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Non-invasive prediction of portal pressure with MR elastography and DCE-MRI of the liver and spleen: preliminary results

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Abstract

Background—Portal hypertension, defined by hepatic venous pressure gradient (HVPG) ≥ 5 mmHg and clinically significant portal hypertension, defined by HVPG ≥ 10 mmHg, are complications of chronic liver disease.

Purpose—To assess the diagnostic performance of MR elastography (MRE) and dynamic contrast-enhanced MRI (DCE-MRI) of the liver and spleen for the prediction of portal hypertension and clinically significant portal hypertension, in comparison with a qualitative portal hypertension imaging scoring system.

Study type—IRB approved prospective study.

Population—34 patients with chronic liver disease who underwent HVPG measurement.

Field strength/sequence—1.5/3T examination including 2D-GRE MRE (n=33) and DCE-MRI of the liver/spleen (n=28).

Assessment—Liver and spleen stiffness were calculated from elastogram maps. DCE-MRI was analyzed using model-free parameters and pharmacokinetic modeling. Two observers calculated qualitative portal hypertension imaging scores based on routine images.

Statistical tests—Imaging parameters were correlated with HVPG. ROC analysis was performed for prediction of PH and clinically significant portal hypertension.

Results—There were significant correlations between DCE-MRI parameters [liver time-to-peak, $r=0.48/p=0.003$, liver distribution volume, $r=0.494/p=0.009$, liver upslope, $r=-0.567/p=0.002$], liver stiffness ($r=0.478/p=0.016$), portal hypertension imaging score ($r=0.441/p=0.009$) and HVPG. Receiving operating curves (ROC) analysis provided significant area under the ROC (AUROCs) for portal hypertension (liver upslope 0.765, liver stiffness 0.809, spleen volume/diameter 0.746–0.731, portal hypertension imaging score 0.756) and for clinically significant portal hypertension (liver and spleen perfusion parameters 0.733–0.776, liver stiffness 0.742, portal hypertension imaging score 0.742). The ratio of liver stiffness to liver upslope had the highest AUROC for diagnosing portal hypertension (0.903) and clinically significant portal hypertension (0.785).

Conclusion—These preliminary results suggest that the combination of liver stiffness and perfusion metrics provide excellent accuracy for diagnosing portal hypertension, and fair accuracy for clinically significant portal hypertension. Combined MRE and DCE-MRI outperformed qualitative imaging scores for prediction of portal hypertension.

Keywords

Magnetic resonance imaging; Magnetic resonance elastography; Dynamic-contrast enhanced MRI; Portal hypertension

INTRODUCTION

Portal hypertension is a common complication of liver cirrhosis and a major cause of morbidity and mortality in cirrhotic patients (1). The definitive diagnosis of portal hypertension is based on transjugular hepatic venous pressure gradient (HVPG) measurement, which is considered the reference standard for the estimation of portal pressure (2). Portal hypertension is defined as an HVPG ≥ 5 mmHg, and clinically significant portal hypertension is defined as an HVPG ≥ 10 mmHg (3). The presence of clinically significant portal hypertension has been shown to carry a high risk of complications, such as variceal bleeding and ascites (4). Direct HVPG measurement is not widely available and is relatively invasive and costly, with potential complications, which limit its use in clinical practice, especially for patient follow-up. Thus, there is a need for non-invasive methods to predict portal pressure in patients with chronic liver diseases.

In this context, several non-invasive tests are under investigation to evaluate if they could replace, or decrease the need for, HVPG measurement. Several parameters have been proposed, including platelet count, spleen size (and their combination), serum markers,

Child-Pugh score, presence of esophageal varices on upper gastrointestinal endoscopy, or imaging composite score (based on presence of varices, spleen size, presence of ascites), with variable accuracy. The highest accuracy has been reported for the ratio between platelet count and spleen size (AUROC 0.64–0.93) (5–9).

Liver stiffness measurement acquired through ultrasound elastographic methods [transient elastography or acoustic radiation force impulse (ARFI)/shear wave elastography (SWE)] or magnetic resonance elastography (MRE) has been most often used for liver fibrosis staging (10, 11). Liver stiffness measurement using transient elastography has been shown to be a robust tool for portal hypertension diagnosis, with AUROC between 0.76 and 0.99 (5, 12–14). ARFI and SWE have demonstrated a slightly better diagnostic value, but are still limited by failures in obese patients and in patients with ascites (15, 16).

Spleen stiffness has been proposed for portal hypertension assessment in most recent studies. The increase in spleen stiffness is likely due to splenic congestion secondary to the increase in portal pressure. Spleen stiffness is a potentially attractive parameter, due to lack of confounding factors (such as liver congestion, biliary obstruction, liver inflammation, cellular infiltration, deposition of amyloid), compared to liver stiffness. Spleen stiffness measurement using ultrasound elastography methods is promising but has a high failure rate, which limits its uses (16, 17).

MRE for liver and spleen stiffness measurements has also been tested, with studies showing strong correlation between both liver and spleen stiffness and portal pressure in pigs, weak to moderate correlation between both liver and spleen stiffness and HVPG or with the grade of esophageal varices (18, 19). Moreover, liver and spleen stiffness measurements with MRE show high reproducibility between MRI field strengths, systems, and observers (20, 21).

In parallel to the liver and spleen stiffness increase, advanced liver fibrosis and cirrhosis can cause hemodynamic changes, with increased splanchnic inflow, hepatic resistance and portal pressure, and decreased portal flow secondary to increased hepatic resistance and the development of portosystemic collaterals (22). This decrease of the portal flow is associated with an increase of the arterial flow, known as the hepatic arterial buffer response (23). The role of Doppler measurement for portal hypertension assessment is limited due to the high variability of the measurement (24). Annet et al suggested the use of flow parameters obtained from dynamic contrast-enhanced (DCE)-MRI for noninvasive portal pressure assessment (25). They found that portal fraction, portal blood flow, and mean transit time were substantially correlated with portal pressure, and that liver blood flow, arterial blood flow and distribution volume/hepatic artery resistance index transit time were weakly correlated with portal pressure (25).

The aim of our initial study was to assess the diagnostic performance of MRE and DCE-MRI of the liver and spleen for the prediction of portal hypertension and clinically significant portal hypertension in patients with liver disease.

MATERIALS AND METHODS

Patients

This single-center prospective study was compliant with the Health Insurance Portability and Accountability Act and approved by the local institutional review board. Written informed consent was obtained from all subjects. From April 2012 to August 2016, 34 patients with chronic liver disease (M/F 16/18) with a mean age of 53 years (range 26 – 75 years) who underwent HVPG measurements were consented to the study protocol.

Clinical data

The following clinical parameters were recorded for all patients at the time of their MRI exam: age, sex, weight, body mass index (BMI) and etiology of chronic liver disease.

HVPG measurements

HVPG measurements were performed either before or after the MRI (78 ± 48 days, range 3–184 days) by 1 of 5 experienced interventional radiologists. Right transjugular access was obtained using ultrasound guidance, under local anesthesia and moderate conscious sedation. A 5F 65-cm MPA diagnostic catheter (Cordis, Bridgewater, NJ) was used to catheterize the right or middle hepatic vein, and venography was performed with iodinated contrast. Then, a 5.8F 1.0-cm flow-directed occlusion balloon (Cook Medical) catheter was placed in the middle or right hepatic vein. The HVPG was calculated as the difference between wedged and free hepatic venous pressures. Free pressure was measured in the vein with the balloon deflated. Measurements were obtained after 45–60s to allow for equilibration using an NAMIC Preceptor transducer (Navilyst Medical, Marlborough, MA). Then, the balloon was inflated to profile in the vein and the wedge pressure was measured using the same transducer. Two measurements were performed, and an average value was determined.

MRI acquisition

The MRI acquisitions were performed on either a 1.5T clinical system (Siemens Aera, Siemens Healthineers, Erlangen, Germany, n=19) or using the combination of a 1.5T (Siemens Avanto, Siemens Healthineers, Erlangen, Germany) and 3.0T systems (General Electric MR 750, GE Healthcare, Waukesha, WI) (n=15). Each system is equipped with a 32-channel spine and flexible body array coil for signal reception. Subjects were asked to fast for 6 hours prior to imaging to eliminate post-prandial effects on portal venous blood flow (27). In cases for which a combination of systems was used, MRE was first performed on the 3.0T system followed by DCE-MRI and additional standard sequences, performed on the 1.5T system.

In addition to MRE and DCE-MRI, the MRI protocol also included the following standard sequences: axial and coronal single-shot T₂-weighted imaging; axial fat-suppressed fast spin echo T₂-weighted imaging; axial 3D T₁-weighted imaging in- and out-of-phase, axial diffusion-weighted imaging; and 3D T₁-weighted imaging breath-hold fat-suppressed spoiled gradient-recalled echo sequence before and at a delayed phase (approximately 4

minutes) after injection of a gadolinium based contrast agent. The acquisition parameters for MRE and DCE-MRI are listed in Table 1.

DCE-MRI acquisition consisted of 100 dynamic acquisitions of a T_1 -weighted 3D-FLASH volumes covering the liver and spleen, before and after an intravenous injection of gadolinium based contrast agent [0.05 mmol/kg of gadobenate dimeglumine (Multihance, Bracco Diagnostics Inc)], followed by a 25 ml saline flush, at a rate of 3 ml/s. The injection began 8 s after the start of the acquisition. Because of the high relaxivity of gadobenate dimeglumine, half dose of the contrast agent was used to avoid saturation of the signal intensity in the DCE-MRI acquisition (26). Before DCE-MRI, an inversion recovery Look-Locker (IR-LL) pulse sequence (180° inversion with 32 post-inversion acquisitions, $TI's = 42\text{--}1576.5$ ms at 48 ms interval, $TR = 2.25$ ms, $TE = 1.04$ ms, $FA = 8^\circ$, $FOV 420 \times 288$ mm², matrix 128×88 , parallel imaging GRAPPA acceleration 2) was used to provide quantitative T_1 mapping in 1–2 slices through mid-liver in a single 18 s breath-hold.

For liver and spleen **MRE acquisitions**, two 19 cm-diameter passive acoustic drivers were placed both at the level of the xiphoid, one on the right side of the abdomen to measure liver stiffness and the other one posteriorly to the left side to measure spleen stiffness. Two different acquisitions were performed. Four axial slices were centered over the portal vein for the liver acquisition and the splenic hilum for the spleen acquisition. A modified phase contrast gradient recalled echo (GRE) sequence was used with motion encoding gradients along the z-axis. The acquisition time was 55 seconds, split in 4 breath-holds for each location. The stiffness maps and a confidence index (ranging from 0–100%) for stiffness measurement were automatically provided by the software. MRE was performed before the contrast injection. MRE failure was defined as the absence of visualized wave propagation on the wave images and/or no pixel with a confidence index higher than 95% on the confidence map (27).

MRI analysis

DCE-MRI analysis—First, motion correction was applied to the DCE-MR images with 3D rigid registration using open-source image analysis software (Firevoxel, CAI²R, New York University, New York, NY, USA) by observer 1 or observer 2 (MRI physicists with 2 and 4 years of experience). Second, free-hand ROIs were drawn in the right hepatic lobe (centered on the portal bifurcation) and the portal vein on the liver-registered images, the spleen parenchyma (centered on the spleen hilum) on the spleen-registered images and the aorta at the level of the celiac trunk on the unregistered images, on 5 slices, by two observers in consensus [observer 1 and observer 3, a body radiologist with 6 years of experience in abdominal imaging] to measure signal intensity (SI, in arbitrary units). Then, the signal-time intensity curves were extracted and analyzed using MATLAB (version R2015a, MathWorks, Natick, MA, USA). In order to reduce inflow artifacts in the mean SI curve in the aorta, a locally weighted linear least-square fit with first degree polynomial (LOWESS) was applied on the curve of the aorta, as described previously (28). Pixel dynamic SI curves were converted to dynamic contrast agent concentration ([CA]) curves by using the signal equation for an SPGR sequence, T_1 values and the contrast agent's relaxivity. Liver and spleen T_1 values were calculated from the Look-Locker acquisition. The Look-Locker

inversion recovery sequence was picked because it was shown that this sequence, if optimized for the liver, has superior test-retest repeatability than a 3D FLASH sequence optimized for the liver (29). Portal vein and aorta T_1 values were based on literature (30). A hematocrit value of 0.45 was used for conversion from blood [CA] to plasma [CA]. A contrast agent relaxivity value of $8.1 \text{ mM}^{-1} \text{ s}^{-1}$ was used (31).

A quantitative analysis was performed using a dual-input single compartment model described by Materne et al. for the liver and a Tofts model for the spleen (32, 33). The following estimated parameters were computed for the liver, arterial flow (F_a , ml/100g/min), portal venous flow (F_p , ml/100g/min), total hepatic flow (F_t , ml/100g/min), mean transit time (MTT, s), distribution volume (DV, %), and arterial fraction ($ART = F_a/F_t$, %); for the spleen: transfer constant (K^{trans} , min^{-1}), extravascular extracellular space (v_e , %), and rate constant (k_{ep} , min^{-1}). In addition, model-free parameters were obtained for both the liver and spleen: time-to-peak (TTP, s), peak concentration (C_{peak} , mmol/L), area-under-the-curve at 60 s (AUC60, mmol/L.s) and upslope (mmol/(L.s)).

MRE analysis—MRE analysis was performed by observer 3 using Osirix software (v 5.5.2, Geneva, Switzerland). Free-hand ROIs were drawn in the liver and spleen parenchyma, as large as possible, avoiding voxels with confidence index less than 95% and large vessels, liver/spleen edge, fissures and regions of ambiguous wave propagation. Stiffness values were extracted for the liver and spleen, and an average organ stiffness value, weighted by the ROI size, was computed from all 4 slices.

Additional MRI analysis—Two radiologists [observer 3 and observer 4 (a radiologist with 3 years of experience in abdominal imaging)] independently reviewed the MR images on PACS (Centricity, GE Healthcare). The observers were blinded to the initial radiological reports, HVPg and pathology results. They were asked to compute a fast semi-quantitative imaging-based portal hypertension score, ranging from 0 to 9, according to Kihira et al. (6), which has been shown to provide fair accuracy for prediction of portal hypertension and clinically significant portal hypertension. The imaging score is based on the number of variceal sites (0: absence of varices, 1: one variceal site, 2: two variceal sites, and 3: 3 or more variceal sites), volume of ascites (0: no ascites, 1: minimal perihepatic and perisplenic fluid, 2: intraperitoneal fluid without marked abdominal wall distension, and 3: fluid causing marked abdominal wall distension), and maximum craniocaudal diameter of the spleen (0: size less than 13 cm, 1: size between 13 and 15 cm, 2: size between 15 and 20 cm, and 3: size greater than 20 cm). Finally, observer 1 measured the spleen volume through manual segmentation on axial single-shot T2-weighted imaging, using Osirix Software (v 5.5.2, Geneva, Switzerland).

Statistical analysis

Quantitative variables are presented as median (interquartile range) (IQR). Categorical variables are presented as number of cases (percentage of cases). Statistical difference between parameters in patients with and without portal hypertension, and patients with and without clinically significant portal hypertension was assessed using Mann-Whitney U tests. Correlations between MRI parameters and HVPg were assessed using Spearman correlation

analysis. ROC analysis was performed for prediction of portal hypertension (HVPG ≥ 5 mmHg) and clinically significant portal hypertension (≥ 10 mmHg). Finally, general linear modeling with stepwise selection of features was employed to select the most predictive (combination of) parameters for assessment of portal hypertension and/or clinically significant portal hypertension. Only parameters that showed significance between no portal hypertension and portal hypertension and between no clinically significant portal hypertension and clinically significant portal hypertension were included as potential variables for the general linear model to avoid overfitting. A two-tailed p-value less than 0.05 was considered to be significant. Statistical analyses were performed using SPSS software (Version 20, Chicago, IL), except the general linear modeling which was performed using Matlab (version R2016B, MathWorks, Natick, MA).

RESULTS

Patients

Among the 34 patients, 2 patients did not have DCE-MRI acquisition due to chronic renal insufficiency, 4 patients had non-usable DCE-MRI data because of major artifacts and 1 patient did not have MRE acquisition. Patient characteristics are presented in Table 2. 12/34 patients (35%) did not have portal hypertension and 22/34 (65%) had portal hypertension including 9 (26%) with clinically significant portal hypertension. On histopathologic examination, half of the patients had advanced fibrosis/cirrhosis [F3 (n=7, 21%) and F4 (n=10, 29%)].

Technical success of liver and spleen stiffness measurements

MRE was successful for liver and spleen stiffness measurements in 31/33 (94%) and 27/33 patients (81%) who underwent MRE, respectively.

Correlation between imaging parameters and HVPG measurements (Table 3, Fig. 1)

There was a moderate significant correlation between liver stiffness ($r = 0.486$, $p = 0.006$) and HVPG measurement. Among the DCE-MRI parameters, liver DV, liver TTP and liver upslope were all significantly correlated with HVPG measurement ($r = 0.494$, $p = 0.009$, $r = 0.487$, $p = 0.003$, and $r = -0.567$, $p = 0.002$, respectively). Liver T_1 was not significantly correlated with HVPG ($r = 0.049$, $p = 0.809$).

None of the spleen parameters were significantly correlated to HVPG measurement, except for spleen volume and spleen craniocaudal diameter, which showed weak non-significant correlations with HVPG measurement ($r = 0.309$ and 0.311 , $p = 0.075$ and $p = 0.073$, respectively). The portal hypertension qualitative score of both observers were moderately correlated to HVPG measurements ($r = 0.441$ – 0.484 , $p = 0.004$ – 0.009).

Diagnostic accuracy for diagnosing portal hypertension (HVPG ≥ 5 mmHg)

Liver upslope and liver TTP were the only liver perfusion parameter significantly different between patients with and without portal hypertension; it was significantly decreased and increased, respectively in portal hypertension ($p = 0.027$ / $p = 0.035$). The qualitative portal hypertension score, liver stiffness, spleen volume and spleen craniocaudal diameter were all

significantly higher in patients with portal hypertension (Table 4). The AUROC analysis is presented in Table 5. Liver stiffness had the highest AUROC (0.809) for diagnosing portal hypertension.

Diagnostic accuracy for diagnosing clinically significant portal hypertension (HVPG 10 mmHg)

Liver TTP, liver DV and spleen TTP, liver stiffness the qualitative portal hypertension score were all significantly increased in patients with clinically significant portal hypertension compared to patients without clinically significant portal hypertension, while liver upslope was significantly decreased (Table 4, Fig. 2). Spleen upslope was decreased and spleen craniocaudal diameter was increased in patients with clinically significant portal hypertension, with a trend towards significance ($p=0.095/p=0.086$). The AUROC analysis is presented in Table 5. To differentiate patients with and without clinically significant portal hypertension, for the significant parameters, AUROCs were approximately 0.75.

Combination of non-invasive methods

Similarly to Kim et al. (34) on the basis of the above results, we combined DCE-MRI and MRE parameters that showed the best correlation with HVPG (liver upslope and liver stiffness). As liver upslope was negatively correlated with HVPG, it was used as the denominator, and as liver stiffness was positively correlated with HVPG, it was used as the numerator, in order to emphasize their relationship with HVPG. The new parameter was called LSLU and was computed as ratio of liver stiffness to liver upslope. LSLU was strongly and significantly correlated to HVPG ($r=0.650$, $p<0.0001$) (Fig. 1). LSLU was significantly higher in patients with portal hypertension than in patients without portal hypertension [median (IQR): 830.28 (971.68) vs. 192.72 (195.65), $p=0.001$]. To diagnose portal hypertension using LSLU, we observed AUROC of 0.903 ($p=0.001$) with sensitivity of 78% and specificity of 100% (using cutoff 433) (Table 5). LSLU was also significantly higher in patients with clinically significant portal hypertension than in patients without clinically significant portal hypertension [median (IQR): 871.82 (1354.31) vs. 363.68 (855.01), $p=0.022$]. To diagnose clinically significant portal hypertension using LSLU, we observed AUROC of 0.785 ($p=0.023$), sensitivity of 88% and specificity of 72% (using cutoff 469) (Table 5).

According to the general linear modeling, the combination of liver stiffness and liver upslope showed high accuracy for prediction of portal hypertension (accuracy 0.769). However, this combination did not outperform liver stiffness alone (accuracy 0.807). For clinically significant portal hypertension, spleen TTP was the best predictor (accuracy 0.778) (Table 6).

Finally, we assessed the number of patients with clinically significant portal hypertension missed by liver stiffness that were correctly diagnosed with the qualitative score and vice-versa. Using liver stiffness, there were 4 false negative cases for clinically significant portal hypertension (among the 9 cases of clinically significant portal hypertension assessed with liver stiffness), including two correctly diagnosed with the qualitative score (Fig. 3). Using

the qualitative score, there were 3 false negative cases; none of them was correctly diagnosed by liver stiffness.

DISCUSSION

In this initial prospective study, we showed that the combination of liver stiffness and perfusion parameters has the potential to identify patients with PH (with excellent accuracy) and clinically significant portal hypertension (with fair accuracy).

Several liver perfusion/flow modifications are known to occur in chronic liver disease and cirrhosis. The increase of the liver resistance and portal pressure are responsible for a decrease in portal flow and an increase in arterial flow as shown previously by Annet et al (25). In contrary to Annet et al., we did not find any significant correlation or modification in the portal blood flow, arterial blood flow or arterial fraction in portal hypertension and clinically significant portal hypertension (25). Of note, these correlations were not always described in other studies (35, 36). These discrepancies could be explained by the high variability of the modeled DCE-MRI parameters and the small sample size (37). Yet, we found that liver upslope, liver TTP and liver DV correlated significantly with HVPG measurements. The increase of liver TTP and the decrease of liver upslope in portal hypertension is concordant with the decrease in liver perfusion in advanced liver disease. None of the spleen DCE-MRI parameters correlated with HVPG measurements, with only a trend found for spleen TTP. The published data on spleen perfusion quantification in portal hypertension is limited with variable results (35, 38, 39). The absence of correlation between spleen blood flow and HVPG is not in accordance with two previous studies, which found a decrease of splenic blood flow in portal hypertension (35, 38). Similarly, a relationship between spleen K^{trans} and HVPG was also observed previously, but not reproduced in our study (35, 39). The splenic perfusion modifications in case of portal hypertension could be linked to an increased interstitial pressure in the splenic tissue, which may increase the blood transit time, decrease the capillary permeability and the blood flow. The absence of correlation in our study may be due to differences in modeling or imaging modality (CT vs MRI).

Liver stiffness was significantly correlated with HVPG and higher in patients with portal hypertension, in accordance with previous results either with ultrasound or MR elastography (5, 13–16, 18). Despite the potential confounding factors, such as liver fibrosis stage, liver stiffness seems to be the best parameter for identification of patients with portal hypertension. Moreover, MRE is an attractive method because it does not require contrast injection, and has a high success rate (at 1.5T using a GRE sequence and at 3T using a spin echo sequence) (27, 40, 41).

Our newly described combined parameter, LSLU, combining liver stiffness measured with MRE and liver upslope, could improve performance of MRE for the diagnosis of portal hypertension (with sensitivity of 78% and specificity of 100%). However, it did not improve the performance of liver MRE for clinically significant portal hypertension. The added value of LSLU should be studied in a larger sample.

The general linear modeling identified the combination of liver stiffness and liver upslope as a good predictor for portal hypertension. However, this combination did not outperform liver stiffness, which had the best accuracy. For prediction of clinically significant portal hypertension, spleen TTP alone was the best predictor according to the general linear modeling.

We found that spleen stiffness was not able to identify patients with portal hypertension. The literature on spleen stiffness in portal hypertension is conflicting. Spleen stiffness is considered by certain authors to be a promising parameter, due to less confounding factors comparing to liver stiffness. For example, Ronot et al. showed that the viscoelastic parameters of the spleen allowed the identification of patients with severe portal hypertension (defined by HVPG ≥ 12 mmHg) and those with high-risk varices (18). Similarly, Shin et al. found a significant correlation between spleen stiffness and grade of esophageal varices (19). The discordance between their results and ours may be related to the fact that they used 3-directional MRE while we used 1-directional MRE. The 1-directional MRE sequence was designed for the liver and 3-directional MRE has been suggested to be more appropriate for spleen anatomy (18, 19).

As expected, the spleen volume and craniocaudal spleen diameter were significantly higher in portal hypertension, however did not correlate significantly with HVPG. The increase of spleen diameter and volume have been previously described with variable accuracy (6, 35, 42). Both, and especially the spleen diameter, are attractive because they are easy to obtain. However, as previously shown, they seem more accurate when combined with other parameters (6, 42). In addition, we confirmed - as in Kihira's study - the diagnostic accuracy of the qualitative portal hypertension score for portal hypertension and clinically significant portal hypertension assessment (6). The qualitative score is easy to assess and could be an alternative to more advanced methods, even if it performs less well than the advanced methods. It could also be useful to identify patients with clinically significant portal hypertension missed by MRE.

Our study has several limitations to be acknowledged. First, the sample size is small, reflecting our initial experience. Our results need to be validated in a larger study. Second, all patients did not undergo examination with each imaging modality because of failure, contra-indications or availability. Third, different platforms were used for MRI acquisition. Some studies have reported that inter-platform reproducibility is close to the repeatability (20, 43). Moreover, for DCE-MRI, the 1.5T systems used are from the same vendor, so we can expect a high reproducibility between those 2 systems, as we used similar 3D GRE sequences and identical injection protocol. Fourth, we used MRE with 1 direction of motion, while most of studies on spleen stiffness used MRE with 3 directions of motion. However, only MRE with 1 direction of motion was available at our institution at time of the study. Fifth, the interval between HVPG and MRI may be quite long. However, logistically, it was not possible to scan the patients within a few days of the HVPG measurement, but all patients had no treatment in the time interval. Finally, we did not include endoscopic findings in our study.

To conclude, our preliminary results suggest that combined liver stiffness and perfusion metrics provide excellent accuracy for diagnosing portal hypertension, and fair accuracy for clinically significant portal hypertension. Combined MRE and DCE-MRI outperformed qualitative portal hypertension imaging scores for prediction of portal hypertension. These results need confirmation in a larger study.

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ABBREVIATIONS (in alphabetic order)

ARFI	acoustic radiation force imaging
AUC₆₀	area-under-the-curve at 60 s
AUROC	area under the receiver operating characteristic curve
C_{peak}	peak concentration
DCE-MRI	dynamic contrast-enhanced MRI
DV	distribution volume
F_a	arterial flow
F_p	portal flow
F_t	total hepatic flow
GRE	gradient recalled echo
HVPG	hepatic venous pressure gradient
IQR	interquartile range
K_{ep}	rate constant
K^{trans}	transfer constant
LSLU	ratio of liver stiffness measured with MRE and liver upslope
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MTT	mean transit time
ROC	receiver operating characteristic
ROI	region of interest
SWE	shear wave elastography

TTP time to peak

References

1. de Franchis R, Baveno V. Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol*. 2010; 53:762–768. [PubMed: 20638742]
2. Escorsell A, Garcia-Pagán JC, Bosch J. Assessment of portal hypertension in humans. *Clin Liver Dis*. 2001; 5:575–589. [PubMed: 11565131]
3. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology*. 2017; 65:310–335. [PubMed: 27786365]
4. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med*. 2005; 353:2254–2261. [PubMed: 16306522]
5. Abraldes JG, Bureau C, Stefanescu H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The “Anticipate” study. *Hepatology*. 2016; 64:2173–2184. [PubMed: 27639071]
6. Kihira S, Kagen AC, Vasudevan P, et al. Non-invasive prediction of portal pressures using CT and MRI in chronic liver disease. *Abdom Radiol N Y*. 2016; 41:42–49.
7. Thabut D, Trabut J-B, Massard J, et al. Non-invasive diagnosis of large oesophageal varices with FibroTest in patients with cirrhosis: a preliminary retrospective study. *Liver Int*. 2006; 26:271–278. [PubMed: 16584387]
8. Giannini EG, Botta F, Borro P, et al. Application of the platelet count/spleen diameter ratio to rule out the presence of oesophageal varices in patients with cirrhosis: a validation study based on follow-up. *Dig Liver Dis*. 2005; 37:779–785. [PubMed: 15996912]
9. Berzigotti A, Gilibert R, Abraldes JG, et al. Noninvasive prediction of clinically significant portal hypertension and esophageal varices in patients with compensated liver cirrhosis. *Am J Gastroenterol*. 2008; 103:1159–1167. [PubMed: 18477345]
10. Singh S, Venkatesh SK, Wang Z, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. *Clin Gastroenterol Hepatol*. 2015; 13:440–451. e6. [PubMed: 25305349]
11. Yoon JH, Lee JM, Joo I, et al. Hepatic fibrosis: prospective comparison of MR elastography and US shear-wave elastography for evaluation. *Radiology*. 2014; 273:772–82. [PubMed: 25007047]
12. Castera L, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. *J Hepatol*. 2012; 56:696–703. [PubMed: 21767510]
13. Lemoine M, Katsahian S, Ziol M, et al. Liver stiffness measurement as a predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis. *Aliment Pharmacol Ther*. 2008; 28:1102–1110. [PubMed: 18691352]
14. Vizzutti F, Arena U, Romanelli RG, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology*. 2007; 45:1290–1297. [PubMed: 17464971]
15. Cassinotto C, Charrie A, Mouries A, et al. Liver and spleen elastography using supersonic shear imaging for the non-invasive diagnosis of cirrhosis severity and oesophageal varices. *Dig Liver Dis*. 2015; 47:695–701. [PubMed: 25959234]
16. Elkrif L, Rautou P-E, Ronot M, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. *Radiology*. 2015; 275:589–598. [PubMed: 25469784]
17. Colecchia A, Montrone L, Scaioli E, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology*. 2012; 143:646–654. [PubMed: 22643348]
18. Ronot M, Lambert S, Elkrif L, et al. Assessment of portal hypertension and high-risk oesophageal varices with liver and spleen three-dimensional multifrequency MR elastography in liver cirrhosis. *Eur Radiol*. 2014; 24:1394–1402. [PubMed: 24626745]

19. Shin SU, Lee J-M, Yu MH, et al. Prediction of esophageal varices in patients with cirrhosis: usefulness of three-dimensional MR elastography with echo-planar imaging technique. *Radiology*. 2014; 272:143–153. [PubMed: 24620910]
20. Yasar TK, Wagner M, Bane O, et al. Interplatform reproducibility of liver and spleen stiffness measured with MR elastography. *J Magn Reson Imaging*. 2016; 43:1064–72. [PubMed: 26469708]
21. Lee YJ, Lee JM, Lee JE, et al. MR elastography for noninvasive assessment of hepatic fibrosis: reproducibility of the examination and reproducibility and repeatability of the liver stiffness value measurement. *J Magn Reson Imaging JMRI*. 2014; 39:326–331. [PubMed: 23589232]
22. Bosch J, García-Pagán JC. Complications of cirrhosis. I. Portal hypertension. *J Hepatol*. 2000; 32(1 Suppl):141–156. [PubMed: 10728801]
23. Lautt WW. Mechanism and role of intrinsic regulation of hepatic arterial blood flow: hepatic arterial buffer response. *Am J Physiol*. 1985; 249(5 Pt 1):G549–556. [PubMed: 3904482]
24. Denys A, Menu Y. Portal and splanchnic blood flow measurements in vivo: US Doppler or MR angiography? *J Hepatol*. 1997; 26:437–438. [PubMed: 9059969]
25. Annet L, Materne R, Danse E, Jamart J, Horsmans Y, Van Beers BE. Hepatic flow parameters measured with MR imaging and Doppler US: correlations with degree of cirrhosis and portal hypertension. *Radiology*. 2003; 229:409–414. [PubMed: 12970464]
26. Schabel MC, Parker DL. Uncertainty and bias in contrast concentration measurements using spoiled gradient echo pulse sequences. *Phys Med Biol*. 2008; 53:2345–2373. [PubMed: 18421121]
27. Wagner M, Corcuera-Solano I, Lo G, et al. Technical Failure of MR Elastography Examinations of the Liver: Experience from a Large Single-Center Study. *Radiology*. 2017; 284:401–412. [PubMed: 28045604]
28. Duan M, Loeffler R, Song R, et al. A Robust Method for Reducing Inflow Artifacts in the Arterial Input Function of Dynamic Contrast Enhanced Data Set. 19th Annual Meeting of ISMRM; Montreal, Canada. Montreal, Canada: 2011.
29. Bane O, Hectors SJ, Wagner M, et al. Accuracy, repeatability, and interplatform reproducibility of T1 quantification methods used for DCE-MRI: Results from a multicenter phantom study. *Magn Reson Med*. 2017; doi: 10.1002/mrm.26903
30. Zhang X, Petersen ET, Ghariq E, et al. In vivo blood T(1) measurements at 1.5 T, 3 T, and 7 T. *Magn Reson Med*. 2013; 70:1082–1086. [PubMed: 23172845]
31. Pintaske J, Martirosian P, Graf H, et al. Relaxivity of Gadopentetate Dimeglumine (Magnevist), Gadobutrol (Gadovist), and Gadobenate Dimeglumine (MultiHance) in human blood plasma at 0.2, 1.5, and 3 Tesla. *Invest Radiol*. 2006; 41:213–221. [PubMed: 16481903]
32. Materne R, Smith AM, Peeters F, et al. Assessment of hepatic perfusion parameters with dynamic MRI. *Magn Reson Med*. 2002; 47:135–142. [PubMed: 11754452]
33. Tofts PS, Brix G, Buckley DL, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. *J Magn Reson Imaging JMRI*. 1999; 10:223–232. [PubMed: 10508281]
34. Kim BK, Han K-H, Park JY, et al. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. *Am J Gastroenterol*. 2010; 105:1382–1390. [PubMed: 20087336]
35. Talaki E, Schaffellner S, Kniepeiss D, et al. CT perfusion imaging of the liver and the spleen in patients with cirrhosis: Is there a correlation between perfusion and portal venous hypertension? *Eur Radiol*. 2017
36. Gouya H, Grabar S, Vignaux O, et al. Portal hypertension in patients with cirrhosis: indirect assessment of hepatic venous pressure gradient by measuring azygos flow with 2D-cine phase-contrast magnetic resonance imaging. *Eur Radiol*. 2016; 26:1981–1990. [PubMed: 26373753]
37. Heye T, Davenport MS, Horvath JJ, et al. Reproducibility of Dynamic Contrast-enhanced MR Imaging. Part I. Perfusion Characteristics in the Female Pelvis by Using Multiple Computer-aided Diagnosis Perfusion Analysis Solutions. *Radiology*. 2013; 266:801–811. [PubMed: 23220897]
38. Tsushima Y, Koizumi J, Yokoyama H, Takeda A, Kusano S. Evaluation of portal pressure by splenic perfusion measurement using dynamic CT. *AJR Am J Roentgenol*. 1998; 170:153–155. [PubMed: 9423623]

39. Sauter AW, Spira D, Schulze M, Horger MS. Explanations for the heterogeneity of splenic enhancement derived from blood flow kinetic measurements using dynamic contrast-enhanced CT (DCE-CT). *Acta Radiol Stockh Swed* 1987. 2014; 55:645–653.
40. Wagner M, Besa C, Bou Ayache J, et al. Magnetic Resonance Elastography of the Liver: Qualitative and Quantitative Comparison of Gradient Echo and Spin Echo Echoplanar Imaging Sequences. *Invest Radiol*. 2016; 51:575–81. [PubMed: 26982699]
41. Mariappan YK, Dzyubak B, Glaser KJ, et al. Application of Modified Spin-Echo-based Sequences for Hepatic MR Elastography: Evaluation, Comparison with the Conventional Gradient-Echo Sequence, and Preliminary Clinical Experience. *Radiology*. 2017; 282:390–398. [PubMed: 27509543]
42. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology*. 2013; 144:102–111. e1. [PubMed: 23058320]
43. Ng CS, Raunig DL, Jackson EF, et al. Reproducibility of perfusion parameters in dynamic contrast-enhanced MRI of lung and liver tumors: effect on estimates of patient sample size in clinical trials and on individual patient responses. *AJR Am J Roentgenol*. 2010; 194:W134–140. [PubMed: 20093564]

Figure 1. Correlation plots displaying significant correlations between imaging parameters and HVPG measurements (DV: distribution volume, HVPG: hepatic venous pressure gradient; LS: liver stiffness; LSLU: ratio of liver stiffness and liver upslope; MRE: magnetic resonance elastography; PH: portal hypertension, TTP: time to peak).

Figure 2.

Top: 59 year-old female patient with chronic hepatitis C and moderate liver fibrosis (METAVIR F2) without portal hypertension (HVPg=3 mm). Bottom: 46 year-old female patient with alcoholic cirrhosis (METAVIR F4) and clinically significant portal hypertension (HVPg=18 mm). Patient with clinically significant portal hypertension had higher liver and spleen stiffness (12 and 14.3 kPa vs. 2.2 and 5.1 kPa, respectively), and increased liver and spleen TTP (time-to-peak) (liver in blue: 69.0 s and spleen in red: 13.6 s vs. 29.5 s and 10.9 s, respectively), with decreased liver upslope (0.007 vs. 0.015 mmol/L.s). LSLU (ratio of liver stiffness and liver upslope) was higher in patient with clinically significant portal hypertension than in patient without PH (1664 vs. 152).

Figure 3.

53 year-old female patient with chronic hepatitis B cirrhosis (METAVIR F4) and clinically significant portal hypertension (HVPg = 27 mmHg). A: Liver stiffness map obtained with MRE. Liver stiffness value was 4.99 kPa, below cutoff value of 5.75 kPa for clinically significant portal hypertension (false negative), while the portal hypertension imaging score correctly diagnosed clinically significant portal hypertension (score of 6 for both readers). Of note, spleen stiffness was not measured in this case. B and C: Axial T1-weighted post-contrast images demonstrate variceal sites (white arrows), D: Coronal T2-weighted image demonstrates moderate ascites and splenomegaly.

Table 1

Acquisition parameters for DCE-MRI and MRE.

	DCE-MRI		MRE	
Scanner	1.5T Siemens Avanto	1.5T Siemens Aera	3.0T GE MR750	1.5T Siemens Aera
Sequence type	3D FLASH	3D FLASH	2D GRE	2D GRE
Orientation	Coronal	Axial	Axial	Axial
TE (ms)	1	1.06	20	25
TR (ms)	2.73	2.74	50	50
Flip angle	12°	11.5°	20°	25°
Matrix	192 × 121	192 × 106	256 × 80	256 × 90
FOV (mm ²)	400 × 400	400 × 275	360 × 360	350 × 262
Slice thickness (mm)	4	4	10	7
Number of slices	36	40	4	4
Parallel imaging	GRAPPA 3	CAIPIRINHA 3	ASSET 2	GRAPPA 2
Sequence-specific parameters	Contrast agent 0.05 mmol/kg Gd-BOPTA; temporal resolution 2.3 s (64–100 dynamic volumes acquired)		Motion-encoding gradient frequency 60 Hz	

TE: echo time; TR: repetition time; FOV: field of view, 3D: 3 dimensional; GRE: gradient recalled echo; GRAPPA: generalized autocalibration partially parallel acquisition; ASSET: array spatial and sensitivity encoding technique; CAIPIRINHA: controlled aliasing in parallel imaging results in higher acceleration.

Table 2

Patients characteristics.

	All patients (n=34)
Sex (M/F)	16 (47%)/18 (53%)
Mean age (y)	52 ± 12
BMI (kg/m²)	29 ± 8
Cause of chronic liver disease	
Alcohol	2 (6%)
Chronic hepatitis C virus infection *	14 (41%)
Chronic hepatitis B virus infection	2 (6%)
Non alcoholic steatohepatitis	7 (21%)
PSC/PBC/AIH	9 (26%)
Fibrosis stage	
F1	7 (21%)
F2	10 (29%)
F3	7 (21%)
F4	10 (29%)
HVPG	
<5 mmHg	12 (35%)
5–10 mmHg	13 (38%)
10 mmHg	9 (27%)

Data are presented as mean ± standard deviation or number of cases (percentage of cases)

* including 3 cases with HCV associated with another etiology

BMI: body mass index

PSC: primary sclerosing cholangitis

PBC: primary biliary cirrhosis

AIH: auto-immune hepatitis

Table 3

Correlation between imaging parameters and HVPG measurements.

	R (correlation coefficient)	p
Liver parameters		
Liver T1 (sec)	0.049	0.809
Model-free DCE-MRI parameters		
TTP (sec)	0.517	0.006
Cpeak (mmol/L)	-0.146	0.467
AUC60 (mmol/L.s)	-0.176	0.380
Upslope (mmol/(L.s))	-0.567	0.002
Modeled DCE parameters		
F _a (ml/100g/min)	0.190	0.343
F _p (ml/100g/min)	-0.108	0.593
F _t (ml/100g/min)	0.047	0.817
MTT (sec)	0.313	0.112
DV (%)	0.494	0.009
ART (%)	0.079	0.694
Liver Stiffness (kPa)	0.486	0.006
Spleen parameters		
Spleen T1 (sec)	0.275	0.165
Model-free DCE-MRI parameters		
TTP (sec)	0.326	0.097
Cpeak (mmol/L)	-0.228	0.253
AUC60 (mmol/L.s)	-0.122	0.545
Upslope (mmol/(L.s))	-0.322	0.101
Modeled DCE parameters		
Total flow (ml/100g/min)	0.019	0.926
MTT (sec)	0.177	0.377
K ^{trans} (min ⁻¹)	0.019	0.926
K _{ep} (min ⁻¹)	-0.177	0.377
V _e (%)	0.278	0.160
Spleen Stiffness (kPa)	0.099	0.714
Spleen volume (cm³)	0.309	0.075
Spleen craniocaudal diameter (cm)	0.311	0.073
Portal hypertension imaging score		
Observer 3	0.447	0.008
Observer 4	0.484	0.004
Average between observers	0.441	0.009

Significant p values are in bold.

ART: arterial fraction, AUC60: area under the curve at 60 sec, Cpeak: concentration at the peak, DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging, DV: distribution volume, Fa: arterial flow, Fp: portal flow, Ft: total flow, Kep: rate constant, K^{trans}: transfer constant, MRE: magnetic resonance elastography, MTT: mean transit time, PH: portal hypertension, TTP: time to peak, Ve: extracellular extravascular volume

Table 4

Imaging parameters in patients without portal hypertension vs. with portal hypertension (< 5 mmHg) and clinically significant portal hypertension (≥ 10 mmHg). Data are presented as median (interquartile ranges: IQR).

	HVPG <5 mmHg (n=12)	HVPG 5 mmHg (n=22)	p (< 5 vs. 5 mmHg)	HVPG <10 mmHg (n=25)	HVPG 10 mmHg (n=9)	p (< 10 vs. 10 mmHg)
Liver parameters						
Liver T1 (sec)	563.40 (391.34)	544.98 (158.20)	0.631	514.06 (192.60)	575.41 (122.41)	0.621
Model-free DCE-MRI parameters						
TTP (sec)	40.99 (22.20)	53.02 (31.80)	0.035	41.47 (25.76)	69.45 (41.98)	0.045
Cpeak (mmol/L)	0.39 (0.23)	0.40 (0.16)	0.527	0.39 (0.17)	0.40 (0.17)	0.735
AUC60 (mmol/L.s)	17.87 (4.98)	17.01 (10.17)	0.631	17.87 (7.71)	16.45 (9.92)	0.658
Upslope (mmol/(L.s))	0.011 (0.011)	0.007 (0.007)	0.027	0.011 (0.007)	0.006 (0.004)	0.039
Modeled DCE parameters						
F _a (ml/100g/min)	50.52 (90.11)	62.11 (76.79)	0.631	50.52 (72.99)	74.94 (268.06)	0.260
F _p (ml/100g/min)	193.63 (215.34)	136.78 (189.66)	0.322	187.70 (205.55)	157.00 (384.56)	0.658
F _t (ml/100g/min)	243.93 (218.98)	203.04 (195.65)	0.596	204.98 (194.33)	266.47 (582.45)	0.307
MTT (sec)	14.79 (14.66)	20.75 (22.90)	0.118	18.01 (17.39)	23.03 (19.74)	0.481
DV (%)	38.27 (38.44)	53.00 (44.98)	0.131	47.28 (24.29)	77.25 (111.01)	0.025
ART (%)	0.21 (0.42)	0.34 (0.33)	0.433	0.33 (0.44)	0.34 (0.18)	1.000
Liver Stiffness (kPa)	2.31 (2.80)	5.14 (2.57)	0.004	3.88 (3.16)	5.86 (6.71)	0.037
Spleen parameters						
Spleen T1 (sec)	770.09 (208.80)	858.17 (376.58)	0.561	797.99 (327.67)	894.01 (279.20)	0.198
Model-free DCE-MRI parameters						
TTP (sec)	15.46 (13.04)	21.51 (37.06)	0.212	15.46 (16.65)	44.90 (40.69)	0.045
Cpeak (mmol/L)	1.11 (0.60)	0.77 (0.65)	0.194	0.88 (0.73)	0.77 (0.57)	0.333
AUC60 (mmol/L.s)	39.44 (30.98)	34.44 (24.32)	0.403	37.21 (25.55)	34.52 (21.76)	0.775
Upslope (mmol/(L.s))	0.064 (0.086)	0.031 (0.070)	0.176	0.051 (0.090)	0.021 (0.57)	0.095
Modeled DCE-MRI parameters						
Total flow (ml/100g/min)	520.81 (490.39)	454.07 (416.19)	0.705	434.45 (482.24)	529.30 (536.66)	0.658
MTT (sec)	15.72 (20.67)	19.17 (17.08)	0.348	18.47 (13.80)	22.74 (42.77)	0.217
K _{trans} (min ⁻¹)	3.91 (3.68)	3.41 (3.12)	0.705	3.26 (3.62)	3.97 (4.02)	0.658

	HVPG <5 mmHg (n=12)	HVPG 5 mmHg (n=22)	p (< 5 vs. 5 mmHg)	HVPG <10 mmHg (n=25)	HVPG 10 mmHg (n=9)	p (< 10 vs. 10 mmHg)
K_{ep} (min^{-1})	3.82 (4.96)	3.13 (2.48)	0.348	3.25 (3.56)	2.79 (3.01)	0.217
V_e (%)	0.61 (0.50)	0.89 (0.37)	0.106	0.74 (0.42)	0.99 (0.56)	0.147
Spleen Stiffness (kPa)	5.90 (2.28)	6.23 (1.98)	0.421	5.87 (1.97)	6.58 (4.21)	0.338
Spleen volume (cm^3)	246 (252)	441 $\pm$ 629	0.018	415 (256)	443 (834)	0.188
Spleen craniocaudal diameter (cm)	11.6 (2.8)	14.0 $\pm$ 4.8	0.028	12.5 (3.1)	14.6 (7.1)	0.086
Portal hypertension imaging score						
Observer 3	0 (1)	2 (5.25)	0.013	1 (1.5)	4 (4.5)	0.027
Observer 4	0 (1)	2 (5)	0.008	1 (1.5)	4 (4.5)	0.037
Average between observers	0 (1)	2 (5.25)	0.013	1 (1.5)	4 (4.5)	0.033

Significant p values are in bold.

ART: arterial fraction, AUC60: area under the curve at 60 sec, Cpeak: concentration at the peak, DCE-MRI: dynamic contrast enhanced magnetic resonance imaging, DV: distribution volume, Fa: arterial flow, Fp: portal flow, Ft: total flow, K_{ep} : rate constant, K_{trans} : transfer constant, MRE: magnetic resonance elastography, MTT: mean transit time, TTP: time to peak, Ve: extracellular extravascular volume

ROC analysis for the diagnosis of portal hypertension (> 5 mmHg) and clinically significant portal hypertension (> 10 mmHg). Only parameters with significant AUROCs are listed.

Table 5

	AUROC (95% CI)	P	Cutoff	Sensitivity (%)	Specificity (%)
Diagnosis of portal hypertension					
Liver Upslope	0.765 (0.583–0.948)	0.027	0.007	100	50
Liver TTP	0.753 (0.565–0.941)	0.035	>41.19	78	77
Liver stiffness	0.809 (0.637–0.981)	0.005	3.01	85	73
Spleen volume	0.746 (0.570–0.922)	0.019	239	95	50
Spleen craniocaudal diameter	0.731 (0.562–0.900)	0.028	12.8	68	75
Portal hypertension score (Observer 3)	0.758 (0.598–0.917)	0.014	3	50	92
Portal hypertension score (Observer 4)	0.777 (0.623–0.930)	0.009	2	55	92
Portal hypertension score (average of 2 observers)	0.756 (0.596–0.915)	0.015	2.25	50	100
LSLU	0.903 (0.787–1.000)	0.001	433	78	100
Diagnosis of clinically significant portal hypertension					
Liver Upslope	0.757 (0.554–0.959)	0.038	0.0094	68	88
Liver TTP	0.750 (0.528–0.972)	0.044	64.34	63	95
Liver DV	0.776 (0.594–0.959)	0.026	68.68	63	84
Spleen TTP	0.750 (0.547–0.953)	0.044	37.38	63	90
Liver stiffness	0.742 (0.552–0.933)	0.037	5.75	55	91
Portal hypertension score (Observer 3)	0.749 (0.540–0.957)	0.029	3	78	80
Portal hypertension score (Observer 4)	0.736 (0.528–0.944)	0.039	2	78	75
Portal hypertension score (average of 2 observers)	0.742 (0.530–0.955)	0.033	2.25	78	84
LSLU	0.785 (0.597–0.972)	0.023	469	88	72

DV: distribution volume, LSLU: ratio of liver stiffness and liver upslope, TTP: time to peak.

Table 6

Results of general linear modeling with stepwise selection of (combination of) significant parameters for prediction of portal hypertension and clinically significant portal hypertension.

	Input data	Model parameters	Accuracy	p
Portal hypertension	Quantitative MRI parameters	Liver Upslope + Liver stiffness	0.769	0.002
	DCE-MRI only	Liver Upslope	0.704	0.008
	MRE only	Liver stiffness	0.807	0.015
	Qualitative Portal Hypertension imaging score	Qualitative Portal Hypertension imaging score	0.677	0.002
Clinically significant portal hypertension	Quantitative MRI parameters	Liver Upslope	0.740	0.031
	DCE-MRI only	Spleen TTP	0.778	0.029
	MRE only	Liver stiffness	0.742	0.047
	Qualitative Portal Hypertension imaging score	Qualitative Portal Hypertension imaging score	0.765	0.019

DCE-MRI: dynamic contrast enhanced magnetic resonance imaging, MRE: magnetic resonance elastography, TTP: time to peak,