < 0.001 |
| **Occipital WM**            |                        |                             |             |                      |     |
| Fixed value method          |                        |                             |             |                      |     |
| $K_{\text{trans}}$          | 0.0204                 | 0.0121                      | 0.0083      | 40.69                | 0.004 |
| $v_e$                       | 6.1912                 | 5.1713                      | 1.0199      | 16.47                | 0.570 |
| $v_p$                       | 0.2286                 | 0.1353                      | 0.0933      | 40.81                | 0.007 |
| T1 map method               |                        |                             |             |                      |     |
| $K_{\text{trans}}$          | 0.0518                 | 0.0093                      | 0.0125      | 24.13                | 0.064 |
| $v_e$                       | 5.4221                 | 3.8081                      | 1.6140      | 29.77                | 0.254 |
| $v_p$                       | 0.1776                 | 0.1080                      | 0.0696      | 39.19                | < 0.001 |
| **All WM**                  |                        |                             |             |                      |     |
| Fixed value method          |                        |                             |             |                      |     |
| $K_{\text{trans}}$          | 0.0175                 | 0.0149                      | 0.0026      | 14.86                | 0.185 |
| $v_e$                       | 5.2472                 | 6.8736                      | -1.6264     | -30.99               | 0.226 |
| $v_p$                       | 0.2347                 | 0.1907                      | 0.0440      | 18.74                | 0.186 |
| T1 map method               |                        |                             |             |                      |     |
| $K_{\text{trans}}$          | 0.0163                 | 0.0115                      | 0.0048      | 29.44                | 0.157 |
| $v_e$                       | 4.4714                 | 6.8295                      | -2.3581     | -52.73               | 0.271 |
| $v_p$                       | 0.1819                 | 0.1338                      | 0.0481      | 26.44                | 0.011 |

Units of $K_{\text{trans}} = \text{min}^{-1}$. *Difference = normal-appearing WM - high signal intensity areas in WM, †Mean difference = difference/normal-appearing WM x 100. $K_{\text{trans}} = \text{volume transfer constant, } v_e = \text{volume of extravascular extracellular space, } v_p = \text{volume of vascular plasma space, WM = white matter}$
measurement method and each individual, even in the same region of the brain, which is one of the necessary values for measuring the pharmacokinetic parameters of DCE MRI. We believe that synthetic MRI has some benefits when measuring the T1 relaxation time of the brain. First, the T1 relaxation time is dependent on the field strength and pulse sequence. Lu et al. [19] reported that the T1 relaxation time was 14–30% longer at 3T when compared to the values at 1.5T. In another study, the T1 values were found to increase with field strength at 1.5, 3, and 7T [20]. They also reported that the values in the same 3T study differed depending on the pulse sequence used in the measurement. In contrast, synthetic MRI is a technique to stably obtain the absolute magnetic properties, such as the T1 relaxation times of the brain tissues, independent of the scanner settings [21]. Second, the T1 relaxation time is different for each individual, especially when considering age and sex. There are significant differences in the T1 relaxation times measured between female and male brains. According to Wansapura et al. [17], females have a longer T1 relaxation time than males in gray matter and WM areas. In addition, age is also a factor affecting the normal T1 relaxation time. Breger et al. [22] reported that the T1 values in the telencephalon tend to increase by approximately 0.1% per year. According to Steen et al. [23], T1 values generally increase with age, and brain aging is associated with occult processes that can begin at a relatively early age. Cho et al. [24] found that brain tissue continues to change throughout the lifespan among healthy subjects with no neurologic deficits. Age-related changes follow a remarkably different schedule in different brain tissues; WM tracts tend to reach a minimum T1 value and increase again earlier than gray matter tracts do. Thus, for the exact measurement of pharmacokinetic parameters in each brain region, such individual variations in T1 values should be considered. In each subject, we obtained reliable T1 relaxation times of the brain regions via synthetic MRI.

The multiple flip angle technique is the most widely used technique for baseline T1 measurement because it requires less acquisition time and thus is more attractive for clinical use. However, the technique has weak reproducibility due to motion artifacts and B1 field inhomogeneity. Although

### Table 4. ICC for the Fixed Value Method and the T1 Map Method Using Synthetic MRI

| Pharmacokinetic Parameters | Fixed Value Method | T1 Map Method |
|----------------------------|--------------------|---------------|
| **Normal-appearing frontal WM** |                    |               |
| $K_{trans}$                | 0.590 (0.392 to 0.723) | 0.574 (0.368 to 0.713) |
| $v_e$                      | 0.690 (0.539 to 0.791)  | 0.728 (0.596 to 0.816)  |
| $v_p$                      | 0.535 (0.311 to 0.687)  | 0.632 (0.454 to 0.752)  |
| **Normal-appearing occipital WM** |                |               |
| $K_{trans}$                | 0.955 (0.929 to 0.971)  | 0.942 (0.908 to 0.963)  |
| $v_e$                      | 0.885 (0.819 to 0.927)  | 0.995 (0.991 to 0.997)  |
| $v_p$                      | 0.843 (0.752 to 0.900)  | 0.852 (0.766 to 0.906)  |
| **High signal intensity areas in frontal WM** |             |               |
| $K_{trans}$                | 0.400 (0.103 to 0.597)  | 0.288 (-0.063 to 0.523) |
| $v_e$                      | 0.625 (0.430 to 0.753)  | 0.527 (0.282 to 0.689)  |
| $v_p$                      | 0.682 (0.527 to 0.786)  | 0.672 (0.512 to 0.779)  |
| **High signal intensity areas in occipital WM** |            |               |
| $K_{trans}$                | 0.817 (0.699 to 0.889)  | 0.865 (0.777 to 0.918)  |
| $v_e$                      | 0.770 (0.613 to 0.863)  | 0.821 (0.699 to 0.894)  |
| $v_p$                      | 0.788 (0.650 to 0.871)  | 0.794 (0.661 to 0.875)  |
| **Putamen**                |                    |               |
| $K_{trans}$                | 0.707 (0.565 to 0.803)  | 0.722 (0.584 to 0.814)  |
| $v_e$                      | 0.587 (0.373 to 0.728)  | 0.776 (0.651 to 0.856)  |
| $v_p$                      | 0.880 (0.818 to 0.920)  | 0.880 (0.817 to 0.921)  |
| **Caudate head**           |                    |               |
| $K_{trans}$                | 0.773 (0.662 to 0.847)  | 0.954 (0.932 to 0.969)  |
| $v_e$                      | 0.836 (0.754 to 0.890)  | 0.821 (0.732 to 0.881)  |
| $v_p$                      | 0.875 (0.813 to 0.916)  | 0.916 (0.875 to 0.944)  |

Values in parentheses indicate the 95% confidence interval. ICC = interclass correlation coefficient, $K_{trans}$ = volume transfer constant, $v_e$ = volume of extravascular extracellular space, $v_p$ = volume of vascular plasma space, WM = white matter.
Fig. 6. Bland-Altman plots showing interobserver reproducibility between the measurements from observer 1 and observer 2 in normal-appearing areas (A) and high signal intensity areas (B). Between both measurements, 95% limits of agreement are similarly observed. Fixed value = fixed value method, $K_{trans}$ = volume transfer constant, SD = standard deviation, T1 map = T1 map method, $v_e$ = volume of extravascular extracellular space, $v_p$ = volume of vascular plasma space, WM = white matter.
the B1 inhomogeneity can be revised, it takes some time and is not properly corrected, making it somewhat difficult for clinical practice [25,26]. On the other hand, the T1 map using the synthetic MRI method can be reproduced and has a reasonable scan time. Some studies recommend a fixed value method. According to Larsson et al. [27], the use of a fixed T1 is recommended when monitoring changes in parameters of DCE MRI in high-grade glioma patients, thereby simplifying the analysis of DCE MRI in a clinical setting. Conte et al. [28] reported that T1 mapping is not mandatory because it does not improve the diagnostic accuracy of DCE MRI for glioma grading, and the use of a fixed T1 value represents a valid alternative to T1 mapping for DCE MRI analysis [28]. However, these two studies did not suggest that the fixed value method is superior (or more efficient). What they meant was a fixed value method can be clinically useful as it could also carry stable and simple applications. If T1 mapping becomes more robust and simple than existing mapping methods, it will no longer be necessary to use the fixed value method clinically as it is currently used.

To calculate the quantitative DCE MRI kinetic parameters, the AIF needs to be defined. There have been many reports establishing the most reliable and accurate method to determine the optimal AIF, but several controversies remain, such as the AIF detection locations and methods [29-31]. We used the population-based AIF for measuring the pharmacokinetic parameters of DCE MRI because the main purpose of this study was to investigate the T1 measurement method-associated differences in DCE MRI.

Fig. 6. Bland-Altman plots showing interobserver reproducibility between the measurements from observer 1 and observer 2 in normal-appearing areas (A) and high SI areas (B). Between both measurements, 95% limits of agreement are similarly observed. Fixed = fixed value method, \( k^\text{trans} \) = volume transfer constant, SD = standard deviation, SI = signal intensity, T1 map = T1 map method, ve = volume of extravascular extracellular space, vp = volume of vascular plasma space, WM = white matter.
parameters. An application of the population-based AIF could minimize the potential AIF-associated errors between the fixed value method group and the T1 map method group.

In this study, we obtained the pharmacokinetic parametric values in the normal-appearing frontal WM, normal-appearing occipital WM. Knowing the parametric values of DCE MRI in normal-appearing regions will provide a better understanding of brain diseases affecting brain-blood barrier permeability. Some studies revealed that the permeability changes measured by DCE MRI in brain lesions without visible contrast enhancement, such as small vessel disease [32-34]. The high signal intensity areas on pre-contrast FLAIR imaging have a longer T1 relaxation time than the normal WM, which requires the correction of the baseline T1 value for the DCE MRI. We also found that there were significant differences in the pharmacokinetic parameters between normal-appearing and high-signal intensity areas on FLAIR imaging. Therefore, we believe that our information can be used for future research on WM diseases.

There are some limitations to this study, in addition to the retrospective design. First, we did not use an automatic segmentation method for ROI selection. However,
the observers carefully drew the ROIs to minimize the location differences among subjects, and we chose brain regions that are visually definite areas. Second, we did not subclassify the high signal intensity lesions in the WM on FLAIR imaging, which could result from various WM affecting diseases, such as small vessel disease, interstitial edema, and demyelinating disease. However, we included non-enhancing lesions, so they could be categorized as inactive lesions, which did not cause significant differences in brain-blood barrier permeability. Third, our study did not include the diagnostic performances of the T1 map method in some specific diseases, including enhancing lesions, for which future studies are warranted.

In conclusion, we found that the pharmacokinetic parameters of DCE MRI in each brain region based on the T1 map method using synthetic MRI were significantly different from those using the fixed baseline T1 value, which could result from the application of the individual T1 values. In addition, the T1 map method also showed comparable interobserver agreements with the fixed baseline T1 value method for measuring the pharmacokinetic parameters of DCE MRI. We believe that the T1 map method using synthetic MRI may be helpful for reflecting individual differences and reliable measurements in clinical applications of DCE MRI.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

Author Contributions
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