

Method and System of MRI Imaging to Estimate Liver Water R_1 and R_2^* VariabilityField of the Invention

The present invention relates to the field of liver imaging using MRI. In particular, the present invention provides means to estimate the variability in liver water R_1 and R_2^* with reference to liver water, iron, and fat content.

Background

T_1 and T_2^* relaxation times, and proton density fat fraction (PDFF), are MRI-derived parameters that have been shown to provide useful information for characterizing liver health.

10 The influence of liver iron concentration (LIC) on liver R_1 ($1/T_1$) and R_2^* ($1/T_2^*$) in subjects with elevated iron is known. Liver T_1 is also sensitive to liver water concentration (LWC) and has been shown to correlate with biopsy-derived measurements of fibrosis and inflammation, due to the elevation in tissue water content associated with these processes.

15 R_2^* is composed of the sum of the following terms: R_2 ($1/T_2$), the spin-spin relaxation rate, and R_2' , the relaxation rate introduced by magnetic field heterogeneities. R_2 is sensitive to both LWC and LIC, and as such changes in either parameter will influence liver R_2^* values.

It is important to understand and correct for these confounding influences on liver R_2^* , which is addressed by the present invention.

Various publications address the influence of iron, water, and fat concentration on liver T_1 and T_2^* .

For example, in relation to liver iron concentration, Wood, J. C. et al. ('Cardiac Iron Determines Cardiac T_2^* , T_2 , and T_1 in the Gerbil Model of Iron Cardiomyopathy.' *Circulation* 112, 535–543 (2005)) demonstrated that iron shortens T_1 , T_2 , and T_2^* relaxation times in the heart and liver, using a gerbil iron-overload model. They present calibration curves relating liver R_1 to biopsy-determined liver iron, which show potential for estimating the influence of iron on liver R_1 values measured in patients with elevated liver iron.

Ghugre, et. al., ('Mechanisms of tissue-iron relaxivity: Nuclear magnetic resonance studies of human liver biopsy specimens.' *Magn. Reson. Med.* 54, 1185–1193 (2005)) found that nuclear magnetic resonance (NMR) relaxometry of human liver biopsy specimens yielded unique insights into the mechanisms of tissue-iron relaxivity. Their study aimed to address the underlying proton relaxation mechanisms within the human tissue environment on non-invasive iron quantification, and inter-site and inter-sequence variability, as well as methodological inaccuracies that limit its widespread clinical use. They performed NMR relaxometry on fresh human liver biopsy specimens taken from patients with transfusion-dependent anaemia and compared NMR parameters to quantitative iron levels and tissue histology. They noted that R_1 and R_2 both increased linearly with hepatic iron content, with R_2 being more sensitive to iron.

In a further study, noting that relaxation rates R_2 and R_2^* measured by MRI have different advantages for hepatic iron concentration (HIC) estimation, Wood, et al. ('MRI R_2 and R_2^* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients.' *Blood* 106, 1460–1465 (2005)) compared non-invasive iron estimates using optimized R_2 and R_2^* methods in patients with iron overload and controls. They found that the R_2 calibration curve was similar to the curve generated by other researchers, despite differences in technique and instrumentation; that combined R_2 and R_2^* measurements did not yield more accurate results than either alone; and that both R_2 and R_2^* can accurately measure hepatic iron concentration throughout the clinically-relevant range of HIC with appropriate MRI acquisition techniques.

St Pierre et al. ('Non-invasive measurement and imaging of liver iron concentrations using proton magnetic resonance.' *Blood* 105.2 (2005): 855-861) have shown how the accumulation of iron in the liver leads to the shortening of T_2 . They presented a calibration curve relating liver R_2 to biopsy-determined LIC.

Hernando et al ('Multicenter Reproducibility of Liver Iron Quantification with 1.5-T and 3.0-T MRI,' *Radiology* 306, e213256 (2023)) quantified cross-vendor reproducibility of R_2^* -based LIC estimation, by comparing liver R_2^* measurements against estimated LIC values. They evaluated the reproducibility of R_2^* -based LIC estimation in a multi-centre, multi-vendor study. Participants with known or suspected liver iron overload underwent single breath-hold, multi-echo gradient-echo MRI for R_2^* mapping at 1.5 T and 3 T (2.89 T or 3.0 T) on the same day. R_2^* maps from the multi-echo images were

reconstructed and analysed. They confirmed a linear relationship between R_2^* and the LIC measurements, and all calibrations within the same field strength were highly reproducible, showing no evidence of statistically significant centre-specific differences.

- 5 An MR technique which is commonly used for mapping T_1 in the liver is *MODified Look-Locker Inversion-recovery (MOLLI)*, which widely known for being a robust and fast (single breath-hold) method for acquiring T_1 data. However, it is known and accepted that MOLLI- T_1 has a dependence on tissue T_2 , which results in an underestimation of the MOLLI- T_1 as T_2 is shortened (Piechnik et al. 'Shortened Modified Look-Locker
10 Inversion recovery (ShMOLLI) for clinical myocardial T_1 -mapping at 1.5 and 3 T within a 9 heartbeat breathhold.' *Journal of cardiovascular magnetic resonance* 12.1 (2010): 1-11). As such, in the presence of elevated liver iron, MOLLI- T_1 will be reduced both directly and indirectly (the latter being due to the shortening of T_2). This acts as a confounding effect to the increase in T_1 resulting from increased tissue water content
15 associated with liver inflammation or fibrosis.

- A correction for the confounding effect of LIC on MOLLI- T_1 is described in Tunnicliffe et al. ('A model for hepatic fibrosis: the competing effects of cell loss and iron on shortened modified Look-Locker inversion recovery T_1 (shMOLLI- T_1) in the liver', *Journal of Magnetic Resonance Imaging* 45.2 (2017): 450-462) and
20 PCT/GB2014/050815. This approach may be implemented in commercial or open source solutions and utilizes Bloch simulations of the acquired MOLLI sequence to estimate the MOLLI T_1 for different levels of LIC and extra-cellular fluid volume fraction (ECF). For a given subject, LIC is estimated using measured T_2^* values, and ECF is estimated by selecting the simulated MOLLI signal (for a given ECF and LIC) which
25 best matches the measured signal. If LIC is elevated, look-up tables are used to estimate the equivalent MOLLI T_1 for the same ECF value and normal LIC. This provides a corrected T_1 (cT_1), in which the confounding effect of LIC is minimized.

- T_2^* is sensitive to microscopic inhomogeneities in magnetic susceptibility within the liver tissue. Similar to iron, hepatic fat droplets induce local magnetic susceptibility
30 inhomogeneities, leading to a decrease in T_2^* (or an increase in R_2^*). As such, increases in PDFF will lead to an increase in liver R_2^* , and in patients with normal iron but elevated PDFF, fat may be the dominant influence on the measured R_2^* , rather than iron.

Various publications discuss this. For example, Wang et al. used Monte Carlo simulations to model the relationship between liver R_2^* and PDFF ('Monte Carlo Modelling of Liver MR Signal in the Presence of Fat', Proc. Intl. Soc. Mag. Reson. Med. 26 (2018)). Their results showed a linear correlation between PDFF and R_2^* (slope of R_2^* (Hz) relative to PDFF (%) = 0.395 at 1.5T, and 0.772 at 3T).

Wang et. al.'s results are consistent with previous *in vivo* studies, in which the slope of R_2^* relative to PDFF (in Hz/%) ranges from 0.77 to 0.87 at 3.0T (Hernando et al. 'Relationship between liver proton density fat fraction and R_2^* in the absence of iron overload', Proc. Intl. Soc. Mag. Reson. Med. 23 (2015), Mamidipalli et al. 'Cross-sectional correlation between hepatic R_2^* and proton density fat fraction (PDFF) in children with hepatic steatosis', J Magn Reson Imaging 2017).

Fat also influences T_1 measurements obtained in the liver. For instance, MOLLI T_1 mapping sequences generally employ a balanced steady-state free precession readout, which is influenced by off-resonance effects between the fat and water signal. This can lead to complex behaviour of the signal during T_1 recovery if the imaged voxels contain a mixture of fat and water. With typical MOLLI imaging parameters, and clinically relevant fat fraction, this leads to an over-estimation of the MOLLI T_1 value, which is at odds with the decreased T_1 expected in a simple fat/water partial volume model (Mozes et al. "Mapping tissue water T_1 in the liver using the MOLLI T_1 method in the presence of fat, iron and B_0 inhomogeneity", NMR in Biomedicine 2018; e4030). The study by Mozes et al. shows how Bloch simulations of the acquired MOLLI sequence can be used to model the water and fat signals independently, which allows a 'water T_1 ' value to be estimated, which is independent of the confounding effect of fat. The authors also show how, by applying a version of the liver model introduced by Tunnicliffe et al., the confounding influence of LIC on water T_1 can also be minimised.

The studies summarized above have investigated changes in T_1 and T_2^* arising predominantly from changes in liver iron or fat. However, these parameters are also sensitive to changes in tissue water content, which may result from inflammation or fibrosis in the liver. For example, Luetkens *et al* ('Quantification of liver fibrosis at T_1 and T_2 mapping with extracellular volume fraction MRI: preclinical results.' *Radiology* 288.3 (2018): 748-754) have described how fibrosis and portal hypertension in the liver might increase the water content of the extracellular matrix, and lead to an increase in the tissue T_1 and T_2 .

- Hamilton et al. ('Relation between T_1 and T_2 of liver water and fat and Proton Density Fat Fraction estimated by a flip angle corrected multi-TR, multi-TE single breath-hold ^1H MRS STEAM sequence.' *Proc. Intl. Soc. Mag. Reson. Med.* (2019)) examined the relationship between the T_1 and T_2 relaxation times of liver water and fat, in adult
5 subjects with known or suspected non-alcoholic fatty liver disease. The use of a multi-TR, multi-TE ^1H MRS sequence allowed the T_1 and T_2 of the liver water and fat signals to be measured independently. They found a significant linear correlation between liver water T_1 and water T_2 , which is likely to reflect the combined response of these parameters to variability in the underlying liver water concentration within this cohort.
- 10 Thompson et al. have presented a novel imaging method known as PROFIT (PDFF imaging with T_1), which provides simultaneous quantification of PDFF, T_2^* , and water T_1 in the liver (Thompson et al., 'Simultaneous proton density fat-fraction and R_2^* imaging with water-specific T_1 mapping (PROFIT1): application in liver', *Magn Reson Med* 2021; 75:223-239). Their method addresses fat-related liver T_1 biases by
15 separation of water and fat signals, and also provides T_2^* and PDFF maps in a single scan. Water T_1 values obtained with this method remain sensitive to both LIC and LWC. In a subsequent paper, the authors suggest using a T_2^* -compensation approach to account for normal physiologic variations which jointly affect water T_1 and T_2^* and lead to increased variability in water T_1 (Thompson et al., 'Reference Values for Water-Specific T_1 of the Liver at 3 T: T_2^* -Compensation and the Confounding Effects of Fat',
20 *J. Magn. Reson. Imaging* 2024). This resulted in reduced variability in liver water T_1 in a cohort of healthy subjects.

However, this approach does not differentiate between the competing influences of LWC and LIC on water T_1 and T_2^* and could potentially eliminate clinically-relevant
25 pathologic signals that affect both T_1 and T_2^* , such as increased tissue water content as a result of fibrosis or inflammation.

- Furthermore, the reduction in T_2^* due to liver fat is not accounted for, and as such, even with water-specific T_1 mapping, a reduced T_2^* due to a high fat content would give rise to an increase in T_2^* -compensated water T_1 .
- 30 In summary, such studies confirm that liver T_1 and T_2^* are sensitive to the fat, water, and iron concentration in the tissue, and these can have opposing effects on measured T_1 and T_2^* values.

While some steps have been made to mitigate these confounding effects, such as measuring water-specific T_1 to remove the influence of fat, or using T_2^* to apply iron-correction to the liver T_1 , there is currently no means to model the simultaneous, combined effects of iron, water and fat content on both water R_1 and R_2^* . The present invention presents such a means.

Summary of the Invention

According to a first aspect of the invention there is a method of liver imaging using MRI as disclosed in claim 1. Further features of the invention are disclosed in dependent claims.

The present invention provides a means to determine the simultaneous and combined effects that iron, fat, and water concentration have on liver water T_1 and T_2^* values.

According to an aspect of the invention there is a method of liver imaging using MRI including: receiving inputs derived from MRI scans of a liver including a map of a transverse relaxation rate R_2^* , a map of PDFF, and raw MOLLI T1 mapping sequence signal data S_{raw} ; for a main magnetic field value B_0 of the MRI scans, presuming a first relation wherein a longitudinal relaxation rate R_1 is linearly dependent on a liver water concentration LWC and separately linearly dependent on a liver iron concentration LIC of the first liver; for the main magnetic field value, presuming a second relation wherein a fat corrected transverse relaxation rate $R_{2^*fat_corr}$ that accounts for an influence of fat in the first liver is linearly dependent on the liver water concentration LWC and separately linearly dependent on the liver iron concentration LIC of the first liver; using the inputs, the first and second linear relations, and known correlations of MRI parameters derived from other MRI scans of other livers or internal body organs determined prior to the MRI scans of the first liver to determine quantitative values of: a first ratio $\beta_{R_2^*/PDFF}$ of change in the transverse relaxation rate R_2^* per change in the PDFF; a difference $\Delta PDFF$ that is a difference in a measured PDFF minus zero PDFF; a change in relaxation rate ΔR_{2^*fat} that is a difference R_2^* due to fat relative to zero PDFF; a longitudinal water relaxation rate wR_1 ; a relaxation rate wR_{1ref} that is a reference water relaxation rate R_1 of a healthy liver; a relaxation rate correction ΔR_2^* is a compensator for the LWC; a relaxation rate $R_{2^*fat_corr}$ is a transverse relaxation rate that is compensated for influence of fat in the liver on the transverse relaxation rate

R_2^* ; a relaxation time R_{2wc}^* that is corrected for the LWC; a liver iron concentration LIC_{wc} that is water corrected to be unconfounded by the LWC; a relaxation rate R_{2wc} is a transverse relaxation rate that is associated with a value of the LIC_{wc} unconfounded by the LWC; a relaxation rate correction ΔR_2 is a compensator for the LWC; and
 5 summing the relaxation rate R_{2wc} plus the relaxation rate correction ΔR_2 to determine a transverse water relaxation rate R_{2wcic} that accounts for influence of the LWC and the LIC. Here R_{2wcic} is the reciprocal of the relaxation time T2 in equation 12 below. The detailed description below provides a detailed explanation of stage 1 inputs, and method of calculation in equations 3, 4 and 12. The method enables the
 10 obtaining of an estimate for liver R2 without direct measurement of this parameter. The estimate is free of the confounding effects of LWC and LIC.

According to another aspect of the invention there is a method of liver imaging using MRI including:

15 receiving inputs derived from MRI scans of a first liver including a map of a second star relaxation rate R_2^* , a map of PDFF, and raw MOLLI T1 mapping sequence signal data S_{raw} ;

for a main magnetic field value B_0 of the MRI scans, presuming a first relation wherein a first relaxation rate R1 is linearly dependent on a liver water concentration LWC and separately linearly dependent on a liver iron concentration LIC of the first liver;

20 for the main magnetic field value B_0 of the MRI scans, presuming a second relation wherein a fat corrected second relaxation rate $R_{2fat_corr}^*$ that accounts for influence fat in the first liver is linearly dependent on the liver water concentration LWC and separately linearly dependent on the liver iron concentration LIC of the first liver;

25 using: known correlations of MRI parameters derived from other MRI scans of other livers or internal body organs determined prior to the MRI scans of the first liver, and the inputs, and the first and second linear relations to determine quantitative values of at least: a relaxation rate R_{2wc} and relaxation rate correction ΔR_2 ,

30 and summing the relaxation rate R_{2wc} plus the relaxation rate correction ΔR_2 to determine a second water relaxation rate R_{2wcic} that accounts for influence of the LWC and the LIC.

Further relationships and quantitative values from the field of MRI imaging and which may be used in determining the second water relaxation rate R_{2WCIC} may be determined by reference to measurements and procedures given in the detailed description. Such relationships or quantitative values may include but are not necessarily limited to or by: a first ratio $\beta_{R_2^*/PDFF}$ of change in the transverse relaxation rate R_2^* per change in the PDFF; a difference $\Delta PDFF$ that is a difference in a measured PDFF minus zero PDFF; a change in relaxation rate ΔR_{2^*fat} that is a difference R_2^* due to fat relative to zero PDFF; a longitudinal water relaxation rate wR_1 ; a relaxation rate wR_{1ref} that is a reference water relaxation rate R_1 of a healthy liver; a relaxation rate correction ΔR_2^* is a compensator for the LWC; a relaxation rate $R_{2^*fat_corr}$ is a transverse relaxation rate that is compensated for influence of fat of the liver on the transverse relaxation rate R_2^* ; a relaxation time R_{2^*wc} that is corrected for the LWC; a liver iron concentration LIC_{wc} that is water corrected to be unconfounded by the LWC; a relaxation rate R_{2WC} is a transverse relaxation rate that is associated with a value of the LIC_{wc} unconfounded by the LWC; a relaxation rate correction ΔR_2 is a compensator for the LWC.

The method provides a means to estimate liver T_2 , for a given value of water T_1 and T_2^* , without the need of a separate MRI acquisition to measure T_2 directly. This is advantageous, as R_2 -based relaxometry methods generally require long acquisition times (10–20 minutes), provide limited spatial coverage of the liver, and are prone to motion artifacts. Conversely, R_2^* -based measurements generally provide good spatial coverage of the liver, and acquisition within a single short breath-hold is feasible (Hernando et al ('Multicenter Reproducibility of Liver Iron Quantification with 1.5-T and 3.0-T MRI', Radiology 306, e213256 (2023))).

Preferably the method of liver imaging includes finding a fit between the raw MOLLI T_1 mapping sequence signal data S_{raw} and simulated MOLLI signals S_{sim} as a function of the longitudinal water relaxation rate wR_1 and a transverse water relaxation rate R_{2WCIC} that accounts for influence of the LWC and the LIC to determine a longitudinal relaxation rate wR_1 that is independent of fat. The detailed description below provides a detailed explanation of stage 4 signal matching. The method helps by obtaining an estimate for liver R_2 without direct measurement of this parameter, the latter being used to accurately simulate the MOLLI raw signal, in order to estimate liver water T_1 . The liver water T_1 is independent of fat.

Preferably the method of liver imaging includes using: a ratio $\beta_{R1/LIC}$ from the first relation as presumed that relates a change in the longitudinal relaxation rate $R1$ to a change in the LIC; a difference ΔLIC of the LIC minus a healthy liver iron concentration reference LIC_{ref} , and determining a product of the longitudinal relaxation rate $wR1_{noFat}$ that is independent of fat times an amount that is a difference of one minus a relaxation time $wT1_{noFat}$ corresponding to the longitudinal relaxation rate $wR1_{noFat}$ that is independent of fat times the ratio $\beta_{R1/LIC}$ times the difference ΔLIC to determine a fat independent and iron corrected water relaxation rate $wR1_{Fe-corr}$. The detailed description below provides a detailed explanation of calculation by equations 14 and 15. The method helps to estimate a corrected liver water $T1$ value, in which the confounding influences of iron, fat, magnetic field strength and inter-vendor variability on liver $T1$ are minimised.

Preferably the method of liver imaging is conducted wherein a constant offset plus a product of the fat independent and iron corrected water relaxation time $wT1_{Fe-corr}$ is multiplied times a constant coefficient, and the constant offset and coefficient are determined from the MRI scans of the first liver at the main magnetic field value B_0 and second MRI scans at a second main magnetic field value $B_{0(2)}$ to quantify an effect of magnetic field on the fat independent and iron corrected water relaxation time $wT1_{Fe-corr}$. The detailed description below provides a detailed explanation of calculation by equation 16. The method helps because the influence of LIC and LWC on liver $R1$, $R2^*$ and $R2$ is able to be estimated.

Preferably the method of liver imaging is conducted wherein the relaxation rate compensators and $\Delta R2^*$ and $\Delta R2$ are both directly proportional to a difference of the longitudinal relaxation rate of water $wR1$ minus the relaxation rate $wR1_{ref}$, and the longitudinal relaxation rate $wR1$ is a reciprocal of a longitudinal relaxation time water $T1$ generated by a Bloch simulation of the raw MOLLI $T1$ mapping sequence signal data S_{raw} , and the relaxation rate $wR1_{ref}$ is a reciprocal of a healthy liver reference water relaxation time $T1$. The detailed description below provides a detailed explanation of calculation by equations 9 and 11.

Preferably the method of liver imaging is conducted to determine the relaxation rate R_{2WC} as a function of the main magnetic field level of the MRI scan and the liver iron concentration LIC_{wc} that is water corrected to be unconfounded by the water concentration LWC. The detailed description below provides a detailed explanation in

stage 3(b)(C) LIC to T_2 Estimation.

Preferably the method of liver imaging is conducted wherein the reciprocal of the relaxation time $R2^*_{wc}$ that is corrected for the LWC is a relaxation time $T2^*_{wc}$, that determines the liver iron concentration LIC_{wc} using a Hernando model which provides
 5 linear regression models relating the transverse relaxation rate $R2^*$ to the LIC by using values of the relaxation time $T2^*_{wc}$. The detailed description below provides a detailed explanation in stage 3(b)(B) LIC estimation.

Each of the water corrected values of the LIC may be converted to corresponding relaxation time $T2$ which is then adjusted for the influence of the LWC on the relaxation
 10 time $T2$, as shown below in equation 11, to provide an estimate of a relaxation time $T2_{wcLIC}$ for a corresponding value of the relaxation time $T1$; thereby preparing for a best-fit liver water $T1$ relaxation time to be estimated via a Bloch simulation of the raw MOLLI $T1$ mapping sequence signal data. The detailed description below provides a detailed explanation in stage 3(b)(C) LIC to $T2$ estimation and in stage 3(b)(D) liver-water-
 15 adjusted $T2$ estimation. Preferably the method of liver imaging is conducted wherein each of the values of relaxation time $T2^*_{wc}$ that is water corrected is associated with a relaxation time water $T1_{noFat}$ generated by a Bloch simulation of the raw MOLLI $T1$ mapping sequence signal data. The detailed description below provides a detailed explanation in stage 4 signal mapping.

20 Preferably the method of liver imaging is conducted to determine the relaxation time $T2^*_{wc}$ as a reciprocal of a difference of the relaxation rate $R2^*_{fat_corr}$ minus a relaxation rate correction $\Delta R2^*$. The detailed description below provides a detailed explanation of calculation by equation 10. Use of the method helps to avoid erroneously attributing changes in $R2^*$ arising from either an elevated fat or water concentration to a change
 25 in liver iron concentration.

Preferably the method of liver imaging is conducted to determine the change in relaxation rate $\Delta R2^*_{fat}$ as directly proportional to both the first ratio $\beta_{R2^*/PDF}$ and the ΔPDF . The detailed description below provides a detailed explanation of calculation by equation 1.

30 Preferably the method of liver imaging is conducted to determine the transverse relaxation rate $R2^*$ as the reciprocal of a transverse relaxation time $T2^*$ within a region of interest ROI in the liver, wherein the MRI scan is performed to collect data to

formulate a relaxation time $T2^*$ map made visible in a display on which the ROI is placed, wherein the relaxation time $T2^*$ is influenced by fat in the liver, the LWC, and the LIC. The detailed description below provides a detailed explanation in stage 1 inputs.

- 5 Preferably the method of liver imaging is conducted wherein the first relation, the longitudinal relaxation rate $R1$ linear dependency on the LWC is scaled by a first 'a1' constant coefficient that is equal to a change in the longitudinal relaxation rate $R1$ per change in the LWC for a constant LIC; and the second relation, the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ linear dependency on the LWC is scaled by a
 - 10 second 'a2' constant coefficient that is equal to a change in the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ per change in the LWC for a constant LIC; whereby a combined variability in the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ per change in the longitudinal relaxation rate $R1$ due to variability in the LWC is determined as a ratio of the second 'a2' constant coefficient to the first 'a1' constant coefficient, and the
 - 15 ratio is determined from a linear correlation between a longitudinal water relaxation rate and a transverse water relaxation rate determined from MRI scans of subjects in whom the LIC is normal with known or suspected non-alcoholic fatty liver disease. The detailed description below provides a detailed explanation of calculation by equations 3, 4, 5c, and 7.
- 20 Preferably the method of liver imaging is conducted wherein the longitudinal relaxation rate $R1$ linear dependency on the LIC is scaled by a first 'b1' constant coefficient that is equal to a change in the longitudinal relaxation rate $R1$ per change in the LIC when the LWC is constant; and the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ linear dependency on the LIC is scaled by a second 'b2' constant coefficient that is equal to
 - 25 a change in the transverse relaxation rate $R2^*_{fat_corr}$ per change in the LIC when the LWC is constant; whereby a combined variability in the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ per change in the longitudinal relaxation rate $R1$ due to variability in the LIC is determined as a ratio of the second 'b2' constant coefficient to the first 'b1' constant coefficient, and the first 'b1' constant coefficient is determined
 - 30 from MRI scan of subjects in whom iron concentration is elevated above normal and second 'b2' constant coefficient is determined from a Hernando model that relates the relaxation rate $R2^*_{fat_corr}$ to LIC. The detailed description below provides a detailed explanation of calculation by equations 3, 4, 6a, 6b, 6c, and 8.

Preferably the method of liver imaging is conducted by adjusting a combined variability in the fat corrected transverse relaxation rate $R2^*_{\text{fat_corr}}$ per change in the longitudinal relaxation rate $R1$ to correlate with a relationship between the main magnetic field value and the water relaxation rates $R2^*_{\text{fat_corr}}$, $R1$ acquired from MRI scans at a plurality of magnetic field levels. The detailed description below provides a detailed explanation of calculation by equations 7 and 8 and illustration in Figure 2.

Preferably the method of liver imaging includes determining from an MRI scan of at least one healthy subject, a water longitudinal relaxation rate ($R1$) reference value $wR1_{\text{ref}}$ at the particular main magnetic field value.

According to another aspect of the invention there is a system of liver imaging to execute the method of liver imaging, the system comprising a computer, an input receiving device by which the computer receives the inputs derived from the MRI scans of the first liver, a data receiving device by which the computer receives the known correlations of MRI parameters derived from other MRI scans, a display by which the computer shows the maps of transverse relaxation rate $R2^*$, PDFF, or transverse water relaxation rate $R2_{\text{WCIC}}$ that accounts for influence of the LWC and the LIC, and a computer program directly loadable into a memory of the computer for controlling the method when the program is run on the computer.

According to another aspect of the invention there is an MRI scanner configured to acquire MRI scans of a liver wherein the MRI scanner is in electronic communication with a system of liver imaging to execute the method of liver imaging, the system comprising a computer, an input receiving device by which the computer receives from the MRI scanner the inputs derived from the MRI scans of the first liver, a data receiving device by which the computer receives the known correlations of MRI parameters derived from other MRI scans, a display by which the computer shows the maps of transverse relaxation rate $R2^*$, PDFF, or transverse water relaxation rate $R2_{\text{WCIC}}$ that accounts for influence of the LWC and the LIC, and a computer program directly loadable into a memory of the computer for controlling the method when the program is run on the computer.

The invention will now be described, by way of example only, with reference to the accompanying figures in which:

Brief Description of the Figures

Figure 1 shows an overview of the processing steps employed in the present invention;

Figure 2 shows plots of the modelled change in liver water R_1 and R_2^* , as a result of changes in the liver water concentration (LWC, dashed line), and liver iron concentration (LIC, dashed line), at (A) 1.5T, and (B) 3T; and the reference, healthy-liver water R_1 and R_2^* values for 1.5T and 3T are represented by black data points;

Figure 3 shows a schematic of the processing steps used to estimate an associated water T_2 value, for each value in the range of water T_1 values; and these water T_1 and T_2 values are used to build the dictionary of synthetic MOLLI raw signals; and

Figure 4 shows the values for the vendor-specific water T_1 correction terms ($\Delta wT_{1\text{vendor}}$).

Detailed Description of the Invention

In an embodiment, the method and system of MRI Imaging to estimate liver water R_1 and R_2^* variability comprises the following stages:

1. **Inputs**
2. **T_2^* Fat-Correction**
3. **Generation of Simulated MOLLI Signals:**
 - (a) LIC-LWC relaxation rate
 - i) estimating the influence of LWC on R_1 and R_2^*
 - ii) estimating the influence of LIC on R_1 and R_2^*
 - iii) healthy-liver reference water R_1 , LIC, and R_2^* values,
 - (b) estimation of water T_2 and
 - (c) generating a dictionary of simulated MOLLI signals,
4. **Signal Matching**
5. **Water T_1 Iron Correction, and**

6. **Water T₁ Standardisation** : (a) water T₁ field strength correction; b) water T₁ vendor correction.

An explanation for each stage is provided below.

1. Inputs

- 5 Processed T₂^{*} and PDFF maps and raw MOLLI signal data are inputs. Regions of interest (ROIs) are placed on the T₂^{*} and PDFF maps to calculate a representative T₂^{*} and PDFF value for the liver (defined as the median value across all voxels within the ROIs). Using these as inputs, the MOLLI raw images are processed on a voxel-by-voxel basis.

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2. T₂^{*} Fat-Correction

- The measured T₂^{*} value is corrected for the known influence of fat on T₂^{*}. The variation in R₂^{*} due to liver fat content can be expressed as a linear relationship between ΔR₂^{*}_{fat} (change in R₂^{*} due to fat, relative to 0% PDFF) and ΔPDFF (the difference in the measured PDFF relative to 0% PDFF), as follows:

$$\Delta R_{2\text{fat}}^* = \beta_{R2^*/PDFF} \cdot \Delta PDFF \quad (1)$$

where $\beta_{R2^*/PDFF}$ relates the change in R₂^{*} (Hz) to a change in PDFF (%). $\beta_{R2^*/PDFF}$ is estimated, for example, using data disclosed by Wang et al ('Monte Carlo Modelling of Liver MR Signal in the Presence of Fat', Proc. Intl. Soc. Mag. Reson. Med. 26 (2018), whereby $\beta_{R2^*/PDFF}$ is 0.772 Hz/% at 3T and 0.395 Hz/% at 1.5T.

- 20 A fat-corrected T₂^{*} is thus calculated (T₂^{*}_{fat-corr}), which represents the measured liver T₂^{*} without the influence of fat:

$$T_{2\text{fat-corr}}^* = \frac{1}{R_2^* - \Delta R_{2\text{fat}}^*} \quad (2)$$

3. Generation of Simulated MOLLI Signals

Bloch simulations of the acquired MOLLI sequence are performed, for example, using the Bloch simulation methodology described in Mozes et al. (Mozes et al. "Mapping tissue water T_1 in the liver using the MOLLI T_1 method in the presence of fat, iron and B0 inhomogeneity", NMR in Biomedicine 2018; e4030) and Tunncliffe et al. (Tunncliffe et al., "A model for hepatic fibrosis: the competing effects of cell loss and iron on shortened modified Look-Locker inversion recovery T_1 (shMOLLI- T_1) in the liver." Journal of Magnetic Resonance Imaging 45.2 (2017): 450-462).

A dictionary of MOLLI signals is generated, by first simulating the raw MOLLI signal from the water and fat compartments of the liver independently.

For the fat compartment, a multi-peak spectral model is used, for example, the six-peak spectral model described by Hamilton et al. ('In vivo characterization of the liver fat ^1H MR spectrum,' NMR Biomed. 2011 Aug;24(7):784-90). Literature values for the T_1 and T_2 of fat are used: at 3T, fat $T_1 = 312\text{ms}$, and fat $T_2 = 62\text{ms}$ (Hamilton et al.); fat T_1 at 1.5T = 253ms, which is estimated by applying a field-strength conversion to the 3T value, derived using the data in Rakow-Penner et. al., ('Relaxation times of breast tissue at 1.5T and 3T measured using IDEAL', JMRI 23:87-91 (2006)); as the T_2 of fat is equivalent at 1.5T and 3T (Rakow-Penner et al.), fat $T_2 = 62\text{ms}$ at 1.5T, to match the 3T value.

For the water compartment, a vector of water T_1 values ($wT_{1\text{range}}$) is used, ranging from 400ms to 3000ms. A dictionary is generated by simulating the signal from the water compartment for each of the water T_1 values in $wT_{1\text{range}}$.

To perform these Bloch simulations, a value of water T_2 must be assigned to each value in $wT_{1\text{range}}$, which accounts for the combined influence of LIC and LWC on both water T_1 and water T_2 . These steps comprise: LIC-LWC relaxation rate estimation and estimating the influence of LWC on R_1 and R_2^*

(a) LIC-LWC Relaxation Rate Estimation

The LIC-LWC relaxation rate estimation stage describes how water R_1 and R_2^* values in the liver jointly-respond to a change in either the iron or water content in the tissue. The R_2^* values used here correspond to the inverse of the $T_{2\text{fat-corr}}^*$ value, therefore the

additional influence of fat on R_2^* has already been accounted for.

The estimation assumes that the combined effect of LWC and LIC on water R_1 and R_2^* can be expressed follows:

$$R_1 = a_1 \cdot LWC + b_1 \cdot LIC + c_1 \quad (3)$$

$$R_2^* = a_2 \cdot LWC + b_2 \cdot LIC + c_2 \quad (4)$$

- 5 where the influence of LWC on R_1 and R_2^* is represented by a_1 and a_2 , and the influence of LIC on R_1 and R_2^* is represented by b_1 and b_2 , respectively. c_1 and c_2 are constants.

For a constant LIC, changes in R_1 (dR_1) and R_2^* (dR_2^*) as a result of changes in LWC (δLWC) can be expressed as:

$$a_1 = \frac{\partial R_1}{\partial LWC} \quad (5a)$$

10

$$a_2 = \frac{\partial R_2^*}{\partial LWC} \quad (5b)$$

and the combined variability in R_2^* and R_1 , due to a variability in LWC, can be expressed as:

$$\left(\frac{\partial R_2^*}{\partial R_1} \right)_{\partial LWC} = \frac{a_2}{a_1} \quad (5c)$$

- 15 Similarly, for a constant LWC, changes in R_1 and R_2^* as a result of changes in LIC can be expressed as:

$$b_1 = \frac{\partial R_1}{\partial LIC} \quad (6a)$$

$$b_2 = \frac{\partial R_2^*}{\partial LIC} \quad (6b)$$

and the combined variability in R_2^* and R_1 , due to a variability in LIC, can be expressed as:

$$\left(\frac{\partial R_2^*}{\partial R_1} \right)_{\partial LIC} = \frac{b_2}{b_1} \quad (6c)$$

5 i) Estimating the Influence of LWC on R_1 and R_2^*

To estimate the $(\delta R_2^*/\delta R_1)_{dLWC}$ term in equation 5c, we can use, for example, the data presented in Hamilton et al. ('Relation between T_1 and T_2 of liver water and fat and Proton Density Fat Fraction estimated by a flip angle corrected multi-TR, multi-TE single breath-hold 1H MRS STEAM sequence.' *Proc. Intl. Soc. Mag. Reson. Med.* (2019)). Here, the authors show a linear correlation between water R_1 and water R_2 in a cohort of adults with known or suspected non-alcoholic fatty liver disease. Water R_2 contributes to R_2^* (specifically, $R_2^* = R_2 + R_2'$), and if R_2' is constant (for instance, when the influence of iron is small), then $\delta R_2 = \delta R_2^*$.

We assume LWC is the primary influence on the variability in liver R_1 and R_2 values in the data presented in Hamilton et al. (the mean water T_2 of 24.7ms at 3T (standard deviation = 3.6ms) suggests LIC is not elevated in these subjects). As such, using these data, $(\delta R_2^*/\delta R_1)_{dLWC}$ in equation 5c can be estimated as 37.1 at 3T.

By applying a field strength conversion to water R_1 (for example via the data in de Bazelaire et al, 'MR imaging relaxation times of abdominal and pelvic tissues measured in vivo at 3.0 T: preliminary results', *Radiology* 230, 652–659 (2004)) and water R_2 (for example, via the method of Ghugre et al, 'Multi-field behaviour of

Relaxivity in an Iron-rich environment', in *Proc. Intl. Soc. Mag. Reson. Med.* (2008)), the $(\delta R_2^*/dR_1)_{dLWC}$ term in equation 5c can be estimated as 18.2 at 1.5T.

Thus:

$$\left(\frac{\partial R_2^*}{\partial R_1}\right)_{\partial LWC} = \begin{cases} 18.2 (1.5T) \\ 37.1 (3T) \end{cases} \quad (7)$$

ii) Estimating the Influence of LIC on R_1 and R_2^*

- 5 When LIC is the primary influence on water R_1 and R_2^* , such as in subjects with elevated iron, the b_1 term in equation 6a can be estimated as, for example, $0.073 \text{ s}^{-1}/\text{mgFe g}^{-1}$, using the data presented in Wood et al. ('Cardiac Iron Determines Cardiac T_2^* , T_2 , and T_1 in the Gerbil Model of Iron Cardiomyopathy', *Circulation* 112, 535–543 (2005)).
- 10 The b_2 value in equation 6b can be estimated using, for example, the model in Hernando et al. ('Multicenter Reproducibility of Liver Iron Quantification with 1.5-T and 3.0-T MRI', *Radiology* 306, e213256 (2023)), which gives $b_2 = 0.026^{-1} (1.5T)$ and $0.013^{-1} (3T) \text{ s}^{-1}/\text{mg Fe g}^{-1}$.

Using equation 6c, we can combine our estimates of b_1 and b_2 , to obtain $(\delta R_2^*/dR_1)_{dLIC}$.

- 15 This gives:

$$\left(\frac{\partial R_2^*}{\partial R_1}\right)_{\partial LIC} = \begin{cases} 527 (1.5T) \\ 1054 (3T) \end{cases} \quad (8)$$

iii) Healthy-Liver Reference Water R_1 , LIC, and R_2^* Values

- A plot of the modelled change in liver water R_1 and R_2^* , resulting from changes in LWC and LIC, is shown in Figure 2. The changes in R_1 and R_2^* in this plot are relative to baseline, healthy-liver water R_1 and R_2^* reference values (represented by the black data points where the dotted line and dashed lines cross). Determination of healthy-liver reference water R_1 , LIC, and R_2^* values is an illustration of the effects mentioned and not necessarily an essential element of the method of liver imaging.
- 20

By way of illustrative example, for water R_1 , a healthy-liver reference value was derived

using in-house data, comprising 83 imaging studies in healthy subjects, acquired at 1.5T (N=38) and 3T (N=45). The median, un-corrected water T_1 values across these healthy subjects, at 1.5T and 3T, were used as healthy-liver reference values. These were $wT_{1ref} = 650\text{ms}$ ($wR_{1ref} = 1.538 \text{ s}^{-1}$) at 1.5T and $wT_{1ref} = 910\text{ms}$ ($wR_{1ref} = 1.099 \text{ s}^{-1}$) at 3T. The 3T wT_{1ref} value is similar to the mean healthy-liver water T_1 value presented in Thompson et al. (952ms), which was obtained in 124 healthy adult subjects imaged at 3T ('Reference Values for Water-Specific T_1 of the Liver at 3 T: T2*-Compensation and the Confounding Effects of Fat', J. Magn. Reson. Imaging 2024).

To obtain a healthy-liver reference T_2^* value, T_2^* measurements acquired in cohorts of healthy subjects, as presented in Obrzut et al. (and references therein) were used ('Value of liver iron concentration in healthy volunteers assessed by MRI', Scientific Reports volume 10, Article number: 17887 (2020)). This provided healthy-liver T_2^* values of 29.2ms ($R_{2ref}^* = 34.19 \text{ s}^{-1}$) at 1.5T and 17.7ms ($R_{2ref}^* = 56.33 \text{ s}^{-1}$) at 3T.

To obtain a healthy-liver reference LIC value, the R_{2ref}^* values described above were converted to an equivalent LIC value, using the model presented by Hernando et al. (Multicenter Reproducibility of Liver Iron Quantification with 1.5-T and 3.0-T MRI. Radiology 306, e213256 (2023), referred to henceforth as the '*Hernando model*'). This resulted in a reference healthy-liver LIC value (LIC_{ref}) of 0.73 mg/g iron dry weight.

As shown in Figure 2, using wR_{1ref} and R_{2ref}^* as a starting point, when LWC changes (but LIC is constant), the method predicts a small change in R_2^* relative to a given change water R_1 ($(dR_2^*/dR_1)_{dLWC} = 18.2$ at 1.5T, 37.1 at 3T). However, when LIC changes (but LWC is constant), a much larger change in R_2^* relative to a given change in water R_1 is expected ($(dR_2^*/dR_1)_{dLIC} = 527$ at 1.5T, 1054 at 3T).

(b) Estimation of Water T_2

The LIC-LWC relaxation rate estimation method is applied to estimate an associated water T_2 value for each water T_1 value in wT_{1range} . With reference to the schematic shown in Figure 3, water T_2 is estimated via the following steps:

(A) T_2^* water correction

In this step, the influence of LWC on T_2^* is minimised. The $T_{2fat-corr}^*$ value and the range of water T_1 values (wT_{1range}) are the inputs. Differences between each water T_1 value

in wT_{1range} and the healthy-liver reference water T_1 values (wT_{1ref} , see above) are assumed to result from differences in LWC. As such, using the LIC-LWC relaxation rate method (equation 7), an R_2^* correction term (ΔR_2^*) is calculated for each value in wT_{1range} , to account for predicted influence of LWC on R_2^* :

5

$$\Delta R_2^* = \begin{cases} 18.2 \cdot (wR_1 - wR_{1ref}) (1.5T) \\ 37.1 \cdot (wR_1 - wR_{1ref}) (3T) \end{cases} \quad (9)$$

where wR_1 represents a given value from the set of values in wT_{1range} . This provides a set of 'water-corrected' T_2^* values (T_{2wc}^*), which are given by:

$$T_{2wc}^* = \frac{1}{(R_{2fat-corr}^* - \Delta R_2^*)} \quad (10)$$

An upper / lower limit of 60ms / 5ms (1.5T) and 35ms / 2.7ms (3T) is applied to T_{2wc}^* , to maintain water-corrected T_2^* values within a plausible range.

- 10 This provides an estimate of T_2^* in which the expected variability due to changes in LWC are minimised.

(B) LIC Estimation

- Each water T_1 value is now associated with a value of T_{2wc}^* . The next step is to convert each T_{2wc}^* value into an estimate of LIC. This is performed using the Hernando model, which provides linear regression models relating R_2^* to LIC for magnetic field strengths of 1.5T, 2.89T, and 3T. By using water-corrected T_2^* values, a value of LIC is estimated which is not confounded by the competing influence of LWC on R_2^* . These LIC values are referred to as 'water-corrected LIC' (LIC_{wc}).
- 15

(C) LIC to T_2 Estimation

- 20 A liver T_2 value for each value of LIC_{wc} is estimated, for example, using the model described by St. Pierre et al. ('Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance.' *Blood* 105.2 (2005): 855-861). This provides an estimate of liver T_2 at 1.5T only, and as such, for data acquired at 3T, a

- field-strength conversion of the T_2 value (to 3T) is performed using the model presented in Ghugre et al. (Multi-field behaviour of Relaxivity in an Iron-rich environment. in *Proc. Intl. Soc. Mag. Reson. Med.* (2008)). These T_2 values do not include the additional influence of LWC on T_2 , and as such are referred to as 'water-corrected T_2 ' (T_{2wc}).

(D) Liver-Water-Adjusted T_2 Estimation

The estimated T_{2wc} values are associated with each value of LIC_{wc} , and correspond solely to the influence of LIC on T_2 , as the additional influence of LWC has been taken out (as described in steps (A) to (C)).

- 10 The T_{2wc} values are adjusted, based on the expected influence of LWC on T_2 , so that the final T_2 estimation reflects both LWC and LIC. This effectively reverses the 'water correction' applied in step (A), however, we are now adjusting T_2 , rather than T_2^* values. This correction is applied as follows:

$$\Delta R_2 = \begin{cases} 18.2 \cdot (wR_1 - wR_{1ref}) & (1.5T) \\ 37.1 \cdot (wR_1 - wR_{1ref}) & (3T) \end{cases} \quad (11)$$

$$T_2 = \frac{1}{(R_{2,wc} + \Delta R_2)} \quad (12)$$

- 15 The time T_2 in equation 12 may also be referred to as time T_{2wclic} to indicate that the effects of the LWC and the LIC have been accounted for.

An upper / lower limit of 100ms / 5ms is applied to the liver-water-adjusted T_2 values estimated using equation 12 to maintain water-corrected T_2^* values within a plausible range.

- 20 The processing steps described in (A) to (D) allow a liver water T_2 value to be estimated for each value of water T_1 , in which the influences of LWC and LIC on T_2 are independently accounted for.

(c) Generating the Dictionary of Simulated MOLLI Signals

For each pair of water T_1 and water T_2 values in wT_{1range} , a Bloch simulation of the acquired MOLLI sequence is performed, to generate a simulated MOLLI signal for the water compartment. This water signal is then combined with the simulated fat signal as follows:

$$S = (1 - PDFF) \cdot S_{water} + PDFF \cdot S_{fat} \quad (13)$$

- 5 where S_{water} is the simulated signal from the water compartment, S_{fat} is the simulated signal from the fat compartment, and PDFF is the proton density fat fraction, expressed as a fraction between 0 (0% fat) to 1.0 (100% fat).

The dictionary comprises a set of simulated MOLLI signals (one for each pair of water T_1 and T_2 values), representing the raw signal intensity over the series of
10 inversion times used in the MOLLI acquisition.

4. Signal Matching

- The measured MOLLI signal is then compared to the simulated signals in the dictionary, by computing the vector dot-product between the measured signal and each
15 simulated signal. The entry in the dictionary which provides the maximum dot-product is selected as the best fit to the measured data, and this entry is used to obtain the best-fit water T_1 value for the measured MOLLI signal. This provides a measure of liver T_1 which relates to the water compartment and is therefore independent of fat.

5. Water T_1 Iron Correction

- 20 The best-fit water T_1 value is then corrected for the known influence of iron on liver T_1 . The variation in R_1 due to LIC ($\Delta R_{1,LIC}$) can be expressed as a linear relationship between $\Delta R_{1,LIC}$ and ΔLIC , in which ΔLIC is the difference between the measured LIC ($LIC_{measured}$) and the healthy-liver reference LIC value ($LIC_{ref} = 0.73$ mg/g iron dry weight), as follows:

$$\Delta R_{1,LIC} = \beta_{R1/LIC} \cdot \Delta LIC \quad (14)$$

where $\Delta LIC = LIC_{\text{measured}} - LIC_{\text{ref}}$, and $b_{R1/LIC}$ relates a change in R_1 (Hz) to a change in LIC (mg/g dry weight).

For this iron-correction step, a whole-liver LIC_{measured} value is used, by converting the fat-corrected T_2^* value to an equivalent LIC value, using the Hernando model. Iron
 5 correction is only applied if $LIC_{\text{measured}} > LIC_{\text{ref}}$ (i.e. the measured liver iron is above the healthy-liver reference value). As such, we do not apply water-correction to the T_2^* value used here, as LIC_{measured} is above the threshold for which we consider iron to be the dominant influence on T_2^* .

$b_{R1/LIC}$ in equation 14 is equal to the b_1 term used in the LIC-LWC relaxation rate model
 10 (equation 6a), which is estimated, for example, using data disclosed by Wood et al. ('Cardiac Iron Determines Cardiac T_2^* , T_2 , and T_1 in the Gerbil Model of Iron Cardiomyopathy.' *Circulation* 112, 535–543 (2005)), which gives $b_{R1/LIC} = 0.073 \text{ Hz/(mg Fe/g)}$.

Iron-corrected water T_1 ($wT_{1FE\text{-corr}}$) is then calculated as follows:

15

$$wT_{1FE\text{-corr}} = \frac{wT_1}{(1 - wT_1 \cdot \beta_{R1/LIC} \cdot \Delta LIC)} \quad (15)$$

where wT_1 is the best-fit (uncorrected) water T_1 value.

6. Water T_1 Standardisation

(a) Water T_1 Field Strength Correction

Iron-corrected water T_1 values are then corrected for the known effect of magnetic field
 20 strength on T_1 relaxation times. By way of illustrative example, a field-strength correction model is used, derived using data acquired in volunteers, who were scanned consecutively at both 1.5T and 3T. Studies were performed across different scanner manufacturers (Siemens, Philips, and GE).

Values of $wT_{1FE\text{-corr}}$, obtained using the steps described above were compared at 1.5T

and 3T for these subjects. Using these data, a linear model was derived which allows T_1 values measured at 1.5T to be 'field strength corrected' to an equivalent 3T value:

$$wT_{1FS-corr} = 0.0072 + (1.44 \cdot wT_{1,1.5T}) \quad (16)$$

where $wT_{1FS-corr}$ is the field-strength corrected water T_1 value, and $wT_{1,1.5T}$ is the water T_1 value measured at 1.5T (both expressed in seconds).

5 (b) Water T_1 Vendor Correction

Variability in water T_1 due to minor differences in the MOLLI sequence used across different scanner manufacturers (e.g. Siemens, Philips, and GE) are then corrected. In an illustrative example, to determine this correction, the same cohort used for the field-strength correction were used. Subjects were included if they had been scanned on a given test scanner (Siemens 1.5T, Philips 1.5T/3T and GE 1.5T/3T) as well as the reference scanner (Siemens 3T). Iron- and field-strength corrected water T_1 values were obtained for each subject, on both the test and reference scanner, and the difference between these was recorded. The median difference in corrected water T_1 (comparing each test scanner against the reference scanner) was used to determine the scanner-specific bias terms.

These bias terms are applied to the $wT_{1FS-corr}$ values, to provide a corrected water T_1 value (cwT_1) which is standardised to the reference scanner (Siemens 3T), as follows:

$$cwT_1 = wT_{1FS-corr} + \Delta wT_{1vendor} \quad (17)$$

The vendor-specific correction terms ($\Delta wT_{1vendor}$) are given in Figure 4.

This provides the final, corrected water T_1 value.

20 The invention has been described by way of examples only. Therefore, the foregoing is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly, all suitable modifications and equivalents may be resorted

to, falling within the scope of the claims.

Claims:

1. A method of liver imaging using MRI including

receiving inputs derived from MRI scans of a first liver including a map of a transverse relaxation rate R_2^* , a map of PDFF, and raw MOLLI T1 mapping sequence signal data S_{raw} ,

for a main magnetic field value B_0 of the MRI scans, presuming a first relation wherein a longitudinal relaxation rate R_1 is linearly dependent on a liver water concentration LWC and separately linearly dependent on a liver iron concentration LIC of the first liver,

for the main magnetic field value, presuming a second relation wherein a fat corrected transverse relaxation rate $R_{2^*fat_corr}$ that accounts for influence fat in the first liver is linearly dependent on the liver water concentration LWC and separately linearly dependent on the liver iron concentration LIC of the first liver,

using the inputs, the first and second linear relations, and known correlations of MRI parameters derived from other MRI scans of other livers or internal body organs determined prior to the MRI scans of the first liver to determine quantitative values of:

a first ratio $\beta_{R_2^*/PDFF}$ of change in the transverse relaxation rate R_2^* per change in the PDFF; a difference $\Delta PDFF$ that is a difference in a measured PDFF minus zero PDFF; a change in relaxation rate ΔR_{2^*fat} that is a difference R_2^* due to fat relative to zero PDFF; a longitudinal water relaxation rate wR_1 ; a relaxation rate wR_{1ref} that is a reference water relaxation rate R_1 of a healthy liver; a relaxation rate correction ΔR_{2^*} is a compensator for the LWC; a relaxation rate $R_{2^*fat_corr}$ is a transverse relaxation rate that is compensated for influence of fat of the liver on the transverse relaxation rate R_2^* ; a relaxation time R_{2^*wc} that is corrected for the LWC; a liver iron concentration LIC_{wc} that is water corrected to be unconfounded by the LWC; a relaxation rate R_{2wc} is a transverse relaxation rate that is associated with a value of the LIC_{wc} unconfounded by the LWC; a relaxation rate correction ΔR_2 is a compensator for the LWC; and

summing the relaxation rate R_{2wc} plus the relaxation rate correction ΔR_2 to determine

- a transverse water relaxation rate R_{2WCIC} that accounts for influence of the LWC and the LIC.
2. A method of liver imaging according to claim 1 finding a fit between the raw MOLLI T1 mapping sequence signal data S_{raw} and simulated MOLLI signals S_{sim} as a function of the longitudinal water relaxation rate $wR1$ and a transverse water relaxation rate R_{2WCIC} that accounts for influence of the LWC and the LIC to determine a longitudinal relaxation rate $wR1_{noFat}$ that is independent of fat.
 3. A method of liver imaging according to claim 2 using: a ratio $\beta_{R1/LIC}$ from the first relation as presumed that relates a change in the longitudinal relaxation rate $R1$ to a change in the LIC; a difference ΔLIC of the LIC minus a healthy liver iron concentration reference LIC_{ref} , and determining a product of the longitudinal relaxation rate $wR1_{noFat}$ that is independent of fat times an amount that is a difference of one minus a relaxation time $wT1_{noFat}$ corresponding to the longitudinal relaxation rate $wR1_{noFat}$ that is independent of fat times the ratio $\beta_{R1/LIC}$ times the difference ΔLIC to determine a fat independent and iron corrected water relaxation rate $wR1_{Fe-corr}$.
 4. A method of liver imaging according to claim 3 wherein a constant offset plus a product of the fat independent and iron corrected water relaxation time $wT1_{Fe-corr}$ is multiplied times a constant coefficient, and the constant offset and coefficient are determined from the from the MRI scans of the first liver at the main magnetic field value B_0 and second MRI scans at a second main magnetic field value B_{0_2} to quantify an effect of level main magnetic field on the fat independent and iron corrected water relaxation time $wT1_{Fe-corr}$.
 5. A method of liver imaging according to any preceding claim wherein the relaxation rate compensators and $\Delta R2^*$ and $\Delta R2$ are both directly proportional to a difference of the longitudinal relaxation rate of water $wR1$ minus the relaxation rate $wR1_{ref}$, and the longitudinal relaxation rate $wR1$ is a reciprocal of a longitudinal relaxation time water $T1$ generated by a Bloch simulation of the raw MOLLI T1 mapping sequence signal data S_{raw} , and the relaxation rate $wR1_{ref}$ is a reciprocal of a healthy liver reference water relaxation time $T1$.
 6. A method of liver imaging according to any preceding claim that determines the relaxation rate R_{2WC} as a function of the main magnetic field level of the MRI scan and the liver iron concentration LIC_{wc} that is water corrected to be unconfounded by

- the water concentration LWC.
7. A method of liver imaging according to any preceding claim wherein the reciprocal of the relaxation time $R2^*_{wc}$ that is corrected for the LWC is a relaxation time $T2^*_{wc}$, that determines the liver iron concentration LIC_{wc} using a Hernando model which
 5 provides linear regression models relating the transverse relaxation rate $R2^*$ to the LIC by using values of the relaxation time $T2^*_{wc}$.
 8. A method of liver imaging according to claim 7 wherein each of the water corrected values of the LIC_{wc} are converted to corresponding relaxation time T2 which is then adjusted for the influence of the LWC on the relaxation time T2 to provide an estimate
 10 of a relaxation time $T2_{WCIC}$ for a corresponding value of the relaxation time T1; thereby preparing for a best-fit liver water T1 relaxation time to be estimated via a Bloch simulation of the raw MOLLI T1 mapping sequence signal data.
 9. A method of liver imaging according to claim 7 wherein each of the values of relaxation time $T2^*_{wc}$ that is water corrected is associated with a relaxation time water $T1_{noFat}$
 15 generated by a Bloch simulation of the raw MOLLI T1 mapping sequence signal data.
 10. A method of live imaging according to claim 7, 8 or 9 that determines the relaxation time $T2^*_{wc}$ as a reciprocal of a difference of the relaxation rate $R2^*_{fat_corr}$ minus a relaxation rate correction $\Delta R2^*$.
 11. A method of liver imaging according to any preceding claim that determines the
 20 change in relaxation rate $\Delta R2^*_{fat}$ as directly proportional to both the first ratio $\beta_{R2^*/PDFF}$ and $\Delta PDFF$.
 12. A method of liver imaging according to any preceding claim that determines the transverse relaxation rate $R2^*$ as the reciprocal of a transverse relaxation time $T2^*$ within a region of interest ROI in the liver, wherein the MRI scan is performed to
 25 collect data to formulate a relaxation time $T2^*$ map made visible in a display on which the ROI is placed, wherein the relaxation time $T2^*$ is influenced by fat in the liver, the LWC, and the LIC.
 13. A method of liver imaging according to any preceding claim wherein
 30 the first relation, the longitudinal relaxation rate R1 linear dependency on the LWC is scaled by a first 'a1' constant coefficient that is equal to a change in the longitudinal

relaxation rate $R1$ per change in the LWC for a constant LIC; and

the second relation, the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ linear dependency on the LWC is scaled by a second 'a2' constant coefficient that is equal to a change in the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ per change in the LWC for a constant LIC;

whereby a combined variability in the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ per change in the longitudinal relaxation rate $R1$ due to variability in the LWC is determined as a ratio of the second 'a2' constant coefficient to the first 'a1' constant coefficient, and the ratio is determined from a linear correlation between a longitudinal water relaxation rate and a transverse water relaxation rate determined from MRI scans of subjects in whom the LIC is normal with known or suspected non-alcoholic fatty liver disease.

14. A method of liver imaging according to any preceding claim wherein

the longitudinal relaxation rate $R1$ linear dependency on the LIC is scaled by a first 'b1' constant coefficient that is equal to a change in the longitudinal relaxation rate $R1$ per change in the LIC as the LWC is constant; and

the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ linear dependency on the LIC is scaled by a second 'b2' constant coefficient that is equal to a change in the transverse relaxation rate $R2^*_{fat_corr}$ per change in the LIC as the LWC is constant;

whereby a combined variability in the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ per change in the longitudinal relaxation rate $R1$ due to variability in the LIC is determined as a ratio of the second 'b2' constant coefficient to the first 'b1' constant coefficient, and the first 'b1' constant coefficient is determined from MRI scans of subjects in whom iron concentration is elevated above normal and second 'b2' constant coefficient is determined from a Hernando model that relates the relaxation rate $R2^*_{fat_corr}$ to LIC.

15. A method of liver imaging according to any preceding claim adjusting a combined variability in the fat corrected transverse relaxation rate $R2^*_{fat_corr}$ per change in the longitudinal relaxation rate $R1$ to correlate with a relationship between the main magnetic field value and the water relaxation rates $R2^*_{fat_corr}$, $R1$ acquired from MRI

scans at a plurality of magnetic field levels.

16. A method of liver imaging according to any preceding claim determining from an MRI scan of at least one healthy subject, a water longitudinal relaxation rate ($R1$) reference value $wR1_{ref}$ at the main magnetic field value.
- 5 17. A system of liver imaging to execute the method according to any of claims 1 to 15 comprising a computer, an input receiving device by which the computer receives the inputs derived from the MRI scans of the first liver, a data receiving device by which the computer receives the known correlations of MRI parameters derived from other MRI scans, a display by which the computer shows the maps of transverse relaxation rate $R2^*$, PDFF, or transverse water relaxation rate $R2_{WCIC}$ that accounts for influence of the LWC and the LIC, and a computer program directly loadable into
10 a memory of the computer for controlling the method when the program is run on the computer.
18. An MRI scanner configured to acquire MRI scans of a liver wherein the MRI scanner
15 is in electronic communication with a system of liver imaging to execute the method according to any of claims 1 to 15, the system comprising a computer, an input receiving device by which the computer receives from the MRI scanner the inputs derived from the MRI scans of the first liver, a data receiving device by which the computer receives the known correlations of MRI parameters derived from other MRI
20 scans, a display by which the computer shows the maps of transverse relaxation rate $R2^*$, PDFF, or transverse water relaxation rate $R2_{WCIC}$ that accounts for influence of the LWC and the LIC, and a computer program directly loadable into a memory of the computer for controlling the method when the program is run on the computer.

25