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Splenic T1ρ as a noninvasive biomarker for portal hypertension

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Abstract

Background: There is a need for noninvasive methods for the diagnosis and monitoring of portal hypertension (PH).

Purpose: To (1) assess the correlation of liver and spleen T_1 and $T_{1\rho}$ measurements with portal pressures in patients with chronic liver disease and (2) to compare the diagnostic performance of the relaxation parameters with radiological assessment of PH.

Study Type: Prospective.

Subjects: 25 patients (M/F 16/9, mean age 56 y, range 21 – 78 y) undergoing portal pressure [hepatic venous pressure gradient (HVPG)] measurements.

Field strength/sequence: 1.5T abdominal MRI scan, including $T_{1\rho}$ and T_1 mapping.

Assessment: Liver and spleen $T_{1\rho}$ and T_1, radiological PH score and (normalized) spleen length were evaluated.

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Statistical tests: Spearman correlation of all MRI parameters with HVPG was assessed. The diagnostic performance of the assessed parameters for prediction of PH (HVPG ≥ 5 mmHg) and clinically significant PH (CSPH, HVPG ≥ 10 mmHg) was determined by ROC analysis.

Results: Mean HVPG measurement was 7.8±5.3 mmHg [PH, n=18 (72%) including CSPH, n=9 (36%)]. PH score, (normalized) spleen length and spleen $T_{1\rho}$ significantly correlated with HVPG, with strongest correlation found for spleen $T_{1\rho}$ (r=0.613, P=0.001). Spleen $T_{1\rho}$ was the only parameter that showed significant diagnostic performance for assessment of PH (AUC 0.817, P=0.015) and CSPH (AUC=0.778, P=0.024). Normalized spleen length also showed significant diagnostic performance for prediction of CSPH, with a slightly lower AUC (AUC=0.764, P=0.031). Radiological PH score, $T_{1\rho}$ and T_1 of the liver and T_1 of the spleen did not show significant diagnostic performance for assessment of (CS)PH (P>0.075).

Data Conclusion: Spleen $T_{1\rho}$ showed a significant correlation with portal pressure and showed improved diagnostic performance for prediction of (CS)PH compared to radiological assessment. These initial results need confirmation in a larger cohort.

Keywords

liver disease; portal hypertension; $T_{1\rho}$; T_1

Introduction

Portal hypertension (PH) is one of the major serious consequences of liver cirrhosis and is associated with severe complications including ascites, hepatic encephalopathy and bleeding from gastro-esophageal varices (1). For clinical management and prognostication of cirrhotic patients, measurement of portal pressure is of key importance (2). The reference standard for the diagnosis and staging is the transvenous measurement of the hepatic venous pressure gradient (HVPG) (3). Limitations of HVPG measurements include the limited availability and invasiveness with risk of complications. In addition to the diagnosis of PH, monitoring of portal pressure is essential to measure the efficacy of medical therapies for PH, including treatment with non-selective beta-blockers (NSBB) (2). It has been shown that a decrease of HVPG of at least 20% from baseline or to a value of 12 mmHg or less greatly reduces their risk of development of bleeding varices, ascites, encephalopathy and death (4). Monitoring of portal pressure is thus essential to identify responders vs. non-responders to NSBB therapy. However, due to its invasiveness, HVPG measurements cannot be longitudinally performed to monitor response to therapy. Therefore, there is a crucial need for noninvasive methods to assess and monitor portal pressure (2).

Ultrasound-based transient elastography (TE) of the liver has shown promise for noninvasive assessment of PH (5). However, the utility of TE is limited by sampling errors and the possibility of inaccurate or failed measurements (6). MRI is currently routinely used for monitoring of cirrhotic patients, including for assessment of liver disease and for detection of HCC (7). MRI also offers quantitative methods that may provide surrogate measurements of portal pressure (8–10). Multiparametric MRI approaches of combined 2D phase contrast and liver T_1 measurements (11) or combined dynamic contrast-enhanced MRI and MR elastography (12) have been proposed, both showing significant correlation with HVPG.

Although these MRI techniques are promising, their clinical implementation is limited by the need for extensive analysis, additional hardware and/or significant prolongation of acquisition time.

Motivated by previous reports on the correlation of MRI relaxation parameter $T_{1\rho}$ with the degree of liver fibrosis (13,14), we hypothesize that this parameter may have utility for prediction of PH. $T_{1\rho}$ (also referred to as T1rho) is sensitive to the interactions between water molecules and macromolecules including collagen (15–17). The pathogenesis of PH includes an increased intrahepatic vascular resistance due to fibrosis and scarring (18). Diffuse fibrosis in the spleen has also been described in patients with PH (19). The pathophysiological changes due to PH in the liver and spleen may potentially be measured by quantitative $T_{1\rho}$ measurements, possibly allowing for measurements of PH. In a previous study, liver T_1 measurements strongly correlated with HVPG measurements, while spleen T_1 measurements only showed a moderate correlation (11). Recently, iron-corrected cT_1 measurements in the spleen were reported to be strongly correlated with HVPG measurements, while liver cT_1 measurements were not (20). These initial results warrant further investigation into T_1 for assessment of PH.

Thus, the aims of this study were to assess the correlation of liver and spleen T_1 and $T_{1\rho}$ with HVPG measurements in patients with chronic liver disease and to compare the diagnostic performance of the relaxation parameters with radiological assessment of PH.

Materials and Methods

Patients

This HIPAA-compliant prospective study was approved by our Institutional Review Board. Informed consent was obtained from all patients. Inclusion criteria were: chronic liver disease; scheduled for or recently performed transjugular liver biopsy with portal pressure measurement. Exclusion criteria were: history of liver transplant or other major abdominal surgery; recent (within last 6 months) onset of beta-blocker treatment because of its effect on PH (21); extrahepatic causes of PH, including portal vein thrombosis; contraindications to MRI including claustrophobia and metal implants.

Between March 2018 and August 2019, 30 patients that matched our inclusion/exclusion criteria were recruited to our study. Five of these patients were excluded from analysis, because they ultimately did not receive portal pressure measurements. Finally, 25 patients with liver disease (M/F 16/9, mean age 56 y, range 21 – 78 y) were recruited to our study. Etiology of liver disease was as follows: non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH), n=9; autoimmune hepatitis, n=4; chronic hepatitis C infection, n=3; cryptogenic cirrhosis, n=3; primary sclerosing cholangitis, n=2; alcoholic or drug induced liver disease, n=2; hemochromatosis, n=1; hepatoportal sclerosis, n=1. The average time between MRI and the portal pressure measurement was −2±48 days.

Portal pressure measurements

The HVPG measurements were performed by 1 of 5 interventional radiologists with over 300 case experience each. A right transjugular access was obtained using ultrasound

guidance. A 5F 65cm MPA diagnostic catheter (Cordis, Santa Clara, CA) was used to catheterize the right or middle hepatic vein and venography was performed with iodinated contrast. A standard disposable pressure transducer was used to measure free hepatic vein pressure through the end hole of the catheter. Then the catheter was moved forward into a wedged position and confirmed with contrast injection to visualized reflux into portal radicals. A wedge pressure was obtained from this location. Measurements were obtained after 45–60 seconds to allow for equilibration. Three measurements were obtained: systolic, diastolic and mean. Neither the transducer position nor table height were changed during pressure measurements. HVPG was measured as the difference between wedge pressure – free mean pressure. Following HVPG measurement, a transjugular liver biopsy (19 gauge) was performed from the hepatic vein using a TLAB biopsy kit (Argon Medical, Frisco, TX) in 23 cases. In two patients, a transjugular intrahepatic portosystemic shunt (TIPS) was placed after the initial portal pressure measurement.

MRI acquisition

The MRI acquisition was performed on a Siemens 1.5T Aera system (Siemens Healthineers, Erlangen, Germany) equipped with an 18-channel flexible body array coil. Patients were instructed to fast for 6 hours prior to the scan to avoid postprandial effects on the assessed liver MRI parameters (22). The research MRI exam consisted of standard abdominal MRI sequences [axial and coronal T_2 HASTE, liver fat and iron assessment with axial multi-echo Dixon, T_1 VIBE pre and post injection of 0.025 mmol/kg gadoxetic acid (Eovist/Primovist, Bayer) and diffusion-weighted imaging] supplemented with research acquisitions. In addition to T_1 and $T_{1\rho}$, the following acquisitions were performed for research purposes: dynamic contrast-enhanced MRI, 4D flow and MR elastography. The single-slice $T_{1\rho}$ acquisition was performed using a custom-written sequence, which was described previously. In short, the sequence consisted of a spin-lock preparation consisting of a pulse scheme of continuous wave radiofrequency (RF) pulses compensating for B_0 and B_1 imperfections (23), followed by a single-shot 2D fast low angle shot (FLASH) read-out. Acquisition parameters were as follows: spin-lock strength 500 Hz, spin-lock time (TSL) 4.8, 9.6, 19.2 and 38.4 ms, echo time (TE) 2.11 ms, repetition time (TR) 15 ms, flip angle (FA) 15°, matrix 128×104, field-of-view (FOV) 380×310 mm^2. The acquisition was performed in a single axial slice covering the largest portion of the liver and spleen. The acquisition was completed during expiration four breath-holds of 10 seconds each to acquire all four spin-lock times.

T_1 measurements were obtained in a single axial slice matching the $T_{1\rho}$ slice using an inversion recovery Look-Locker (IR-LL) sequence. The acquisition was triggered with a simulated ECG signal with an R-R interval of 2000 ms. Other acquisition parameters were: 32 inversion times (TI) (82.5 – 1417.5 ms), TE 1.27 ms, TR 41.7 ms, FA 8°, matrix 192×156, FOV 380×310 mm^2.

The $T_{1\rho}$ and T_1 measurements were both acquired before contrast injection.

$T_{1\rho}$ and T1 analysis

$T_{1\rho}$ and T_1 images were imported in FireVoxel (CAI^2R, NYU) for region-of-interest (ROI) analysis. ROIs in the right liver lobe and spleen were drawn by observer 1 (SJH, an MRI physicist with 4 years of experience). The ROIs were drawn as large as possible, avoiding large vessels or other non-parenchymal tissue. The ROIs were propagated to all TSL's (for $T_{1\rho}$) and TI's (for T_1) and adjusted if necessary to correct for motion or presence of artifacts. The ROIs were the same for all TSL's or TI's. The ROIs were exported to MATLAB (version R2016b, The MathWorks, Natick, MA, USA) for further analysis. A mono-exponential fit (17) through the ROI-averaged signal data at the different spin-lock times was performed to estimate $T_{1\rho}$ in the spleen and liver for each patient. Spleen and liver T_1 values were also calculated from the ROI-averaged signal curves from the IR-LL images using a previously described fitting algorithm (24).

In order to assess interobserver variability of the T_1 and $T_{1\rho}$ measurements, an additional observer (observer 2; OB, an MRI physicist with 6 years of experience), performed the $T_{1\rho}$ analysis in 5 consecutive patients of the cohort.

Radiological analysis

Observer 3 (DS, a radiologist with 5 years of experience in abdominal MRI) performed radiological assessment of PH. The maximal craniocaudal diameter of the spleen was measured from the coronal T2 HASTE images, since spleen size has been shown to be a significant predictor of PH (25). In addition, to correct for non-pathological variation in spleen size, a normalized spleen length was calculated by dividing the spleen length by the maximal normal spleen length calculated based on the patient's gender and height (26). The previously described PH score, which allows for fast assessment of PH based on imaging, was calculated as composite of spleen size, number of variceal sites and volume of ascites (details described in (27)).

Two additional observers, observer 4 and 5 (SL and GC, both body MRI radiologists with 9 and 3 years of experience, respectively) also performed the radiological assessment to evaluate interobserver reproducibility of the spleen size and PH score measurements. However, only the measurements of observer 3 were used for further statistical analysis in terms of correlation with portal pressure.

Statistical analysis

Data is presented as mean ± standard deviation (SD). As this represents an observational, exploratory study, no formal sample size calculation was performed. Given the relatively small sample size in this preliminary study, non-parametric tests were used for statistical analysis. Interobserver reproducibility of the liver and spleen T_1 and $T_{1\rho}$ measurements and radiological parameters (spleen size, PH score) among the observers was assessed using intra-class correlation (ICC) analysis.

The correlation of imaging parameters [T_1 and $T_{1\rho}$ in liver and spleen, (normalized) spleen length and PH score] with HVPG was assessed using Spearman correlation tests. Differences in MRI parameters between patients with and without PH (HVPG ≥ 5 mmHg

vs. HVPG < 5 mmHg) and with and without clinically significant (CS)PH (HVPG ≥ 10 mmHg vs. HVPG < 10 mmHg) (4) were assessed using Mann-Whitney U tests. ROC analysis was performed to determine the diagnostic performance of each of the parameters for assessment of (CS)PH. Logistic regression with feature selection was performed to evaluate the utility of combination of parameters for improved assessment of (CS)PH. Statistical analysis was performed in MATLAB and SPSS (version 20, IBM, Armonk, NY, USA). For all tests, a significance level of 0.05 was used.

Results

Portal pressure measurements

Mean HVPG measurement was 7.8±5.3 mmHg (range 0 – 18 mmHg). Of the 25 patients, 18 patients (72%) had PH including 9 patients (36% of entire population) with CSPH. Liver fibrosis stage was as follows: F0, n=2 (8%); F1, n=2 (8%); F2, n=4 (16%); F3, n=3 (12%); F4, n=14 (56%).

Liver and spleen T_1 and $T_{1\rho}$ for prediction of PH

Spleen T_1 was not assessed in one patient because the spleen was not included in the acquisition. All other measurements were successfully obtained. Excellent interobserver reproducibility was observed for liver T_1 and $T_{1\rho}$ (ICC 0.99, P<0.001 and 0.834, P=0.004, respectively) and spleen T_1 and $T_{1\rho}$ (ICC 0.87, P=0.009 and 0.99, P<0.001, respectively).

Representative T_1 and $T_{1\rho}$ maps of patients with no PH, PH and CSPH are shown in Figure 1. While $T_{1\rho}$ in the liver and T_1 measurements in both liver and spleen did not show substantial differences between degrees of PH severity, $T_{1\rho}$ in the spleen showed visual increase in patients with PH. This observation was also reflected in the quantitative correlation analysis. $T_{1\rho}$ in the spleen was significantly positively correlated with HVPG (r=0.613, P=0.001; Figure 2), while the other relaxation parameters did not show significant correlation (P>0.076).

Radiological assessment of PH

Varices and ascites were observed in 15 patients (60%) and 3 patients (12%), respectively. Fourteen patients (56%) exhibited splenomegaly (spleen length larger than expected maximal normal spleen length based on height and gender (26)). All assessed radiological parameters (spleen length, normalized spleen length and PH score) showed a significant moderate positive correlation with HVPG (r range 0.429 – 0.475, P<0.032; Figure 2).

Radiological evaluation by two additional observers indicated excellent interobserver reproducibility for spleen size (ICC 0.96, P<0.001) and good interobserver reproducibility for PH score (ICC 0.87, P<0.001).

Diagnostic performance (Table 1).

Spleen $T_{1\rho}$ was the only parameter that showed significant diagnostic performance for differentiation between no PH and PH (AUC 0.817, P=0.015). For prediction of CSPH, the strongest diagnostic performance was also observed for spleen $T_{1\rho}$ (AUC=0.778, P=0.024).

Normalized spleen length also showed significant diagnostic performance for prediction of CSPH (AUC=0.764, P=0.031). The other parameters ($T_{1\rho}$ liver, T_1 liver and spleen, spleen length and PH score) did not show significant diagnostic performance for assessment of (CS)PH (P>0.051). Logistic regression with feature selection identified spleen $T_{1\rho}$ as independent predictor for both PH and CSPH (P<0.013), without added value of combined features.

Discussion

Accurate diagnosis and monitoring of PH is essential for management of patients with liver cirrhosis. In our preliminary study, we found that splenic $T_{1\rho}$ showed a highly significant positive correlation with HVPG. Splenic $T_{1\rho}$ showed improved diagnostic performance of PH compared to radiological assessment, including the previously described radiological PH score (27).

The significant correlation of spleen $T_{1\rho}$ with portal pressure may be counterintuitive, since the pathophysiology of splenomegaly in PH is generally believed to be caused by hemodynamic changes (increased vascular pressure) and consequent pooling of blood in the red pulp (congestion) (19). The congestive splenomegaly does not likely affect $T_{1\rho}$. However, a study describing pathologic assessment of splenic tissues has shown other effects of PH on the splenic parenchyma, including hyperplasia of histiocytes and increase of reticuloendothelial fibers that evolves into diffuse fibrosis (19). The elevation in $T_{1\rho}$ in the spleen with increased PH severity may reflect the deposition of collagen during the fibrogenesis. In the liver, we did not find significant correlation of HVPG with $T_{1\rho}$, while it would be expected that the increase in portal pressure would be related to the amount of scarring/fibrosis in the liver leading to obstructed flow (28). We believe that the lack of correlation in the liver may be attributable to possible confounding factors to accurate $T_{1\rho}$ measurement in the liver, including iron deposition and inflammation (29). Indeed, while a significant positive correlation of liver $T_{1\rho}$ with fibrosis severity has been reported (30), another study reported a lack of correlation with fibrosis (31). The discrepancy between results may possibly be explained by the variability in liver disease etiology in the patient cohort included in the latter study (31), while the significant correlation with liver fibrosis was found in a cohort of patients all diagnosed with hepatitis C (30). Liver $T_{1\rho}$ may thus be affected by the large variability in pathophysiological characteristics between liver diseases (32), precluding universal use of this parameter for prediction of liver fibrosis. The pathophysiological changes in the spleen due to PH may be less sensitive to differences in disease etiology, which may explain the significant results for spleen $T_{1\rho}$ in our study.

Liver and spleen T_1 measurement did not show utility for prediction of PH in our study. A previous study has shown significant positive correlation of liver T_1 with HVPG (11), which was not reproduced in our study. The discrepancy may be due to other factors, including inflammation, fat and iron content, that may influence T_1 quantification (33). Iron corrected cT_1 measurements eliminate the dependence of T_1 values on iron content. Liver cT_1 has shown to be strongly correlated with liver fibrosis (34). More recently spleen cT_1 showed strong correlation with HVPG measurements in a proof-of-concept study (20), suggesting that this parameter may also be a suitable biomarker for noninvasive PH assessment. In

our study, T_1 correction was not performed. $T_{1\rho}$ may be easier to implement in clinical settings compared to cT_1, as the $T_{1\rho}$ analysis does not require proprietary software, which is currently necessary for the cT_1 measurements. In addition, $T_{1\rho}$ only requires a single acquisition, while the cT_1 needs a combination of T_1 and T_2* acquisitions.

Spleen $T_{1\rho}$ outperformed the radiological PH score, in particular for differentiation of patients with and without PH. Addition of $T_{1\rho}$ to liver MRI protocols may thus allow for improved and objective assessment of PH. Compared to the routine abdominal MRI protocol, the used $T_{1\rho}$ protocol only adds 40 seconds of acquisition time in 4 brief breath-holds.

For clinical application, the $T_{1\rho}$ acquisition could potentially be further optimized to provide 3D coverage rather than a single slice. Nevertheless, the spleen is usually a homogeneous organ, also in the presence of PH (35). In addition, an adiabatic $T_{1\rho}$ pulse sequence could possibly allow for measurement with higher spin-lock times without exceeding specific absorption rate (SAR) limits, potentially resulting in improved sampling of the $T_{1\rho}$ decay (36). Also, other spin-lock strengths may be evaluated, which may improve the observed $T_{1\rho}$ contrast in PH. In addition to optimization of the technique, test-retest repeatability splenic $T_{1\rho}$ needs to be determined, although excellent robustness of $T_{1\rho}$ evaluation has been observed in other abdominal organs, including liver (13) and kidney (17). The potential confounding influence of potential other co-existing splenic pathologies (e.g. sickle cell disease, Gaucher disease, etc. (35)) on splenic $T_{1\rho}$ would also need to be evaluated, although the prevalence of multiple spleen pathological conditions would be expected to be rare. Moreover, potential influence of age and sex on spleen relaxometry, including $T_{1\rho}$, needs to be studied, as age- and sex-dependent changes in spleen iron deposition may affect the measurements (37).

After further validation and optimization of the splenic $T_{1\rho}$ measurement, its clinical introduction may have implications for management of cirrhotic patients, as it would allow for a noninvasive diagnosis and monitoring of PH. This could ultimately reduce the need for invasive HVPG and endoscopic procedures.

LIMITATIONS

Our study had several limitations, including the small sample size. Our study should therefore be considered as exploratory and hypothesis-generating. In addition, portal pressures were not obtained at the same day as the MRI exam. Another limitation includes the lack of pathological validation of the observed significant correlation of splenic $T_{1\rho}$ with PH. However, pathological sampling of the spleen is extremely rare and therefore further investigation of pathophysiological factors contributing to $T_{1\rho}$ may rather be performed in animal models.

CONCLUSION

We found that spleen $T_{1\rho}$ was significantly correlated with portal pressure and showed improved diagnostic performance for prediction of (CS)PH compared to radiological assessment. The results of our preliminary study need to be validated in a larger cohort.

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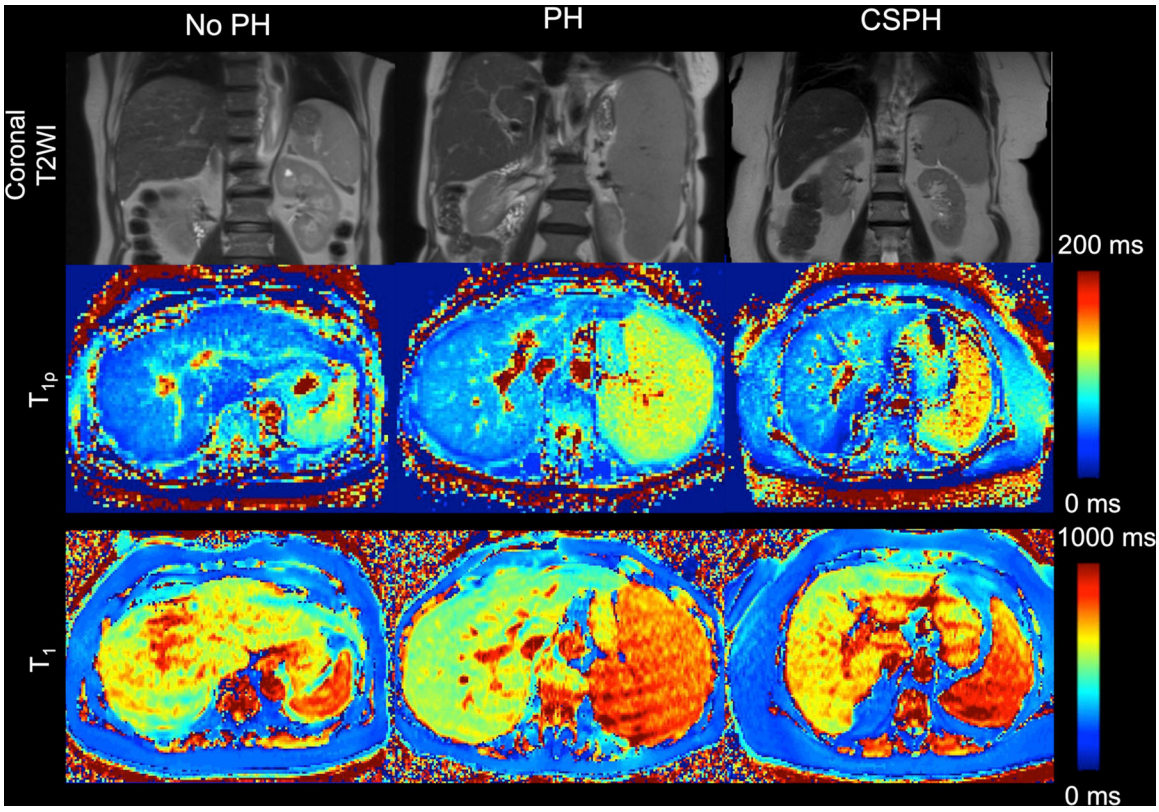

Figure 1.

Coronal T_2-weighted images and $T_{1\rho}$ and T_1 maps in a single slice through the liver and spleen of (left) a 59-year old male HCV patient without PH (HVPG=0 mmHg), (middle) a 78-year old female patient with drug-induced liver disease with PH (HVPG=6 mmHg) and (right) a 63-year old patient with primary sclerosing cholangitis with CSPH (HVPG=14 mmHg). Spleen showed a clear $T_{1\rho}$ elevation with increased PH severity (from left to right: 99.0, 109.6 and 131.4 ms), while liver $T_{1\rho}$ and liver and spleen T_1 did not show a visual trend with PH severity (from left to right 47.9, 55.7 and 53.1 ms for liver $T_{1\rho}$; 594.4 ms, 540.9 and 638.9 ms for liver T_1; 774.2 ms, 777.1 ms and 833.3 ms for spleen T_1). Spleen lengths were 10.0 cm, 20.2 cm and 13.4 cm, respectively.

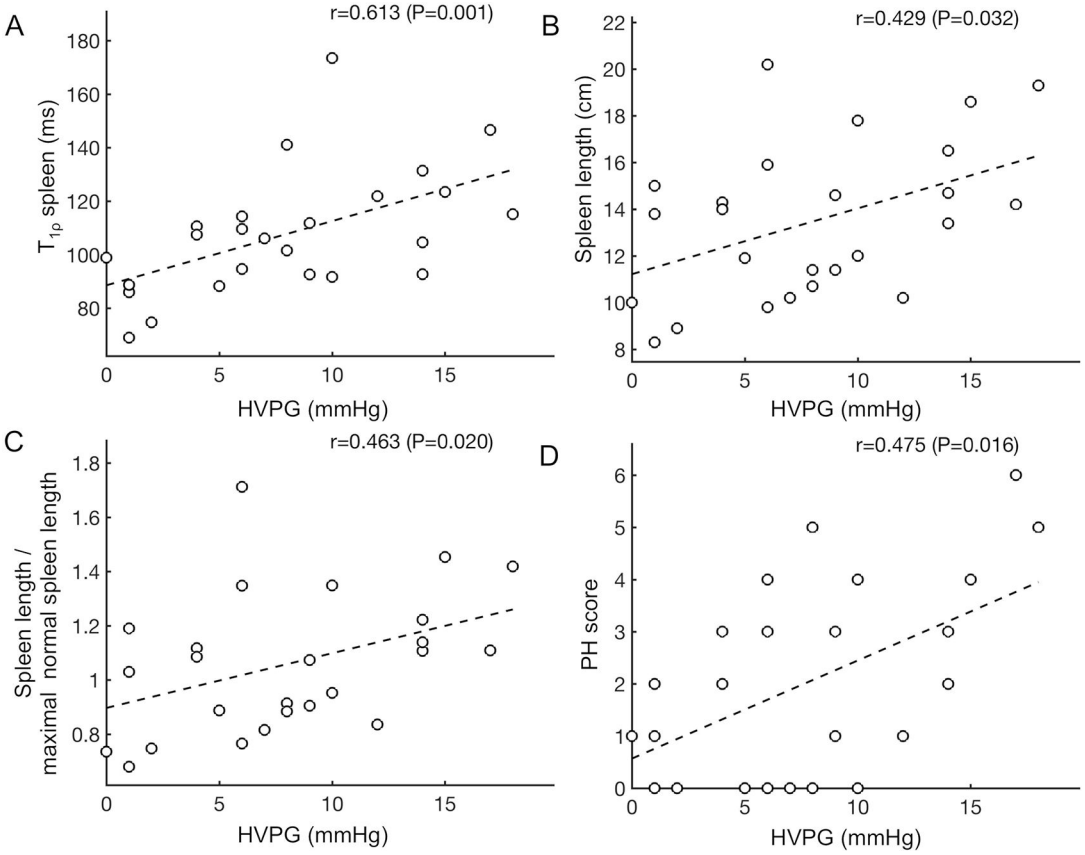

Figure 2.

Correlation plots of (A) $T_{1\rho}$ in the spleen, (B) spleen length, (C) normalized spleen length and (D) radiological PH score with hepatic venous pressure gradient (HVPG).

Table 1.

Mean ± standard deviation and diagnostic performance of the assessed parameters for differentiation between no PH and PH and between no CSPH and CSPH.

		$T_{1\rho}$ liver (ms)	$T_{1\rho}$ spleen (ms)	T_1 liver (ms)	T_1 spleen (ms)	Spleen length (cm)	Spleen length/ maximal normal length	PH score
Normal vs. PH	**No PH**	47.4±8.5	90.8±15.8	553.8±76.0	728.1±34.0	15.2±3.1	1.18±0.21	3.0±1.9
	PH	50.0±8.5	114.5±22.4	558.8±57.9	763.1±50.9	14.0±3.4	1.11±0.26	2.4±2.0
	p *	0.318	**0.017**	0.832	0.134	0.193	0.173	0.242
	AUC (95% CI)	0.635 (0.39 – 0.88)	0.82 (0.63 –1)	0.53 (0.24 – 0.82)	0.71 (0.49 – 0.94)	0.68 (0.43 – 0.92)	0.68 (0.44 – 0.93)	0.66 (0.44 –0.87)
	p #	0.304	**0.015**	0.809	0.125	0.183	0.164	0.238
	Threshold	51.1	90.2	594.1	775.7	10.1	0.76	2.5
	Sensitivity	56%	94%	83%	44%	94%	100%	50%
	Specificity	86%	57%	57%	100%	43%	43%	86%
No CSPH vs. CSPH	**No CSPH**	49.3±6.8	99.7±17.3	542.1±64.2	743.6±42.6	12.5±15.2	0.99±0.27	1.6±1.6
	CSPH	49.2±11.2	122.4±26.2	584.5±49.6	772.3±57.1	15.2±3.1	1.18±0.21	3.0±1.9
	p *	0.756	**0.025**	0.183	0.190	0.054	**0.034**	0.074
	AUC (95% CI)	0.54 (0.29 – 0.80)	0.78 (0.58 – 0.98)	0.67 (0.45 – 0.89)	0.67 (0.42 – 0.91)	0.74 (0.54 – 0.94)	0.76 (0.57 – 0.96)	0.72 (0.57 – 0.96)
	p #	0.734	**0.024**	0.174	0.180	0.051	**0.031**	0.075
	Threshold	52.0	114.7	550.8	778.0	12.0	1.10	1.5
	Sensitivity	56%	67%	78%	56%	89%	78%	78%
	Specificity	69%	94%	63%	87%	56%	75%	56%

*from Mann-Whitney U test.

#from ROC analysis

AUC = area-under-the-curve; CI = confidence interval; CSPH = clinically significant portal hypertension; PH = portal hypertension