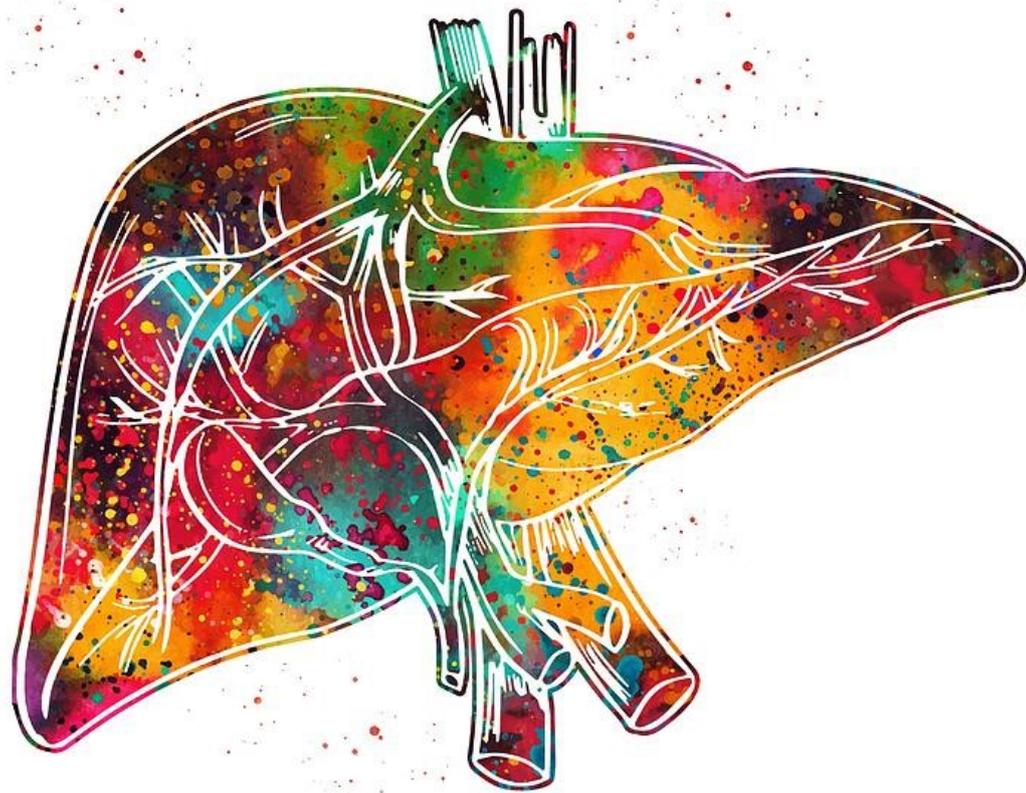# Intravoxel Incoherent Motion and Dynamic Contrast Enhanced Quantitative Magnetic Resonance Imaging in the Preoperative Evaluation of Liver Function

Technical Medicine master thesis project
Amsterdam University Medical Center, Delft University of Technology, Leiden University, Erasmus University Rotterdam

Fenna van der Zijden

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Intravoxel Incoherent Motion and Dynamic Contrast Enhanced Quantitative Magnetic Resonance Imaging in the Preoperative Evaluation of Liver Function

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Fenna van der Zijden

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Supervisor(s):
Dr. F.M. Vos, technical supervisor
O.J. Gurney Champion, technical supervisor
Dr. J.I. Erdmann, medical supervisor
P.J. Arntz, daily medical supervisor
B. Ariens, daily technical supervisor

Thesis committee members:

Dr. F.M. Vos, TU Delft (chair)
Dr. J.I. Erdmann, Amsterdam UMC
Dr. M.G.J. Thomeer, Erasmus MC

Universiteit Leiden   TUDelft Delft University of Technology   ERASMUS UNIVERSITEIT ROTTERDAM

Summary

Background: Surgical removal of liver tumors necessitates a thorough preoperative assessment to ensure adequate future liver remnant function, which is crucial for hepatic regeneration. Imaging techniques like hepatobiliary scintigraphy (HBS) and dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) assess liver function by measuring the uptake of liver-specific contrast agents. Intravoxel incoherent motion (IVIM)-MRI measures both molecular diffusion and perfusion-related motion of water molecules in the liver. This provides valuable insights into tissue microenvironment changes that can indicate liver dysfunction. However, the potential of IVIM-MRI in this context remains unexplored. This study aims to evaluate the feasibility of IVIM-MRI for liver function assessment and its relationship with DCE-MRI. *Methods:* Twenty-one patients scheduled for major hepatectomy underwent preoperative assessment involving HBS, a 20-minute DCE-MRI series, and IVIM-MRI with 15 b-values. DCE-MRI parameters (hepatocyte uptake K_i(min^{-1}), arterial plasma flow F_a (mL/min/100 mL), and venous plasma flow F_v (mL/min/100 mL)), were analyzed using the Sourbron model. IVIM-MRI parameters (diffusion D (mm^2/s), pseudo-diffusion D_p (mm^2/s), and perfusion fraction f (%)) were extracted using a UNET model developed at Amsterdam University Medical Centers. Correlation between parameters was assessed using Pearson correlation analysis. Furthermore, Blant-Altman was employed to assess the inter-observer variability and the reproducibility of the DCE-MRI parameters. *Results:* In 19 patients, weak correlations were observed between DCE- and IVIM-MRI parameters, with correlation coefficients ranging from $r = -0.326$ to $r = 0.443$. Despite the lack of significant correlations between these parameters, strong correlations were observed between DCE-MRI K_i and HBS ($r = 0.80$, $p < 0.001$). Moreover, DCE-MRI parameters demonstrated high reproducibility, with Bland-Altman mean biases ranging from -1.79 to -0.08. *Conclusion:* The weak correlation observed between DCE- and IVIM-MRI parameters suggests that IVIM-MRI may have limited utility in preoperative liver function assessment. Nevertheless, DCE-MRI may serve as an alternative to HBS, potentially providing a one-stop shop for preoperative liver assessment with MRI. Further research is necessary to explore its potential in diverse populations with varying liver function.

Keywords: *quantitative magnetic resonance imaging, liver function, hepatectomy*

List of Abbreviations:
CLD - Chronic Liver Disease
HCC - Hepatocellular Carcinoma
PHLF - Post Hepatectomy Liver Failure
FLR - Future Liver Remnant
HBS - Hepatobiliary Scintigraphy
^{99m}Tc - Technetium-99m
MRI - Magnetic Resonance Imaging
CT - Computed Tomography
DWI - Diffusion Weighted Imaging
IVIM - Intravoxel Incoherent Motion
Gd-EOB-DTPA/Primovist - Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid
DCE - Dynamic Contrast Enhanced
K_i - Hepatic uptake rate
F_a - Arterial plasma flow
F_v - Venous plasma flow
T_f - Total plasma flow
f_a - Arterial flow fraction
D - True diffusion coefficient
D_p - Pseudo-diffusion coefficient
f - Perfusion fraction
TIC - Time Intensity Curve
AIF - Arterial Input Function
VIF - Venous Input Function
ROI - Region of Interest
MUR - ^{99m}Tc-mebrofenin Uptake Rate
TLF - Total Liver Function

Introduction

2.1 The liver

The liver is a vital organ responsible for many essential functions, including the regulation of metabolic processes, immunity, digestion, detoxification, and the storage of vitamins and other nutrients[1]. In addition, the liver has the capability to regenerate, as hepatocytes can proliferate, enabling the liver to restore and regain function after injury[2]. Anatomically, the liver is located in the upper right quadrant and is subdivided into eight independent segments by the Couinaud classification (Fig. 1a and 1b). The branches of the portal vein subdivide the liver horizontally into two parts, while the branches of the hepatic veins divide the liver vertically into four sections. Each segment is supplied by an individual Glissonian pedicle, which consists of a branch of the hepatic artery, the portal vein, and the bile duct[3].
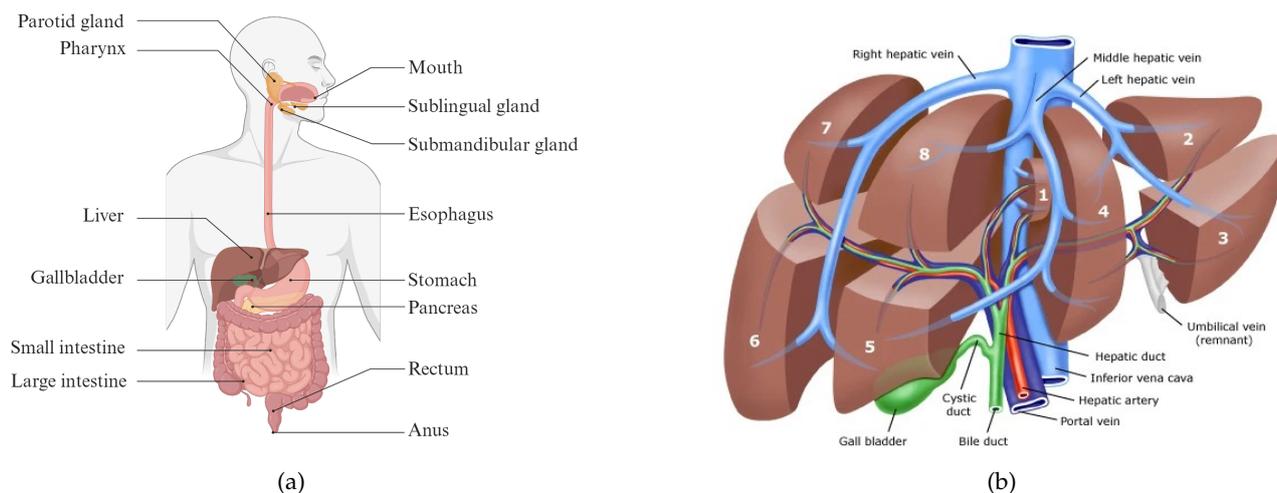

Figure 1: (a) Digestive system with the liver located in the upper right abdomen (b) Couinaud segments.

2.2 Liver diseases

The incidence of chronic liver disease (CLD) has increased dramatically over the past few decades, presenting a significant global health concern. This increase is attributed to several factors, such as the higher prevalence of viral infections like hepatitis B and C, rising rates of obesity and metabolic syndrome, widespread alcohol consumption, and an aging population[4]. Typically, CLD progresses through stages beginning with steatosis, inflammation and fibrosis, which can ultimately result in cirrhosis. Steatosis is defined as the pathological accumulation of fat within hepatocytes, which can lead to cellular dysfunction and inflammation. This can lead to hepatomegaly and impair metabolic functions. If left untreated, it may progress to fibrosis. This progression is driven by the activation of hepatic stellate cells into proliferative myofibroblasts, leading to excessive deposition of extracellular matrix. The resulting accumulation of extracellular matrix disrupts liver architecture, obstructs blood flow, and contributes to the progression of CLD into the irreversible stages of cirrhosis and hepatocellular carcinoma (HCC)[5, 6, 7]. HCC is the most prevalent primary liver malignancy. Besides primary liver malignancies, the liver is a common site for secondary malignancies[8]. Moreover, the biliary tract, which connects the liver to the intestines can be affected by cancers such as cholangiocarcinoma[9].

2.3 Liver treatment options

Treatment of liver disease and malignancies is dependent on the underlying etiology and stage. Early-stage CLD is often managed with lifestyle modifications and medication to prevent the progression of fibrosis. In contrast, liver malignancies, including primary, secondary and biliary tract tumors often may require interventions such as chemotherapy, radiotherapy, or surgical procedures. Local treatments, including ablation and resection, are the only curative options and provide the highest probability of long-term survival for patients with primary and secondary liver tumors. Surgery is recommended when radical excision with tumor-free margins is possible. Nevertheless, surgical removal carries significant risks, including post hepatectomy liver failure (PHLF), with mortality rates up to 18%[9]. For this reason, a comprehensive preoperative assessment is essential

for determining patient suitability and ensuring adequate future liver remnant (FLR) volume and function.

2.4 Preoperative liver assessment

In patients with assumed healthy livers, a standardized volume of 20-30% is generally considered sufficient. However, smaller liver remnant volumes are associated with an increased risk of hepatic dysfunction and postoperative complications. Moreover, in patients with steatosis, fibrosis or injury from drugs or chemotherapy, the hepatic function and regenerative capacity of the liver may be diminished due to the architectural disruption of the liver tissue (Fig. 2)[10, 11]. Therefore, for these patients functional assessment is required. Methods of assessing liver function include the indocyanine green clearance test and the ^{13}C-methacetin breath test[11]. However, these have limitations in assessing regional liver function and may not always correlate with the true functional capacity of the remnant liver. To address these limitations, advanced imaging techniques, including Technetium-99m (^{99m}Tc)-mebrofenin hepatobiliary scintigraphy (HBS) and Magnetic Resonance Imaging (MRI) have emerged as promising alternatives[11].
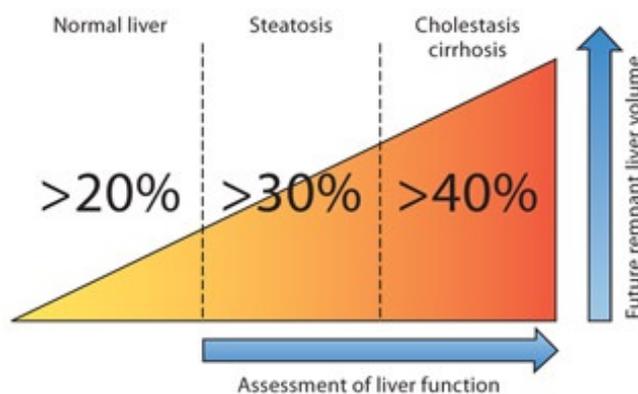

Figure 2: The diagram illustrates the minimum future liver remnant volumes required for safe liver resection based on underlying liver disease. Accurate liver function assessment is essential to determine the appropriate future liver remnant volume for ensuring postoperative safety.

2.5 Hepatobiliary scintigraphy

HBS has been developed for the assessment of total and regional liver function, employing radiotracers to measure hepatic uptake and excretion. The radiotracer ^{99m}Tc-mebrofenin is taken up from the blood through organic anion transporting polypeptides into hepatocytes and subsequently excreted through the bile ducts and gallbladder. As the radiopharmaceutical travels through the body, it emits gamma rays, which are captured by a gamma camera. When hepatocyte function is impaired in specific regions, these areas appear darker due to reduced excretion. HBS is used as standard of care in many centers to assess the risk of PHLF-related complications in patients undergoing major liver surgery. This risk increases when FLR function is below the cut-off value of 2.7%/min[12]. HBS has been shown to be effective in predicting PHLF. However, it focuses on hepatocyte uptake capacity, without assessing other indicators of liver disease that may impact liver function. Moreover, due to its limited spatial resolution, there is a necessity to provide an anatomical reference with a low-dose computed tomography (CT) imaging[13]. Alternatively, MRI has been suggested as a potential one-stop shop examination for preoperative planning of hepatectomy due to integration of anatomical imaging and its potential to measure function as well (Appendix D).

2.6 Magnetic resonance imaging

MRI employs a magnetic field to align the hydrogen nuclei present in body tissues. Radiofrequency pulses are applied to excite nuclei, thereby causing them to transition to a higher energy state. Following the application of the radiofrequency pulse, the nuclei emit radiofrequent signals as they return to their equilibrium states. A T1 image represents the degree to which the magnetization has returned to equilibrium following a period of time, whereas a T2 image represents the amount of magnetization that remains in the excited state after a period of time. Differences in relaxation times between tissues create contrast in images. Diffusion weighted imaging

(DWI) assesses the Brownian motion of water molecules. Variations in the organization and structure of liver parenchyma affect the diffusion coefficient of water, providing image contrast. T1, T2 and DWI sequences provide anatomical information of soft tissue, tumor, vascular structure, and anatomy[14].

However, these MRI sequences provide complementary signals in arbitrary units as pixel intensities. To extract functional information from these signals, several quantitative MRI techniques have been developed. For example, by measuring the DWI signal at various diffusion weightings, the apparent diffusion coefficient can be computed, offering valuable insights into tissue characteristics. Additionally, bi-exponential analysis using intravoxel incoherent motion (IVIM)-MRI helps to distinguish between perfusion-related and diffusion-related components[15].

T1-relaxometry, combined with liver-specific contrast agents such as Gadolinium-ethoxybenzyl- diethylenetri-amine pentaacetic acid (Gd-EOB-DTPA; Primovist®), is employed to assess hepatocyte capacity for contrast agent uptake. By measuring differences in signal intensity or relaxation rate during the arterial and hepatobiliary phases, liver function can be evaluated[16]. Moreover, dynamic contrast enhanced (DCE)-MRI assesses hepatobiliary function by monitoring the dynamics of a hepatocyte-specific contrast agent over time. Pharmacokinetic models are then employed to compute parameters such as permeability, flow, and hepatocyte excretion[17].

2.7   Rationale

DCE-MRI has demonstrated correlations with traditional liver function tests, including the indocyanine green clearance test and HB S[18, 19, 20]. Nevertheless, DCE-MRI is limited by its reliance on contrast agents and complexity in acquisition and post-processing. Complementary, IVIM-MRI offers information on microcirculation and molecular diffusion without the need for contrast agents[21]. As liver fibrosis affects perfusion and cell density, IVIM-MRI has the potential to offer valuable insights into hepatic function. Phonlakrai et al. demonstrated moderate correlations between IVIM-MRI parameters and hepatic uptake fraction in patients undergoing radiation therapy[22]. Additionally, Hectors et al. reported correlations between DCE- and IVIM-MRI parameters in the liver parenchyma of patients with HCC[23]. However, to date, no studies have investigated the degree to which IVIM-MRI correlates with DCE-MRI and HBS in patients scheduled for major hepatectomy.

Therefore, the aim of this study was to explore the feasibility of IVIM-MRI in assessing liver function and its relationship to DCE-MRI in the evaluation of liver function before hepatectomy. By considering alternative aspects of liver perfusion and diffusion with IVIM-MRI, liver function may be assessed more comprehensively. We hypothesize that DCE- and IVIM-MRI parameters will correlate, as both techniques measure aspects of liver diffusion and perfusion. A correlation between the DCE-MRI hepatic uptake rate (K_I) and the diffusion coefficient (D) was expected because both parameters are influenced by the tissue microenvironment, which affects molecular mobility. Furthermore, a correlation was expected between the arterial and venous plasma flows (F_A and F_V) from DCE-MRI and the pseudo-diffusion coefficient (D_p) from IVIM-MRI, as both parameters are influenced by microvascular blood flow. As a secondary objective, repeated analysis was conducted to assess the inter observer variability of the DCE-MRI measurements and their correlation with HBS.

Methods

3.1   Patients

This internal validation study used the dataset derived from a study comparing HBS and DCE-MRI, encompassing patients from the Amsterdam University Medical Centers during the period from December 2014 to July 2018[18]. Inclusion criteria were adult patients (age above 18 years) diagnosed with one or more liver lesions scheduled for major hepatectomy. Exclusion criteria included patients with contraindications to MRI, chronic renal impairment or history of congenital prolonged QT-syndrome, arrhythmia after the use of cardiac repolarization time prolonging drugs, bronchial asthma and allergies to gadolinium. The principle investigator from the previously conducted study by Rassam et al. approved reuse of the dataset and extended on the informed consent given. The study was registered at Amsterdam University Medical Centers under ID NL45755.018.13.

3.2 Image acquisition

Patients scheduled for major hepatectomy received ^{99m}Tc-mebrofenin and underwent DCE- and IVIM-MRI, within two weeks of the surgery.

3.2.1 HBS

A dual-head SPECT-CT camera (Siemens Symbia T16) with low-energy high-resolution collimators was used for acquisition. The energy window was 140 KeV. The dynamic acquisition started immediately after the intravenous bolus injection of the radiopharmaceutical ^{99m}Tc-mebrofenin (200 MBq; 5.41 mCi, Bridatec, GE Healthcare). Two dynamic acquisitions were conducted to measure the hepatic uptake and biliary excretion phases. Acquisition settings included 38 frames of 10 seconds per frame in a 128 × 128 matrix size for the uptake phase. In the biliary excretion phase 15 frames of 60 seconds per frame in a 128 × 128 matrix size were used. After the first dynamic acquisition, a SPECT imaging (60 projections of 8 seconds per projection, 128 × 128 matrix) combined with low-dose CT imaging was performed. This combination was used as an anatomical reference and for attenuation correction.

3.2.2 DCE- and IVIM-MRI

DCE images were acquired on a Philips 3.0 Tesla Ingenia MR scanner (Philips Healthcare). T1-weighted gradient echo DCE images were acquired in the axial orientation. Scanning parameters included a 15 degree flip angle, 2.30 ms echo time, 3.75 ms repetition time, 3x3x5 mm^3 voxel size and 128x128x44 matrix size. The DCE-MRI protocol consisted of four acquisition phases (0 s, 22 s, 3 min, 12 min), spread out over 20 minutes. After the first acquisition, a bolus of Primovist contrast agent was injected (0.1 mL/kg). Sampling intervals during the first two acquisitions were 2.2 s, while a sampling interval of 30 s and 60 s was used for the third and fourth acquisition phases, respectively. Increasingly higher values were used as the uptake of contrast slows down over time. This resulted in 108 volumes in total. For IVIM-MRI, a multi-slice diffusion-weighted single shot echo-planar imaging sequence with multiple b-values (0, 1, 2, 4, 6, 9, 12, 17, 24, 37, 54, 98, 147, 220, 294 mm²/s) was used. IVIM images were acquired in the coronal orientation. Parameters for the sequence included a 56 ms echo time, 3.9 ms repetition time, a 3.5x3.5x5 mm^3 voxel size and 80x80x25 matrix size.

3.3 Image analysis

3.3.1 HBS

The Hermes software platform (Hermes Medical Solutions) was used for image analysis. Image analysis was performed in line with the joint EANM/SNMMI/IHPBA HBS procedure guideline[24]. Signal attenuation correction was applied to address differences in signal intensity between the anterior and posterior datasets by computed the geometric mean of both datasets. The first step in post-processing was to identify the starting point, defined as the first image in the hepatic uptake phase with inflow of the radiopharmaceutical in the aorta. All images prior to this point were discarded. Regions of interest (ROIs) were then defined. The ROI for the blood pool was manually delineated on the initial image by defining the boundaries of the left ventricle and the aortic root (Fig. 3a). The liver ROI was defined semi-automatically using a threshold based approach (Fig 3c). The field of view was employed as the third ROI for the computation of the total body activity. The FLR was manually delineated on the SPECT-CT images, based on the planned resection (Fig. 3b). The liver ROI was employed to compute the ^{99m}Tc-mebrofenin uptake rate (MUR; %/min), which was defined by equation:

$$\text{MUR} = \frac{L(t_2) - L(t_1)}{A(t_1) \int_{t_1}^{t_2} C_{\text{norm}}(t)\, dt} \tag{1}$$

where $L(t_2) - L(t_1)$ represents the change in liver activity between the time points t_1 and t_2, $A(t_1)$ is the total activity in the blood pool at the initial time point t_1, and $\int_{t_1}^{t_2} C_{\text{norm}}(t)\, dt$ is the normalized concentration of the radiotracer in the blood over the time interval[25]. The total liver function (TLF) was defined as the percentage of radio tracer that has accumulated in the liver over a certain period of time. The functional share of the FLR was defined as the ratio of the FLR counts to the total liver counts measured in SPECT-CT volumes. The FLR function was then computed by multiplying this functional share by the total liver MUR.
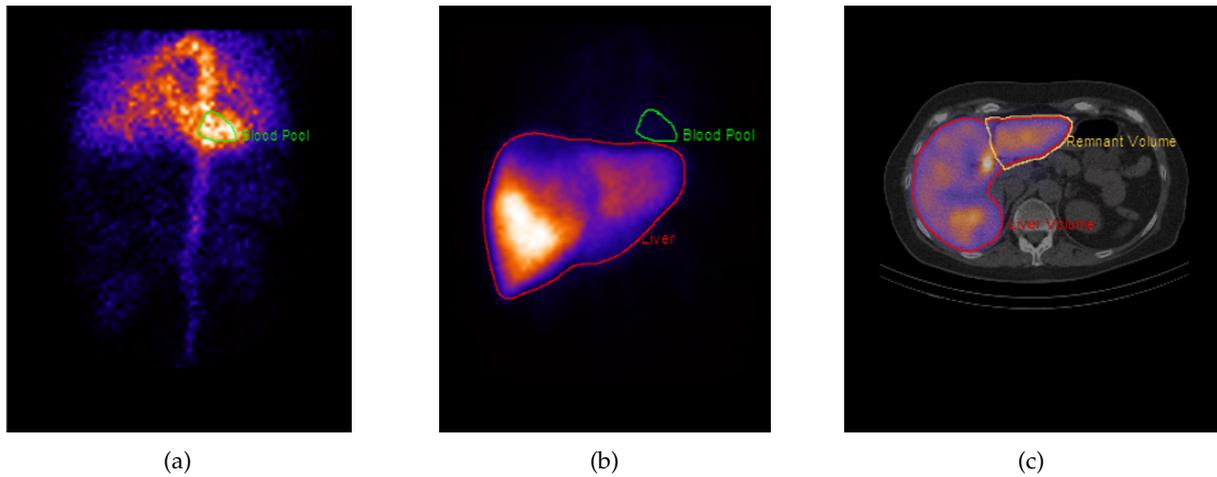
Figure 3: HBS postprocessing steps in the Hermes software platform: (a) Manual delineation of the blood pool and aortic root, (b) semi-automatic delineation of the liver, (c) manual delineation of the future liver remnant volume.

3.3.2 DCE

The analysis of DCE-MRI data in our study involved several steps: 1) pre-processing; 2) extraction of time intensity curves (TICs); 3) conversion to gadolinium concentration; 4) application of Orton's model to analytically represent the vascular input functions[26]; and 5) use of Sourbron's model to estimate biological parameters from the fitted data[27].

The modality independent neighborhood descriptor method was employed to register the DCE images over time. This method employs a pixel neighborhood approach, focusing on image structures for image registration rather than signal intensities. This renders it particularly useful for contrast-enhanced images. The last time frame was selected as the reference image, as the liver is enhanced with contrast in this time frame. Automatic segmentation of the aorta and a manually delineated ROIs of the portal vein were employed at peak TIC to determine the arterial input function (AIF) and venous input function (VIF). Subsequently, voxel-based TICs were extracted from both regions and normalized. A mean TIC for both AIF and VIF were computed from the three individual curves with the greatest contrast enhancement. TICs were converted into plasma concentration by taking into account the flip angle, repetition time, native T1-relaxation times, Primovist relaxivity and hematocrit concentration. A hematocrit value of 0.46 and a contrast agent relaxivity value of 7.3 L/s/mmol were used[28, 29]. A modified Orton's model was used to analytically derive the AIF input function[30]. If patient-based VIF and AIF computation was not possible (e.g., due to early contrast inflow), population-based AIF and VIF were applied. The population-based AIF and VIF were derived by fitting parameters from all individual curves within the study cohort. First, the median of these fitting parameters was computed. Then, a population based curve was generated by fitting the median parameters. In the last step, the Sourbron pharmacokinetic model was applied (Fig. 4). This is a dual-inlet, two-compartment model that represents the physiological structure of the liver and was specifically designed for the Primovist contrast agent[27]. Extracted parameters were the arterial and venous plasma flows (F_a, F_v (mL/min/100mL)) and the hepatic uptake rate (K_i (min^{-1})). Besides the computed parameters, the total in-flow ($T_f = (F_a + F_v)$(mL/min/100mL)) and the arterial flow fraction ($f_a = (F_a/F_a + F_v)$(%)) were derived. These parameters reflect the balance between arterial and venous contributions, which may shift in response to underlying liver disease[31].
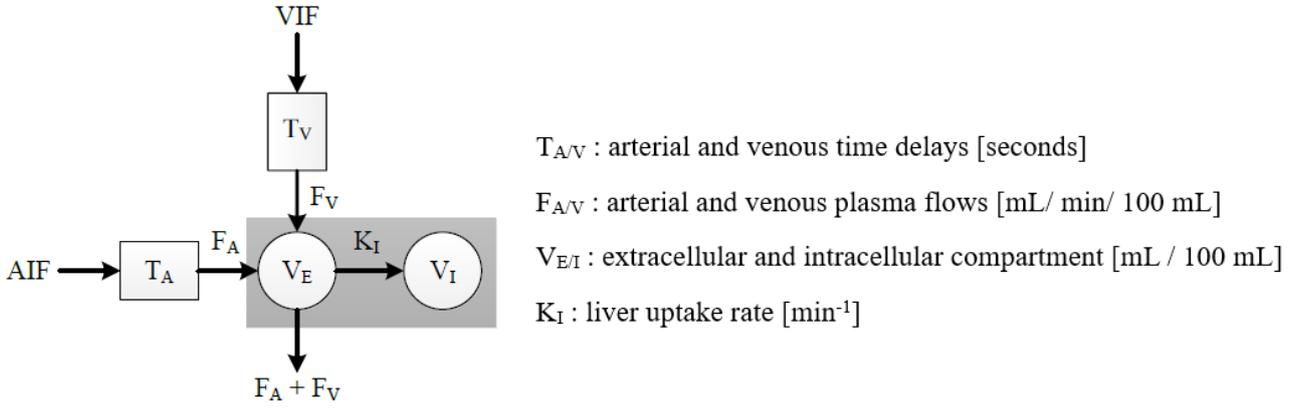
Figure 4: The Sourbron dual compartment dual inlet model employed in DCE-MRI with Primovist for analyzing tissue perfusion and permeability. The gray rectangle represents the liver. AIF, Arterial Input Function; VIF, Venous Input Function.

3.3.3 IVIM

ITKsnap Version 3.8.0 (US National Institutes of Health) was employed to perform image post-processing[32]. Manual segmentation of the liver was performed in ITKsnap with a threshold based region growing approach. The resulting segmentation was used for image registration. To align the 4D image dataset across different b-values, affine image registration was performed using Elastix for MATLAB. Principle component analysis and maximum intensity projection were applied to minimize artifacts and enhance signal to noise ratio.

Image analysis was performed in the Python programming language within the PyTorch environment. Images were transformed for analysis by converting them from 4D to 2D arrays, representing each voxel across all b-values. Data normalization was performed using the zero b-value as a reference. Subsequently, a publicly available IVIM UNET was employed to estimate IVIM-MRI parameters (D (mm^2/s), D_p (mm^2/s), f (%))[33, 34]. The IVIM model was described by the formula:

$$S(b) = S_0 \left(f \cdot e^{-bD_p} + (1 - f) \cdot e^{-bD} \right) \tag{2}$$

where $S(b)$ is the signal intensity at a given b-value (b), S_0 is the signal intensity without diffusion weighting ($b = 0$), D is the true diffusion coefficient, D_p is the pseudo-diffusion coefficient, and f is the perfusion fraction. The neural network was trained on an image array comprising all patients to estimate these parameters. After training, the same neural network was applied to estimate the IVIM-MRI parameters for each patient separately.

3.4 DCE- and IVIM-MRI parameter extraction

DCE and IVIM images were acquired in different orientations (axial and coronal). Consequently, rigid registration was applied to align the images and facilitate voxel-wise comparison within ROI. Due to the superior spatial resolution of the DCE images relative to the IVIM images, the IVIM images were registered to the DCE images. Automatic segmentation of the entire liver, along with manual delineation of the FLR, was performed on the DCE-MRI K_i map. Additionally, a standardized approach for ROI-based measurements was employed to extract data from the Couinaud liver segments[35]. Binary masks were generated from the segmentations and overlaid on the DCE-MRI K_i, F_a, F_v parametric maps as well as on the IVIM-MRI D, D_p, and f parametric maps. Within the entire liver and the FLR delineation, the sum values of K_i were computed to determine the functional share of the FLR. FLR function values were calculated by multiplying the functional share with the mean K_i of the FLR.
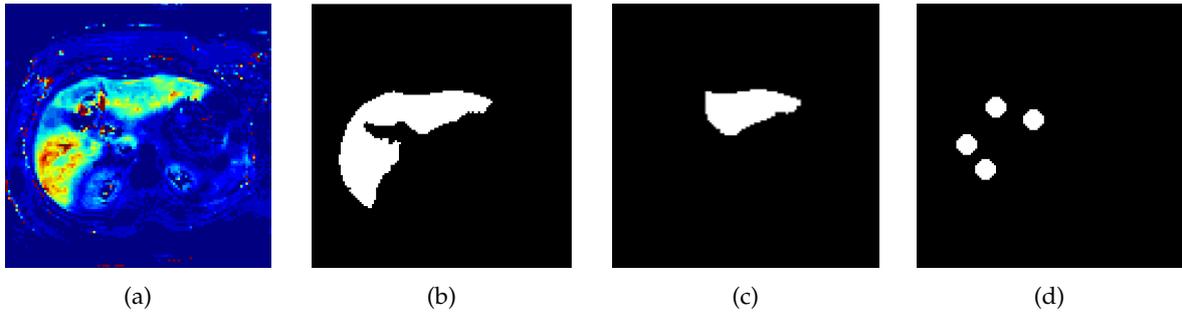
Figure 5: DCE-MRI K_i parametric map and corresponding masks of patient 19. (a) K_i parametric map, (b) entire liver mask, (c) FLR mask, (d) ROI mask of 4 mm^2 on the Couinaud segments at the level of the splenic vein.

3.5   Histological analysis

The intraoperative liver biopsy of the future remnant liver was performed by the operating surgeon, according to the standard of care for regular (i.e., non-research) intraoperative liver biopsies. Approximately 1 cm^3 of liver tissue was removed for all patients. The degree of fibrosis in the resected liver was computed based on the METAVIR scoring system by a pathologist.

3.6   Statistical analysis

Statistical analysis was conducted using SPSS. The minimum and maximum values, mean, and standard deviation range were calculated for the extracted DCE- and IVIM-MRI parameters. Correlations between DCE- and IVIM-MRI parameters, as well as between DCE-MRI parameters and HBS results, were analyzed using the Pearson correlation analysis. Additionally, the same correlation analysis were used to evaluate the relationships between derived IVIM-MRI parameters and histological parameters. P-values less than 0.05 were considered to indicate statistical significance. In order to evaluate the reproducibility of DCE-MRI parameters and assess agreement with previously published results, a Bland-Altman analysis was conducted on corresponding data sets from the same patients. Furthermore, agreement between functional share values measured on DCE-MRI and HBS was assessed using the same analysis.

Results

4.1 Patient characteristics

A total of 21 patients were scanned; two were excluded from the study due to protocol violations, one patient did not receive Primovist, and the MRI scan for a different patient was terminated at the patient's request. Histological data was not available for four patients; two of these patients did not undergo surgery, and two did not receive a FLR biopsy. All included patients underwent HBS and MRI within a two-week interval. Histological analysis demonstrated that 12 of the patients were classified as F0, four as F1, two as F2, and one as F4 according to the METAVIR scoring system. Patients with METAVIR score above F0 had HCC, intrahepatic cholangiocarcinoma or benign liver tumors. Five patients received neoadjuvant chemotherapy; however, no chemotherapy-associated liver injury was observed. Patient characteristics are summarized in Table 1.

4.2 Image processing

4.2.1 HBS

The image analysis was successfully conducted using the Hermes software platform in accordance with the procedural guidelines. Average values of the TLF and FLR are displayed in Table 2.

4.2.2 DCE

DCE-MRI images were processed using the described methodology (Appendix A). TICs were extracted from the ROI and converted to contrast concentration values (Fig. 6). In two patients, contrast inflow was observed directly at the start of the image series. In one patient, the fitting was unsuccessful. For these cases, population-based median AIF and VIF values were computed from the mean values of the individual curves (Appendix C). Subsequently, pharmacokinetic modeling using Sourbron's model was applied to all images. DCE-MRI parameters (F_a, F_v and K_i) were computed for the entire liver, FLR and ROIs in the FLR (Table 2 and 3). Besides the values derived from the parametric maps, the total in-flow ($T_f = F_a + F_v$) and arterial plasma flow fraction ($f_a = (F_a/F_a + F_v)$) were computed.

Table 1: Patient Characteristics

Age (mean)	63 years
Sex female/male	8/11
Type of Liver Disease	
HCC	3/19
Benign	4/19
CRLM	8/19
PHC	1/19
IHC	3/19
Resection left/right	15/4
METAVIR	
F0	12/19
F1	4/19
F2	2/19
F3	0/19
F4	1/19

Hepatocellular Carcinoma (HCC), Colorectal Liver Metastases (CRLM), Perihilar Cholangiocarcinoma (PHC), Intrahepatic Cholangiocarcinoma (IHC)
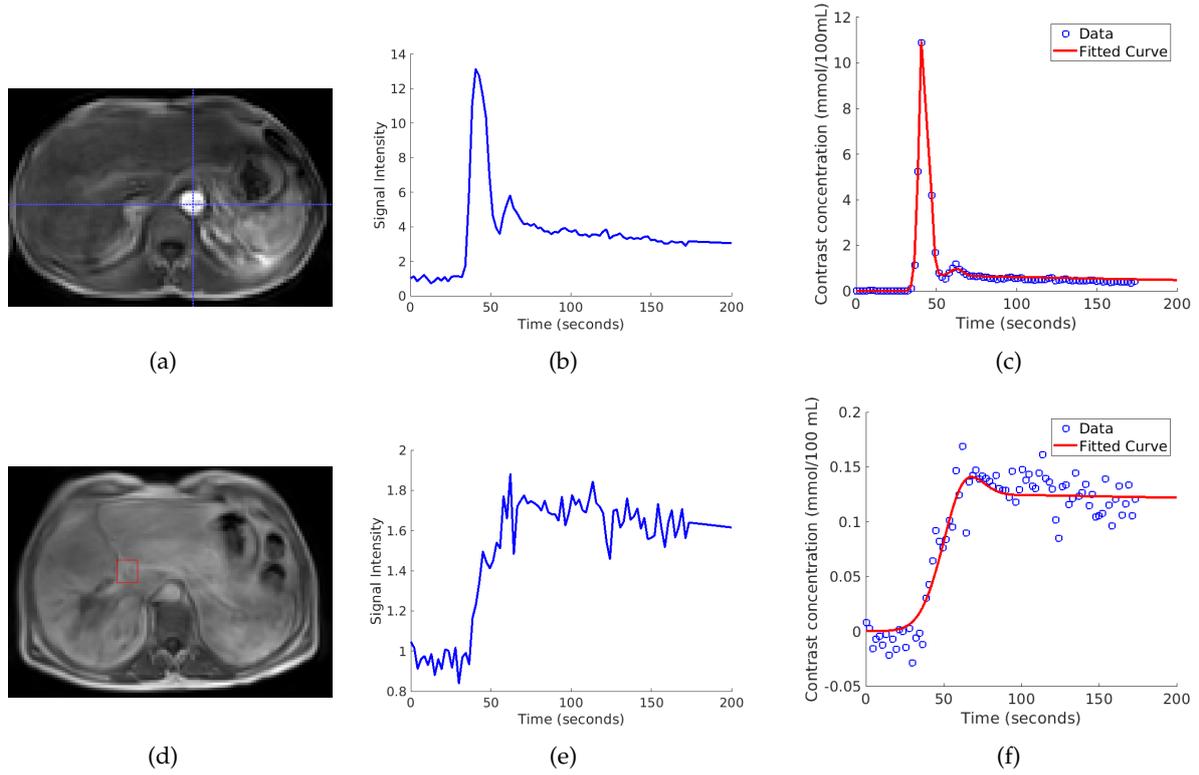
Figure 6: Computation of AIF and VIF. Image (a) and (d) display axial magnetic resonance imaging slices highlighting regions of interest for arterial and venous inputs. Graph (b) and (e) depict the derived TICs from these regions. Graph (c) and (f) display the analytical fits for AIF and VIF, respectively.

Table 2: Descriptive Statistics for TLF and FLR Values

	Parameter	N	Minimum	Maximum	Mean	SD
HBS	MUR TLV	19	7,50	20,47	15,22	3,41
	MUR FLR	19	2,10	12,60	4,89	2,84
DCE	K_i TLV	19	2,69	11,45	6,91	2,93
	K_i FLR	19	2,44	12,28	7,09	1,65
	F_a TLV	19	6,46	52,77	22,90	15,46
	F_a FLR	19	5,11	53,32	20,97	14,64
	F_v TLV	19	7,42	67,55	30,73	18,67
	F_v FLR	19	7,28	91,94	31,91	23,17

MUR, mebrofenin uptake rate (%/min); K_i, Primovist uptake rate (min^{-1}); TLV, Total Liver Volume; FLR, Future Liver Remnant.

4.2.3 IVIM

The methodology was successfully applied to process the IVIM images (Appendix B). However, parameter extraction from the entire liver, FLR segmentation, and several Couinaud segments was not feasible due to these segments being outside the field of view. Consequently, IVIM-MRI parameters ((D, D_p, and f) were extracted from the available ROIs. The mean values of IVIM-MRI ROI measurements within the FLR are displayed in Table 3.

Table 3: Descriptive Statistics for ROI Values in the FLR

	Parameter	N	Minimum	Maximum	Mean	SD
DCE	K_i	19	2.44	19.22	8.47	3.92
	F_a	19	2.60	53.26	21.65	16.34
	F_p	19	2.40	93.33	36.42	30.39
IVIM	D	19	0.67	2.34	1.60	0.40
	D_p	19	39.43	122.73	85.30	22.59
	P_F	19	4.24	24.92	13.65	6.61

K_i, Primovist uptake rate (min^{-1}); D, diffusion coefficient ($10^{-3}\ \text{mm}^2/\text{s}$); D_p, pseudodiffusion coefficient ($10^{-3}\ \text{mm}^2/\text{s}$); f, perfusion fraction (%); F_a, arterial plasma flow (mL/min/100mL); F_p, venous plasma flow (mL/min/100mL);

4.3 Statistical analysis

4.3.1 Correlation of DCE-MRI and HBS parameters

A Bland-Altman analysis was conducted to assess the agreement between the functional share values from HBS and DCE-MRI. The analysis revealed a mean difference of 0.52 with limits of agreement ranging from -15.21 to 16.24, indicating a generally strong agreement with some variability between the measurements. A Pearson correlation analysis was conducted to assess the relationship between the TLF function and FLR function from both DCE-MRI and HBS. Additionally, a sub-analysis was conducted for patients who underwent right hepatectomy. The correlation between the DCE-MRI parameter K_i and the HBS parameter MUR showed a moderate positive correlation (r = 0.49, p = 0.03) (Fig. 7a). Additionally, there was a strong, significant correlation between the FLR MUR and K_i (r = 0.80, p <0.001) (Fig. 7b) in the whole patient group. Whereas a weak correlation was observed between the FLR MUR and K_i in the right hepatectomy group (r = 0.214, p = 0.443) (Fig. 7c).

(a)   (b)   (c)
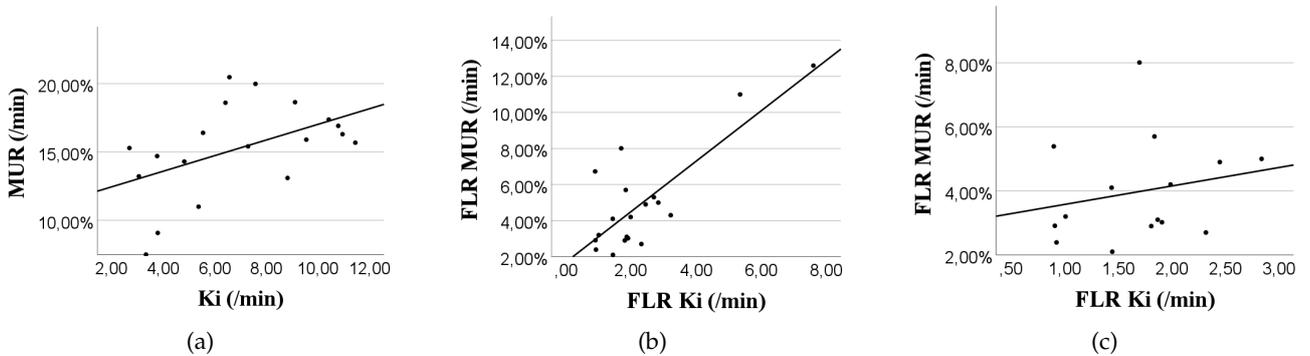
Figure 7: Pearson correlation between total liver function, as measured with HBS and DCE. Results are demonstrated for the total liver (a), the future liver remnant of all patients (b) and the future liver remnant in patients who underwent right hepatectomy (c). FLR, Future Liver Remanant; K_i, Primovist uptake rate (min^{-1}); MUR, Mebrofenin uptake rate (min^{-1}).

4.3.2 Interobserver variability DCE-MRI

The Bland-Altman analysis was employed to assess the reproducibility of the DCE-MRI measurements. The results demonstrated a mean bias of -0.08 for functional share, with limits of agreement from -1.98 to 1.82, indicating strong reproducibility. FLR Function had a mean bias of -0.12 and limits from -4.85 to 4.60. TLF demonstrated more variability, with a mean bias of -1.79 and limits from -20.07 to 16.49.

4.3.3 Correlation of DCE- and IVIM-MRI parameters

Table 4 presents the Pearson correlations between the DCE-MRI parameters (K_i, F_v, F_a, T_f and f_a) and the IVIM-MRI parameters (D, D_p, and f). This analysis demonstrated negative weak to positive moderate correlations ($r = -0.326$ to $r = 0.443$).

Table 4: Pearson correlations between DCE parameters and IVIM parameters

DCE		IVIM		
		D	D_p	f
K_i	r	0.149	-0.143	0.059
	p	0.542	0.560	0.811
F_a	r	0.443	-0.326	-0.064
	p	0.057	0.173	0.793
F_v	r	0.074	0.144	-0.169
	p	0.763	0.555	0.489
T_f	r	0.300	-0.030	-0.196
	p	0.211	0.904	0.422
f_a	r	0.055	-0.200	0.130
	p	0.823	0.411	0.597

The significance level was set at $p < 0.05$. K_i, Primovist uptake rate (min^{-1}); F_a, arterial plasma flow (mL/min/100mL); F_v, venous plasma flow (mL/min/100mL); T_f, total plasma flow (mL/min/100mL); f_a, arterial plasma flow fraction (%). D_p, pseudodiffusion coefficient (10^{-3} mm^2/s); D, diffusion coefficient (10^{-3} mm^2/s); f, perfusion fraction (%).

4.3.4 Correlation of IVIM-MRI and histological parameters

Correlation between IVI-MRI parameters and the histological METAVIR score was examined. The correlation coefficients were as follows: D (r = 0.374, p = 0.115), D_p (r = -0.199, p = 0.415), and f (r = -0.252, p = 0.298). These results suggest a weak correlation between the IVIM-MRI parameters and METAVIR scores.

Discussion

The aim of this study was to examine the relationship between IVIM- and DCE-MRI in the assessment of preoperative liver function in patients scheduled for major hepatectomy. The results indicated a negative weak to positive moderate correlation between IVIM- and DCE-MRI parameters. Additionally, strong correlations were observed between the hepatic uptake rate K_i measured by DCE-MRI and the MUR measured by HBS. High reproducibility with minimal bias was also observed in the repeated DCE-MRI analysis.

The lack of correlation between DCE- and IVIM-MRI parameters may be attributed to the fundamental differences in measurement techniques and the physiological processes they detect. DCE-MRI quantifies liver-specific contrast uptake, determined by multiple physiological factors, including perfusion, permeability, diffusion, and active hepatocyte transport. In contrast, IVIM-MRI measures diffusion and perfusion without the use of contrast agents. Previous studies have demonstrated that IVIM-MRI has good diagnostic accuracy in detecting and staging liver fibrosis. However, the limited representation of advanced fibrosis stages in our patient cohort may have contributed to the lack of correlations observed with histological parameters. This may also explain the discrepancies between our findings and those of Hectors and Phonlakrai et al., who assessed the correlation between IVIM- and DCE-MRI in a cohort of patients with HCC[22]. Unlike our cohort, which almost exclusively included patients undergoing major liver resections without evident liver pathology, patients with HCC often present with fibrosis or cirrhosis[23]. These underlying conditions may contribute to the moderate correlations (f_a and D_p ($r = -0.443$, $P = 0.028$); f_a and f ($r = -0.536$, $P = 0.006$); F_a and f ($r = -0.455$, $P = 0.023$)) observed in their findings. This is supported by studies demonstrating a correlation

between IVIM-MRI measurements and the Child-Pugh scoring system, which is employed to assess the severity of cirrhosis[36].

IVIM-MRI values reported in the literature vary widely due to differences in imaging protocols, MRI systems, and analysis methods[21]. Nevertheless, our IVIM-MRI results align with previously reported values, which range from 0.66–1.50 for D (10^{-3} mm^2/s), 13.60–136 (10^{-3} mm^2/s) for D_p, and 5.50–47.7% for f[21, 37, 38]. The mean D in our study (1.60) was slightly higher compared to other studies, which may have attributed to the limited range of b-values used (0 to 294 mm²/s). These b-values primarily capture perfusion effects rather than pure diffusion, potentially reducing sensitivity to slow diffusion components and affecting the accuracy of D measurements. This limitation might also explain the correlations observed between D and K_i measured with DCE-MRI. In contrast, previous research by Hectors et al. employed a broader range of b-values, allowing for a more accurate separation of diffusion from perfusion effects[23]. This wider range likely enhanced the quantification of diffusion and may account for the moderate correlations observed in their study.

The low bias observed in the Bland-Altman tests indicates high consistency and reliability across the repeated DCE-MRI post-processing analysis, despite the variability introduced by manual processing steps. The variability may be attributed to different registration methods employed compared to the previous study[18]. In addition, in our study, population-based parameters for VIF and AIF were applied in three patients. However, this may not accurately reflect the individual input function, leading to significant errors in the computation of pharmacokinetic parameters[39]. The slightly weaker correlation observed in DCE-MRI measurements in our analysis ($r = 0.80$, $p < 0.001$) compared to the correlations reported by Rassam et al. ($r = 0.89$, $p < 0.001$) may be a result of the observed variability[18].

Moderate correlations were observed in the whole liver, while strong correlations were found in the FLR. However, in the patients that underwent right hepatectomy, the correlation between FLR MUR and K_i was weak ($r = 0.214$, $p = 0.443$). This indicates that the relationship between the FLR MUR and K_i is less evident in the left liver lobes. The correlation observed between the FLR in all patients may be based on the functional dominance of the right liver lobe segments, rather than indicating a direct relationship between DCE-MRI and HBS[40].

The strong correlation observed between DCE-MRI and HBS indicates that DCE-MRI may serve as an alternative for evaluating preoperative liver function. This could create a "one-stop shop" MRI for preoperative planning, allowing for simultaneous assessment of liver function, anatomy, and tumor characterization. However, future studies are needed to address the challenges of clinical implementation, which is currently unfeasible due to complex pharmacokinetic models, variability in post-processing measurements, and a lack of standardization. While IVIM-MRI did not demonstrate strong correlations with DCE-MRI parameters in this specific patient cohort, it may still provide valuable complementary information for preoperative planning. For instance, the diagnostic performance of IVIM-MRI for detecting liver fibrosis demonstrated high accuracy across fibrosis stages, with AUCs of 0.862 (95% CI: 0.811–0.914) for $\geq F1$, 0.883 (95% CI: 0.856–0.909) for $\geq F2$, 0.886 (95% CI: 0.865–0.907) for $\geq F3$, and 0.899 (95% CI: 0.866–0.932) for $F4$[41]. Moreover, compared to the conventional tumor characterization with DWI-MRI to distinguish benign from malignant lesions and primary from secondary tumors[42].

In addition to the investigated MRI techniques in our study, other quantitative MRI techniques have been developed to evaluate liver characteristics. For instance, fat fractions and stiffness quantification through proton density fat fraction MRI and magnetic resonance elastography MRI are already employed in clinical practice[43, 44]. Additionally, there is no evidence demonstrating a direct correlation between individual liver pathology measurements and liver function[11]. However, it is possible that the collective effects of different types of liver pathology influence overall liver functionality in varying ways. Integrating various MRI techniques into a multiparametric approach could significantly enhance our understanding of liver disease and its relation to liver function and regenerative capacity. LiverMultiScan has developed a tool that quantifies liver steatosis, fibrosis, and iron overload using multiparametric MRI[45, 46]. The impact of underlying liver disease on the risk of PHLF requires careful consideration. Distinguishing borderline resectable patients presents a challenge due to the resilience of the liver, which often obscures underlying pathology in individuals with compromised liver

function.

This study has several limitations that should be considered when interpreting the results. First, the manual delineation of the portal vein, future remnant liver, and ROIs may have introduced observer bias. Manual processing can lead to variability in results, affecting the reliability of the findings, especially when performed by an inexperienced or non-clinician. Additionally, due to the incomplete coverage of the liver in the field of view in the scan, whole liver or segmental liver delineation on IVIM images was impossible. As a result, ROIs only capture a small portion of the liver, which may not represent the heterogeneity of the whole liver or individual segments. This limitation can lead to a biased or incomplete assessment of liver conditions.

Another limitation was the change in the imaging protocol during the study, which resulted in variations in the volumes and timing of contrast inflow. This made post-processing more complex and could have affected the consistency of the data. Furthermore, our patient group was relatively homogeneous, primarily consisting of patients with CRLM, who generally have adequate liver function. This homogeneity may impact the observed correlations due to the lack of variability in liver function within our patient group. Finally, T1-relaxometry values from the literature were employed instead of patient-specific T1 maps, which could have impacted the accuracy of the imaging analyses.

These limitations highlight the need for further studies with larger and more diverse patient populations, as well as standardized imaging protocols, to validate our findings. Future research should explore these imaging modalities in different liver diseases and heterogeneous liver function cohorts. Standardization of image acquisition and post-processing techniques is crucial for enhancing the reliability and comparability of liver imaging studies. For instance, the incorporation of automated liver segmentation algorithms will improve reproducibility and consistency in post-processing compared to manual segmentation methods. Moreover, other potential sources of bias, such as variability across scanners and inter-time variability, should be considered to ensure the reproducibility and accuracy of the results.

Conclusion

The lack of correlation between DCE and IVIM-MRI parameters indicates the limited utility of IVIM-MRI in preoperative liver function evaluation. The strong correlations observed between DCE-MRI and HBS parameters suggest that DCE-MRI may serve as a viable alternative for assessing liver function in preoperative settings. However, further studies in a patient cohort with varying degrees of liver function are essential to validate the observed correlations and assess the clinical applicability of IVIM- and DCE-MRI.

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Appendix A

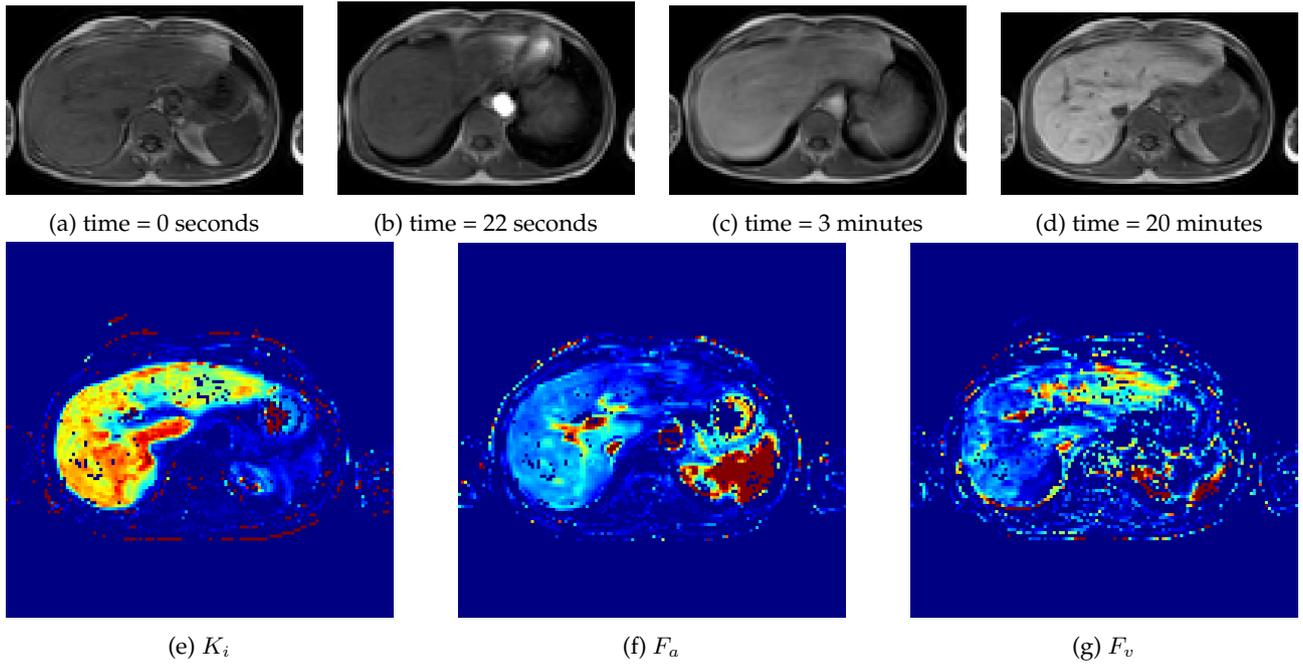| (a) time = 0 seconds | (b) time = 22 seconds | (c) time = 3 minutes | (d) time = 20 minutes |

(e) K_i (f) F_a (g) F_v

Figure A.1: DCE MRI images at various stages: (a) initial image at time 0, (b) arterial phase post-contrast injection, (c) portal venous phase, (d) hepatobiliary phase at 20 minutes, (e) hepatic uptake rate map K_i (min^{-1}), (f) arterial plasma flow F_a map (mL/min/100mL), and (g) venous plasma flow F_v map (mL/min/100mL).

Appendix B

(a) b = 0

(b) b = 1

(c) b = 2

(d) b = 4

(e) b = 6

(f) b = 9

(g) b = 12

(h) b = 17

(i) b = 24

(j) b = 37

(k) b = 54

(l) b = 98

(m) b = 147
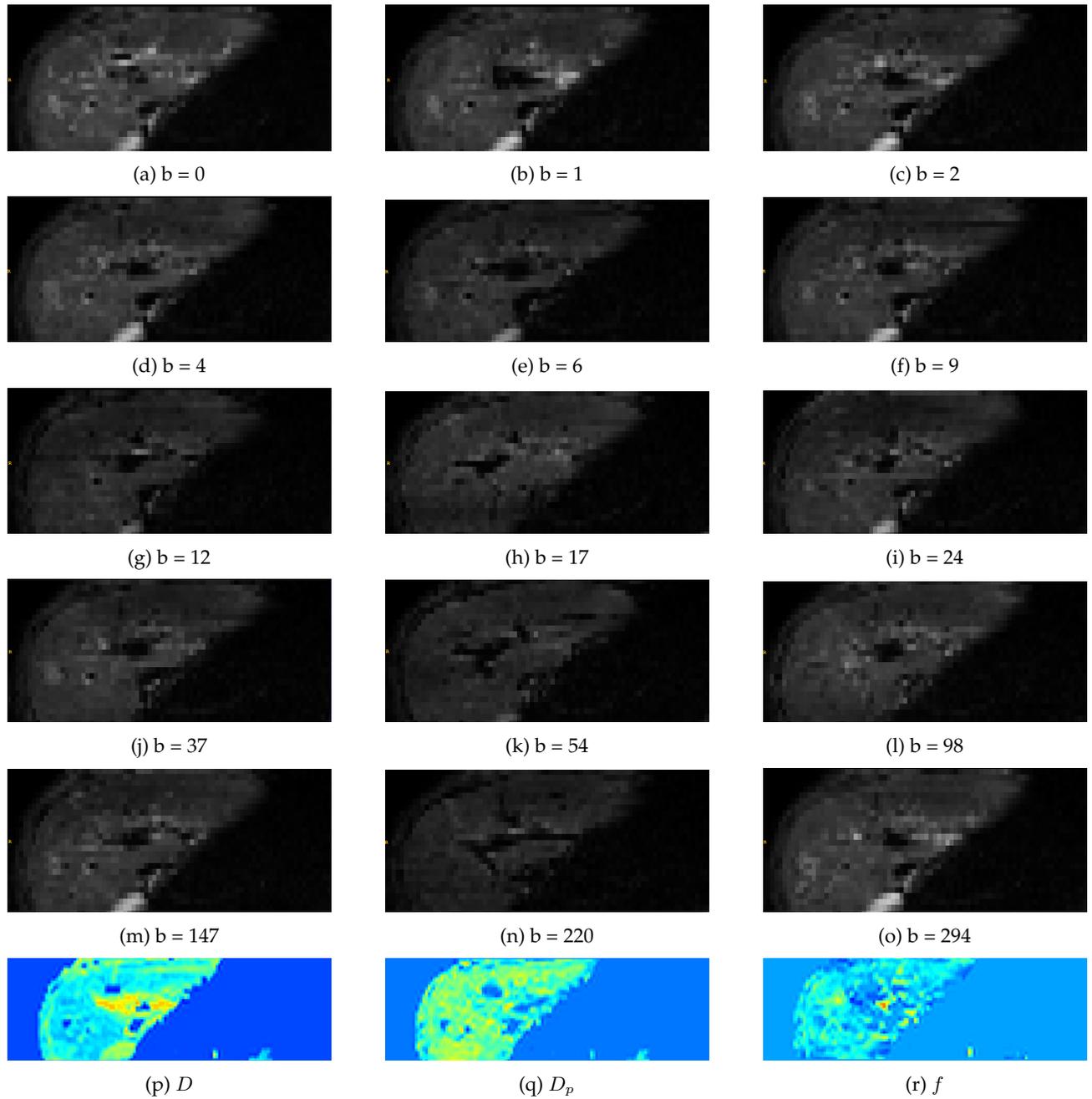
(n) b = 220

(o) b = 294

(p) D

(q) D_p

(r) f

Figure B.1: (a-o) Diffusion weighted images with different b-values. Each subfigure corresponds to a specific b-value. (p-q) Reoriented parametric maps after IVIM image processing. D, diffusion (mm^2/s); D_p, pseudodiffusion (mm^2/s); f, perfusion fraction (%).

Appendix C

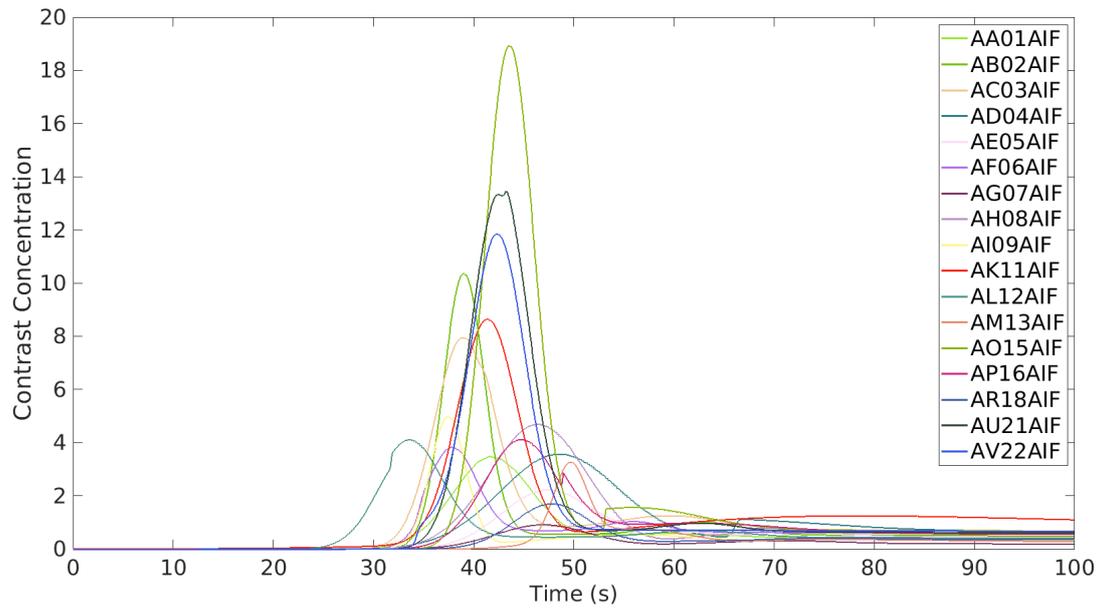## C.1 Individual AIF and VIF curves

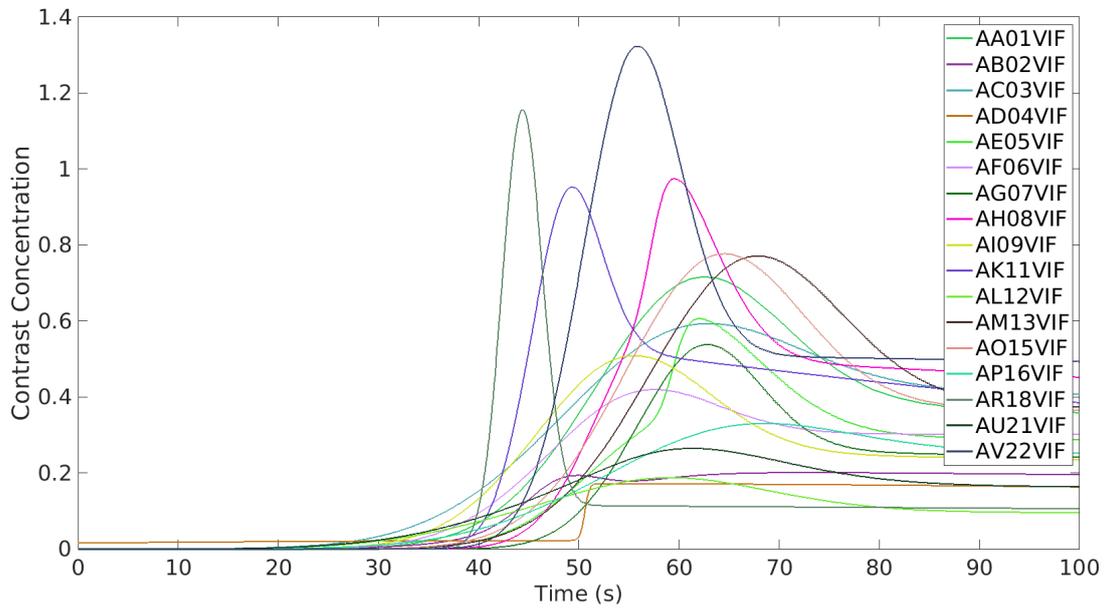Figure C.1: Individual arterial input functions

Figure C.2: Individual venous input functions
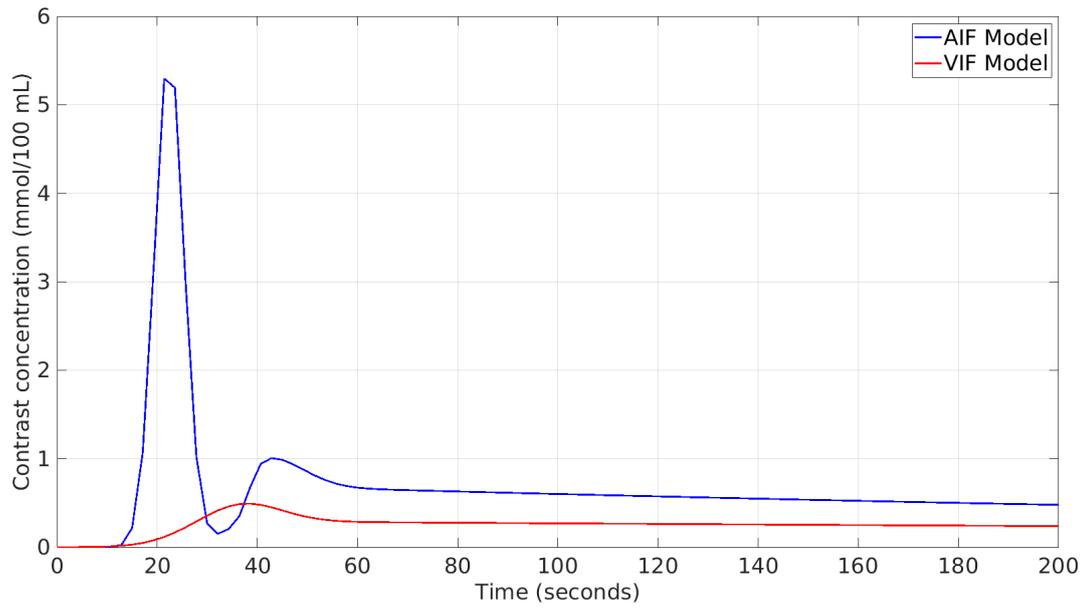
C.2 population based AIF and VIF curves

Figure C.3: Population based arterial and venous input function

Appendix D

Quantitative MRI in the pre-operative evaluation of liver function for hepatectomy – a scoping review

Fenna A. van der Zijden [a,b], Pieter J.W. Arntz [b,c]

[a] *MSc Student Technical Medicine, Technical University Delft, Leiden University Medical Center, Erasmus Medical Center, The Netherlands* [b] *Cancer Center Amsterdam, The Netherlands* [c] *Department of Surgery, Amsterdam UMC, University of Amsterdam, The Netherlands*

Abstract

Background: Careful assessment of remnant liver function before liver resection is essential to minimize the risk of post-hepatectomy liver failure (PHLF). Quantitative magnetic resonance imaging (qMRI) has emerged as potential technique for evaluating liver function, predicting PHLF, and assessing underlying liver diseases. However, the application of qMRI in the preoperative evaluation for liver surgery is limited. The aim of this review is to present an overview of the role of qMRI in the preoperative assessment for liver surgery. Methods: A systematic review was conducted for qMRI sequences compared to preoperative tests to measure liver function as mentioned in the E-AHPBA-ESSO-ESSR (EAEE) Innsbruck consensus guidelines or to liver pathology affecting liver function. In compliance with PRISMA-ScR guidelines, systematic searches of the Embase, Web of Science, and Medline databases were conducted until October 9, 2023. Results: A total of 216 studies were included. The current applications and limitations of T1-relaxometry, magnetic resonance elastography (MRE), diffusion-weighted imaging (DWI), proton density fat fraction (PDFF), and multiparametric MRI for conducting quantitative liver assessment before hepatectomy are discussed. T1-relaxometry is primarily used for assessing liver function and predicting PHLF, whereas other qMRI techniques evaluate underlying liver disease. Nevertheless, their application in the preoperative setting remains limited. Conclusion: This review highlights the potential of qMRI techniques in preoperative assessment for liver surgery. Integration of individual qMRI techniques into multiparametric approaches holds promise for enhancing preoperative liver evaluation.

Keywords: *quantitative magnetic resonance imaging, liver function, hepatectomy*

List of Abbreviations:
ADC - Apparent Diffusion Coefficient
ALBI - Albumin-Bilirubin Score
cT1 - corrected T1
DCE - Dynamic Contrast Enhanced
DWI - Diffusion-Weighted Imaging
EAEE - E-AHPBA-ESSO-ESSR Innsbruck consensus guidelines
FLR - future liver remnant
HBS - Hepatobiliary Scintigraphy
ICG - Indocyanine Green
IVIM - Intravoxel Incoherent Motion
Ki - Hepatocellular Uptake Rate
LiMAX - liver maximum capacity test
LSR - Liver-to-Spleen Ratio
mpMRI - Multiparametric MRI
MRI - magnetic resonance imaging
MRE - Magnetic Resonance Elastography
PDFF - Proton Density Fat Fraction
PHLF - Post hepatectomy Liver Failure
Primovist - Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid
qMRI - quantitative magnetic resonance imaging
RE - Relative Enhancement
SI - Signal Intensity
T1rr - Relative Reduction in T1
TE - Transient Elastography
TIC - Time Intensity Curves

Introduction

Advancements in major hepatobiliary surgery have enabled more extensive and precise resection, demonstrating improved quality of life and extending life expectancy[1;2;3]. Maintaining a balance between maximizing tissue removal for successful radical resection and ensuring ample future liver remnant (FLR) is crucial to minimize the risk of post-hepatectomy liver failure (PHLF)[4]. Despite advanced preoperative and intraoperative techniques, the incidence of PHLF and subsequent death in patients with primary malignancies undergoing major liver resection remains high (8-12%)[5]. Hence, an accurate preoperative assessment of FLR function plays a critical role in the risk evaluation of PHLF, which is essential for clinical decision-making and treatment planning.

In patients without underlying liver disease and with an assumed homogeneous distribution of functional capacity, volumetric estimation of the FLR is currently the standard method for predicting preoperative risk[6]. Therefore, determination of underlying liver disease is crucial and should be addressed by additional diagnostic evaluation. Although the demand for non-tumoral liver biopsy has been reduced by the introduction of non-invasive tests and histological assessment is not indicated for the estimation of liver function, it continues to play an important role in the diagnosis and staging of underlying liver disease[7].

The E-AHPBA-ESSO-ESSR (EAEE) Innsbruck consensus guidelines highlight that a combined volumetric and functional assessment of the FLR in patients with suspected or known underlying liver disease is essential for the preoperative risk evaluation of PHLF[6]. Several methods, including Indocyanine green clearance (ICG), liver maximum capacity test (LiMAx, 13C-Methacetin Breath test), hepatobiliary scintigraphy (HBS) either with technetium-99m labelled mebrofenin or galactosyl human serum albumin are available for the quantitative assessment of liver function[8]. HBS, unlike LiMAx and ICG, evaluates regional variations in liver function, making it more applicable for defining resection margins in patients with heterogeneous distribution of function[9].

Magnetic resonance imaging (MRI) may offer an alternative approach in the current preoperative assessment for the evaluation of underlying liver disease and the assessment of liver function. Quantitative (q)MRI techniques have been developed for a more measurable evaluation of underlying liver disease and have been suggested as an alternative to liver biopsy[10]. Alternatively, several qMRI approaches based on liver-specific contrast agents such as gadoxetic acid have been developed for the assessment of liver function, though the extent to which qMRI techniques correlate with liver function remains largely unknown[11]. The development of both functional and histopathological qMRI techniques is progressing, and their integration into a multiparametric (mp)MRI approach holds significant promise for enhancing comprehensive assessment in clinical practice[12;13;14].

Given the potential of these advanced imaging techniques, we conducted a systematic review with the aim to identify qMRI techniques for the assessment of preoperative liver function, the risk assessment of PHLF, and evaluation of underlying liver disease. The findings in this review highlight the current applications and limitations of qMRI techniques individually and in combination in a mpMRI approach.

Methods

The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for systematic reviews guidelines and was registered in the Prospective Register of Systematic Reviews[15;16]. Specifications of eligibility criteria, information sources, search strategy, selection, and data collection process, and data extraction were independently performed by two authors (FvdZ, PA).

2.1 Information sources and search strategy

A systematic literature search was conducted in collaboration with a librarian from the Amsterdam University Medical Center on October 9, 2023, using Embase, Web of Science, and Medline as search engines. Search terms 'MRI' and 'liver' were restricted to title, abstract or keywords. In addition, preoperative tests to measure liver function (section 2.1.1) or liver pathology affecting liver function (section 2.1.2) were used as a third term. Articles published between October 2013 and October 2023 were included, as MRI technology continues to rapidly evolve and older articles lose relevance. Additionally, reference lists of retrieved articles were evaluated for additional sources using backward snowballing. Endnote was used as a reference management tool and for deduplication[17].

2.2 Definition of methods to assess preoperative liver function before hepatectomy

Surgery is considered if the patient is fit, and the procedure is oncologically beneficial. Subsequently, surgical approach and FLR function will be determined. The EAEE-guidelines provide an overview of dynamic methods (ICG, LiMAx, HBS) and static blood markers (albumin-bilirubin (ALBI) and AST to Platelet Ratio Index (APRI)) to evaluate liver function and PHLF risk.

2.3 Definition of liver pathology affecting liver function

The ability of the remaining hepatocytes to regenerate is crucial for restoring ample function. Hence, the preoperative assessment for hepatectomy requires a precise understanding of the underlying liver diseases that lead to liver pathology affecting liver function. The EAEE-guidelines mention fibrosis, steatosis, and liver injuries from drugs or chemotherapy potentially impair liver function and regeneration. Liver biopsy is recommended to stage and differentiate liver pathology in patients with suspected or known underlying liver disease. Additionally, liver stiffness measurement with transient elastography (TE) should be considered for risk evaluation in these patients[18]. Therefore, the mentioned pathologies, biopsy and TE were included in the literature search[6].

2.4 Study selection procedure

Articles were included if they reported qMRI techniques compared with dynamic functional tests and static blood markers

to assess liver function or were deemed predictive of PHLF. Articles were included if they reported qMRI techniques that were compared to histopathological scoring systems to assess liver pathology. Exclusion criteria were as follows: (1) non-English articles; (2) no full text, reviews, commentary, conference abstracts, reports, protocols and guidelines; (3) animal, phantom or ex vivo research; (4) humans < 18 years; (5) functional test used as a reference not mentioned in the EAEE-guideline; (6) MRI used as a reference standard. Additional deduplication and title/abstract study selection were independently performed by two authors in a systematic review collaboration platform[19]. Conflicting selections were discussed per study till consensus was met, yielding the studies selected for inclusion.

2.5   Synthesis of results
The included articles were sorted into categories according to qMRI techniques. The identification of existing systematic reviews evaluating the techniques described in the defined groups were separately conducted. Full-text screening of articles was performed when topics were not covered by existing systematic reviews.

Results
3.1   Search results
The search across three databases yielded 10,889 articles. After removing duplicates in Endnote and Rayyan, 7,373 articles were screened by title and abstract. 216 articles were included after title and abstract screening. Figure 1 illustrates the selection process according to the PRISMA-ScR guidelines. MRI techniques were classified into T1-relaxometry, diffusion-weighted imaging (DWI), magnetic resonance elastography (MRE), proton density fat fraction (PDFF) and mpMRI. T1-relaxometry studies predominantly focused on the assessment of liver function, whereas the majority of other qMRI techniques focused on histopathological outcomes (Fig 2a). 22 studies included surgical patients, mostly investigating the relationship with T1-relaxometry and the assessment preoperative liver function. A total of 16 studies explored qMRI as a potential tool for prediction of PHLF. Of these, 15 employed T1-relaxometry and one study used MRE.

3.2   T1-relaxometry
A total of 87 articles and three systematic reviews on T1-relaxometry were included in this category. T1-relaxometry involves measuring the longitudinal or spin-lattice relaxation time of hepatic tissue, which depends on the transfer of energy to the surrounding tissue. The amount of energy transferred varies with different tissue characteristics, thereby generating contrast in images. This effect can be enhanced using liver-specific contrast agents such as Gadolinium-ethoxy benzyl- diethylenetriamine pentaacetic acid (Gd-EOB-DTPA; Primovist®). Contrast agents are taken up and excreted by hepatocytes, reaching a maximum accumulation in the hepatobiliary phase approximately 20 minutes after administration. Paramagnetic properties of these contrast agents reduce T1-relaxation times, thus enhancing signal intensity (SI). Based on this effect several indices were established.
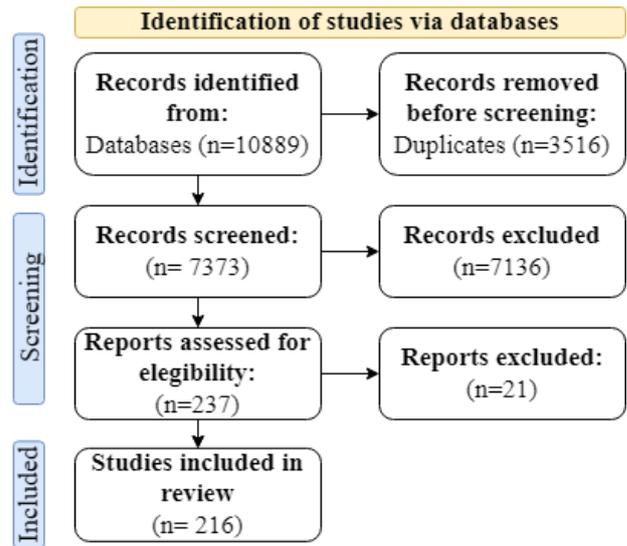

Figure 1: Identification of included studies and classification of selected articles into quantitative MRI groups. T1; T1-relaxometry, DWI; Diffusion weighted imaging, SWI; susceptibility weighted imaging, MRE; magnetic resonance elastography, PDFF; proton density fat fraction
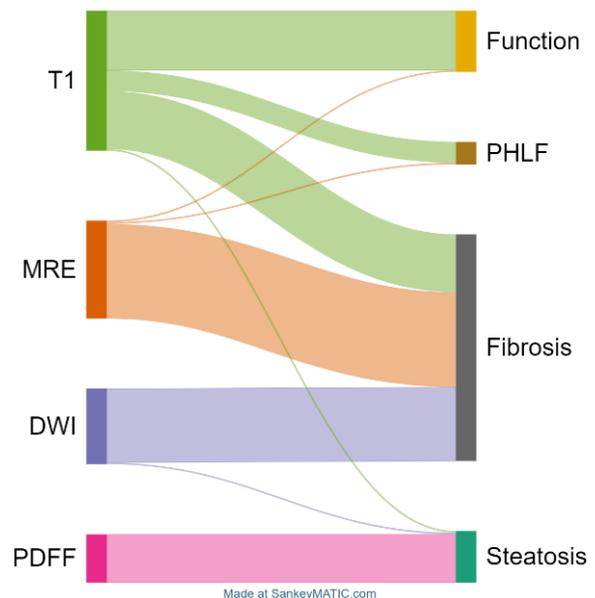

Figure 2: Sankey diagram illustrating the relationships between qMRI and clinical outcomes in liver disease assessment. DWI; diffusion weighted imaging, PDFF; proton density fat fraction, MRE; magnetic resonance elastography, PHLF; posthepatectomy liver failure

3.2.1   Contrast enhanced indices
SI and relaxometry-based indices (Table 1) estimate liver function by measuring SI and relaxation rates before and after contrast injection. This uptake of contrast agents is indicative of hepatocyte excretion. In cases where liver function may be heterogeneous, whole liver measurements can provide information about the distribution of functional capacity. A meta-analysis comparing the most commonly used indices (Table 1. Relative enhancement (RE), liver to spleen

3

ratio (LSR), liver to muscle ratio and T1 relaxation rate (T1rr)) with ICG demonstrated moderate correlations [20]. However, additional studies not included in this meta-analysis showed moderate to strong correlations, which also applied to the less frequently used indices [21;22;23;24]. Moreover, SI-histogram analysis enabled the differentiation between groups with high (> 20) and low (< 20) ICG clearance [25]. Among SI-based and relaxometry-based indices, the T1rr index exhibited the strongest correlation ($r = 0.83$) with ICG clearance [22]. Integrating liver volume into these indices resulted in no or only marginal improvement in correlation coefficients with ICG clearance [26]. Comparative studies of RE and T1rr with LiMAX revealed moderate correlations for RE and strong correlations for T1rr [27;28;29;30]. A study by Wang et al., examined multiple correlations between HBS and SI-indices, demonstrating considerable variability in the comparisons. A derivative of HBS demonstrated a strong correlation with LSR, while the clinically used HBS value showed moderate correlation [31]. Additionally, moderate correlations with the hepatocellular uptake index were observed, whereas Geisel et al. found strong correlations in the remnant liver lobe [32]. In accordance with previous findings, the results indicated that RE and HBS exhibited moderate correlations [33]. Mori et al., measured the LSR one hour after contrast injection and found a strong correlation with HBS parameters [34]. In addition to dynamic comparisons, static serum markers were correlated to T1-values to assess liver uptake function. Included studies consistently demonstrate a moderate negative correlation between the ALBI score and liver enhancement ratios [35;36;37;38]. Moreover, a combination of T1rr with height, weight, and liver volume demonstrated a moderately negative correlation with the ALBI score [39].

A recent systematic review reported on the potential of contrast-enhanced T1-relaxometry to distinguish PHLF from nonPHLF [40]. Subsequently, a study was published which predicted PHLF with LSR, yielding results consistent with the findings of the systematic review [41]. However, further studies using prospective, large-scale samples and standardized parameters are required to confirm these findings and to establish clinically applicable cut-off values [40;41].

Besides the potential of T1-relaxometry to estimate liver function and predict PHLF, one systematic review and 25 studies focussed on the correlation between T1-relaxometry and fibrosis. Fibrosis results in a reduction in tissue perfusion and permeability, which potentially makes contrast enhanced T1-relaxometry an appropriate tool for quantification. Moreover, estimation per voxel may be valuable in resection planning as it provides insights into the distribution of fibrotic tissue throughout the liver. The included systematic review and meta-analysis showed a good diagnostic efficacy for several gadoxetic acid-enhanced MRI based SI and relaxometry based indices in the staging of liver fibrosis [42]. Several articles demonstrated good to excellent diagnostic accuracy for the detection of no and mild levels of fibrosis (F0-F2). Alternatively, several articles showed good to excellent diagnostic accuracy for detection of low and high levels of fibrosis when multiple fibrosis stages where combined into groups, representing a more binary division [43;44;45;46]. Nevertheless, the diagnostic performance of MRE for fibrosis was found superior to any T1 based method [47;48]. Additionally, T1 relaxation times may be affected by inflammation, the presence of iron and acute elevation in liver enzymes and bile parameters [49;50;51]. Failing to account for these confounders may affect diagnostic accuracy.

3.2.2 Dynamic contrast enhanced

In contrast to the previously mentioned T1-techniques, dynamic contrast-enhanced (DCE)-MRI enables the measurement of changes in tissue signal intensity over time. Seven studies were included in the current review, which reported on DCE-MRI. Four of these studies focused on liver function, three assessed the correlation with fibrosis. Time intensity curves (TIC) of the contrast agent dynamics provide a visual representation of the hepatic uptake over time. Pharmacokinetic models can be applied to extract biological parameters from TIC. The maximum slope of increase, derived from the TIC, was compared to HBS to estimate remnant liver function. However, none of the results were found to be statistically significant [33]. The employed PK models differed in terms of number of inputs and compartments, which makes direct comparisons between studies challenging. Studies indicate that hepatic perfusion and hepatocellular uptake rate (Ki) can effectively quantify liver function, showing strong correlations with ICG clearance [52;53]. Moreover, hepatic uptake and excretion of technetium-labelled mebrofenin in HBS and Primovist in DCE-MRI use similar transporters and show a strong correlation with remnant liver function ($r = 0.89$), suggesting the potential of DCE-MRI as an alternative to HBS [33]. Nevertheless, moderate correlations were found in comparison to technetium-99 m galactosyl human serum albumin [54].

Four studies were included in the analysis, which quantified fibrosis with DCE-MRI. DCE-MRI parameters, including Ki and TIC-derived values, demonstrate significant correlations with fibrosis stages, with AUROC values between 0.71 and 0.84 indicating strong diagnostic performance [55;56]. However, a Ki correlation of R = -0.55 reported by Juluru suggests a moderate relationship [57]. No statistically significant correlation was observed between Ki and the fibrosis stages determined by TE [58].

3.2.3 Non-contrast

Non-contrast T1-mapping and T1-rho techniques allow for the measurement of liver properties without the need for contrast agents. Non-contrast T1-mapping quantifies the T1 relaxation time of tissues by acquiring images at different inversion times. Although no correlation with T1-mapping and ALBI to estimate liver function has been identified [59]. T1rho measures T1 relaxation with a continuous radio frequency pulse. This technique is sensitive to the movement of low-frequency protons, enabling the detection of changes in macromolecules and disrupted proton movement, which are characteristic of fibrosis. Studies have demonstrated that T1rho correlates strongly with the severity of liver fibrosis even in the presence of fat, when compared with histological scoring systems and TE [60;61;62;63]. However, differentiating early stages of fibrosis (F0 vs. F1-2) was not possible with

Abbreviation	Meaning	Formula
RE	Relative Enhancement	$RE = \frac{SI_{post} - SI_{pre}}{SI_{pre}} \times 100$
LSR	Liver-to-Spleen Ratio	$LSR = \frac{SI_{\text{liver}}}{SI_{\text{spleen}}}$
LSM	Liver-to-Muscle Ratio	$LSM = \frac{SI_{\text{liver}}}{SI_{\text{muscle}}}$
HUI	Hepatic Uptake Index	$HUI = \frac{SI_{\text{liver}}}{SI_{\text{liver}} + SI_{\text{background}}}$
rHUI	Relative Hepatic Uptake Index	$rHUI = V_l \left(\frac{SI_{\text{liver, 20}}}{SI_{\text{spleen, 20}}} - 1 \right)$
T1rr	T1 Relaxation Rate	$T1rr = \frac{1}{T1}$
ΔLSR	Increase Rate of Liver-to-Spleen Ratio	$\Delta LSR = \frac{LSR_{post} - LSR_{pre}}{LSR_{pre}} \times 100$
ΔLSM	Increase Rate of Liver-to-Muscle Ratio	$\Delta LSM = \frac{LSM_{post} - LSM_{pre}}{LSM_{pre}} \times 100$
ΔR1	Change in Relaxation Rate	$\Delta R1 = \frac{1}{T1_{\text{post}}} - \frac{1}{T1_{\text{pre}}}$

Table 1: Summary of T1-relaxometry and signal intensity indices

T1rho[64].

3.3 DWI

In DWI, the MRI signal is sensitized to random Brownian motion of water molecules within a tissue voxel. Differences in organization of structure of the liver parenchyma affect the diffusion of water and contribute to image contrast. By measuring the signal at different diffusion-weightings, the apparent diffusion coefficient (ADC) can be calculated. Intravoxel incoherent motion (IVIM) is an extended model that employs a bi-exponential rather than a mono-exponential DWI model. It has the ability to quantify perfusion and diffusion separately, providing additional parameters such as the perfusion fraction, true diffusion coefficient, and pseudo-diffusion coefficient.

One study used a complex DWI model that accounts for the non-gaussian distribution of water to assess liver function directly and found moderate correlations when compared to ICG and ALBI[65]. The remaining 31 studies, including two systematic reviews, focused on the staging of fibrosis using DWI or extended DWI models.

Results from a systematic review suggest that DWI can accurately differentiate between stages of liver fibrosis compared with histological fibrosis scoring[66]. Studies not included in the systematic review have shown that ADC values can distinguish between fibrotic and non-fibrotic groups, and ADCs decrease significantly as fibrosis increases[67;68;69;70;71;72;73;74;75;76;77;78;79;80;81]. However, other studies have reported a decrease in ADC with increasing fibrosis that was not statistically significant[78;82]. Moreover, the ability of DWI to distinguish between different fibrosis stages varies across studies, particularly between intermediate stages[68;77;80;81]. Compared to TE, moderate correlations were found[83;84].

A meta-analysis conducted by Ye et al. (2020) highlighted the diagnostic potential of IVIM for both detecting and staging liver fibrosis, with AUC values of 0.862 for $\geq$ F1, 0.883 for $\geq$ F2, 0.886 for $\geq$ F3, and 0.899 for F4[85]. Subsequent studies have confirmed these results[86;87;88]. Nevertheless,

considerable heterogeneity was observed within the included studies[85]. Furthermore, studies indicated that values were not reproducible due to confounding factors[89;90].

The efficacy of advanced diffusion models, including diffusion kurtosis imaging, diffusion tensor imaging, and the distribution diffusion coefficient, has been evaluated for the detection and staging of liver function and fibrosis[91;92;93;94]. However, two studies that used diffusion kurtosis imaging and distribution diffusion coefficient demonstrated a diagnostic enhancement over DWI and IVIM in the staging of fibrosis[93;94].

3.4 PDFF

A total of 22 articles were included that reported on PDFF, a non-invasive modality for the measurement of hepatic fat fractions. Eleven of the included articles were discussed in recent systematic reviews and demonstrated the high diagnostic accuracy of PDFF in the quantitative grading of hepatic steatosis when compared with histological assessment as reference standard[95;96;97;98]. Liver biopsy was found to overestimate steatosis grade compared to PDFF[99;100;101]. Moreover, PDFF showed high diagnostic accuracy for hepatic fat fractions and outperformed several other imaging modalities, such as magnetic resonance spectroscopy and TE[102;103;104;105;106]. Comparative results were found in the remaining included articles[107;108;109;110;111]. Particularly high diagnostic accuracy was observed for moderate and severe grade steatosis[108;112]. Potential confounding factors, such as iron overload, inflammation and fibrosis can be mitigated in PDFF measurements when complemented with multi-echo sequences and T2* corrections[113;114;115;116].

3.5 MRE

A total of 52 articles were included that reported on MRE, which quantifies liver stiffness or elasticity by transmitting shear waves using an external wave generator and a passive driver. 25 of the included articles in the present study were discussed in recent systematic reviews.

One systematic review reported on liver stiffness assessed by MRE as a prognostic value for postoperative outcomes. How-

ever, PHLF was not explicitly identified as a primary outcome measure[117]. Two studies have demonstrated that hepatic stiffness values may be predictive of PHLF[118;119]. Another study directly compared MRE measurements to ICG clearance in hepatocellular carcinoma patients, demonstrating a correlation between increased non-tumour liver stiffness and higher ICG levels. This suggests that MRE may have potential for assessing functional reserve in hepatocellular carcinoma patients[120].

The majority of systematic reviews reported on the staging of fibrosis and cirrhosis across various liver conditions. These consistently demonstrated the excellent diagnostic accuracy of MRE for significant (F0-1 vs. F2-4) and advanced (F0-2 vs F3-4) fibrosis and cirrhosis stages (F0-3 vs F4), in comparison to biopsy[96;121;122;123;124;125;126;127;128;129;130]. In addition to the systematic reviews, 26 articles provide a comparison of MRE with histopathological scoring systems and blood markers to assess fibrosis. Compared to histopathology, MRE demonstrated equivalent or superior performance in the detection of significant fibrosis, consistent with the findings of the discussed systematic reviews[104;111;120;131;132 133;134;135;136;137;138;139]. Furthermore, MRE also showed improved diagnostic accuracy compared to serum markers and other qMRI methods (DWI, DCE, T1-relaxometry and T2-relaxometry)[134;137;140;141;142;143;144;145].

Remaining articles present technical conclusions that demonstrate the comparable performance of different 2D and 3D acquisition methods, despite the potential to image the entire liver with 3D MRE[146;147;148]. However, 3D-MRE can detect early necroinflammation and distinguish it from liver fibrosis[149]. Clinically, MRE provides an accurate, reproducible, and non-invasive assessment of liver fibrosis, regardless of the aetiology, and is not limited by obesity or ascites[125;150].

3.6 mpMRI

MpMRI integrates multiple individual qMRI techniques into a single acquisition, which is hypothesized to mitigate some of the limitations and confounders associated with individual techniques. To date, there have been no studies reporting on the use of mpMRI for the preoperative assessment of liver function or for the risk evaluation of PHLF. Furthermore, no studies compared mpMRI to dynamic liver function tests.

Several studies have reported on mpMRI for the assessment of underlying liver disease. One study reported promising diagnostic performance of mpMRI for diagnosing and staging steatosis, fibrosis and disease activity in non-alcoholic fatty liver disease and analysed several imaging parameters from magnetic resonance spectroscopy, PDFF, IVIM and MRE[151]. Feier et al., Combined DWI, susceptibility-weighted imaging and RE parameters and demonstrated excellent diagnostic performance for staging the severity of liver fibrosis[152]. Another study combined corrected (c)T1, T2*- relaxometry, and PDFF, and effectively evaluated fibrosis, hemosiderosis, and steatosis, respectively[153]. The three studies discuss the potential of mpMRI as substitute for liver biopsy. However, in these studies no combination of individual outcomes were analysed in a multivariate regression to investigate the relationship between parameters. McDonald et al. identified a significant correlation between cT1 values and fibrosis across different inflammation severity levels in a multivariate analysis[154]. An additional study found that combining several qMRI techniques in a mpMRI protocol with volume predicts postoperative outcomes, suggesting its potential for future personalized treatment[155].

Discussion

This review was conducted to investigate the potential role of qMRI techniques for the preoperative assessment liver function, the ability to predict PHLF and for the evaluation of underlying liver disease either individually or in a mpMRI approach.

Results demonstrate the promising role of T1-relaxometry in the assessment of preoperative liver function and prediction of PHLF, however methodological variability and small study cohorts limit standardization and complicates reproducibility. Despite their potential to be combined, no studies have explored a mpMRI approach to assess liver function or predict PHLF. MRE, DWI and PDFF were employed primarily for the diagnosis and staging of underlying liver disease. Nevertheless, a direct comparison between the influence of underlying liver disease on liver function was not determined.

Reviews have reported on the role of contrast-enhanced T1-relaxometry in measuring liver function[11;156]. Unal et al. indicated the use of SI indices for identifying different liver dysfunction patterns in patients with chronic liver disease[156]. However, these reviews did not address the use of DCE for measuring liver function and other qMRI techniques for assessing parenchymal status. Moreover, single blood markers, Child-Pugh and model for end-stage liver disease clinical grading systems have been used as surrogates for predicting PHLF. However, these lack precision in determining the perioperative risk of PHLF, as defined by the EAEE-guidelines and were therefore excluded from our review[6].

Despite the promising results of SI-indices to assess liver function, it should be acknowledged that contrast-enhanced measurements primarily reflect the hepatic uptake and bile excretion of hepatocytes. Moreover, SI values are affected by paramagnetic field inhomogeneities due to technical parameters, rendering them non-absolute and therefore semi-quantitative. Therefore, deriving indices from relaxation rates is more reliable than relying on a single SI measurement. However, direct correlation between the uptake of Primovist and T1 relaxation rates due to the influence of physiological and aetiology of underlying liver disease. Moreover, correct determination of the hepatobiliary phase is not standardized between centres and still varies significantly between patients[157;158;159]. Continuous measurement of contrast uptake with DCE is regarded as a more quantitative approach, also given its ability to extract more intricate biological parameters. However, implementation of DCE has not yet been feasible due to the complexity of pharmacokinetic models and lack of standardization[66].

T1-relaxometry and MRE have been applied to predict major post-operative outcomes. However, the correlation between T1-relaxometry and PHLF remains unclear due to

small study groups and the low incidence of PHLF. To establish a clear correlation between T1-relaxometry and PHLF, larger-scale studies with more diverse patient populations are necessary. While liver stiffness has been demonstrated to predict PHLF, it is predominantly evaluated through TE[6]. Nevertheless, MRE demonstrates superior diagnostic performance, a lower technical failure rate, applicability in patients with obesity and ascites, and better reproducibility in measuring liver stiffness compared to TE[160;161].

MRE, DWI, and T1 are all effective methods for assessing fibrosis, with MRE demonstrating the highest accuracy. However, MRE is limited by the need for specialized hardware. Numerous factors related to tissue composition affect relaxation times, complicating interpretation of measurements. For example, the presence of fat can influence DWI imaging and iron overload complicates MRE, rendering it non-diagnostic in patients with steatosis or hemosiderosis respectively[161;162]. Moreover, while PDFF is an accurate method for quantifying liver fat, it may also be influenced by the presence of iron.

Challenges posed by confounders make qMRI complex, but they also increase the potential for success with mpMRI over other modalities if these interactions can be accurately interpreted[163]. T2*-relaxometry and advanced MRI-PDFF techniques are currently employed in an mpMRI approach for the quantification of iron and the assessment of regional liver fat content, respectively. While another commercially available product also offers quantification of fibrosis and inflammation, there are currently no studies that have incorporated qMRI techniques for liver function assessment in an mpMRI approach. 'Liver health,' as measured by the LiverMultiScan (Perspectum, Oxford, UK), has been proposed as a potential pre-operative method to predict the risk of PHLF[155]. However, while the LiverMultiScan has been validated against liver biopsy, it is crucial to recognize the limitations of biopsy in the context of preoperative liver function assessment and subsequent risk of PHLF[12]. The HepaT1ca trial would potentially benefit from correlations with validated methods for the assessment of liver function to enhance its clinical application.

PDFF and MRE are employed in clinical practice, demonstrating the feasibility of qMRI in routine practice. However, challenges such as variability across scanners, complex interpretation, and the lack of standardized protocols hinder their widespread adoption. Furthermore, other qMRI techniques are currently limited to research settings and cannot be implemented in clinical practice due to the predominant use of in-house analysis within single-center studies, which impedes comparability across different studies. To ensure reproducibility and effective implementation of qMRI in preoperative settings, future multi-center studies are needed. Adoption of guidelines from organisations such as the Quantitative Imaging Biomarker Alliance and the National Cancer Institute Quantitative Imaging Network could standardise protocols, thereby providing accurate liver function quantification in preoperative settings[163].

Despite the promising potential of qMRI in preoperative liver assessment, limitations within this review should be acknowledged. The review primarily focused on fundamentals of qMRI techniques a and their application, omitting technical aspects. However, the ongoing development of qMRI through technical innovations is essential for expanding its clinical applicability. Additionally, various underlying liver pathologies and comparative techniques within our methodology introduce complexities in synthesizing results and drawing definitive conclusions.

Conclusion

Identified techniques, including T1-relaxometry, DWI, PDFF and MRE offer valuable insights in assessment of liver function, prediction of PHLF and evaluation of parenchymal status. Integration of individual qMRI techniques into multi-parametric approaches holds promise for enhancing preoperative liver evaluation. However, further studies are essential to establish more robust correlations between qMRI techniques and dynamic liver function tests, as well as to identify the role of underlying liver disease on liver function. Additionally, standardizing imaging protocols and conducting large-scale multi-center studies are required in order to enhance diagnostic accuracy and clinical applicability.

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