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The influence of iron deposition on the quantitative estimation of proton density fat fraction in patients with comorbid hepatic siderosis and steatosis: An MRI study

Dimosthenis E. Gkotsis[1,2], Efstathios D. Gotsis [3], Ioannis Seimenis [1]

[1]National & Kapodistrian University of Athens, School of Medicine, Department of Medical Physics, Athens, Greece

[2]GE HealthCare, Pharmaceutical Diagnostics, Global R&D, Imaging and Digital Technology Evaluation Group

[3]Diagnostic Center Euromedica Encephalos, Radiology, MRI Department, Athens, Greece

1. Background - Aim

Fat infiltration and **abnormal iron deposition** in the liver may be concurrently present. In such cases, an accurate quantification of both liver iron and fat is needed to guide patient management and overall treatment plan[1][2] .

In our **previous work**[3] we proposed a novel framework that allows **simultaneous characterization of PDFF and iron contents** in a single-breathhold, using signal intensities measured from multi-echo gradient echo images and then manually least-squares-fitted with a **customized bi-exponential equation** that treats water and fat protons as distinct entities, considers baseline noise, accounts for fat-induced signal oscillation.

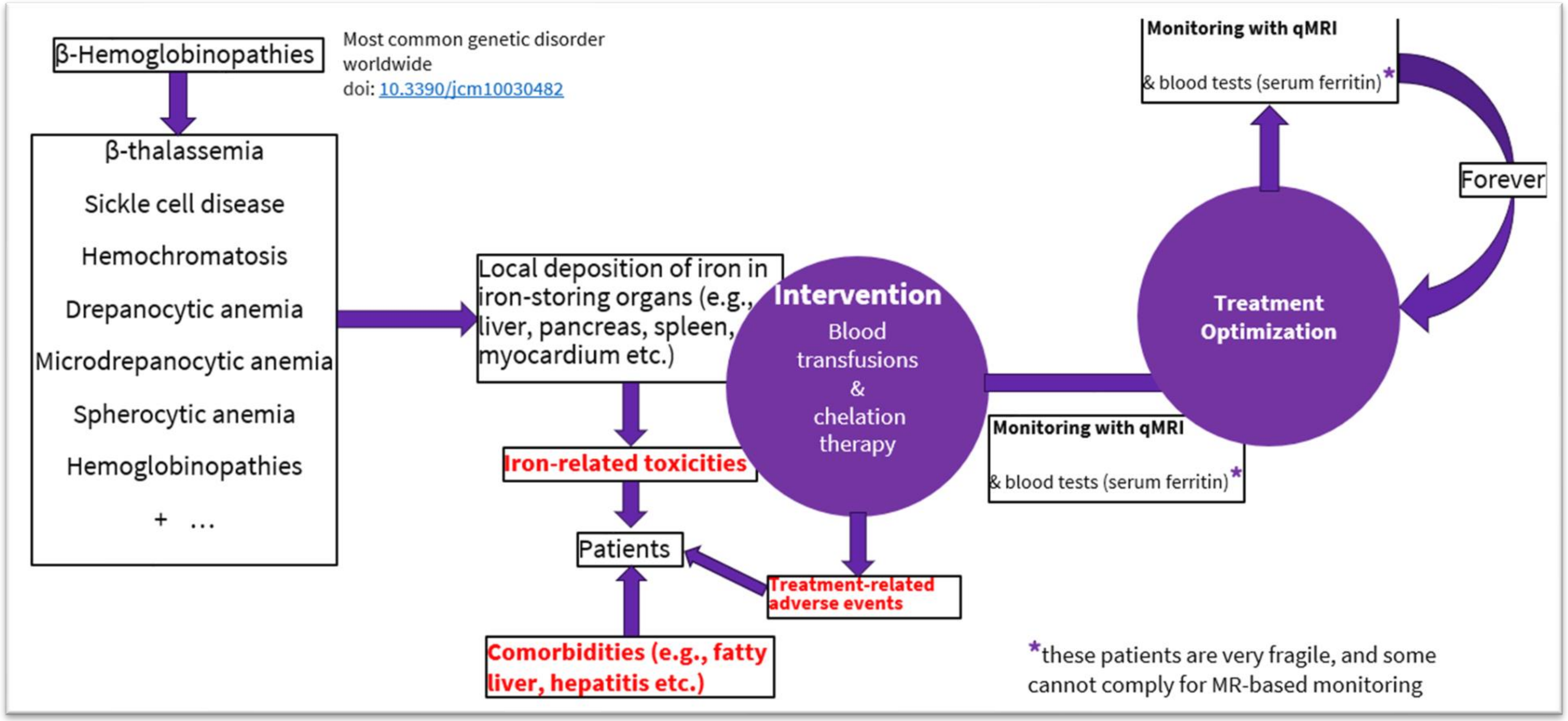


Figure 1. Care pathway for patients with b-hemoglobinopathies and related diseases.

The purpose of this retrospective study was to **evaluate the influence of iron presence on the quantitative estimation of the proton density fat fraction (PDFF) of the liver** with magnetic resonance imaging (MRI), which exhibits adequate sensitivity to assess both iron deposition and fat infiltration, whereas in our previous work we mainly assessed the inverse problem (e.g., the influence of fat deposition on the quantitative estimation of iron concentration.

2. Materials & Methods

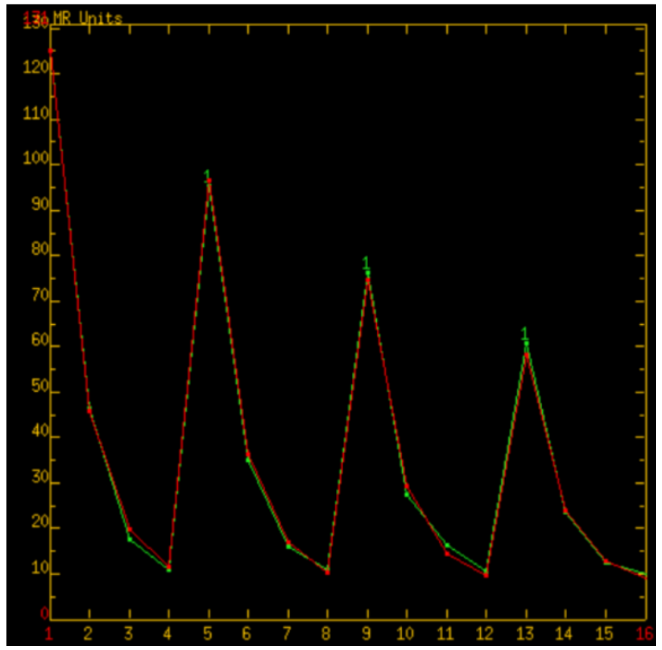


Figure 2. Signal intensity as a function of the number of gradient echoes. Four trains of four echoes each, minimum TE = 1.2 msec, maximum TE = 4.0 msec, 16 echoes

MR System Characterization

Scanner: 1.5T GE Signa HDxt

Software version: 26.0

Coil: 32 elements

MRS Acquisition parameters

Mode: STEAM

TR/TE = 3000/14 msec

NEX=16

Water suppression: No

Post-processing: SIVIC[4]

Table 1. Acquisition parameters for the imaging protocol; Protocols 1, 2, and 3 for our methodology; IDEAL-IQ commercial comparator.

Acquisition parameter	Protocol 1	Protocol 2	Protocol 3	IDEAL IQ
Number of echoes	16	16	16	6
Minimum Echo Time (TE_{min}) (ms)	1.1–1.3	1.1–1.3	1.1–1.3	0.9
Maximum Echo Time (TE_{max}) (ms)	12.2–12.8	4.0–4.1	26.4–28.1	8.7
Inter-echo spacing (ms)	0.8	0.2	1.8	Variable
Field of view (cm)	36.0–42.0	36.0–42.0	36.0–42.0	36.0–42.0
Bandwidth (Hz/pixel)	976.6	976.6	976.6	651
Acquisition matrix (phase × frequency)	128 × 128	128 × 128	128 × 256	128 × 256
Acquisition mode	Two-dimensional	Two-dimensional	Two-dimensional	Three-dimensional
Thickness (mm)	8	8	8	10
Gap (mm)	8	8	8	0
Number of slices	11	11	6	40
Repetition time (TR) (ms)	115	68	150	13.5
Flip angle (°)	20	20	20	7
Number of breath-holds	2	1–2	2	1

2. Materials & Methods

MRI **indications** for the subjects were **diverse**:

(a) β-thalassemia, (b) transfusion-dependent thalassemia, (c) sickle-cell disease, (d) hemochromatosis, (e) diabetes, (f) microdrepanocytic anemia, (g) drepanocytic anemia, (h) aplastic anemia, (i) spherocytic anemia, (j) cirrhosis, (k) low ferritin, (l) high ferritin, (m) sideroblastic anemia

- 80/193 with grade 0 siderosis, normal HIC (HIC ≤ 1.8 mg Fe/g dwt)
- 41/193 with grade 1 siderosis, stable HIC (1.8 mg Fe/g dwt < HIC < 3.2 mg Fe/g dwt)
- 47/193 with grade 2 siderosis, mild iron overload (3.2 mg Fe/g dwt ≤ HIC ≤ 7.0 mg Fe/g dwt)
- 19/193 with grade 3 siderosis, moderate iron overload (7.0 mg Fe/g dwt < HIC < 15.0 mg Fe/g dwt)
- 6/193 with grade 4 siderosis, severe iron overload (HIC ≥ 15.0 mg Fe/g dwt)

- 50/193 with grade 0 steatosis (FF: 0%–6.5%)
- 113/193 with grade 1 steatosis (FF: 6.6%–17.5%)
- 21/193 with grade 2 steatosis (FF: 17.6%–22.1%)
- 9/193 with grade 3 steatosis (FF: > 22.1%)

$$y = \underbrace{S_w \cdot e^{-TE \cdot R_{2w}^*}}_{\text{Water relaxation}} + \underbrace{S_f \cdot e^{-TE \cdot R_{2f}^*}}_{\text{Fat relaxation}} \cdot \underbrace{\cos\left(\frac{2\pi \cdot TE}{\Delta T} - 2\pi\right)}_{\text{Water-fat IOP correction factor}} + \underbrace{B}_{\text{Bias term}}$$

$$S_w = \frac{1}{2}(S_{IP} + S_{OP})$$ **Water signal**

$$S_f = \frac{1}{2}(S_{IP} - S_{OP})$$ **Fat signal**

$$PDFF = \left(\frac{S_f}{S_f + S_w}\right)$$

Fat fraction

$$PDFF = \left(\frac{S_{IP} - S_{OP}}{2S_{IP}}\right)$$

3. Results

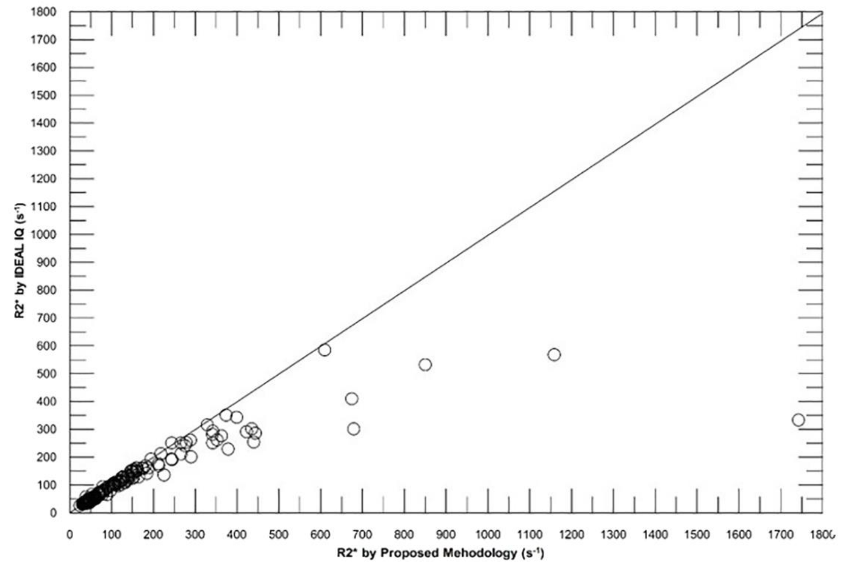


Figure 3A. Our previous results[3], without the visualization of PDFF grades.

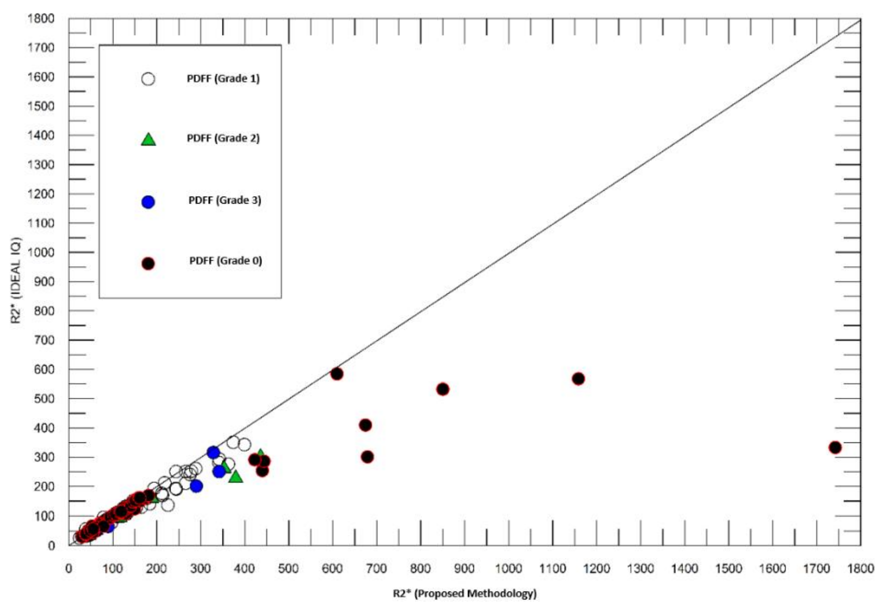


Figure 3B. Same (revisited) figure for the same dataset as in figure 3A, only now the visualization of PDFF grades is clear.

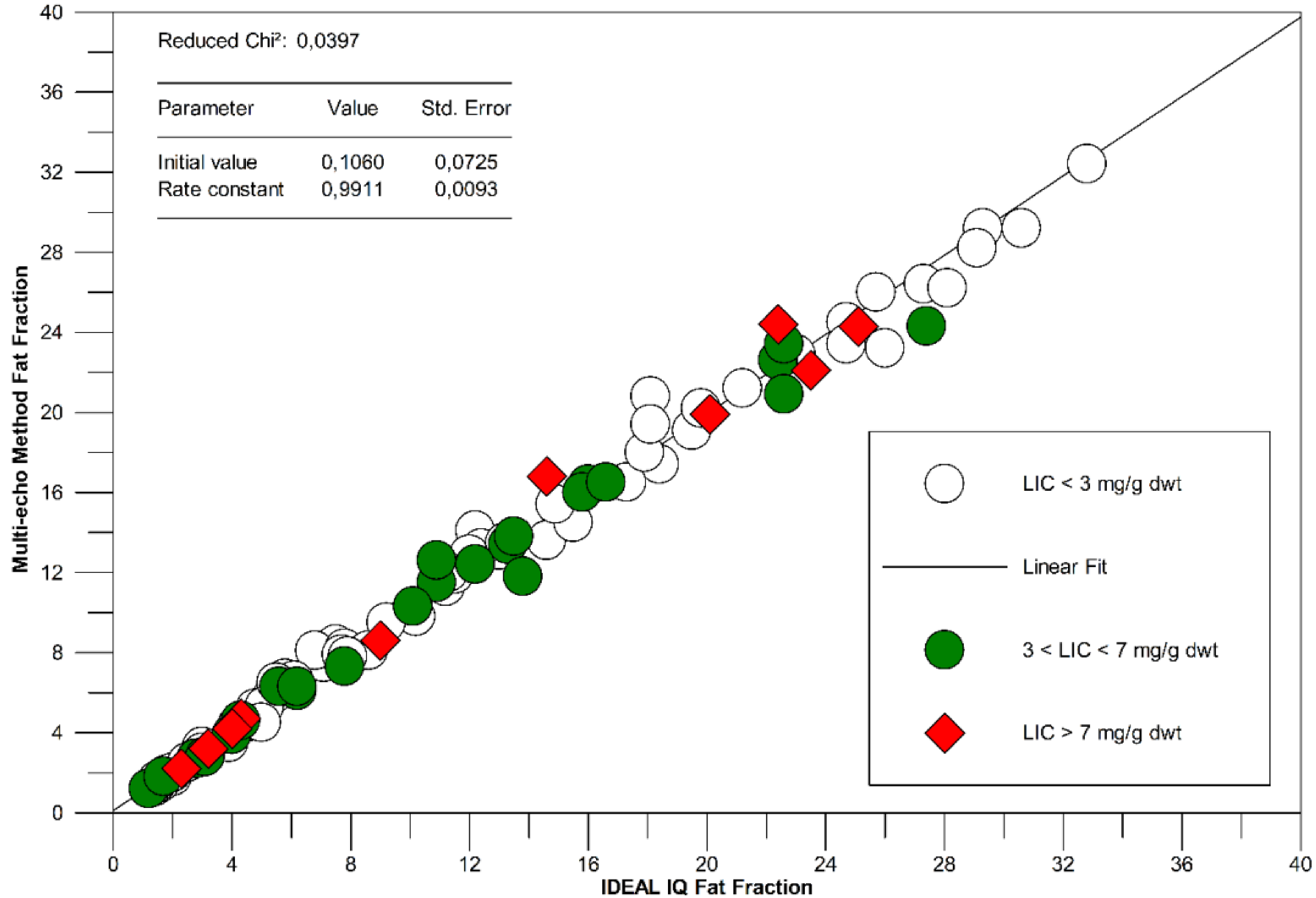


Figure 4. Scatter plot (for the same dataset as in Figures 3A and B) between the PDFF estimation as measured by our proposed methodology, and by IDEAL IQ. No significant differences were obtained between the two methods, regardless of liver siderosis.

3. Results

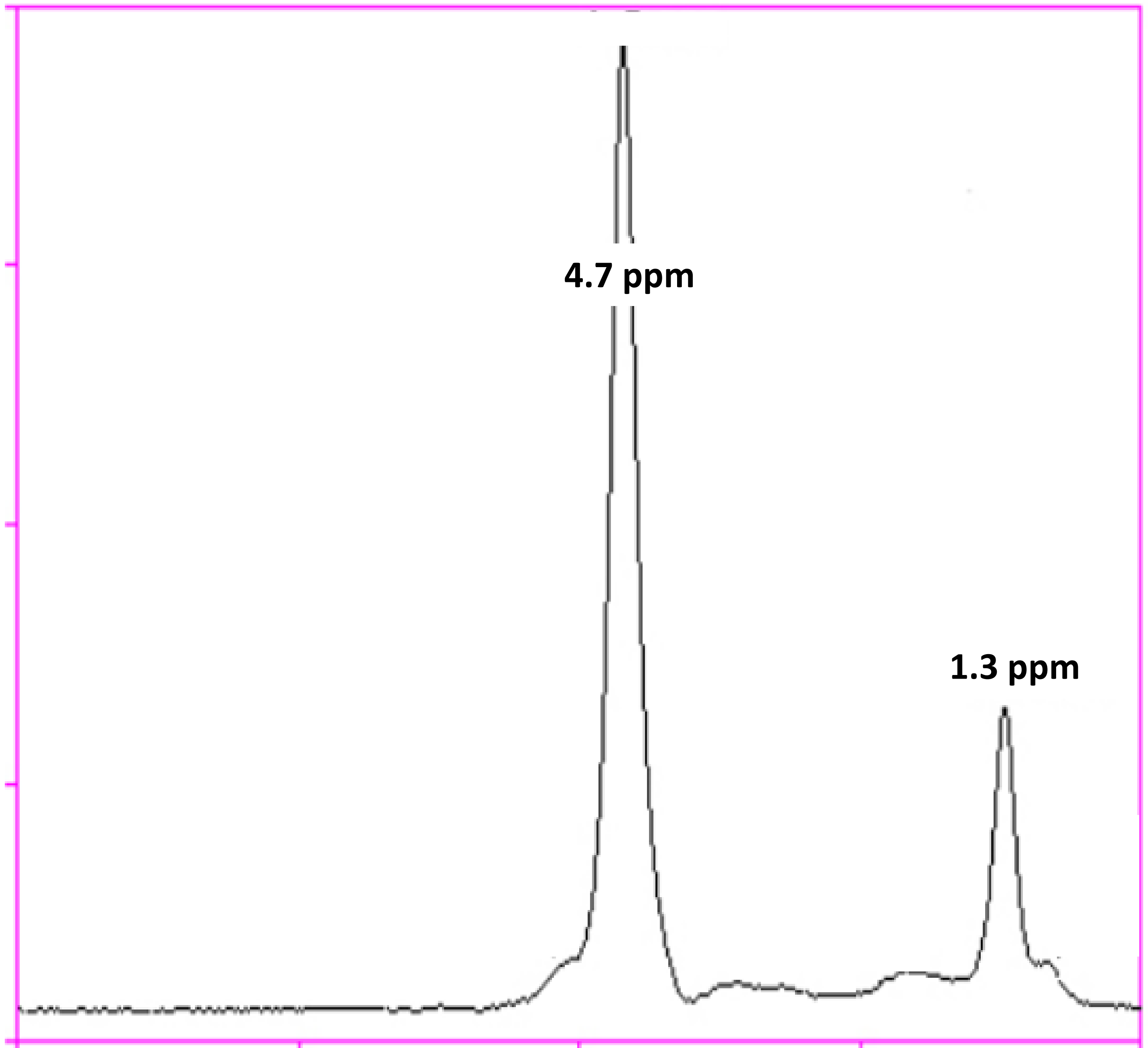


Figure 5. Post-processed MRS of a subject with grade 0 HIC (1.1 mg [Fe]/g.dwt) and grade 2 PDFF (18.3%)

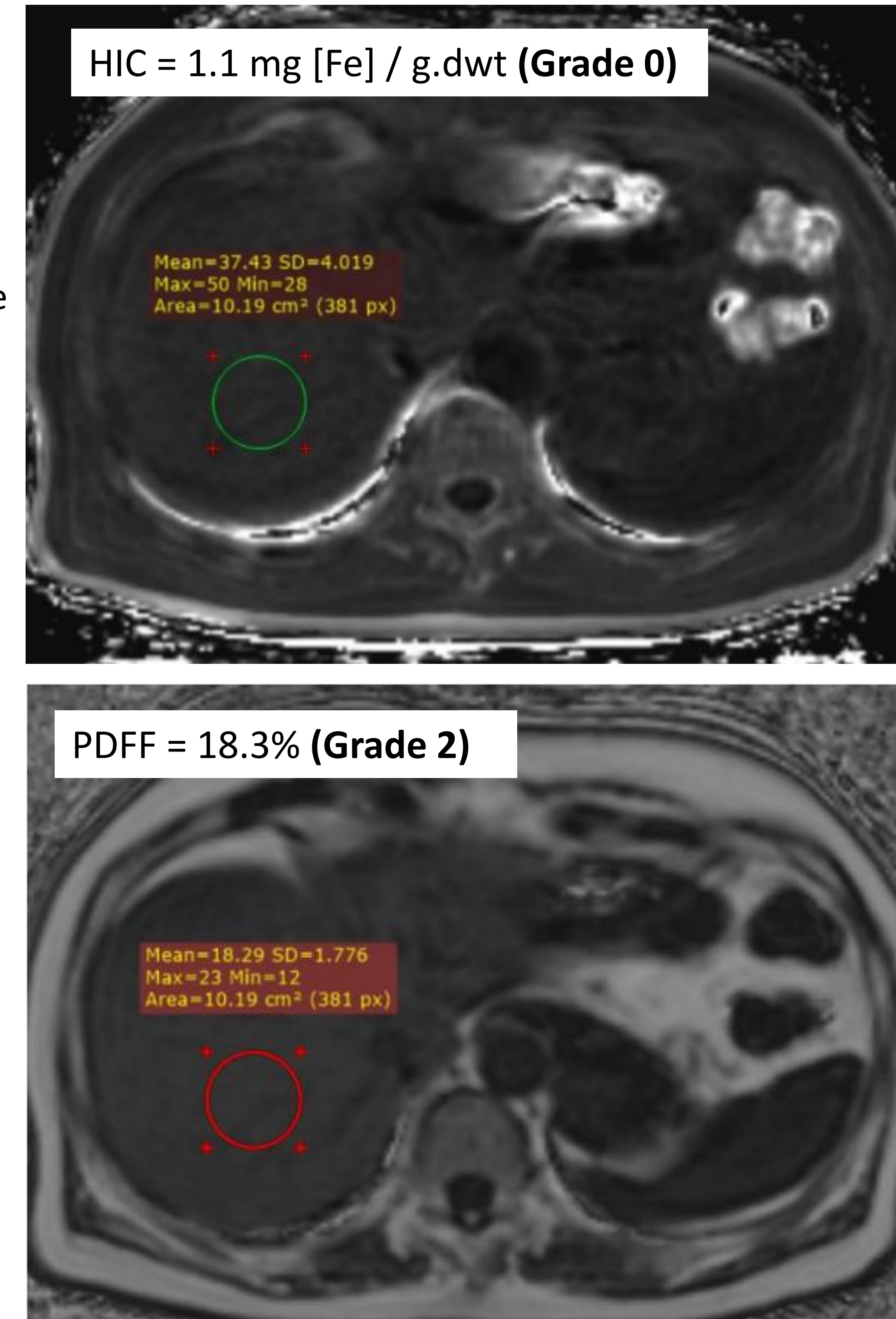


Figure 6. Corresponding images with regions of interest and ROI statistics, for the same subject as in Figure 5. Top image showcases the R2* map produced from the IDEAL IQ sequence, and the bottom image showcases the PDFF map produced from the IDEAL IQ sequence. R2* value was transformed to HIC by using the John Wood calibration equation.

3. Results

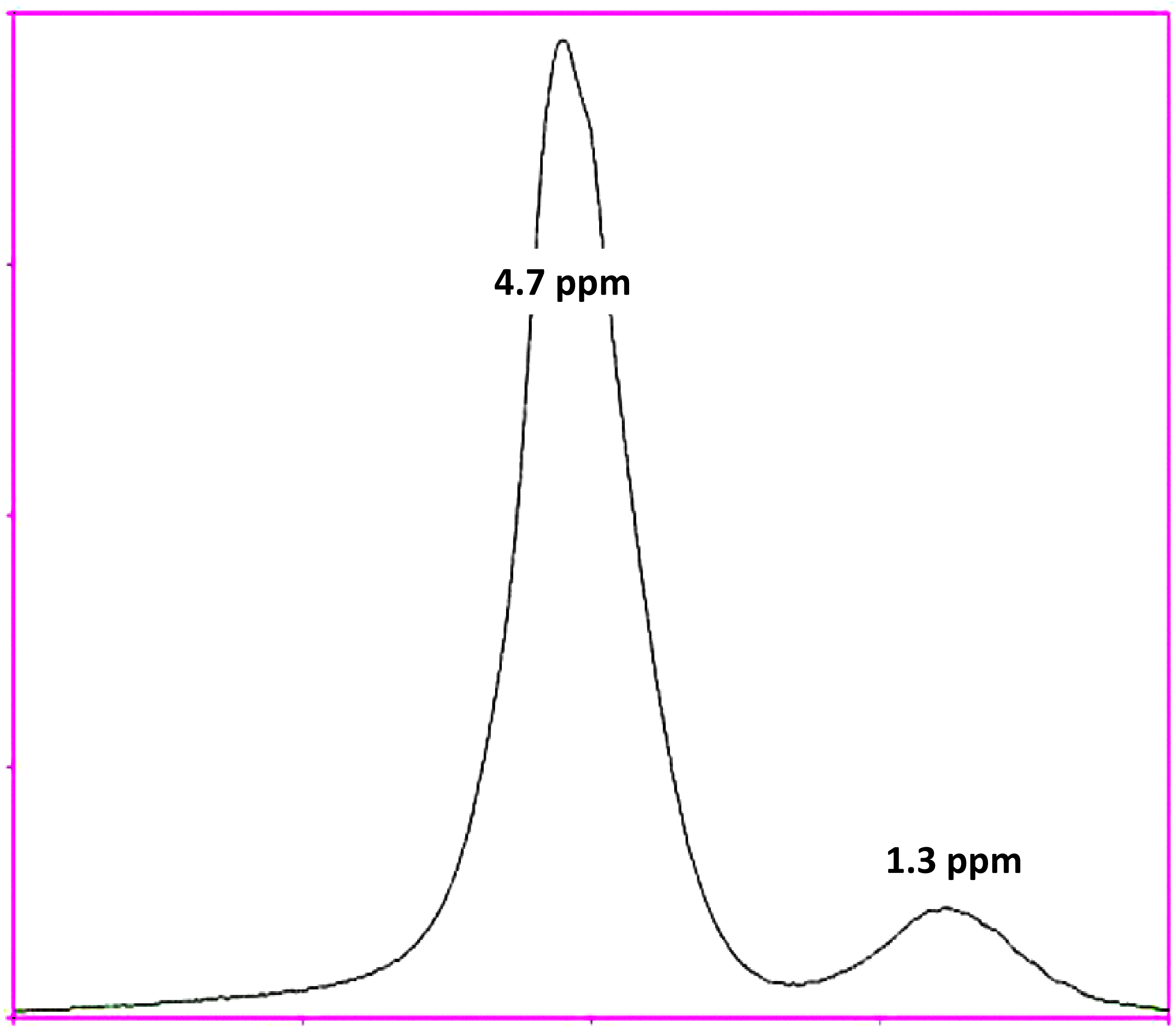
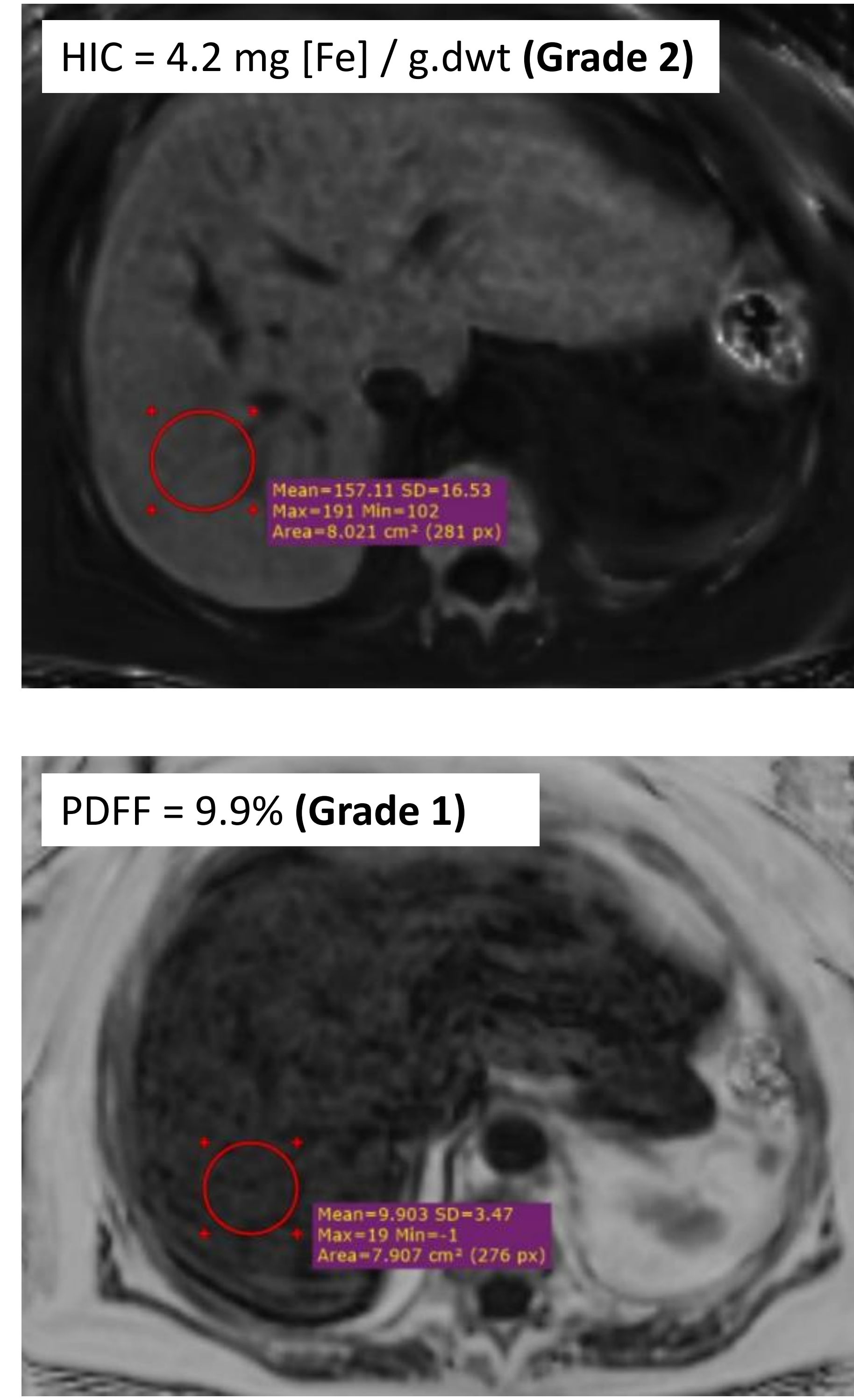


Figure 7. Post-processed MRS of a subject with grade 2 HIC (4.2 mg [Fe]/g.dwt) and grade 1 PDFF (9.9%).

Figure 8. Corresponding images with regions of interest and ROI statistics, for the same subject as in Figure 7. Top image showcases the R2* map produced from the IDEAL IQ sequence, and the bottom image showcases the PDFF map produced from the IDEAL IQ sequence. R2* value was transformed to HIC by using the John Wood calibration equation.



4. Conclusions

- Acquired imaging data suggest that the quantitative determination of **PDFF is not significantly influenced** by the extent of comorbid **hepatic siderosis**.
- Specifically, while **fat fraction seems to influence the determination of HIC** (e.g., the scatter plot outliers occurred for subjects with large R2* values that belonged to the normal PDFF class), the determination of **fat fraction is minimally influenced by the co-existence of iron**.
- Acquired data (from MR spectroscopy) [albeit limited; n = 2] seem to indicate that *indeed*, the paramagnetic effect of iron overload may in fact hinder the precise quantification of both PDFF and iron. However, in the case where **simultaneously there exists high iron contents (grades 2, 3, and 4) & low PDFF (grades 0, and 1),** there will be severe peak overlap due to the paramagnetic broadening that will render the PDFF estimation unreliable (this could explain the point below)
- Although **the study is not powered (**$1 - \beta < 0.2$**)** to allow detection of significant associations in the dataset, according to our study data size, and the relative populations within each group/grade, *the probability (as per the hypergeometric test) of having 5 out of the 5 outliers correspond to highest grade of HIC* ***and*** *lowest grade of PDFF at the same time*, is given by: $P(X = k) = \frac{\binom{K}{k}\binom{N-K}{n-k}}{\binom{N}{n}}$ and is found to be **0.0016%**.

5. References

[1] Eskreis-Winkler, Sarah, et al. "IDEAL-IQ in an oncologic population: meeting the challenge of concomitant liver fat and liver iron." Cancer Imaging 18 (2018): 1-7.

[2] Reeder, Scott B., et al. "Iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL): application with fast spin-echo imaging." Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine 54.3 (2005): 636-644.

[3] Gkotsis, D. E., et al. "Determination of the R2* relaxation rate constant for estimating hepatic iron concentration: A customized approach that considers liver fat infiltration." Physica Medica 76 (2020): 150-158.

[4] https://github.com/SIVICLab/sivic