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Agreement between region-of-interest- and parametric map-based hepatic proton density fat fraction estimation in adults with chronic liver disease

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Abstract

Purpose—To compare agreement between region-of-interest (ROI)- and parametric map-based methods of hepatic proton density fat fraction (PDFF) estimation in adults with known or suspected hepatic steatosis secondary to chronic liver disease over a range of imaging and analysis conditions.

Materials and Methods—In this IRB approved HIPAA compliant prospective single-site study, thirty-one adults with chronic liver disease undergoing clinical gadoxetic acid-enhanced liver magnetic resonance imaging at 3T were recruited. Multi-echo gradient-echo imaging at flip angles of 10° and 50° was performed before and after administration of gadoxetic acid. Six echoes were acquired at successive nominally out-of-phase and in-phase echo times. PDFF was estimated with

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COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conflict of interest:

Author Paul M. Manning declares that he has no conflict of interest.

Author Gavin Hamilton declares that he has no conflict of interest.

Author Kang Wang declares that he has no conflict of interest.

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a non-linear fitting algorithm using the first two, three, four, five, and (all) six echoes. Hence, 20 different imaging and analysis conditions were used (pre/post contrast $\times$ low/high flip angle $\times$ 2/3/4/5/6 echoes). For each condition, PDFF estimation was done in corresponding liver locations using two methods: a region-of-interest (ROI)-based method in which mean signal intensity values within ROIs were run through the fitting algorithm, and a parametric map-based method in which individual signal intensities were run through the fitting algorithm pixel by pixel. Agreement between ROI- and map-based PDFF estimation was assessed by Bland-Altman and intra-class correlation (ICC) analysis.

Results—Depending on the condition and method, PDFF ranged from -2.52 to 45.57% . Over all conditions, mean differences between ROI- and map-based PDFF estimates ranged from 0.04 to 0.24% , with all ICCs > 0.999 .

Conclusion—Agreement between ROI- and parametric map-based PDFF estimation is excellent over a wide range of imaging and analysis conditions.

Keywords

MRI; fat quantification; hepatic steatosis; proton density fat fraction; PDFF; quantitative imaging biomarker; QIB; analysis methods

INTRODUCTION

Proton density fat fraction (PDFF) is an emerging non-invasive biomarker of hepatic steatosis [1-3]. PDFF estimation using a magnitude-based multi-echo magnetic resonance imaging (MRI) acquisition technique (MRI-M) has been shown to agree with PDFF estimation using MR spectroscopy (MRS) at 1.5T [4] and 3.0T [5]. Intra- [5] and inter-exam repeatability [6] of MRI-M-estimated PDFF has been shown to be high, and reproducibility has been demonstrated across scanner manufacturers [7], sites [8], and field strengths [7, 9]. Compared to other techniques used to estimate PDFF, MRI-M currently has the added advantage of widespread accessibility [4]. For these reasons, MRI-M PDFF estimation has been investigated extensively as an MR-based biomarker of hepatic steatosis and is used as an endpoint in clinical trials [10].

To estimate PDFF, MRI-M uses a multi-echo spoiled-gradient-echo technique to generate images at consecutive echo times (TEs) at which water and the dominant methylene fat peak are nominally out of phase and in phase [1]. The images are analyzed with a non-linear fitting algorithm that fits image signal intensity values to a previously-validated mathematical model describing the relationship between signal intensity and PDFF [4, 5]. The model corrects for factors that may confound PDFF estimation including $T2^*$ exponential decay and the spectral complexity of fat [11, 12]. The analysis can be done two ways: using a region-of-interest (ROI)-based method, or using a parametric map-based method. The difference between the two methods is that in the ROI-based method, signal intensities of multiple pixels within an ROI are averaged prior to application of the fitting algorithm (average first). In the map-based method, the fitting algorithm is applied to individual pixels first to generate a parametric PDFF map, and an ROI is then placed on the map to average multiple per-pixel PDFF values (fit first). This difference may affect how

image noise propagates through the fitting algorithm, potentially altering PDF estimates [13]. In recent publications, both ROI- [4, 5, 7, 14] and map- [2, 3, 9, 15] based MRI-M methods have been used to estimate PDF, but not in the same study. Hence, although agreement between ROI- and map-based methods is likely, agreement has not yet been demonstrated, and it is currently unknown whether any error in their agreement is clinically meaningful. Such demonstration would indicate that either method can be used. This would validate the use of either method in clinical care settings or clinical trials where map-based methods are not always possible due to the financial constraints of software expenses, or the hardware constraints of older MRI machines unable to run the sequence. Furthermore, it would allow data to be pooled from different studies regardless of the applied method.

Therefore, the purpose of this study was to compare agreement between ROI- and map-based methods of MRI-M PDF estimation. To accomplish this, we assessed agreement between the two methods over a range of imaging and analysis conditions in adults with liver disease and spanning a spectrum of hepatic steatosis. Simulations were also performed to better understand the results.

MATERIALS AND METHODS

Study design and subjects

This prospective, cross-sectional, observational, single-site study was approved by an Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. Between June 2012 and March 2014, adults with known or suspected hepatic steatosis secondary to chronic liver disease who were scheduled for gadoxetic acid- (GA; Bayer-Schering Pharma AG, Berlin, Germany) enhanced clinical MRI were recruited consecutively to have research sequences added to their clinical MR protocols. Recruitment, consenting, and enrollment were done by coordinators in our research facility with the knowledge and approval of the patients' referring clinicians. The clinical indications, as confirmed by biopsy, for these patients to receive contrast-enhanced MRI are summarized in Table 2. This patient group was selected in order to capture the clinically relevant range of hepatic steatosis among patients with various etiologies of liver disease receiving MR contrast for clinical purposes. This scanner was chosen because it is staffed by research coordinators able to consent clinical patients for add-on research sequences. Recruitment was by convenience and based on scanner schedule to accommodate the add-on sequences. Eligible patients over 18 years of age who gave written informed consent were enrolled in this study. Exclusion criteria included patients with contraindication to receive GA contrast and patients with contraindication to receive MRI, including claustrophobia and pregnancy. Basic demographic, clinical, and anthropometric data were collected.

MR exams

All exams were performed by experienced MR technologists on a 3T scanner (GE Signa EXCITE HDxt, GE Healthcare, Waukesha, WI). Subjects were positioned supine with an 8-channel torso phased-array coil placed over the liver. A magnitude-based fat quantification sequence (described below) was acquired as a research add-on to their clinical exam. This

was performed before and after injection of GA (0.025 mmol/kg), and at both low (10°) and high (50°) flip angle (FA).

These conditions encompass a range of circumstances that may affect PDFF estimation, including different T1 weightings and signal-to-noise ratios (SNRs) [16, 17]. To minimize bias due to acquisition order, the order of imaging at the two tested flip angles was randomized.

Image sequence parameters are provided in Table 1. For each sequence, six magnitude images were obtained at consecutive nominally out-of-phase and in-phase TEs (TE: 1.15, 2.30, 3.45, 4.60, 5.75, and 6.90 ms). Source images generated at each of the six TEs were transferred offline for further processing with open-source image processing and viewing software (Osirix; Osirix Foundation, Geneva, Switzerland).

Fitting algorithm

A previously-published MATLAB- (The Mathworks, MA, USA) based non-linear fitting algorithm was used for all analyses, including the simulation analyses [4, 5, 17]. This fitting algorithm models the spectral complexity of fat and, in cases where more than two echoes are used, also corrects for T2* exponential decay. For two-echo methods, no correction for T2* is made.

ROI selection

One author placed a single 1-cm radius circular ROI in the right hepatic lobe of the 5th-TE images (5.75 ms), avoiding large hepatic vessels, bile ducts, liver edges, liver lesions, and artifacts. These images were chosen because they consistently provide adequate anatomic visualization for ROI placement. The ROIs were automatically propagated at the same anatomic location to the remaining TE images as well as to the parametric PDFF maps (described below). A typical ROI contained 96 pixels.

ROI-based analysis

Signal intensities within each ROI were averaged and recorded. To calculate PDFF, mean signal intensities of the first two, three, four, five, and six echoes were analyzed using the fitting algorithm. Thus, five ROI-based PDFF estimates were generated for each sequence (Figure 1a).

Map-based analysis

Signal intensities from the source images were analyzed pixel by pixel using the fitting algorithm using the first two, three, four, five, and six echoes. Thus, five parametric PDFF maps were generated for each sequence. The previously-selected ROIs were propagated to the maps, and the mean PDFF value from each map-based ROI was recorded (Figure 1b).

Simulation analysis

To further understand potential differences in methods, simulations were performed. Using the previously described non-linear fitting model, we simulated three PDFF values (10, 20, and 30%) and computed the corresponding normalized signal intensity at each TE. Rician-

distributed noise was added to each computed signal intensity [18]. This process was repeated 96 times to represent the 96 pixels within a typical ROI. Thus, for each of the six echoes, 96 simulated 'noisy' signal intensities were generated.

PDFF was then estimated from these 'noisy' signal intensities using both the ROI- and the map-based methods. For the ROI-based method, the 96 simulated pixel values were averaged for each echo, and the averages were analyzed by the fitting algorithm to generate a PDFF estimate. For the map-based method, the fitting algorithm was applied to each simulated pixel value at each echo to generate a per-pixel PDFF estimate, and the mean PDFF value of the 96 simulated pixels was calculated. Each simulation was repeated 50 times, each time with a new addition of Rician-distributed noise, and these repeated measurements were averaged to obtain final PDFF estimates for each method (Figure 2).

Finally, each set of simulations was repeated by varying the magnitude of the added noise to simulate a range of image SNR values in the range 5 - 25, as this range is representative of images typically acquired using the MRI-M technique at 3T. SNR was defined as the ratio of squared signal intensity at simulated TE = 0 ms to the variance of the Rician-distributed noise.

Statistical analysis

Subject characteristics were summarized descriptively.

A total of 20 different conditions were tested: two contrast conditions (pre- or post-), two flip angles (10° or 50°), and five numbers of echoes (two, three, four, five, and six). For each condition, descriptive summaries were generated. Mean differences between ROI- and map-based PDFF estimates, limits of agreement, and intra-class correlation coefficients (ICCs) were calculated. Limits of agreement were defined as mean difference $\pm$ 1.96 standard deviations (SDs). Paired t-tests were performed and Bland-Altman plots were generated. Results of simulations were plotted graphically.

The R software package was used for all statistical analysis (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>).

RESULTS

Thirty-one adult subjects (19 male, 12 female) were included. Mean age was 53 yrs (range 23 - 75 yrs) and mean BMI was 29.5 kg/m² (range 18.0 - 42.1).

Results are summarized in Table 3. Depending on the method and condition, PDFF values ranged from -2.52 to 45.57% and mean PDFF values ranged from 5.39 to 12.61%. The distribution of PDFF is provided in Figure 3 for representative conditions (six-echo, pre contrast, FA 10), which shows that the majority of patients had PDFF in the 0-10% range. Agreement between ROI- and map-based methods was excellent with ICCs 0.999 for every condition. ROI-based PDFF estimates were consistently larger than the map-based estimates with mean differences ranging from 0.04 to 0.24%. Although significant ($p < 0.05$ for all conditions), the differences were small and likely not clinically meaningful.

Informally, the differences were greater at FA 10° (representing a lower SNR condition) compared to FA 50° (representing a higher SNR condition). This is demonstrated by representative Bland-Altman plots for six-echo conditions, shown in Figure 4. From the Bland-Altman plots it can be seen that differences between methods did not change appreciably as PDFF increased.

Figure 5 demonstrates the results of the simulation analyses where PDFF estimates are plotted as a function of SNR. The horizontal black line represents 'true' PDFF. The vertical dashed line represents the lower bound of SNR (~8) typically observed with MRI-M at 3T; thus, data to the right of this line is in the range of expected SNR while data to the left is noisier. Results from simulations were similar to results from experimental conditions. Simulated ROI-based PDFF estimates were consistently higher than simulated map-based PDFF estimates, by 0.01 to 0.51% depending on SNR and PDFF. Both simulated methods underestimated the 'true' PDFF (for each simulation - i.e., 10, 20, or 30%), but map-based underestimation was greater than ROI-based underestimation. For both simulated methods, the magnitude of underestimation was greater at lower SNR and converged to the 'true' value as SNR increased. As PDFF increased (10, 20, or 30%) differences between methods decreased.

DISCUSSION

In this study, we demonstrated excellent agreement between ROI- and parametric map-based methods of hepatic PDFF estimation in adults with variable degrees of hepatic steatosis and various liver abnormalities over a wide range of imaging and analysis conditions, as well as in simulations. Although both methods agreed closely, for all experimental conditions and simulations, PDFF estimates from the ROI-based method were consistently slightly larger than those from the map-based method.

The differences between ROI- and map-based PDFF estimates plausibly may be attributable to the non-linear fitting. With such fitting, averaging before fitting (as is done in the ROI-method) and averaging after fitting (as is done in the map-method) may lead to differences in error propagation and ultimately to small differences in PDFF estimation. Since the simulations held all other potential sources of error constant, the order of averaging must be at least partially responsible.

In the simulations, both methods underestimated 'true' PDFF. This may be because in magnitude imaging, the noise distribution is Rician and biased with a nonzero positive mean [19]. This causes spurious elevations of signal intensity at all echo times, while (on average) the differences between any consecutive pair of out-of-phase and in-phase echo times remain constant. This reduces relative signal oscillation, and hence estimated PDFF. Previous studies have demonstrated that in magnitude imaging, the effect of this bias increases as SNR decreases [18, 19]. This may explain why for both methods underestimation from the 'true' value increased as the simulated SNR decreased. The underestimation from the 'true' value increased more for the map- than for the ROI-based method. Thus, in the simulations, the greatest differences between map- and ROI-based methods were observed at low SNR.

Similarly, we found that differences between methods tended to be larger in FA 10° conditions (lower SNR) than in FA 50° conditions (higher SNR).

As expected, PDFF estimates made under pre-contrast FA 50° conditions were larger compared to other conditions. This is because higher FA conditions like FA 50° are more T1 weighted, which causes PDFF to be overestimated. For this reason, lower FA is normally favored. Our results corroborate previous investigations showing that higher flip angle conditions produce similarly increased PDFF estimates [1, 4, 5]. For post-contrast acquisitions, both FA 10° and FA 50° conditions gave similar results. This corroborates a previous study that showed FA dependence is eliminated with gadolinium contrast administration [16]. PDFF estimates made under two-echo conditions were smaller than estimates made under three-, four-, five-, and six- echo conditions. This is due to the lack of T2* correction in the two-echo model. Our results are consistent with previous studies showing that two-echo methods which do not correct for T2* effects lead to underestimation of PDFF [14]. For these reasons, M-MRI PDFF estimation is typically preformed using FA 10°, pre-contrast, and more than two echoes. This set of conditions has been shown to provide the most accurate PDFF estimates compared to MRS [5, 4, 14].

Although there were differences between ROI- and map-based methods, these differences were small. For comparison, the intra- and inter-exam repeatability for MRI-M PDFF ($\pm$ SD) has been reported to be as high as $\pm 0.87\%$ [4] and $\pm 0.61\%$ [6], respectively, both larger than the maximum differences found between analysis methods in this study.

Overall, our results showed that agreement between methods was excellent and the degree of error was not clinically meaningful, suggesting that in the future either ROI- or map-based methods can be used. Agreement held true regardless of conditions tested, including for two-echo methods which are known to underestimate PDFF but remain in use due to limitations of some scanners. Our results suggest that data from different studies can be pooled regardless of the applied method. Comparing methods, one advantage of map-based estimation is that it is more fully automated and keeps the complicated fitting algorithm hidden from the user [20]. For this reason, it is likely that the map-based method will be the favored technique for future MRI-M PDFF estimation in research and potentially in clinical settings. However, on current MR scanners map-based methods are not always possible due to financial and hardware constraints, so ROI-based methods may be favored in these cases.

A limitation of this study was that all exams were performed on a single 3T scanner from one manufacturer. Although reproducibility of PDFF estimation has been established, agreement between the map- and ROI-based methods across scanners and sites has not yet been demonstrated. Assuming that other scanners operate in a similar noise range, we do not suspect that the choice of scanner would meaningfully impact agreement. The majority of patients in this study had PDFF in the 0-10% range, therefore the results may be less generalizable to patients with higher ranges of PDFF. However, the range captured reflects clinically relevant PDFF which spans from normal to mild to moderate. Furthermore, agreement did not appreciably change for the minority of patients with high PDFF. At the highest simulated PDFF (30%) the differences between methods were smallest, suggesting that in our cohort of patients with relatively low PDFF we would expect the greatest

differences. Agreement of $R2^*$ was not assessed in this study because the clinically relevant range of $R2^*$ was not captured, all patients had essentially normal $R2^*$ values. We did not compare accuracy of PDFF estimates to a reference standard such as MRS because such analyses have been done previously [4, 5, 9] and were outside the scope of this study. Finally, we did not address complex-based techniques of fat quantification or hybrid techniques which use a combination of magnitude- and complex-based fat quantification [18]. However, current implementations of these techniques allow only map-based quantification, making comparison to ROI-based methods irrelevant.

In conclusion, agreement between MRI-M PDFF estimation using ROI- and parametric map-based methods is excellent, indicating that either method is suitable for fat quantification. Our results suggest that data from different studies can be pooled regardless of whether ROI- or map-based methods are used, provided optimal acquisition parameters of low FA and more than two echoes are used. Because the parametric map-based method is more fully automated and easy to use, it may provide a more practical route for research and clinical applications.

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Figure 1.

Example of ROI-based method (a) and map-based method (b) using four echoes. For the ROI-based method, ROIs were placed and co-localized onto each out-of-phase and in-phase image. Signal intensities within ROIs were averaged and analyzed by the fitting algorithm to estimate PDFF. For the map-based method, signal intensities were analyzed by the fitting algorithm pixel by pixel to generate a parametric PDFF map. An ROI was placed on the map at the corresponding anatomic location, and mean PDFF within the ROI was recorded.

Figure 2.

Schema describing simulation analyses. Three PDFF values were selected for simulation (10, 20, and 30%). These values were analyzed by the fitting algorithm to generate signal intensity values pertaining to images acquired at six echoes, and plotted against TE. Rician noise was added to each of the six signal intensity values (range of values plotted at each TE). This was repeated 96 times to represent realistic estimates of the 96 pixels within an ROI. Using these noise-enhanced estimates, PDFF was calculated by the ROI-based method, and then the map-based method.

Figure 3. Histogram displaying distribution of PDFFF for representative conditions (Six echo, pre contrast, FA 10).

Figure 4.

Bland-Altman analyses of ROI- and map-based PDFF estimation. Difference in ROI- and map-based PDFF (%) (ROI-based minus map-based) is plotted as a function of mean ROI- and map-based PDFF (%) for all conditions using six echoes including a) pre-contrast FA 10°, b) pre-contrast FA 50°, c) post-contrast FA 10°, d) post-contrast FA 50°. The blue line in the middle of each graph indicates the mean difference. The two blue lines above and below indicate the 95% limits of agreement.

Figure 5.

Simulation analyses showing simulated PDFF (%) estimates as a function of SNR, for simulated PDFF values of (a) 10%, (b) 20%, and (c) 30%. The solid black line represents the 'true' PDFF value. The dashed vertical line represents SNR of 8; data to the right of this line represents SNR found in our anecdotal experience in typical clinical settings (SNR > 8).

Table 1

Parameters for MRI-M sequences

Parameter	Values
Pulse sequence	Spoiled GRE
Slice thickness	6 - 8 mm
Interslice gap	0 mm
TEs	1.15, 2.30, 3.45, 4.60, 5.75, 6.90 ms
TR	125 - 165 ms
Image matrix	224 × 224 base matrix
FOV	44 × 44 cm base FOV
NEX	1
Parallel imaging accelerating factor	None
BW	± 142 kHz

Notes: MRI-M = magnitude-based magnetic resonance imaging; GRE = gradient recalled echo; TE = time to echo; TR = repetition time; FOV = field of view; NEX = number of excitations; BW = bandwidth

Table 2

Summary of indications for clinical scans. Number of subjects per indication is shown. Note that some subjects had multiple indications.

Indication	Number of subjects
NASH or NASH cirrhosis	11
Alcoholic cirrhosis	1
Hemochromatosis	1
Cystic fibrosis	1
HCV infection	1
HBV infection	1
HCC	3
Metastatic colorectal cancer	8
Metastatic breast cancer	1
Metastatic melanoma	1
More than one indication	2

Notes: NASH = nonalcoholic steatohepatitis; HCV = hepatitis C virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma

Table 3

Summary of results for ROI- and map-based methods of PDFF (%) estimation for all conditions tested including pre- and post-contrast, 10° and 50° flip angles, and two to six echoes used for analysis. Mean differences (ROI-based minus map-based) with 95% limits of agreement (LOA), significance of paired t-test, and ICC are provided for each combination of conditions.

Contrast	FA (°)	Number echoes	ROI-based PDFF (%)		Map-based PDFF (%)		Mean difference (%)	95% LOA (%)	ICC
			Mean	Range	Mean	Range			
pre	10	2	5.88	−1.08, 31.21	5.72	−1.2, 31.13	0.15***	−0.17, 0.48	0.999
pre	10	3	8.15	1.08, 32.45	8.00	1.19, 32.43	0.15***	−0.09, 0.39	0.999
pre	10	4	8.00	0.85, 32.44	7.81	0.93, 32.39	0.19***	−0.05, 0.44	0.999
pre	10	5	7.91	0.73, 32.35	7.76	0.82, 32.31	0.15***	−0.11, 0.41	0.999
pre	10	6	7.78	0.43, 32.33	7.63	0.52, 32.28	0.15***	−0.08, 0.39	0.999
pre	50	2	10.39	−1.61, 44.62	10.3	−1.2, 44.51	0.09***	−0.20, 0.39	0.999
pre	50	3	12.61	0.81, 45.31	12.55	0.91, 45.36	0.06***	−0.11, 0.24	0.999
pre	50	4	12.46	0.56, 45.31	12.37	0.63, 45.26	0.09***	−0.08, 0.26	0.999
pre	50	5	12.41	0.48, 45.54	12.34	0.56, 45.50	0.07***	−0.07, 0.20	0.999
pre	50	6	12.28	0.27, 45.57	12.2	0.24, 45.52	0.07***	−0.06, 0.20	0.999
post	10	2	5.39	−2.33, 31.92	5.27	−2.02, 31.84	0.12**	−0.32, 0.56	0.999
post	10	3	8.07	0.83, 33.70	7.88	0.82, 33.69	0.19***	−0.07, 0.45	0.999
post	10	4	7.95	0.67, 33.69	7.72	0.62, 33.66	0.24***	−0.03, 0.50	0.999
post	10	5	7.9	0.52, 33.80	7.72	0.48, 33.78	0.16***	−0.12, 0.47	0.999
post	10	6	7.79	0.38, 33.81	7.6	0.31, 33.80	0.18***	−0.06, 0.43	0.999
post	50	2	5.52	−2.52, 30.64	5.47	−2.39, 30.63	0.04*	−0.11, 0.19	0.999
post	50	3	8.59	0.84, 32.57	8.54	0.87, 32.57	0.04**	−0.14, 0.23	0.999
post	50	4	8.48	0.64, 32.56	8.42	0.67, 32.57	0.06***	−0.13, 0.24	0.999
post	50	5	8.45	0.56, 32.98	8.41	0.64, 32.97	0.04*	−0.15, 0.23	0.999
post	50	6	8.35	0.40, 33.05	8.31	0.39, 33.02	0.04*	−0.11, 0.18	0.999

Notes: FA = flip angle; ROI = region of interest; PDFF = proton density fat fraction; LOA = limits of agreement; ICC = intra-class correlation coefficient. Paired t-tests comparing methods with p-values 0.05, 0.01, and 0.001 are indicated by *, **, *** respectively. Positive mean difference values indicate that the ROI-based PDFF estimates were higher than map-based PDFF estimates.