Intravoxel Incoherent Motion Diffusion-Weighted MR Imaging of Breast Cancer at 3.0 Tesla: Comparison of Different Curve-Fitting Methods

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**Background:** To compare three different curve-fitting methods for intravoxel incoherent motion (IVIM) analysis in breast cancer.

**Methods:** Diffusion-weighted imaging was acquired in 30 patients with breast cancer using seven b-values (0–800 s/mm²). Three curve-fitting methods were used for biexponential IVIM analysis: a. Direct estimation of D (diffusion coefficient), D* (pseudodiffusion coefficient) and f (perfusion fraction) (Method 1), b. Estimation of D first and then D* and f (Method 2), c. Estimation of D and f first and then D* (Method 3). Goodness-of-fit, parameter precision (coefficient of variance [CV]), parameter difference and correlation with relative enhancement ratio (RER) and initial area under the curve (IAUC) from dynamic contrast-enhanced (DCE) MRI of the three methods were determined and compared.

**Results:** Among the three biexponential methods, Method 1 best described most of the pixels (63.20% based on R²; 44.52% based on Akaike Information Criteria). The CV of D calculated from Method 2/3 (14.95%/13.90%), the CV of D* from Method 2 (77.04%) and the CV of f from Method 3 (80.87%) were the lowest among the three methods. Significant difference was observed for each IVIM-derived parameter calculated from all the three methods (P = 0.000–0.005). Only the perfusion-related f value calculated from Method 2 was correlated with RER (r = 0.548; P = 0.002) or IAUC (r = 0.561; P = 0.001).

**Conclusion:** IVIM-derived parameters differ depending on the calculation methods. The two-step fitting method with D value estimation first was correlated with DCE MRI perfusion.


Diffusion-Weighted Imaging (DWI) is a functional magnetic resonance imaging (MRI) technique which has the ability to detect water molecule’s Brownian motion in vivo. In the assumption of a monoexponential behavior, signal intensity (SI) can be fitted between two or more b-values, and as a result, a quantitative metric known as apparent diffusion coefficient (ADC) can be obtained. ADC measures apparent diffusion properties of the tissue, influenced by the effects of water diffusion in the extracellular extravascular space and capillary perfusion. Assessment of breast DWI and ADC maps has proven useful in characterization and differentiation of breast cancer.1–4 Typically, breast cancer (containing more densely packed cells than normal) exhibits restricted diffusion with hyperintensity on diffusion-weighted image and a corresponding low ADC value.5

One main limitation of the conventional DWI model is that this approach assumes a monoexponential SI decay curve with b-values and the obtained ADC is a combination...
of diffusion and perfusion components. However, many studies have found that with a range of $b$-values, the SI follows a nonmonoeXponential behavior in breast lesions.\textsuperscript{6–11} Numerous attempts have been made to model and analyze the complex diffusion patterns within breast tissues, of which the intravoxel incoherent motion (IVIM) model has recently received a growing interest.\textsuperscript{8–10} The IVIM theory was first proposed by Le Bihan et al., suggesting that using a more sophisticated approach to describe the relationship between SI and $b$-values would tease out the contribution of perfusion to the diffusion signal.\textsuperscript{12} Microcirculation of the blood in the capillaries in each voxel (perfusion) can be considered as an incoherent motion. In normal perfused tissue at low $b$-values ($< 200$ s/mm$^2$), perfusion effect predominantly contributes to the diffusion signal, while at high $b$-values ($> 200$ s/mm$^2$), pure diffusion component accounts for a large portion of the measured signal.\textsuperscript{13,14} By acquiring DWI with a range of $b$-values, followed by fitting the biexponential curve using a nonlinear least squares technique, diffusion coefficient ($D$) and pseudodiffusion coefficient ($D^*$) can be resolved separately, as well as perfusion fraction ($f$), a weight for pseudodiffusion in the acquired DWI signal.

Although IVIM has shown potential to give new insights into the perfusion and diffusion characteristics of breast tissues noninvasively, and provide accurate identification of breast cancer, the IVIM-derived parameters for breast cancer vary considerably among the published studies, especially for $D^*$ and $f$.\textsuperscript{8–11,15} (Table 1). Several factors may account for this variability, such as instrument differences, $b$-values used, patient population and calculation methods. Studies have rarely investigated the influence of these factors on the IVIM results, although many have demonstrated the utility of IVIM analysis for disease assessment.\textsuperscript{8–11,14,16–20} To our knowledge, till now, at least three calculation methods have been reported to produce the final breast IVIM results.\textsuperscript{8–11,15}

Therefore, the purpose of the study was to compare the three commonly used IVIM curve-fitting methods in breast cancer and validate their associations with dynamic contrast-enhanced (DCE) MRI.

**MATERIALS AND METHODS**

**Patient Population**

The retrospective study was approved by the local Institutional Review Board with waiver of informed consent. Between March and November 2013, 30 consecutive female patients (mean age, 50 years; age range, 27–79 years) who underwent breast MRI (including multi-$b$-value DWI) and subsequently had their diagnosis confirmed by histopathology as invasive ductal carcinoma (IDC) were included in the study. Detailed characteristics of patients and lesions are listed in Table 2. Subjects were excluded from our analysis if they received neoadjuvant chemotherapy or hormonal therapy before MRI ($n = 9$). Lesions were excluded if they were smaller than 6 mm ($n = 3$), or if the diffusion-weighted images had obvious artifacts ($n = 2$). In each subject, one largest lesion located in one side of her breast was selected, resulting in a total number of 30 lesions.

**MRI Examination**

All breast MRI scans were performed using a 3.0 Tesla (T) system (Achieva, Philips Medical Systems, Best, the Netherlands) equipped with a dedicated four-channel SENSE breast coil. Patients were placed in the prone position. Conventional axial T1- and T2-weighted imaging with and without fat suppression was first performed for anatomical investigation. Axial DWI examination was performed by using a single shot spin echo sequence with echo-planar imaging readout at seven $b$-values ($b = 0, 50, 100, 150, 200, 500,$ and $800$ s/mm$^2$). For each $b$-value, three orthogonal directions were used to generate isotropic DWI images. Detailed imaging parameters included: echo time (TE) = 67 ms, repetition time (TR) = 2000 ms, flip angle (FA) = 90°, matrix size = 108 × 162, field of view (FOV) = 211 mm, slice thickness/gap = 4/0.5 mm, number of excitations (NEX) = 4, and scan time = 202 s.

Axial T1-weighted DCE MRI was acquired using T1 high resolution isotropic volume excitation (THRIVE) sequence before (scan time: 43 s) and at six consecutive points (time interval: 60 s) after an injection of 0.1 mmol/kg of dimeglumine gadopentetate contrast agent (Magnevist, Bayer Healthcare, Berlin, Germany), at a rate of 1.5 mL/s, followed by a 20-mL saline flush. Other imaging parameters included: TE = 2.3 ms, TR = 4.7 ms, FA = 10°, matrix size = 400 × 320, FOV = 320 mm, slice thickness/gap = 1/0 mm, and scan time = 360 s.

**Diffusion Data Analysis**

Diffusion parameter quantification and image analysis were all conducted by using an in-house developed program based on MATLAB (version 2011b, Mathworks, Natick, MA).

The ADC maps were generated using the traditional monoeXponential model from diffusion-weighted images at all $b$-values:

$$S(b) = S_0 \exp(-(b \times ADC))$$

where $S(b)$ and $S_0$ denote the diffusion-weighted signal intensity obtained with $b$-value of $b$ and zero, respectively.

The IVIM behavior of the diffusion-weighted signal $S(b)$ was described by a biexponential model according to Le Bihan et al.\textsuperscript{12}

$$S(b) = S_0 [(1 - f) \exp(-(b \times D)) + f \exp(-(b \times D^*))]$$

where $D$ is the diffusion coefficient, $D^*$ is the pseudodiffusion coefficient, and $f$ is the perfusion fraction. In recent studies, three curve-fitting methods based on the Levenberg-Marquardt algorithm have been proposed for breast IVIM analysis.\textsuperscript{8–11,15} as follows:

**Method 1**

Direct estimation of $D$, $D^*$, and $f$ using a nonlinear fitting algorithm with the following bound constraints: $0 < D < 5 \times 10^{-3}$ mm$^2$/s, $0 < D^* < 0.1$ mm$^2$/s, $D < D^*$ and $0 < f < 1$.\textsuperscript{21,22}
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Lesion no.</th>
<th>Magneticfield strength</th>
<th>DWI sequence</th>
<th>B-Values (6/mm²)</th>
<th>Curve-fitting method</th>
<th>$D_1$ ($10^{-3}$ mm²/s)</th>
<th>$D_2$ ($10^{-3}$ mm²/s)</th>
<th>$f$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigmund et al., 2011</td>
<td>24 including 19 IDC</td>
<td>3.0 T</td>
<td>Single shot spin-echo EPI</td>
<td>0, 30, 70, 100, 150, 200, 300, 400, 500, 800</td>
<td>Method 3</td>
<td>1.15 ± 0.35</td>
<td>15.1 ± 10.4</td>
<td>9.8 ± 4.8</td>
</tr>
<tr>
<td>Iima et al., 2013</td>
<td>11</td>
<td>3.0 T</td>
<td>Single shot spin-echo EPI</td>
<td>0, 5, 10, 20, 30, 50, 70, 100, 200, 400, 600, 800, 1000, 1500, 2000, 2500</td>
<td>Method 3</td>
<td>0.98 ± 0.22</td>
<td>6.8 ± 1.2</td>
<td>13.6 ± 2.2</td>
</tr>
<tr>
<td>Bokacheva et al., 2013</td>
<td>9</td>
<td>3.0 T</td>
<td>Single shot spin-echo EPI</td>
<td>0, 30, 60, 90, 120, 400 (450 in 7 cases), 600, 800, 1000</td>
<td>Method 3</td>
<td>1.29 ± 0.28</td>
<td>21.7 ± 11.0</td>
<td>6.4 ± 3.1</td>
</tr>
<tr>
<td>Liu et al., 2013</td>
<td>10</td>
<td>3.0 T</td>
<td>Single shot spin-echo TSE</td>
<td>0, 250, 800</td>
<td>Method 1</td>
<td>0.85</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Nilsen et al., 2013</td>
<td>13</td>
<td>1.5 T</td>
<td>Single shot spin-echo EPI</td>
<td>0, 50, 100, 250, 800</td>
<td>Method 1</td>
<td>0.90 ± 0.30</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

IDC, invasive ductal carcinoma; EPI, echo-planar imaging; TSE, turbo spin-echo; $D_1$, diffusion coefficient; $D_2$, pseudodiffusion coefficient; $f$, perfusion fraction; $D_1$, $D_2$, and $f$ are expressed as mean ± standard deviation or median (quartile); N/A, not available.
Method 2
Considering that $D^*$ is significantly greater than $D$ (at least 10 times) and its influence on diffusion-weighted signal is weak when $b$-value is large enough (typically $> 200 \text{ s/mm}^2$), thus, in this higher $b$-value regime, the pseudodiffusion component $D^*$ can be neglected and $D$ can be obtained by a simplified monoexponential fit equation:

$$S(b) = S_0 \exp(-b \times D)$$

Then $D^*$ and $f$ were calculated by using a nonlinear fitting algorithm for all $b$-values.

Method 3
A segmented analysis procedure was proposed as follows. First, as suggested in Method 2, at a high $b$-value, the influence of the pseudodiffusion coefficient $D^*$ is negligible. Therefore, the diffusion coefficient $D$ can be determined from the data within an interval of higher $b$-values ($b > 200 \text{ s/mm}^2$):

$$S_{\text{high}}(b) = S_{\text{high}0} \exp(-b \times D)$$

where $S_{\text{high}0} = S_0 (1-f)$. Second, the perfusion fraction $f$ can be determined using zero intercept $S_{\text{high}0}$ along with the unweighted ($b = 0$) signal $S_0$ as $f = (S_0 - S_{\text{high}0}) / S_0$. Finally, the pseudodiffusion coefficient $D^*$ can be obtained from the monoexponential fit using the precalculated $D$ and $f$ values.

The decision whether the diffusion-weighted signal follows a certain curve behavior strongly depends on the quality of image and the signal-to-noise ratio (SNR) that is obtained in the measurements. Therefore, before curve-fitting, diffusion-weighted images were smoothed by convolving with a $5 \times 5$ Gaussian filter (standard deviation $= 0.5$).

Two statistics were used to test the curve-fitting performances of different calculation methods in each voxel: $R^2$ value and Akaike Information Criteria (AIC). $R^2$ value is the simplest measure of goodness-of-fit for non-linear curve fit:

$$R^2 = 1 - \frac{\text{ESS}}{\text{TSS}}$$

where $\text{ESS}$ is the sum of squared errors between the data points and the fitting curve and $\text{TSS}$ is the sum of squared differences between the data points and the mean value of all data points. $R^2$ values range from 0 to 1 and a higher $R^2$ value means a better estimation of the curve fit on sample observations.

AIC is a statistical information criterion proposed by Akaike to analyze which model fits best to sample observations:

$$\text{AIC} = N \ln (\text{SS}) + 2p$$

where $N$ is the number of data points, $\text{SS}$ the sum of squared deviance, and $p$ the number of estimated parameters. Different from $R^2$ value, AIC deals with the trade-off between the goodness-of-fit and the complexity of the model. For a given set of candidate models for data points, the preferred model is the one with the minimum AIC value.

For each voxel in a selected region of interest (ROI), if $R^2$ value based on one calculation method (for example, Method $n$) was higher than that of any other method, the voxel was classified as best fit with Method $n$ based on $R^2$ value. Likewise, the voxel was classified as best fit with the method with a lowest AIC value based on AIC strategy. Therefore, within one ROI, the percentage of overall number of voxels classified as best fit for each calculation method, using the two statistics respectively, can be determined.

DCE MRI Data Analysis
Time intensity curve (TIC) for each lesion was constructed from SI values obtained from all time points after contrast injection. Two model-free semiquantitative parameters, relative enhancement ratio (RER) and initial area under the curve (IAUC) were calculated from TIC.

$$\text{RER} = \left( \frac{\text{SI}_{\text{post}} - \text{SI}_{\text{pre}}}{\text{SI}_{\text{pre}}} \right) \times 100$$

where $\text{SI}_{\text{pre}}$ is the SI before contrast injection and $\text{SI}_{\text{post}}$ is the SI of the first postcontrast dynamic acquisition.

$$\text{IAUC} = \int_0^t \text{SI}(t') \, dt'$$

where $\text{SI}(t')$ represents SI in the tissue at time at time $t'$. In the study, a value of $t = 5 \text{ min}$ was selected.

ROI Delineation
For DCE MRI data, a ROI was placed selectively on the areas of the most rapid and strongest enhancement. For diffusion data, another ROI was manually placed on the lesion area on a single slice of ADC map with the maximum diameter of lesion as large as possible, and meanwhile, large cystic or necrotic areas by visual inspection were excluded to focus on viable tumor tissue only. Then, the ROI was copied to the corresponding $D$, $D^*$, and $f$ maps. DCE images were used for lesion localization to guide the

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>30</td>
</tr>
<tr>
<td>Age (y) b</td>
<td>50 (27–79)</td>
</tr>
<tr>
<td>Lesion size (mm) b</td>
<td>25 (8–60)</td>
</tr>
<tr>
<td>Lesion location</td>
<td></td>
</tr>
<tr>
<td>Left breast</td>
<td>15</td>
</tr>
<tr>
<td>Right breast</td>
<td>15</td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
</tr>
<tr>
<td>HER2</td>
<td>9</td>
</tr>
<tr>
<td>Luminal</td>
<td>13</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>8</td>
</tr>
</tbody>
</table>

*Lesion size was measured on DCE MRI with the maximum transverse diameter of lesion.
*Data are expressed as mean (range).
ROI delineation. The whole ROI processing was independently conducted by two blinded observers (J.H. and N.L., with experiences of 15 and 4 years of breast MRI diagnosis, respectively).

**Statistical Analysis**
Statistical analysis was performed using SPSS software for Windows (version 17.0; SPSS, Chicago, IL) and GraphPad Prism 5 for Windows (version 5.01; GraphPad Software Inc, San Diego, CA). A P value less than 0.05 was considered to indicate a statistically significant difference.

To assess interobserver agreement in DWI and DCE MRI parameters, intraclass correlation coefficient (ICC) were calculated for ADC, IVIM-derived parameters ($D$, $D^*$, and $f$) and DCE-derived parameters (RER and IAUC) provided by both observers.

We calculated the precision of the parameter estimates by means of the coefficient of variation (CV) of the parameter estimates.$^{25,26}$ The statistical significance of the difference in the precision of the parameter estimates for the IVIM-derived parameters calculated from different methods was examined using Wilcoxon signed rank test. The Kruskal-Wallis test was used to assess the differences in each IVIM-derived parameter calculated from different methods, followed by Wilcoxon signed rank test with Bonferroni correction for pairwise comparisons. Spearman’s rank correlation was used to characterize the association of IVIM-derived perfusion-related parameters ($f$, $D^*$, and $f \times D^*$) from all the three methods and DCE-derived parameters (RER and IAUC).

**RESULTS**

**Interobserver Agreement**
Overall interobserver agreement was excellent. The ICC value was 0.93 for ADC map. The ICC values for IVIM-derived parameters ranged from 0.88 to 0.98 for Method 1, 0.92 to 0.98 for Method 2, and 0.89 to 0.98 for Method 3. Similarly, the ICC values for RER and IAUC were 0.93 and 0.94, respectively.

**Curve-Fitting Performance**
Based on $R^2$ criteria, the majority of voxels were best described by the Method 1 biexponential model (63.20%). Based on AIC strategy, the majority of voxels were best described by the monoexponential model (48.53%) and Method 1 biexponential model (44.52%), and there was no significant difference between AICs of the two models (Wilcoxon signed rank test, $P = 0.992$). The results are listed in Table 3.

**IVIM-Derived Parameter Precision**
Figure 1 depicts the bar plots of the CVs over the 30 subjects for the IVIM-derived parameters. The CV of $D$ calculated from Method 1 was significantly higher compared with Method 2 or Method 3 (both $P < 0.001$), while no significant difference was found between Method 2 and Method 3 ($P = 0.382$). The CV of $D^*$ calculated from Method 2 was significantly lower compared with Method 1 or Method 3 (both $P < 0.001$). The CV of $f$ calculated from Method 3 was also significantly lower compared with Method 1 or Method 2 (both $P < 0.001$) (Fig. 2).

**Difference of IVIM-Derived Parameters**
Table 4 shows IVIM-derived parameters calculated from all the three methods, and results of the Kruskal-Wallis test. Significant difference was observed for each IVIM-derived parameter in breast cancer ($P = 0.000–0.005$). Wilcoxon signed rank test with Bonferroni correction for pairwise comparisons showed that except $f$ values calculated from Method 3 was also significantly different ($P = 0.013$), all other IVIM-derived parameters between each two methods were significantly different ($P = 0.000–0.008$). An example of IVIM-derived parameter maps of breast cancer derived using the three methods is shown in Figure 2.

**Correlation With DCE MRI**
Mean values for DCE MRI parameters were as follows: RER = 142.15 (range, 60.41–218.69; units: au), and IAUC = 7.11 (range, 5.10–8.73; units: au). Among the IVIM-derived perfusion-related parameters ($f$, $D^*$, and their product, $f$ $\times$ $D^*$), only $f$ calculated from Method 2 was significantly correlated with RER ($r = 0.548$; $P = 0.002$) or

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**TABLE 3. Diffusion-Weighted Signal Attenuation Behavior of Voxels in Comparison of Different Curve-Fitting Methods in Breast Cancer**

<table>
<thead>
<tr>
<th>Linear curve fit</th>
<th>Nonlinear curve fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Method 1</td>
</tr>
<tr>
<td>$R^2$</td>
<td>9.85%</td>
</tr>
<tr>
<td>AIC</td>
<td>48.53%</td>
</tr>
</tbody>
</table>

Percentages of voxels best fit with certain method behavior were recorded based on $R^2$ and Akaike Information Criteria (AIC), respectively.
The results of correlation analysis are shown in Table 5.

**DISCUSSION**

The major limitation of IVIM model is its lack in producing reliable estimates of diffusion- and perfusion-related parameters from the diffusion-weighted signals, mainly because of the nonlinear nature of the IVIM model, and the more parameters to be estimated. Several different curve-fitting procedures with or without prior assumptions have been developed to get more reliable estimates of IVIM-derived parameters. However, different results have been reached using different calculation methods as shown in previous studies, and the potential confounding role of different calculation methods has not yet been investigated in breast cancer.

In the present study, we compared the three commonly used IVIM curve-fitting methods in breast cancer from aspects of parameter fitting performance, precision, difference, and their association with DCE MRI. Among the three biexponential calculation models, Method 1 best described most of the pixels. Though Method 1 has three free parameters to be estimated which seems less stable than Method 2 or Method 3, Method 2 and Method 3 are hypothesis-driven and simplified models, which may influence the goodness-of-fit. Nevertheless, in a previous study by Wittsack et al., noise simulations showed that Method 1 was easily influenced by image noise and reliable only in the presence of a sufficiently high SNR.

We assessed the quality of IVIM-derived parameter maps calculated from the three methods using the CV as the quantitative precision measure. The precision of $D$ determination was higher using Method 2 or Method 3 compared with Method 1. The precision of $D^*$ and $f$ determination reached a maximum using Method 2 and Method 3, respectively. For each method, the $D$ determination got higher precision compared with $D^*$ or $f$ determination; the result was consistent with that reported by Freiman et al.

Our results showed that using different curve-fitting methods, the IVIM-derived parameters differed significantly.
except the \( f \) values calculated from Method 2 and Method 3. The preliminary results may offer part of the explanation for why large variations in IVIM-derived parameters existed among previously published studies using different calculation methods (\( b \)-value combination is another major concern). The variations between different calculation methods might be caused by the complexities of mathematical approaches using different numbers of free parameters. In a study conducted by Heusch et al, they evaluated different calculation methods for IVIM model in transplanted kidneys and reached similar results.\(^{28}\) However, in their study, they did not assess \( D^* \) values.\(^{28}\)

The results of the present study revealed moderate correlations between IVIM-derived perfusion-related parameter \( f \) (calculated from Method 2) and DCE parameters in patients with breast cancer. Although the exact “perfusion” nature of what is measured with IVIM MRI deserves further investigation due to the complex vascular architecture and various fluid exchange mechanisms in vivo, it is universally recognized that the \( f \) value is linked to the blood volume within the capillary network.\(^{8,18,29–33}\) In IVIM studies of gliomas, Federau et al and Kim et al respectively reported a positive correlation between the \( f \) value and normalized CBV derived from DSC MRI perfusion (\( r = 0.59 \) and \( r = 0.67 \), respectively).\(^{29,31}\) In another IVIM study, Chandarana et al conducted a comparison between the \( f \) value and IAUC in renal tumors, and found they were strongly correlated (\( r = 0.82 \)).\(^{18}\) Similar correlation between the \( f \) value and tumor blood volume derived from DCE MRI was also found in head and neck squamous cell carcinoma by Fujima et al (\( r = 0.65 \)).\(^{30}\) Another two meaningful studies reported recently by Lima et al and Lee et al, respectively, found a positive correlation between the \( f \) value and microvessel density in a rat brain tumor model (\( r = 0.56 \)),\(^{32}\) and in a rat colorectal cancer model (\( r = 0.75 \)),\(^{34}\) which may potentially strengthen the biologic relevance between IVIM and microvascular blood volume. In our study of breast cancer, a moderate correlation between the \( f \) value and RER (\( r = 0.55 \), as well as a correlation between the \( f \) value and IAUC (\( r = 0.56 \)), was found, which was consistent with the above studies, and revealed the promising role of IVIM in characterizing tumor perfusion features in breast cancer. However, the correlation coefficient between the \( f \) value and RER/IAUC was not as high as we had expected. Many reasons may account for this result. Most important of all is the different focuses of the two perfusion-related parameters.

### Table 4. IVIM-Derived Parameter Values for Breast Cancer Using Three Calculation Methodsa

<table>
<thead>
<tr>
<th>Method</th>
<th>( D ) (10(^{-3}) mm(^2)/s)</th>
<th>( D^* ) (10(^{-3}) mm(^2)/s)</th>
<th>( f )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method 1</td>
<td>0.70 ± 0.11</td>
<td>98.24 ± 59.25</td>
<td>16.33 ± 5.21</td>
</tr>
<tr>
<td>Method 2</td>
<td>0.83 ± 0.19</td>
<td>159.50 ± 90.32</td>
<td>7.61 ± 2.33</td>
</tr>
<tr>
<td>Method 3</td>
<td>0.77 ± 0.15</td>
<td>69.28 ± 46.19</td>
<td>6.10 ± 3.19</td>
</tr>
<tr>
<td>( P ) Value</td>
<td>0.005</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

\(^a\)D, diffusion coefficient; \( D^* \), pseudodiffusion coefficient; \( f \), perfusion fraction; \( D, D^* \) and \( f \) are expressed as mean ± standard deviation.

\(^b\)Indicates difference among three calculation methods using the Kruskal-Wallis test.

### Table 5. Correlation Coefficients (\( P \) Values) Between IVIM-Derived Perfusion-Related Parameters (\( f, D^* \) and \( f \times D^* \)) From All the Three Methods and DCE-Derived Parameters (RER and IAUC)a

<table>
<thead>
<tr>
<th></th>
<th>RER</th>
<th>IAUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( f )</td>
<td>−0.113 (0.551)</td>
<td>−0.176 (0.352)</td>
</tr>
<tr>
<td>( D^* )</td>
<td>0.046 (0.809)</td>
<td>0.146 (0.441)</td>
</tr>
<tr>
<td>( f \times D^* )</td>
<td>0.006 (0.977)</td>
<td>0.044 (0.816)</td>
</tr>
<tr>
<td>Method 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( f )</td>
<td>0.548 (0.002)</td>
<td>0.561 (0.001)</td>
</tr>
<tr>
<td>( D^* )</td>
<td>−0.033 (0.862)</td>
<td>0.009 (0.964)</td>
</tr>
<tr>
<td>( f \times D^* )</td>
<td>0.121 (0.523)</td>
<td>0.202 (0.284)</td>
</tr>
<tr>
<td>Method 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( f )</td>
<td>−0.061 (0.748)</td>
<td>−0.106 (0.577)</td>
</tr>
<tr>
<td>( D^* )</td>
<td>0.001 (0.994)</td>
<td>0.098 (0.608)</td>
</tr>
<tr>
<td>( f \times D^* )</td>
<td>−0.121 (0.525)</td>
<td>−0.067 (0.725)</td>
</tr>
</tbody>
</table>

\(^a\)\( D^* \), pseudodiffusion coefficient; \( f \), perfusion fraction; RER, relative enhancement ratio; IAUC, initial area under the curve. The statistically significant correlations are displayed in bold.
The $f$ value reflects the fractional blood volume in the capillary network, or more exactly the ratio of the volume of water flowing in the microvascular compartment (plasma and blood cell content), whereas RER/IAUC measures contrast agent kinetics determined by a combination of blood flow, blood volume, and endothelial permeability.35

However, the IVIM analysis using Method 1 or Method 3 failed to reveal any association between perfusion parameters derived from IVIM and DCE MRI. We suspect that for Method 1, direct fitting of all three free parameters was largely influenced by image noise and outliers in the SI of a range of $b$-values as the SI of EPI sequence may include large outliers caused by susceptibility.36 As for Method 3, we suspect that in the higher $b$-value regime when perfusion effects were neglected, the calculation of the $f$ value may be rough, because IVIM has a differential sensitivity to vessel types according to the $b$-values used,35 and the $f$ value calculated only from the higher $b$-value regime would eliminate the perfusion component influenced by vessel types sensitive to low $b$-values. In addition, the calculation of the $f$ value was simplified as $f=\frac{S_0-S_{\text{ ADC}}}{S_0}$ in Method 3, which is a nonfitting approach and susceptible to $S_0$, whereas the $f$ value calculated from Method 2 was fitted using all $b$-values.

Our study had several limitations. First, only patients with pathologically proven IDC were included and evaluated in the study. A larger patient cohort with broader histological types of breast malignant and benign lesions was evaluated in the study. A larger patient cohort with broader histopathological types of breast malignant and benign lesions was needed to make a more comprehensive analysis. Second, our study was retrospective and the optimal $b$-value combination for breast IVIM analysis was not assessed. Different $b$-value combinations may lead to bias and variability in the IVIM-derived parameter estimates, especially $f$.37,38 Additionally, more $b$-values could strengthen the IVIM effect, at the cost of increasing acquisition time. Therefore, some researchers have suggested the imaging protocol could be abbreviated to a range of $b$-values.39 Taking both clinical tolerance and IVIM characterization into consideration, we used 7 $b$-values in the current study and most of them were not larger than 200 s/mm². Third, we did not compare some other newly introduced methods for IVIM estimation which have not been used in breast IVIM analysis, like fusion bootstrap moves and data driven Bayesian modeling.25,40

In conclusion, we assessed different IVIM analysis methods on DWI data acquired from breast cancer patients in the current study. IVIM-derived parameters differ depending on the calculation methods. It was found that the two-step fitting method with $D$ value estimation first was more correlated with DCE MRI perfusion compared with the other two methods. Cautious selection of an appropriate calculation method is necessary for measurement of diffusion- and perfusion-related parameters obtained with IVIM. Maybe a unified standard for IVIM data collection and analysis needs to be reached; otherwise, the clinical utility of IVIM analysis will perhaps be diminished.

References


