**Specialty Area**: Quantitative Biomarkers in Liver MRI: How to Use Them in the Real World

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**Highlights:**

- $R_2$ and $R_2$* relaxometry MRI is emerging as quantitative imaging biomarkers for liver iron
- $R_2$ MRI has been extensively validated and available for clinical use
- $R_2$* MRI is promising and has distinct advantages but validation data is less extensive
- Remaining challenges for $R_2$* as a liver iron biomarker include technical standardization, addressing confounding effects such as noise and fat, and cross-vendor/platform validation

**TALK TITLE**: Iron (8311)

**AUDIENCE**: MRI scientists and radiologists working in liver iron quantification

**OBJECTIVES:**

*Understand –*

- Clinical need for quantitative biomarker of liver iron
- The biophysical basis of iron's effect on transverse relaxation
- Similarity and differences of spin-spin relaxation ($R_2$) and bulk relaxation ($R_2$*)
- Basic strategies for liver $R_2$ and $R_2$* quantification by MRI

*Familiarize with –*

- Currently available techniques for liver $R_2$/$R_2$ * relaxometry MRI
- Existing validation data of $R_2$/$R_2$ * as biomarker of liver iron
- Real-life challenges in iron quantification – confounding effects of noise, field inhomogeneity, fat

**PURPOSE**: Iron overload, or excessive accumulation of iron in the body, occurs frequently in patients with genetic hemochromatosis and various hematological disorders [1]. Excess iron deposition in various organs, including the liver and the heart, causes cell injury, organ dysfunction, and failure [2]. Liver is the primary organ of body iron storage [3] and high liver iron levels are associated with risks of hepatic and extrahepatic complications [4-7].

The traditional reference standard for evaluation of hepatic iron overload has been liver biopsy with biochemical LIC determination [8]. However, biopsy is impractical for routine clinical care, because it is invasive, painful, and frequent repeat biopsies are often necessary for longitudinal patient care [8-10]. MRI is an appealing noninvasive alternative, as it allows direct quantitative measurement of liver iron. The purpose of this talk is to describe the MRI techniques for liver $R_2$ and $R_2$* relaxometry and show how these MRI-derived metrics may serve as quantitative biomarkers of liver iron in clinical practice.

**METHODS:** Excess iron is stored in the liver as small water-soluble ferritin-iron complex and/or large water-insoluble hemosiderin granules. These iron-containing paramagnetic molecules cause rapid transverse relaxation in a concentration-dependent manner [11-13]. The transverse relaxation rate on spin-echo (SE) sequences due to spin-spin interaction is called $R_2$. The relaxation rate on gradient-recalled-echo (GRE) sequences due to the combined or "bulk" effect of macroscopic field inhomogeneity *and* spin-spin interaction is called $R_2$*. These rates are reciprocal of their respective time constants, $T_2$ and $T_2$*. By acquiring images at progressively longer echo-times (TEs) and fitting the measured signal to a mathematical model, the relaxation rates can be calculated pixel-by-pixel, and cross-sectional $R_2$ and $R_2$* maps can be reconstructed. Therefore, $R_2$ and $R_2$* values by relaxometry MRI have potential of serving as quantitative biomarkers of liver iron.

**RESULTS:** Calculated $R_2$ by SE MRI increases in a monotonic curvilinear fashion with increasing iron load [14, 15] and clinically validated against biopsy-LIC in various patient populations and on different 1.5T

scanners [16]. The calculated $R_2$ values can be converted to LIC values (e.g. μg/g dry tissue) by referring to a calibration normograms [14, 15]. However, long exam time, image artifacts associated with free-breathing acquisition, incomplete anatomical coverage, as well as the cost and time associated with off-line data processing has thus far limited its widespread clinical use.

On the other hand, calculated $R_2$* by GRE increases in a linear fashion with increasing iron load [15, 17]. It has practical advantage of rapid breath-hold acquisition, automatable online data processing, and ease of integrating into standard clinical exam and workflow. While $R_2$*-LIC normograms have been proposed and validated in several single-center studies [15, 17-21], the concern for technique-dependent biases and lack of consensus technical standardization [17, 22-24] has thus hampered wide implementation of liver $R_2$* MRI in clinical practice.

**DISCUSSION:** Liver iron can be noninvasively quantified using $R_2$ or $R_2$* relaxometry MRI. These metrics differ in the underlying biophysical mechanisms, mathematical models for relaxometry, and the pattern of correlation with LIC (curvilinear vs. linear). $R_2$ MRI has the advantage of being specific for iron, has been extensively validated, and is now considered as a biomarker of liver iron in clinical use. It is commercially available (FerriScan®, Resonance Health, Ltd., Australia) and has regulatory-clearance in many countries including United States. On the other hand $R_2$* MRI may be more practical for real-life clinical care but several challenges remain, including (1) technical challenges in clinically significant severe iron overload, (2) effect of acquisition parameters and mathematical models, (3) other confounding factors such as field-inhomogeneity and presence of liver fat, and (4) less extensive cross-vendor/cross-platform validation data. Further technical refinement, standardization, and clinical validation are likely necessary to facilitate more widespread use of $R_2$* MRI.

**CONCLUSION:** $R_2$ relaxometry MRI for liver iron quantification has been extensively validated is available for clinical use. $R_2$* relaxometry MRI may be more practical for real-life clinical care, but further technical refinement, standardization, clinical validation are likely needed.

## REFERENCES


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