Survey of water proton longitudinal relaxation in liver in vivo

John Charles Waterton1,2

Received: 20 January 2021 / Revised: 5 April 2021 / Accepted: 27 April 2021 / Published online: 12 May 2021
© The Author(s) 2021

Abstract
Objective To determine the variability, and preferred values, for normal liver longitudinal water proton relaxation rate $R_1$ in the published literature.
Methods Values of mean $R_1$ and between-subject variance were obtained from literature searching. Weighted means were fitted to a heuristic and to a model.
Results After exclusions, 116 publications (143 studies) remained, representing apparently normal liver in 3392 humans, 99 mice and 249 rats. Seventeen field strengths were included between 0.04 T and 9.4 T. Older studies tended to report higher between-subject coefficients of variation (CoV), but for studies published since 1992, the median between-subject CoV was 7.4%, and in half of those studies, measured $R_1$ deviated from model by 8.0% or less.
Discussion The within-study between-subject CoV incorporates repeatability error and true between-subject variation. Between-study variation also incorporates between-population variation, together with bias from interactions between methodology and physiology. While quantitative relaxometry ultimately requires validation with phantoms and analysis of propagation of errors, this survey allows investigators to compare their own $R_1$ and variability values with the range of existing literature.

Keywords Liver · Magnetic resonance imaging · Biomarker · $T_1$ relaxation time · Reproducibility

Introduction
The liver longitudinal water proton relaxation rate $R_1$ is important for several reasons. Native $R_1$ is a biomarker of liver pathology [1, 2]. Also, other liver biomarkers are secondarily derived from $R_1$ measurements: for example, increase in $R_1$ post-gadoxetate is a biomarker of hepatocyte function [3, 4]; extracellular volume is derived by comparing $R_1$ pre and post contrast [5]; and baseline $R_1$ is required for rate constants in dynamic contrast-enhanced MR [6], for tissue oxygen tension in oxygen-enhanced MR [7], and for relaxivity measurements in contrast agent research[8]. Measurements of $R_1$ in individual livers or liver regions suffer from both systematic errors and random errors [9]. Systematic errors (bias) arise because measurements are imperfectly performed. Other systematic deviations occur because different methods, even when perfectly performed, yield $R_1$ values with different dependences on liver composition and physiology. Random (repeatability) errors arise from physiologic and instrument noise, and can be high particularly when regions-of-interest are small. In addition, even in the absence of bias and noise, there are, in each study, genuine between-subject differences in $R_1$ due to between-subject variation in physiology or subclinical pathology.

To mitigate the effects of random error in establishing a “normal” or “baseline” liver $R_1$, investigators sometimes employ a "compromise" $R_1$, averaged from all subjects in their study. This likely reduces the "noise" variance, but introduces other errors by ignoring true between-subject variation. Other investigators may obtain $R_1$ from literature reports, although this will introduce additional bias if different measurement methods had been used, or different populations had been studied.
Reported liver $R_1$ (symbol area $\propto N$)
- human
- rat
- mouse

- dotted line: fit to heuristic Eq. 2.
- solid line: fit to model Eq. 3: $R_{1,\infty} = 0.213$ s$^{-1}$
- dashed line: fit to model Eq. 3: $R_{1,\infty} = 0.4, 0.6, \text{ or } 0.8$ s$^{-1}$
The aim of this study was to survey values, and variabilities, of normal liver $R_1$ from the published literature. This would give investigators an indication of whether the liver $R_1$ or $T_1$ values and variabilities they measure are broadly consistent with, or discordant from, the prior literature.

**Methods**

**Literature searching**

Literature was searched manually using “Ovid Medline” (www.ovid.com) for “magnetic resonance imaging” AND “liver” AND “relaxation”. Additional literature reports were retrieved from citations, supplemented by a more intensive search for data with $B_0$ = 4.7 T, 7 T, 9.4 T, 11.7 T, 14.1 T or 21.1 T (see supplementary material 1 for further details). Liberal inclusion criteria were employed: any report, in any language, which claimed to measure liver $R_1$ or $T_1$ values and variabilities they measure are broadly consistent with, or discordant from, the prior literature.

**Analysis**

The mean and variance of $R_1$ across all subjects in each study was estimated from the publications, with the coefficient of variation given by $\text{CoV} = \sqrt{\text{variance}/\text{mean}}$. Where measurements were made on the same subjects using the same method (repeatability), the weighted mean ± SD was used, however where measurements were made on the same subjects using different method (e.g., different field strengths) the measurements were treated as if from two different studies. Any $R_1$ measurement method was allowed, as long as $T_1$ (s) or $R_1$ (s$^{-1}$) was reported. Where $T_1$ ± SD was reported, a point estimate of $R_1$ was estimated as $T_1^{-1}$ and the between-subject variance in $R_1$ was estimated (see supplementary material 2) as:

$$0.25\left(\left(\frac{1}{T_1 - \text{SD}}\right) - \left(\frac{1}{T_1 + \text{SD}}\right)\right)^2$$

In a few cases, the between-subject variance in $R_1$ was estimated from a bar or scatterplot depicted in the publication, or from the range rule [10]. To aggregate the data, individual studies were weighted by the inverse of their between-subject variance in $R_1$. Studies with $N = 1$, or where a variance could not be extracted, were included in Figs. 1 and 2, but their $R_1$ was assigned zero weight in the fits. In addition, a method to account for the well-known $B_0$-dependence of liver $R_1$ [11–15] was needed. Two methods of representing this $B_0$ dependence were used: a heuristic log–log relationship, and a biophysical power-law model developed by Diakova et al. [12]. $R_1$ was fitted to $B_0$ using the weighted non-linear least squares function nls() in R[16] (see supplementary material 3). The fitted parameters in the heuristic were $M$ and $C$:

$$\log \left(\frac{R_1}{M}\right) = M \log \left(\frac{B_0}{C}\right) + C$$

The fitted parameters in the model were $A$ and $B$:

$$R_1 = A o^k + B T_{\text{D}} \ln \left(1 + \left(\frac{\omega T_{\text{D}}}{\tau_D}\right)^{-2}\right) + 4 \ln \left(1 + \left(\frac{2\omega T_{\text{D}}}{\tau_D}\right)^{-2}\right)$$

$R_{1,\infty}$ is the high-frequency asymptote, i.e., the extreme narrowing condition, set here to 0.213 s$^{-1}$ at 310 K[17]; $\tau_D$ is the translational correlation time from Diakova et al. [12] adjusted for temperature to $1.43 \times 10^{-11}$ s; $k = -0.6$ also from Diakova et al. [12]; and $\omega = 2\pi \times 42.58 \times 10^6 \times B_0$ s$^{-1}$. In the summaries, lower (LQ) and upper (UQ) quartiles, and medians, are reported. For exploratory fits using other weightings, see Supplementary Material 4.

**Results**

Approximately 500 publication abstracts were read, from which around 270 publications were selected and reviewed. After exclusions, 116 publications remained, with publication dates between 1981 and 2020. Some publications reported multiple studies, or multiple groups within a single study, so that 143 studies were available to contribute to this analysis. These represented 3392 humans [1–4, 7, 11, 14, 15, 18–94], 99 mice [95–105] and 249 rats [5, 33, 105–126]. The number of subjects per study varied between 1 and 1037 (median 12). A very wide variety of $T_1$ measuring methods was used. Frequently used approaches (see supplementary material 5) were inversion-recovery (18% of studies), saturation-recovery (21%) or variable-flip-angle (10%), which
compare signal arising respectively when inversion time, repetition time, or flip angle are incremented. The median number of increments was 3 (range 2–20). Various read-outs were employed including spin-echo, gradient-echo, echo-planar or localized spectroscopy. Other studies employed variants of Look-Locker (24%) or MR fingerprinting (1%). Some studies reported that they suppressed fat, and/or corrected for iron-induced $T_1$-shortening; some reported motion suppression, registration, triggering, gating or breath-hold; some reported $B_1$ correction or phantom-based validation. Some studies analysed quite small regions of interest often avoiding blood vessels and bile ducts; others included most or all of the liver. Seventeen field strengths were included between 0.04 T and 9.4 T. No values were found in reports using $B_0 > 9.4$ T: one report of $T_1^* = 1.0 \pm 0.1$ s at 14.1 T was excluded[127]. Figures 1 and 2 show plots of $R_1$ against $B_0$, in which $R_1$ shows the expected decrease with increasing field: Table 1 gives values for the most important field strengths. The fit to Eq. 2 gave $M = -0.3611 \pm 0.0115$ and $C = 0.2956 \pm 0.0073$. The fit to Eq. 3 gave $A = (8.663 \pm 0.681) \times 10^4$ and $B = (1.294 \pm 0.082) \times 10^9$. An exploratory attempt at a three-parameter fit to Eq. 3 (i.e., to $A$, $B$, and $R_1,\infty$) failed to provide evidence for $R_1,\infty > 0$ (supplementary material 4). When data were subgouped by species or by method, no evidence was found that the subgoup $R_1$ values deviated systematically from Eq. 3 (supplementary material 6). Across all studies, the median between-subject CoV was 9.1% (LQ 5.9%, UQ 16.5%, rms 17.0%). There was, however, a tendency for early studies to report high between-subject CoV (Fig. 3 and supplementary material 7): no study published after 1992 had CoV ≥ 20%, and for post-1992 studies the median between-subject CoV was 7.4% (LQ 5.6%, UQ 11.0%, rms 9.6%). In half those studies, the measured $R_1$ deviated from Eq. 3 by 8.0% or less (LQ 2.8%, UQ 16.6%).

At each field strength, there was considerable variation in $R_1$ between studies: the between-study CoV was 16% for post-1992 studies. Six publications[2, 37, 98, 119, 128, 129] also reported liver $R_1$ repeatability (same subject, different scan, same measurement conditions): the rms CoV was 1.9%. These CoVs allowed a crude estimate (supplementary material 8) of the relative size of the three main variance components: repeatability variance contributed ~ 1%; within-study-between-subject variance contributed ~ 25%; and between-study variance contributed ~ 74%.

![Fig. 2 Dependence of longitudinal relaxation rate on field strength. Each symbol represents one study. Dashed black line: Eq. 2. Solid black line: Eq. 3. Dotted line: $R_{1,\infty} = 0.213 s^{-1}$](image-url)

### Table 1: Preferred $R_1$ values (s$^{-1}$) for five commonly used field strengths, derived from the data and from the fits

| $B_0$ (T) | Mean over studies (N studies) | Weighted mean over studies (N studies) | Mean over subjects (N subjects) | Fitted to heuristic Eq. 2 | Fitted to model Eq. 3 |
| --- | --- | --- | --- | --- | --- |
| 9.4 | 0.90 (4) | 1.01(4) | 0.89(38) | 0.88 | **0.92** |
| 7 | 1.02 (9) | 1.02(9) | 1.00(56) | 0.98 | **1.02** |
| 4.7 | 1.12 (5) | 1.22 (5) | 1.05(34) | 1.13 | **1.15** |
| 3 | 1.34 (36) | 1.42(36) | 1.29(989) | 1.33 | **1.33** |
| 1.5 | 1.66 (37) | 1.47(37) | 1.55(1700) | 1.71 | **1.66** |

Five different methods of generating a preferred $R_1$ are illustrated: the model fit (in bold) makes greatest use of the available information.
Discussion

In liver, as in pure water, both intramolecular and intermolecular water $^1$H-$^1$H dipolar relaxation contribute to $R_1$. Specific additional contributors to water $^1$H $R_1$ in liver arise from $^1$H-$^1$H dipolar relaxation between water and other molecules, and $^1$H-electron dipolar relaxation between water and various iron- or copper-containing substances or dioxygen. These $^1$H-containing and unpaired-electron-containing substances differ in concentration between subjects. The liver $^1$H resonance arises mostly from tissue water in hepatocytes. Other contributions come from water in other intracellular compartments (e.g., Kupffer cells, erythrocytes), and in extracellular compartments (e.g., bile, plasma, space of Disse). Signal from triglyceride and inflowing blood may contribute, depending on the sequence used. Macromolecules contribute to the signal, notably collagen and glycogen which have different concentrations in different subjects. These factors likely account for some of the variation between subjects and between studies.

Fits from the heuristic and from the model were very similar. The main difference is that the heuristic forces $R_1$ to zero at infinite field, while the model forces $R_1$ to asymptote in the extreme narrowing condition. This difference might become important at fields above 7 T (Fig. 1). In this study, following Diakova et al.[12], the asymptote $R_{1,\infty}$ was fixed at 1/4.7 s$^{-1}$, equal to the $R_1$ of pure deoxygenated water at 310 K at high field [17]: a slightly higher value would be more appropriate if $R_1$ values from liver water and pure water do not converge as illustrated in Fig. 1.

The relative magnitude of the major variance components was estimated. This is very crude, and given the heterogeneity and variable quality of the raw data, should be considered a rough guide only. The within-study between-subject CoV reflects not only repeatability error (~1% of the variance), but also the expected between-subject variation (~25% of the variance). Between-study variation (~74% of the variance) also includes between-population variation, together with bias from interactions between each study’s measurement method and its livers’ variation in flow, motion, fat, oedema, collagen, glycogen and iron. $R_1$ may also change after a meal [89], during the menstrual cycle [25] or with drug treatment [25].

The literature survey was not fully PRISMA-compliant [130] and is unlikely to be complete. Studies explicitly of liver $R_1$ or $T_1$ as a biomarker are readily retrieved, because
appropriate keywords are generally used in the title and abstract. However, for studies where liver $R_1$ or $T_1$ measurement is incidental to another objective, for example extracellular volume, relaxivity, or dynamic contrast-enhanced studies, suitable keywords may not have been included.

There is no single “correct” value for any liver’s $1H \ R_1$. $R_1$ may vary spatially across the liver [60, 119]. Water $1H \ R_1$ is multiexponential, particularly with sequences where macromolecule-associated fast-relaxing water contributes to the measurement. Other substances in the liver may also contribute to the $1H$ signal, such as glycogen [87] or triglyceride [76, 131]. Inflowing blood [110, 132], physiologic motion [71], magnetization transfer, and iron affect the measured $R_1$ in ways which depend both on the sequence and on the analysis employed. There may be systematic differences in $R_1$ between fat-suppressed vs. non-fat-suppressed acquisitions; 2D acquisitions more vulnerable to inflow effects than 3D; breathhold or gated vs. free-breathing; and so on. Some investigators advocate the use of a “corrected” $T_1$ to avoid bias caused by the relaxivity of iron-containing substances [65]. Because of these biases in the literature, studies which deviate from these survey data should not immediately be considered “incorrect”, but if large deviations are observed, then an explanation on methodological or physiological grounds should be sought.

There are some other limitations. While some publications reported carefully designed and conducted biomarker validation studies, in other publications, the precise value of $T_1$ was only of incidental interest and possibly acquired with less care. However, in this survey, the study design and objectives were not incorporated into the weightings. Most studies did not report validation of their liver $R_1$ by means of a phantom, so accuracy is unknown. It was difficult to explore the effect of methodology on $R_1$, because some studies used methodology which was poorly described or did not appear robust, and because of correlation between field strength and methodology (old studies used old methodology and lower fields). Likewise, there was correlation between field strength and species (humans at low-medium fields, rats at medium–high fields and mice at high fields), so it was difficult to compare between species.

**Conclusion**

Quantitative relaxometry requires validation with phantoms and analysis of propagation of errors. However, it is also good scientific practice to compare one’s own findings with prior literature. An investigator who finds their average liver $R_1$ in normal liver to be within 8% of the fit to Eq. 3, with between-subject CoV <8%, can conclude that their measurements are in agreement with the majority of the literature: for measurements far outside these limits, a physiological or methodological explanation should be sought.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10334-021-00928-x.

**Acknowledgements** The research leading to these results received funding from the Innovative Medicines Initiatives 2 Joint Undertaking under grant agreement No 116106 (IB4SD-TRISTAN). This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.

**Author contributions** Waterton, JC. Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript and critical revision.

**Declarations**

**Conflict of interest** John Waterton holds stock in Quantitative Imaging Ltd and is a Director of, and has received compensation from, Bioxydyn Ltd, a for-profit company engaged in the discovery and development of MR biomarkers and the provision of imaging biomarker services.

**Research involving human and animal participants** Not applicable, as this is a survey of previously published research.

**Informed consent** Not applicable, as this is a survey of previously published research.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

**References**

1. Smith FW, Mallard JR, Reid A, Hutchison JMS (1981) Nuclear magnetic resonance tomographic imaging in liver disease. Lancet 317:963–966
2. Banerjee R, Pavlides M, Tunnicliffe EM, Piechnik SK, Sarania N, Philips R, Collier JD, Booth JC, Schneider JE, Wang LM, Delaney DW, Fleming KA, Robson MD, Barnes E, Neubauer S (2014) Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. J Hepatol 60:69–77
3. Haimerl M, Utpatel K, Verloh N, Zeman F, Fellner C, Nickel D, Teufel A, Fichtner-Feigl S, Evert M, Stroszczynski C, Wiggermann P (2017) Gd-EOB-DTPA-enhanced MR relaxometry for the detection and staging of liver fibrosis. Sci Rep 7:41429
4. Haimerl M, Verloh N, Fellner C, Zeman F, Teufel A, Fichtner-Feigl S, Schreyer AG, Stroszczynski C, Wiggermann P (2014) MRI-based estimation of liver function:
9. Raunig DL, McShane LM, Pennello G, Gatsonis C, Carson  
8. Ziemian S, Green C, Sourbron S, Jost G, Schütz G, Hines CDG  
11. Araya YT, Martínez-Santiesteban F, Handler WB, Harris CT,  
6. Li Z, Sun J, Chen L, Huang N, Hu P, Hu X, Han G, Zhou Y, Bai  
14. Keevil SF, Dolke G, Brooks AP, Armstrong P, Farthing MJG,  
15. Henriksen O, de Certaines JD, Spisni A, Cortsen M, Muller RN,  
16. R Development Core Team (2018) R 3.5.1., A language and  
17. Krynicki K (1966) Proton spin-lattice relaxation in pure water  
18. Kamimura K, Fukukura Y, Yoneyama T, Takumi K, Tateyama  
20. Heye T, Yang SR, Bock M, Brost S, Weigand K, Longerich T,  
21. Block W, Reichel C, Träber F, Skodra T, Lemairichs R, Kreft B,  
22. de Certaines JD, Henriksen O, Spisni A, Cortsen M, Ring PB (1993) IV. In vivo measurements of proton relaxation times in human brain, liver, and skeletal muscle: A multicenter MRI study. Magn Reson Imaging 11:841–850  
23. Van Lom KJ, Brown JJ, Perman WH, Sandstrom JC, Lee JKT (1991) Liver imaging at 1.5 Tesla: Pulse sequence optimization based on improved measurement of tissue relaxation times. Magn Reson Imaging 9:165–171  
24. Steudel A, Harder T, Träber F, Dewes W, Schlolaut KH, Koster O (1989) Relaxation times measurements in Der Kernspintomographischen Differentialdiagnose Von Lebertumoren. RöFo Fortschritte auf dem Gebiete der Röntgenstrahlen und der Neuen Bildgeb Verfahren 151:449–455  
25. Richards MA, Webb JAW, Jewell SE, Gregory WM, Reznihk RH (1988) In-vivo measurement of spin lattice relaxation time (T1) of liver in healthy volunteers: The effects of age, sex and oral contraceptive usage. Br J Radiol 61:34–37  
26. Thomsen C, Christoffersen P, Henriksen O, Juhl E (1990) Prolonged T1 in patients with liver cirrhosis: An in vivo MRI study. Magn Reson Imaging 8:599–604  
27. Cassinotto C, Feldis M, Vergniol J, Mournies A, Cochet H, Lapuyade B, Hocquetau A, Juanola E, Foucher J, Laurent F, De Ledingen H (2015) MR relaxometry in chronic liver diseases: Comparison of T1 mapping, T2 mapping, and diffusion-weighted imaging for assessing cirrhosis diagnosis and severity. Eur J Radiol 84:1459–1465  
28. Henninger B, Kremser C, Rauch S, Eder R, Zoller H, Finkenstedt A, Michaely HJ, Schocke M (2012) Evaluation of MR imaging with T1 and T2* mapping for the determination of hepatic iron overload. Eur Radiol 22:2478–2486  
29. Weinrebc FC, Brateeman L, Maravilla KR (1984) Magnetic resonance imaging of hepatic lymphoma. Am J Roentgenol 143:1211–1214  
30. Belt TG, Cohen MD, Smith.JA, Cory DA, McMenna S, Weetman R (1986) MRI of Wilms’ tumor: Promise as the primary imaging method. Am J Roentgenol 146:955–961  
31. Ohtomo K, Itai Y, Furai S, Yoshikawa K, Yashiro N, Iio M (1985) Magnetic resonance imaging (MRI) of primary liver cancer. MRI-pathologic correlation. Radiat Med - Med Imaging Radiat Oncol 3:38–41  
32. Nyman R, Ericsson A, Hemmingsson A, Jung B, Sperber G, Thoumas KA (1986) T1, T2, and relative proton density at 0.35 T for spleen, liver, adipose tissue, and vertebral body: Normal values. Magn Reson Med 3:901–910  
33. Stark DD, Moseley ME, Bacon BR (1985) Magnetic resonance imaging and spectroscopy of hepatic iron overload. Radiology 154:137–142  
34. Gilligan LA, Dillman JR, Tkach JA, Xanthakos SA, Gill JK, Trout AT (2019) Magnetic resonance imaging T1 relaxation times for the liver, pancreas and spleen in healthy children at 1.5 and 3 tesla. Pediatr Radiol 49:1018–1024  
35. Kim JE, Kim HO, Bae K, Choi DS, Nickel D (2019) T1 mapping for liver function evaluation in gadoxetic acid–enhanced MR imaging: comparison of look-locker inversion recovery and B1 inhomogeneity–corrected variable flip angle method. Eur Radiol 29:3584–3594  
36. Yang L, Ding Y, Rao S, Chen C, Zeng M (2020) T1 mapping on Gd-EOB-DTPA-enhanced MRI for the prediction of oxaliplatin-induced liver injury in a mouse model. J Magn Reson Imaging 53:896–902
of iron and copper disease states. AJR Am J Roentgenol 141:943–948

Ebara M, Ohto M, Watanabe Y, Kimura K, Saisho H, Tsuchiya Y, Okuda K, Arimizu N, Kondo F, Ikereha H (1986) Diagnosis of small hepatocellular carcinoma: Correlation of MR imaging and tumor histologic studies. Radiology 159:371–378

Brasch RC, Wesbeey GE, Gooding CA, Koerper MA (1984) Magnetic resonance imaging of transfusional hemosiderosis complicating thalassemia major. Radiology 150:767–771

Ehman RL, McNamara MT, Pallack M, Hricak H, Higgins CB (1984) Magnetic resonance imaging with respiratory gating: Techniques and advantages. Am J Roentgenol 143:1175–1182

Rödl W (1984) Differentialdiagnose von Lebererkrankungen im Kernspintomogramm. RöFo Fortschritte auf dem Gebiete der Rontgenstrahlen und der bildgeb Verfahren 142:505–510

Rupp N, Reiser M, Stetter E (1983) The diagnostic value of morphology and relaxation times in NMR-imaging of the body. Eur J Radiol 3:68–76

Buonocore E, Borkowski GP, Pavlick w, Ngo F (1983) NMR imaging of the abdomen: Technical considerations. Am J Roentgenol 141:1171–1178

Brown DW, Henkelman RM, Poon PY, Fisher MM (1985) Nuclear magnetic resonance study of iron overload in liver tissue. Magn Reson imaging 3:275–282

Mozes FE, Tunncliffle EM, Moolla A, Marjot T, Levick CK, Pavlides M, Robson MD (1990) Mapping tissue water T1 in the liver using the MOLLI T1 method in the presence of fat, iron and B0 inhomogeneity. NMR Biomed 32:e4030

Ding Y, Rao SX, Zhu T, Chen C, Li RC, Zeng MS (2015) Liver fibrosis staging using T1 mapping on gadoxetic acid-enhanced MRI compared with DW imaging. Clin Radiol 70:1096–1103

Moss AA, Goldberg HI, Stark DB, Davis PL, Margulis AR, Kaufman L, LEC, (1984) Hepatic tumors: Magnetic resonance and CT appearance. Radiology 150:141–147

Träber F, Steudel A, Harder T (1990) In-vivo-messung von geweberelaxationszeiten mit lokalisierter 31P- und 1H-MR-Spektroskopie. RöFo Fortschritte auf dem Gebiete der Rontgenstrahlen und der Neuen Bildgeb Verfahren 153:209–215

Wang C, Wang ZC, Ding Y, Zeng MS, Rao SX (2018) Value of gadoxetate disodium-enhanced magnetic resonance on hepatobiliary phase T1 mapping for predicting liver injury. Zhonghua GanZang Bing ZaZhi 27:547–551

Ehman RL, Kjos BO, Hricak H, Higgins CB (1985) Relative intensity of abdominal organs in MR images. J Comput Assist Tomogr 9:315–319

Flak B, Ajzen S, Li DKB, Cooperberg PL, Clark C (1989) Hemangioma of the liver: Characteristics exhibited on a 0.15 Tesla scanner. Can Assoc Radiol J 40:135–138

Fletcher BD, Kopiwoda SY, Strandjord SE, Nelson AD, Pickering SP (1985) Abdominal neuroblastoma: Magnetic resonance imaging and tissue characterization. Radiology 155:699–703

Foley WD, Kneeband J, Cates JD, Kellman GM, Lawson TL, Middleton WD, Hendrick RE (1987) Contrast optimization for the detection of focal hepatic lesions by MR imaging at 1.5 T. Am J Roentgenol 149:1155–1160

Schmidt HC, Tscholakoff D, Hricak H, Higgins CB (1985) MR image contrast and relaxation times of solid tumors in the chest, abdomen, and pelvis. J Comput Assist Tomogr 9:738–748

Rödl W (1984) Differential diagnosis of liver diseases with the aid of nuclear magnetic resonance imaging. In: Demling L, Lutz H, Wenz W, Wiltiirt H (eds) Diagnostic Imaging Methods in Hepatology: proceedings of the 37th Falk Symposium, held during Basel Liver Week, Basel, September 29–October 2, 1983. MTP Press, Lancaster, MA USA, pp 153–158

Weis J, Kullberg J, Ahlström H (2018) Multiple breath-hold proton spectroscopy of human liver at 3T: Relaxation times and concentrations of glycogen, choline, and lipids. J Magn Reson Imaging 47:410–417

Hoad CL, Palaniyappan N, Kaye P, Chernova Y, James MW, Costigan C, Austin A, Marciani L, Gowland PA, Guha IN, Francis ST, Aithal GP (2015) A study of T1 relaxation time as a measure of liver fibrosis and the influence of confounding histological factors. NMR Biomed 28:706–714

O’Connor JPB, Jackson A, Buonaccorsi GA, Buckley DL, Roberts C, Watson Y, Cheung S, McGrath DM, Naish HJ, Rose CJ,黑暗 PM, Jayson GC, Parker GM (2007) Organ-specific effects of oxygen and carbogen gas inhalation on tissue longitudinal relaxation times. Magn Reson Med 58:490–496

Nyman R, Rhen S, Ericsson A, Glimelius B, Hagberg H, Hemmingsson A, Sundström C (1987) An attempt to characterize malignant lymphoma in spleen, liver and lymph nodes with magnetic resonance imaging. Acta Radiol 28:527–533

Hardy CJ, Edelstein WA, Vatis D, Harms R, Adams WJ (1985) Calculated T1 images derived from a partial saturation-inversion recovery pulse sequence with adiabatic fast passage. Magn Reson Imaging 3:107–116

Kinami Y, Yokota H, Takata M, Takashima S, Yamamoto I (1988) Magnetic resonance imaging in the diagnosis of tumors of the liver. Gastroenterol Jpn 23:139–146

Leung A, Bydder G, Steinert R, Bryant D, Young I (1984) Magnetic resonance imaging of the kidneys. AJR Am J Roentgenol 143:1215–1227

Okada M, Murakami T, Yada N, Numata K, Onoda M, Hyodo T, Inoue T, Ishii K, Kudo M (2015) Comparison between T1 relaxation time of Gd-EOB-DTPA-enhanced MRI and liver stiffness measurement of ultrasound elastography in the evaluation of cirrhotic liver. J Magn Reson Imaging 41:329–338

Chow AM, Gao DS, Fan SJ, Qiao Z, Lee FY, Yang J, Man K, Wu EX (2012) Measurement of liver T1 and T2 relaxation times in an experimental mouse model of liver fibrosis. J Magn Reson Imaging 36:152–158

Ding Y, Yang L, Rao SX, Zeng MS (2019) Gadoxetic disodium-enhanced MRI to characterize T1 relaxation values and expression level of organic anion transporters and multidrug resistance protein on hepatocyte surface membrane of normal C57BL/6 mice. Zhonghua Gan Zang Bing Za Zhi 27:547–551

Matsuo-Tezuka Y, Sasaki Y, Iwai T, Kurasawa M, Yorozu K, Tashiro Y, Hirata M (2019) T1 relaxation time obtained from magnetic resonance imaging of the liver is a useful parameter for use in the construction of a murine model of iron overload. Contrast Media Mol Imaging 2019:7463047

Faller TL, Trottier AJ, Miraux S, Ribot EJ (2019) Radial MR fingerprinting (RIPE-MRF) for enhanced motion artifact suppression in preclinical cartesian MR fingerprinting. Magn Reson Med 79:2176–2182

Jackson LH, Vlachoudimitropoulou E, Shangaris P, Roberts TA, Ryan TM, Campbell-Washburn AE, David AL, Porter JB, Lythgoe MF, Stuckey DJ (2017) Non-invasive MRI biomarkers for the early assessment of iron overload in a humanized mouse model of β-thalassemia. Sci Rep 7:43439

Eberhard C, Wurzig MC, Wirsching A, Rossi C, Feldman I, Lesurtel M, Boss A (2018) Prediction of small for size syndrome after extended hepatectomy: Tissue characterization by relaxometry, diffusion weighted magnetic resonance imaging and magnetization transfer. PLoS ONE 13:e0192847
102. Li H, Gray BD, Corbin I, Lebherz C, Choi H, Lund-Katz S, Wilson JM, Glickson JD, Zhou R (2004) MR and fluorescent imaging of low-density lipoprotein receptors. Acad Radiol 11:1251–1259

103. Oostendorp M, Douma K, Hackeng TM, Post MJ, Van Zandvoort MAMJ, Backes WH (2010) Gadolinium-labeled quantum dots for molecular magnetic resonance imaging: R1 versus R2 mapping. Magn Reson Med 64:291–298

104. Ramasawmy R, Campbell-Washburn AE, Wells JA, Johnson SP, Pedley RB, Walker-Samuel S, Lythgoe MF (2015) Hepatic arterial spin labelling MRI: An initial evaluation in mice. NMR Biomed 28:272–280

105. Polasek M, Fuchs BC, Uppal R, Schüble DT, Alford JK, Loving GS, Yamada S, Wei L, Lauwers GY, Guimaraes AR, Tanabe KK, Caravan P (2012) Molecular MR imaging of liver fibrosis: A feasibility study using rat and mouse models. J Hepatol 57:549–555

106. Müller A, Hochrath K, Stroeder J, Hittatiya K, Schneider G, Lammert F, Buecker A, Fries P (2017) Effects of liver fibrosis progression on tissue relaxation times in different mouse models assessed by ultrahigh field magnetic resonance imaging. Biomed Res Int 2017:8720367

107. Braren R, Curric J, Remmele S, Alfonte J, Ebert O, Rummeny EJ, Stein.goetter A (2011) Free-breathing quantitative dynamic contrast-enhanced magnetic resonance imaging in a rat liver tumor model using dynamic radial T1 mapping. Invest Radiol 46:624–631

108. Cheng HLM, Haedicke IE, Cheng W, Nofiele JT, Zhang XA (2014) Gadolinium-free T1 contrast agents for MRI: Tunable pharmacokinetics of a new class of manganese porphyrins. J Magn Reson Imaging 40:1474–1480

109. Oostendorp M, Douma K, Hackeng TM, Post MJ, Van Zandvoort MAMJ, Backes WH (2010) Gadolinium-labeled quantum dots for molecular magnetic resonance imaging: R1 versus R2 mapping. Magn Reson Med 64:291–298

110. Chouhan MD, Ramasawmy R, Bainbridge A, Campbell-Washburn AE, Wells JA, Johnson SP, Pedley RB, Walker-Samuel S, Lythgoe MF (2015) Hepatic arterial spin labelling MRI: An initial evaluation in mice. NMR Biomed 28:272–280

111. Marzola P, Maggioni F, Vicinanza E, Daprà M, Cavagna FM, Gneiting T, Margulis AR, Watts J, Hoenninger J, Arakawa M, McRee R, Caravan P, Pedley RB, Walker-Samuel S, Lythgoe MF (2015) Hepatic arterial spin labelling MRI: An initial evaluation in mice. NMR Biomed 28:272–280

112. Hazle JD, Narayana PA, Dunsford HA (1991) In vivo NMR, biochemical, and histologic evaluation of alcohol-induced fatty liver in rat and a comparison with CCl4 hepatotoxicity. Magn Reson Med 15:211–228

113. Hazle JD, Narayana PA, Dunsford HA (1990) Chronic carbon tetrachloride and phospholipase D hepatotoxicity in rat: In vivo IH magnetic resonance, total lipid analysis, and histology. Magn Reson Med 15:211–228

114. Ding M, Brauer M (1992) Ethanol-induced fatty liver in the rat examined by in vivo IH chemical shift selective magnetic resonance imaging and localized spectroscopic methods. Magn Reson Imaging 10:663–677

115. Herfkens R, Davis P, Crooks L, Kaufman L, Price D, Miller T, Margulis AR, Watts J, Hoenninger J, Arakawa M, McRee R (1981) Nuclear magnetic resonance imaging of the abdominal live rat and correlations with tissue characteristics. Radiology 141:211–218

116. Davis PL, Kaufman L, Crooks LE, Miller TR (1981) Detectability of hepatomas in rat livers by nuclear magnetic resonance imaging. Invest Radiol 16:354–359

117. Moy AM, McDonald N, Lennen RJ, Milanese M, Herlihy AH, Kendall TJ, Mungall W, Gyngell M, Banerjee R, Janiczek RL, Murphy PS, Jansen MA, Fallowfield JA (2018) Non-invasive assessment of liver disease in rats using multiparametric magnetic resonance imaging: a feasibility study. Biol Open 7:bios033910

118. Zhou IY, Jordan VC, Rotile NJ, Akam E, Krishnan S, Arora G, Krishnan H, Slattery H, Warner N, Mercialdo N, Farrar CT, Wollen J, Martinez R, Schlerman F, Tanabe KK, Fuchs BC, Caravan P (2020) Advanced MRI of liver fibrosis and treatment response in a rat model of nonalcoholic steatohepatitis. Radiology 296:67–75

119. Li J, Liu H, Zhang C, Yang S, Wang Y, Chen W, Li X, Wang D (2020) Native T1 mapping compared to ultrasound elastography for staging and monitoring liver fibrosis: an animal study of repeatability, reproducibility, and accuracy. Eur Radiol 30:337–345

120. Gao Y, Erokwu BO, Desantis DA, Croniger CM, Schur RM, Lu L, Mariapprumur J, Dell KM, Flask CA (2016) Initial evaluation of hepatic T1 relaxation time as an imaging marker of liver disease associated with autosomal recessive polycystic kidney disease (ARPKD). NMR Biomed 29:84–89

121. Gambarota G, Veltien A, Van Laarhoven H, Philipsen M, Jonker A, Mook OR, Frederiks WM, Heerschap A (2004) Measurements of T1 and T2 relaxation times of colon cancer metastases in rat liver at 7 T. Magn Reson Mater Phys, Biol Med 17:281–287

122. Fan YD, Vanzieleghem B, Achten E, De Deene Y, Defreyne L, Praet M, Van Huyse J, Kunnen M, De Hemptinne B (2001) T1 relaxation times for viability evaluation of the engrafted and the native liver in a rat model of heterotopic auxiliary liver transplantation: A pilot study. NMR Biomed 14:350–359

123. Nakakoshi T, Kajiyama M, Fujita N, Jong-Hon K, Takeichi N, Miyasaka K (1996) Quantitative analyses of correlations of signal intensity on T1-weighted images and T1 relaxation time with copper concentration in the rat liver. Acad Radiol 3:36–39

124. Chamuleau RAFM, De Nie JHNCI, Moerland MA, Van der Lende OR, Smidt J (1988) Is the magnetic resonance imaging proton spin-lattice relaxation time a reliable noninvasive parameter of developing liver fibrosis? Hepatology 8:217–221

125. Ganesh T, Estrada M, Yeger H, Duffin J, Margaret Cheng HL (2017) A non-invasive magnetic resonance imaging approach for assessment of real-time microcirculation dynamics. Sci Rep 7:4768

126. Sheng RF, Wang HQ, Yang L, Jin KP, Xie YH, Fu CX, Zeng MS (2017) Assessment of liver fibrosis using T1 mapping on Gd-EOB-DTPA-enhanced magnetic resonance. Dig Liver Dis 49:789–795

127. Soares AF, Lei H (2018) Non-invasive diagnosis and metabolic consequences of congenital portosystemic shunts in C57BL/6 J mice. NMR Biomed 31:e3873

128. Steudel A, Traber F, Krahe T, Schiffmann O, Harder T (1990) Qualitatskontrole der quantitativen mr-tomographie: in-vitro und in-vivo-überprüfung von relaxationszeitmessungen. RoFo Fortschritte auf dem Gebiete der Rontgenstrahlen und der Neuen Bildgeb Verfahren 152:673–676

129. Bachtiar V, Kelly MD, Wilman HR, Jacobs J, Newbould R, Kelly CJ, Gyngell ML, Groves KE, McKay A, Herlihy AH, Fernandes CC, Halberstadt M, Maguire M, Jayaratne N, Linden S, Neu-bauer S, Banerjee R (2019) Repeatability and reproducibility of liver fibrosis assessed by ultrahigh field magnetic resonance imaging. J Magn Reson Imaging 7:147–152
(2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 6:e1000097

131. Haimerl M, Probst U, Poelsterl S, Fellner C, Nickel D, Wiegand K, Brunner SM, Zeman F, Stroszczynski C, Wiggermann P (2018) Evaluation of two-point Dixon water-fat separation for liver specific contrast-enhanced assessment of liver maximum capacity. Sci Rep 8:13863

132. Axel L (1984) Blood flow effects in magnetic resonance imaging. Am J Roentgenol 143:1157–1166

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.