Proton-Density Fat Fraction Biomarker Committee: A Meta-Analysis Interim Report 2016

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Quantitative Imaging Biomarkers Alliance — RSNA

PDFF - Biomarker of Hepatic Steatosis

Proton-density fat fraction (PDFF) is a **quantitative imaging biomarker** (**QIB**) of hepatic triglyceride concentration that can be measured using magnetic resonance imaging (MRI) or spectroscopy (MRS). PDFF is a fundamental property of tissue and represents the ratio of MR-visible triglyceride protons to the sum of triglyceride and water protons.

As the only standardized **QIB** for hepatic steatosis, PDFF holds promise for multi-center research studies and in clinical practice.

Compelling published data indicate that MRI-PDFF has high linearity and negligible bias against MRS as the reference, as well as excellent test-retest repeatability. In comparison there are limited data on the performance of MRI-PDFF in multi-center or clinical settings where individuals may undergo MRI-PDFF measurements on different scanners of different vendors, field strengths, and possibly using different reconstruction algorithms.

Working Criteria for PDFF by MRI

Proton-density fat fraction (PDFF) is mathematically defined as:

$$PDFF = \sum_{all} PD_{fat\ peak} / (PD_{water\ peak} + \sum_{all} PD_{fat\ peak})$$

where PD is the MR-visible proton-density at resonance frequencies corresponding to water (4.7 ppm) and triglyceride (multiple frequencies [1]). Various MRI-based methods for measuring PDFF have been proposed, including 2D and 3D spoiled gradient recalled echo (SGRE) sequences at 1.5T and 3.0T field strengths, using different reconstruction algorithms.

The QIBA PDFF Committee currently adopts the following criteria for MRI acquisition and reconstruction methods to estimate PDFF.

Acquisition Criteria

- *Vendor* : Any
- *Field strength* : 1.5 or 3.0T
- *Pulse sequence* : 2D or 3D SGRE
- *Flip angle* : Low flip-angle relative to TR to minimize T1 related bias
- *# of TE's* : ≥3 TEs to enable estimation and correction for T2* signal decay
- *Echo spacing* : ¼ - ¾ of full fat-water cycle (4.6/2.3 ms at 1.5T/3T)
- *Echo train* : Single shot or interleaved shot
- *Field of view, slice thickness and imaging matrix* : Any, compatible with required echo spacing
- *First TE* : Typically 0.5-3.0 ms
- *Parallel imaging* : Any, permitted by the scanner vendor
- *Respiration* : Breath-hold or respiratory gated/triggered

Reconstruction Criteria

- *T2* estimation & correction* : mono-exponential or bi-exponential
- *Fat-peak modeling* : ≧4 of the most dominant triglyceride peaks
- *Data fitting algorithm* : Magnitude, complex, or hybrid

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Purpose

Using a meta-analysis, summarize existing literature on MRI-PDFF, to obtain pooled linearity, bias, and precision estimates across different field strengths, scanner vendors, and reconstruction algorithms.

Materials and Methods

A *PubMed* literature search was performed for primary research articles using the following inclusion criteria:

For linearity/bias study: liver "fat fraction" (imaging AND spectroscopy) "magnetic resonance" NOT Review [Publication Type]

For precision study: liver "fat fraction" imaging (repeatability OR reproducibility OR precision) "magnetic resonance" NOT Review [Publication Type]

Abstracts, then the full paper, were screened using the following exclusion criteria: secondary analysis of previously published data; not meeting criteria for PDFF; not *in vivo* human study; no MRS-PDFF (i.e. not long-TR multi-TE STEAM sequence, for linearity/bias study); no repeated PDFF measurements (for precision study). The authors of the articles meeting all inclusion/exclusion criteria were invited to submit de-identified source PDFF data for this meta-analysis.

For each subject's MRI PDFF measurements, the following data were recorded in a pooled database:

- Field strength : 1.5 or 3.0T
- Vendor : GE, Siemens, or Philips
- Reconstruction : Magnitude, complex, or hybrid
- Exam number : Repeated exam setup (coil, calibration, etc.)
- Acquisition number : Repeated acquisition with identical exam setup
- Region of Interest : Region of interest (ROI) label in the liver
- MRI-PDFF (%) : Average PDFF within an ROI
- MRS-PDFF (%) : Co-localized to MRI ROI, if available

The pooled data were analyzed using R ver3.1.3 (The R Foundation for Statistical Computing). Linearity was evaluated using linear regression of MRI- vs. MRS-PDFF. Bias, defined as the difference in PDFF between MRI and MRS (as the reference technique), was evaluated using a linear mixed model, with field strength, vendor, and reconstruction as fixed effects, and subject, ROI, exam and acquisition as random effects. Precision, defined as variability of MRI-PDFF upon repeated measurements, was also evaluated using a linear mixed effects model, with field strength, vendor, reconstruction, subject, ROI, exam, and acquisition as random effects.

Results

Out of 74 and 54 articles meeting the search criteria for the linearity/bias and precision studies, respectively, a total 23 articles were selected. All corresponding authors agreed to submit the original datasets, 21 of which were available at the time of this interim analysis [2-22].

A total of 1,470 subjects from 18 different studies were included in the linearity and bias analyses, and 1,656 subjects from 17 studies were included in the precision analysis.

Results (cont'd)

Fig 1 (right) shows excellent linearity of MRI-PDFF across entire observed MRS-PDFF range of 0.0 - 46.2%. The regression intercept did not deviate significantly from 0. The regression slope was <1, but this deviation from unity (by 0.025) is unlikely to be significant clinically or in clinical trials.
Fig 2 (below) demonstrates that MRI agreed closely with MRS in PDFF measurements, with negligible mean bias. Overall limits of agreement were approximately ±4%. The vendor, field strength and reconstruction algorithms had small (mostly <2%) impact in bias.

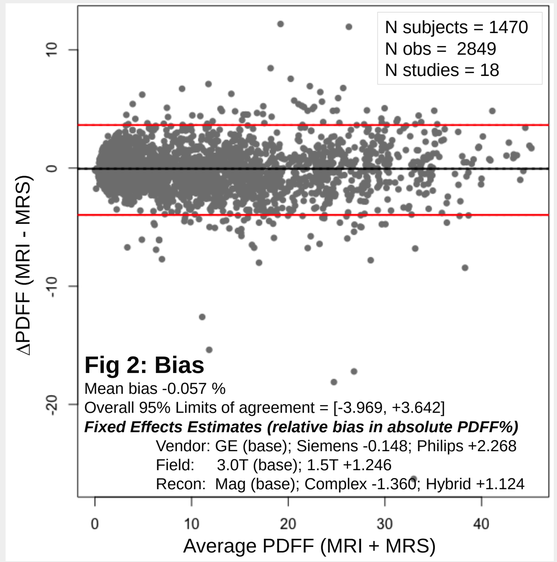
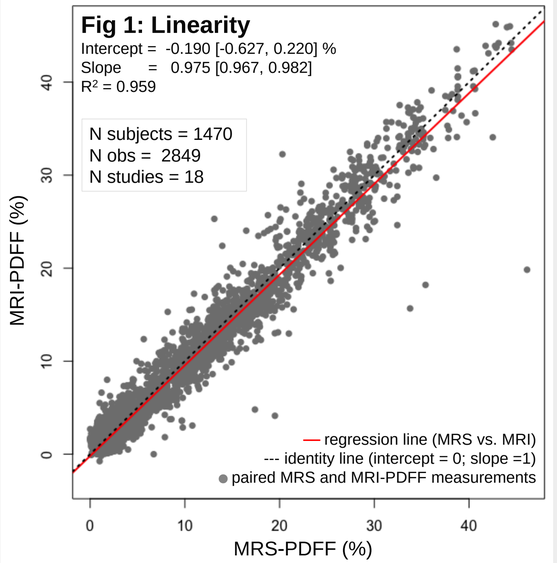
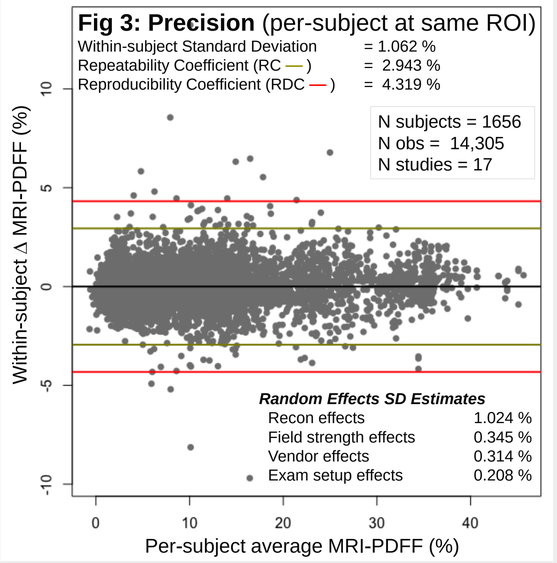


Fig 3 (right) shows excellent precision of MRI-PDFF across the observed PDFF range with repeatability coefficient of 2.9%. Reproducibility coefficient - which incorporates additional sources of variability (field strength, vendor, reconstruction, and exam-setup effects) was 4.3%.





Conclusion

This interim meta-analysis of liver MRI-PDFF data from multiple published studies demonstrated excellent linearity, negligible bias, and high precision across different field strengths, vendors, and reconstruction algorithms.

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