Japanese Journal of Gastroenterology and Hepatology[R]

ISSN 2435-1210 | Volume 11

Research Article Open Access

Limitations of MR Spectroscopy-Derived PDFF in the Quantification of Hepatic Steatosis in MASH

Atul Kapoor*

Advanced Diagnostics, Kennedy Avenue, Amritsar, India

***Corresponding author:**

Atul Kapoor,
Advanced Diagnostics, Kennedy Avenue,
Amritsar, India

Received: 08 Oct 2026
Accepted: 03 Nov 2026
Published: 06 Nov 2026
J Short Name: JJGH

Copyright:

©2026 Atul Kapoor, This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially

Citation:

Atul Kapoor, Limitations of MR Spectroscopy-Derived PDFF in the Quantification of Hepatic Steatosis in MASH. Japanese Jour of Gastro and Hepatology® 2026; V11(1): 1-4

1. Abstract

MR-derived proton density fat fraction (PDFF), measured by single-voxel MR spectroscopy (HISTO) or by chemical-shift-encoded multi-echo Dixon, is widely accepted as the non-invasive reference standard for hepatic fat quantification. However, in the setting of metabolic dysfunction-associated steatohepatitis (MASH) where hepatocyte ballooning, inflammatory infiltrate, sinusoidal edema, and (later) fibrotic extracellular matrix expansion increase the MR-visible water signal PDFF systematically underestimates true tissue triglyceride content. Because PDFF is mathematically a ratio of fat to total proton signal, any process that inflates the water denominator lowers the calculated fat fraction without any change in absolute triglyceride mass. Concurrent iron overload further confounds the chemical-shift-encoded variant of the technique. This discussion reviews the biophysical mechanisms, clinical implications, and the rationale for combining MRS with iron-insensitive ultrasound techniques ultrasound-derived fat fraction (UDFF), attenuation imaging (ATI), and shear wave dispersion to obtain a more accurate picture of the inflamed, steatotic liver.

1.1. Background and the Mathematical Definition of PDFF

PDFF is defined as the fraction of MR-visible mobile proton signal arising from triglyceride methylene/methyl protons relative to the total mobile proton signal in the voxel:

PDFF (%) = [Fat signal / (Fat signal + Water signal)] × 100

This ratio formulation is its strength in healthy livers, where water content is biologically stable, but is also its principal weakness in diseased livers, where the water signal is anything but stable. PDFF is therefore not a measure of absolute fat content; it is a measure of fat relative to a variable denominator. The clinically meaningful endpoint tissue mass fat fraction (TMFF), the actual triglyceride-to-tissue mass ratio measured histologically diverges from PDFF whenever the water signal in the voxel changes from its healthy baseline.

2. Mechanisms by Which Active Inflammation Lowers Apparent PDFF

In MASH, several histopathological processes coexist and each contributes additional MR-visible water signal to the spectroscopy voxel. The cumulative effect can be substantial sufficient to deflate the calculated fat fraction by 30–50 percent of its true value in moderate-to-severe steatohepatitis.

2.1. Hepatocyte Ballooning

Ballooned hepatocytes are a defining histological feature of steatohepatitis. They are swollen with intracellular water and disorganized cytoskeletal proteins. Within an MRS voxel, ballooned cells contribute disproportionately to the water proton pool while contributing little to the fat pool, because their lipid droplets are often displaced or poorly visible. The net effect is an increase in the water denominator without a matching increase in fat numerator.

2.2. Inflammatory Cellular Infiltrate

Lobular and portal inflammation introduces lymphocytes, neutrophils, and activated Kupffer cells into the parenchyma. These inflammatory cells are water-rich and lipid-poor, and they replace some volume that would otherwise be occupied by hepatocytes. Their cumulative contribution to the water signal can be considerable in active disease.

2.3. Sinusoidal and Interstitial Edema

Cytokine-mediated permeability changes (TNF-α, IL-6, and others released by activated stellate and Kupffer cells) lead to interstitial fluid accumulation and sinusoidal congestion. The extracellular water compartment expands, again increasing the water denominator. This is the same phenomenon that gives inflamed liver its high T2-weighted MRI signal.

2.4. Prolongation of Liver Water T2

Inflammation lengthens the T2 relaxation time of liver water by reducing the tightness of water-macromolecule binding. In standard multi-echo MRS sequences, longer water T2 means more water

signal survives at each echo time, further inflating the apparent water fraction in T2-corrected fat fraction calculations even when the underlying water proton density is unchanged.

2.5. Glycogen Accumulation in Diabetic Livers

In diabetic patients and particularly in those with poor glycemic control or insulin therapy hepatic glycogen content can be markedly elevated (so-called glycogenic hepatopathy). Glycogen is associated with a hydration shell that contributes to the bound and semi-bound water pool, subtly inflating the water signal in the MRS voxel. This is an under-appreciated confounder specific to the diabetic MASH population.

2.6. Fibrotic Matrix Expansion

In more advanced disease (F2–F4), expansion of the extracellular matrix with collagen and proteoglycans is accompanied by increased extracellular water. This is the mechanism investigated in detail by Hooker and colleagues (2022), who demonstrated a progressive divergence between PDFF and biopsy-derived digital image analysis (DIA) fat fraction with increasing fibrosis stage. Their water-content correction reduced but did not eliminate the underestimation.

3. Quantitative Illustration

To illustrate the magnitude of the bias, consider a liver with a true triglyceride load corresponding to a tissue mass fat fraction of 27%. The table below shows the calculated PDFF when progressively larger volumes of inflammatory water are added to the voxel:

A liver with true 27% steatosis can therefore read 14–18% on MRS in active MASH a clinically important reclassification from S2 to S1 if the operator anchors on the MRS number alone. This corresponds closely to the Hooker et al. (2022) observation that mean PDFF at the highest steatosis grade was 24 ± 9% in fibrotic grades 0–2 versus 17 ± 6% in fibrotic grades 3–4, at matched histological steatosis severity.

Pathological state	Fat signal	Water signal	Calculated PDFF
Healthy / no inflammation	27	73	**27.0%**
Mild inflammation (+25% water)	27	91	**22.9%**
Moderate inflammation (+40% water)	27	102	**20.9%**
Marked inflammation (+70% water)	27	124	**17.9%**
Severe inflammation (+90% water)	27	139	**16.3%**

4. The Parallel Confounder: Iron Overload

Whereas inflammation deflates the apparent fat fraction, hepatic iron has the opposite and even more dramatic effect on chemical-shift-encoded Dixon PDFF. Iron-induced T2* shortening corrupts the fat-water decomposition, sometimes producing fat fractions of 80–95% when the true value is well under 20%. Critical points:

• MR spectroscopy is comparatively iron-resistant, because the multi-echo HISTO sequence explicitly fits and corrects T2 decay; the R^2-water value reported alongside PDFF is itself a measure of iron loading.

• Multi-echo Dixon PDFF requires accurate T2* correction. When iron is severe enough that water signal decays faster than the fitting algorithm can model, fat-water swap or systematic over-attribution to fat occurs.

• Ultrasound-derived methods (UDFF, ATI, sound speed) are essentially iron-insensitive, since acoustic propagation at diagnostic frequencies is not significantly affected by iron deposition.

In a patient with combined steatosis, inflammation, and iron loading a common phenotype in MASH and dysmetabolic iron overload syndrome MRS may underestimate fat (inflammation effect) while Dixon may grossly overestimate fat (iron effect), and ultrasound-derived methods then become the most reliable iron-and-inflammation-corrected reference.

5. The Role of Multi-Parametric Ultrasound

Modern ultrasound platforms now integrate multiple quantitative parameters that together resolve the confounders MRS cannot:

Shear wave dispersion is particularly relevant to the present discussion. Because dispersion directly reflects the viscous component of liver tissue and viscosity is increased by exactly the same processes (cellular edema, inflammatory infiltrate, ballooning) that inflate the MRS water denominator an elevated dispersion value in a patient with a low MRS-PDFF is a strong, modality-independent signal that the MRS value is being suppressed by inflammation. Reported normal liver dispersion is in the range of 10–13 (m/s)/kHz; values above 16–17 indicate active inflammation.

Parameter	What it measures	Clinical role
UDFF	Ultrasound-derived fat fraction; integrates attenuation, backscatter coefficient, and sound speed via a calibrated model.	Iron- and inflammation-insensitive estimate of hepatic fat. Serves as an independent tiebreaker when MRS and Dixon disagree.
ATI	Attenuation coefficient (dB/cm/MHz) of the ultrasound beam through liver parenchyma.	Surrogate marker of fat content; cut-offs of 0.62 / 0.72 / 0.82 dB/cm/MHz separate steatosis grades S0–S3.
Shear wave dispersion (SWD)	Frequency dependence of shear wave speed; an indirect measure of tissue viscosity rather than elasticity.	Direct correlate of necroinflammation, hepatocyte ballooning, and cellular edema. Independent of fat content.
LSM (SWE/TE)	Shear wave speed converted to tissue stiffness in kPa.	Fibrosis assessment; however, native LSM is artifactually elevated by inflammation, iron, and severe steatosis and must be cross-corrected.
ISEI	Ultrasound-derived iron index from acoustic and statistical parameters.	Identifies iron loading without an MRI-based R2/R2* measurement.

6. A Practical Reconciliation Algorithm

When MRS-PDFF, Dixon-PDFF, and ultrasound fat estimates disagree in a single patient, the following stepwise approach yields a coherent interpretation:

• Check R2/R2*. An elevated R2-water (>30 s^{-1}) or R2* indicates iron loading sufficient to corrupt Dixon PDFF. Discard the Dixon number; the spectroscopic PDFF is the more reliable MR-based estimate.

• Check inflammation surrogates. Elevated SWD, raised LFTs, or imaging features of hepatitis warn that MRS is also being suppressed. The true fat fraction is likely 20–50% higher than the MRS value.

• Anchor on iron-insensitive ultrasound. UDFF (corrected) and ATI provide the cleanest fat estimate when both iron and inflammation are present.

• Cross-correct stiffness. Native LSM is unreliable in the inflamed liver. After correction for inflammation and iron contributions, the residual stiffness reflects true fibrosis.

• Synthesize. Report a single integrated impression steatosis grade, inflammation grade, iron status, fibrosis stage rather than four discordant numbers.

7. Clinical Implications

Several practical consequences follow from recognizing this systematic MRS underestimation in MASH:

• Treatment-response trials that use MRS-PDFF as the primary endpoint may underestimate the true magnitude of fat reduction in patients whose inflammation also resolves; conversely, an apparent fat reduction on MRS may partly reflect resolving inflammation rather than true triglyceride loss.

• Histological correlation studies have repeatedly shown that visual or digitally-assessed biopsy fat exceeds PDFF in fibrotic and inflamed livers a finding now formalized in the PDFF-vs-TMFF distinction.

• In clinical practice, a low MRS-PDFF in a patient with raised transaminases, type 2 diabetes, and abdominal discomfort should not reassure the clinician; the true fat burden may be considerably higher, and MASH should be actively considered.

• Multi-parametric ultrasound UDFF, ATI, dispersion, LSM is increasingly positioned as the front-line non-invasive workup, with MRI/MRS reserved for confirmatory or therapy-monitoring use.

8. Conclusion

MR spectroscopy-derived PDFF remains an excellent, reproducible biomarker for hepatic fat in uncomplicated steatosis. In active MASH with hepatocyte ballooning, inflammatory infiltrate, edema, and (in diabetics) glycogenic loading it systematically underestimates true triglyceride content because its denominator is no longer biologically constant. Concurrent iron overload further compromises chemical-shift-encoded variants of the technique. A multi-parametric workup combining MRS, multi-echo Dixon, ultrasound-derived fat fraction, attenuation imaging, and shear wave dispersion converges on a more accurate picture of the inflamed, fatty, sometimes iron-loaded liver than any single modality can provide. Reporting practice should reflect this: a single number is rarely the truth in MASH.

References

1. Hooker JC, Hooker C, Bass E, Schlein A. Comparing magnetic resonance liver fat fraction measurements with histology in fibrosis: the difference between proton density fat fraction and tissue mass fat fraction. Magn Reson Mater Phys (MAGMA). 2022.
2. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024.
3. Caussy C, Reeder SB, Sirlin CB, Loomba R. Noninvasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology. 2018.
4. Popa A, Bende F, Sirli R. Shear Wave Dispersion in Chronic Liver Disease: From Physical Principles to Clinical Usefulness. J Pers Med. 2023.
5. Caroli A. Multiparametric ultrasound for non-invasive assessment of liver steatosis, fibrosis, and inflammation in metabolic dysfunction-associated steatotic liver disease. World J Gastroenterol. 2025.

6. Sugimoto K. Viscoelasticity measurement in rat livers using shear-wave dispersion imaging. Studies on shear wave dispersion as a marker of hepatic necroinflammation in NAFLD/MASH (Aplio i800). Radiology / Ultrasound Med Biol, multiple years.
7. Multi-echo Dixon and MRS in quantifying hepatic fat content and staging liver fibrosis. Sci Rep. 2023.