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MR-based Measurements of Portal Vein Flow and Liver Stiffness for Predicting Gastroesophageal Varices

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Objectives: We evaluated flow parameters measured by phase-contrast magnetic resonance (MR) imaging (PC-MRI) of the portal venous system and liver stiffness measured by MR elastography (MRE) to determine the usefulness of these methods in predicting gastroesophageal varices (GEV) in patients with chronic liver disease (CLD).

Methods: In patients with CLD and controls, we performed PC-MRI on the portal (PV) and superior mesenteric veins; calculated mean velocity (V , cm/s), cross-sectional area (S , mm²), and flow volume (Q , mL/min); and determined markers of liver fibrosis (liver stiffness [kPa] and aspartate aminotransferase (AST) platelet ratio index [APRI]). We visually assessed GEV and development of collateral pathways of the PV on routine contrast-enhanced dynamic MR imaging and compared patient characteristics, flow parameters, liver stiffness markers, and visual analysis among 3GEV groups, those with mild, severe, or no GEV with reference to endoscopic findings.

Results: Child-Pugh grade, V_{PV} , S_{PV} , liver stiffness, APRI, and visually identified GEV (visible GEV) differed significantly among the 3 groups ($P < 0.05$). We investigated V_{PV} , S_{PV} , liver stiffness, and visible GEV as independent markers to distinguish patients with and without GEV and examined V_{PV} and visible GEV to predict severe GEV. Visible GEV showed low sensitivity (14 to 30%) and high specificity (98%) for predicting GEV in patients with CLD. A subgroup analysis that excluded cases with collateral pathway demonstrated slightly improved diagnostic performance of V_{PV} and liver stiffness.

Conclusions: Portal vein flow parameters and liver stiffness can be useful markers for predicting GEV in patients with CLD.

Keywords: *gastroesophageal varices, MR elastography, phase-contrast MRI*

Introduction

Gastroesophageal varices (GEV) and bleeding from them are severe complications of portal hypertension in patients with chronic liver disease (CLD). GEV develop in 7% of patients with cirrhosis each year, and occurrence of a first variceal hemorrhage at one year from diagnosis is approximately 12%.¹ Mortality associated with GEV bleeding ranges from 30 to 70%.² Combined treatments, such as vasoactive drugs (beta-blockers),

endoscopic ligation, and transjugular intrahepatic portosystemic shunt, have been developed to prevent GEV bleeding.^{3,4}

Liver fibrosis, a cause of portal hypertension, plays a fundamental role in the development of GEV, and clinicians must monitor patients with liver fibrosis for them. Endoscopy is commonly used to identify GEV, but screening is time consuming and costly, and serious complications, though rare, can occur. Ideally, endoscopic screening for GEV would be restricted to a well targeted population of patients with cirrhosis.

Phase-contrast MR imaging (PC-MRI) has been developed in many fields to measure flow in the

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cardiovascular system, pulmonary artery, cerebrospinal fluid, and portal venous system.⁵⁻⁸ Liver cirrhosis and portal hypertension change the hemodynamics of the portal venous system.⁹ Demonstration by a previous study of altered rate of flow in the portal vein (PV) in patients with GEV suggested that flow in the vessel might serve as a predictor of GEV bleeding.¹⁰

Patients with high risk of developing GEV can also be targeted by estimating degree of liver fibrosis using recently developed methods or a clinically useful blood biochemical index, such as aspartate aminotransferase (AST) platelet ratio index (APRI).¹¹⁻¹⁵ MR elastography (MRE) is a state-of-the-art tool for evaluating liver stiffness that offers high reproducibility, repeatability, and validity.¹⁶⁻²¹

MR examination of the liver can be shortened by performing both PC-MRI and MRE during the delay before equilibrium- or hepatocyte-phase after administration of a contrast agent.^{22,23} Use of these examinations to predict GEV would significantly enhance the utility of MR imaging in managing patients with cirrhosis.

We evaluated the utility of flow parameters measured by PC-MRI of the portal venous system and liver stiffness measured by MRE of the liver for predicting GEV in patients with CLD.

Materials and Methods

Subjects

Our institutional review board approved this retrospective study, and written informed consent was waived. March 1 through December 31 in 2011, 697 patients underwent both PC-MRI of the portal venous system (PV) and superior mesenteric vein (SMV) and MRE at our institution; 305 of the 697 had CLD. We randomly selected 60 control subjects from the patients without CLD who exhibited no liver abnormality other than hepatic cyst or hemangioma, which was confirmed by clinical follow-up and multi-imaging modalities. Of the 305 patients with CLD, we excluded 110 patients who met at least one of the following 5 criteria: 64 patients who did not undergo upper endoscopic examination within 6 months of MR examination; 28 with history of interventional treatment for GEV, such as endoscopic ligation and balloon-occluded retrograde transvenous obliteration; five with PV thrombus confirmed by contrast-enhanced computed tomography; four for whom PC-MRI failed because of motion artifact; and nine with history of lobectomy or more than one segmentectomy of the liver. This yielded a study cohort of 195 patients with CLD who underwent at least one upper endoscopic examination within 6 months of PC-MRI (Fig. 1).

CLD types included 130 cases positive for hepatic

Fig. 1. Schematic diagram of inclusion/exclusion criteria and selection process of study cohort.

tis C virus, 27 positive for hepatitis B virus, 17 with alcoholic liver disease, three with autoimmune liver disease, and 18 other types. Characteristics of controls were: age, 63 ± 13 years; body weight, 54 ± 9 kg; and male-to-female ratio, 40/20. Characteristics of the CLD group were: age, 69 ± 9 years; body weight, 59 ± 10 kg; and male-to-female ratio, 118/75. These characteristics did not differ significantly between the control and study subjects.

Reference standard of GEV

Gastroenterologists specialized in endoscopy from our institution's Department of Digestive Medicine performed all upper endoscopic examinations, recording the presence or absence of GEV. When GEV was present, they identified the form of GEV and type of red color (RC) sign, according to the general rules for recording endoscopic findings of esophagogastric varices (Second Edition of the Japanese Research Society for Portal Hypertension).²⁴ This system categorizes forms of varices as: straight and small, F1; moderately enlarged and beady, F2; markedly enlarged and nodular or tumor-shaped, F3. Results of endoscopic examinations of patients with history of GEV bleeding within 6 months of PC-MRI were designated posi-

tive for RC sign regardless of other endoscopic findings.

We divided patients into 3 groups by GEV form and RC sign on endoscopic findings: 85 patients with no GEV (Fig. 2a); 62 patients with mild GEV, with F1 and negative RC sign (Fig. 2b); and 48 patients with severe GEV, with either F2–F3 or positive RC sign (Fig. 2c). We recommended endoscopic treatment in our institution for patients with severe GEV (Fig. 2c).

PC-MRI

To avoid confounding effect of increased mesenteric blood flow from eating,^{25,26} all subjects fasted at least 3 hours before undergoing MR imaging examination using a 1.5-tesla scanner (Signa; GE Healthcare, Milwaukee, WI, USA). For reference, we acquired images of 4-mm thick coronal slices of the portal venous system using FIESTA sequence (fast imaging employing steady-state acquisition). All patients underwent breath-hold 2-dimensional (2D) PC-MRI to measure flow in the PV and SMV. Slices were set as cross-sections perpendicular to the direction of flow of the PV and SMV (Fig. 3). Imaging parameters for PC-MRI were: repetition time (TR)/echo time (TE), 12.5/5 ms; flip angle,

Fig. 2. Representative endoscopic findings of gastroesophageal varices (GEV). (a) None, (b) mild, and (c) severe.

Fig. 3. Left, reference coronal steady-state acquisition images (FIESTA) of the portal venous system. White lines represent cross-sections perpendicular to flow direction of the portal and superior mesenteric veins. Right, magnitude images of phase-contrast magnetic resonance (MR) imaging of corresponding cross-sections with circular regions of interest placed on each vein.

Table 1. Magnetic resonance imaging parameters

Parameters	Phase-contrast MR imaging	MR elastography
Sequence	Gradient echo	Gradient echo
TR/TE (ms)	12.5/5.0	100/27
Flip angle	20°	30°
Slice thickness (mm)	10	10
Field of view (cm)	40 × 28	30 to 34 × 40 to 45
Matrix	256 × 128	256 × 64
Number of slices	2*	2
Others	Velocity encoding parallel to flow direction: 30 cm/s	Frequency of pneumatic driver: 60 Hz

MR, magnetic resonance; TE, echo time; TR, repetition time; * One slice each for portal vein and superior mesenteric vein was applied.

20°; slice thickness, 10 mm; FOV, 40 × 28 cm; matrix, 256 × 126; number of slices, one; number of phases, 30; velocity encoding parallel to flow direction, 30 cm/s (Table 1). During PC-MRI, periph-

eral arterial pulses were monitored on the fingertip and synchronized to the pulse sequence of the MR imaging.

A radiologist with 7 years' experience in abdomi-

nal radiology selected a region of interest (ROI) on each vein in which to measure mean velocity (V , cm/s), area (S , mm²), and flow volume (Q , mL/min) of the PV and SMV. The ROI placed on the magnitude image first was copied onto the phase image. We calculated flow-related parameters using Advantage Workstation software (GE Healthcare). Because flow velocity fluctuates during the cardiac cycle in the portal venous system, we calculated flow volume by integrating flow volume during a cardiac cycle and then multiplying that value by the number of heartbeats.

Visual analysis

We visually assessed routine dynamic contrast-enhanced MR imaging in all patients for the presence or absence of GEV (visible GEV), defined as luminal dilated vessels abutting or protruding into the luminal space,²⁷ and visible collateral pathways of the PV, defined as tortuously dilated paraumbilical vein, spleno-renal shunt, and paraesophageal vein.

MR elastography

MRE was performed by attaching a cylindrical passive driver across the patient's right chest wall using an elastic (rubber) belt to deliver a pneumatic vibration to the chest wall and liver via a plastic cylinder from a generator placed outside the MR examination room. The generator of the vibration and passive driver were developed at the Mayo Clinic (Rochester, MN, USA).

We employed a breath-hold 2D gradient-echo MRE sequence to acquire axial wave images, setting the scanning position above the gallbladder and below the subphrenic region of the liver.¹⁴ MRE imaging parameters were: (TR/TE), 100/27 ms; continuous sinusoidal vibration, 60 Hz; FOV, 30 to 34 cm $\times$ 40 to 45 cm; matrix size, 256 $\times$ 64; flip angle, 30°; slice thickness, 10 mm; number of slices, 2; evenly spaced phase offsets, 4; and a single cycle of a 60-Hz trapezoidal motion-encoding gradient, with zero- and first-moment nulling along the through-plane direction. We did not use parallel imaging. Total acquisition time was 64 s (four 16-s breath holds) (Table 1). The MR scanner automatically generated elastograms by processing the acquired propagating shear wave images using a previously described inversion algorithm. Shear stiffness of the tissue was determined as a pixel value (kPa).

We evaluated the ROI in the right lobe of the liver on the elastogram in the slice proximal to the center of the passive driver placed on the patient's chest wall. We did not use the left lobe for ROI

measurement to avoid the effects of cardiac motion on the MRE phase image. Generally, we placed ROIs of 1.0 to 1.5 cm² near the anterior edge of the liver where the penetrating wave was well visualized and no interference was observed on the phase image. The magnitude image was also used to place the ROI in the liver region to avoid intrahepatic vessels or bile ducts. The average value in the ROI was used as an indicator of liver stiffness by MRE.

Blood test-based hepatic fibrosis marker

As a blood test-based marker of liver fibrosis, we used AST platelet ratio index (APRI), calculated as²⁸: $APRI = (AST \text{ level} / \text{upper limit of AST}) / (\text{platelet counts} / 10^6) \times 100$. We consider the upper limit of AST as 32 IU/L at our institution.

Statistical analysis

We used Mann-Whitney U test to compare flow-related parameters by PC-MRI between patients with CLD and control subjects and Kruskal-Wallis test to assess univariate analysis of patients' characteristics (age, sex, body weight, and Child-Pugh grade), flow-related parameters, liver stiffness by MRE, and APRI among the 3 GEV groups. We then compared these findings with the proportions of visible GEV among the 3 GEV groups.

We used logistic regression to perform multivariate analyses to discriminate presence and absence of GEV and severe GEV from absent to mild GEV and included only the variables showing significant differences in the univariate analysis. Before multivariate analyses, we calculated a correlation coefficient between the variables to assess colinearity. We performed receiver operating characteristic (ROC) analysis to estimate the efficacy of discrimination. We also performed subgroup analysis that excluded patients with collateral pathways. All statistical analyses were performed using JMP version 9 software (SAS Institute Japan, Tokyo, Japan). Data are presented as mean $\pm$ standard deviation.

Results

Comparison of parameters by PC-MRI between patients with and without CLD

We observed statistically significant differences in V_{PV} , V_{SMV} , S_{PV} , S_{SMV} and Q_{SMV} between patients with CLD and control subjects (Table 2).

Comparison of parameters by PC-MRI and liver stiffness by MRE in patients with CLD

We observed statistically significant differences in Child-Pugh class, V_{PV} , S_{PV} , liver stiffness, APRI,

and distribution of visible GEV among the GEV groups (Table 3).

Multivariate analysis for discriminating presence or absence of GEV

None of the parameters showing significant differences in the univariate analyses (Child-Pugh

Table 2. Comparison of parameters measured by phase-contrast magnetic resonance (MR) imaging between patients with and without chronic liver disease (CLD)

Flow measurement parameter	Control subjects n = 60	Patients with CLD n = 195	P-value
V _{PV} (cm/s)	12.3 ± 3.0	8.5 ± 2.7	<0.0001
S _{PV} (mm ²)	106 ± 35	141 ± 50	0.002
Q _{PV} (mL/s)	734 ± 207	713 ± 298	0.33
V _{SMV} (cm/s)	7.4 ± 2.6	6.5 ± 2.4	0.029
S _{SMV} (mm ²)	59 ± 23	88 ± 39	0.001
Q _{SMV} (mL/s)	261 ± 126	336 ± 186	0.03

Values are expressed as mean ± standard deviation. CLD, chronic liver disease; PV, portal vein; Q, flow volume; S, cross-sectional area; SMV, superior mesenteric vein; V, mean velocity.

grade, V_{PV}, S_{PV}, liver stiffness, APRI, and visible GEV) showed a square of correlation coefficient greater than 0.5; therefore, we included all these parameters in our multivariate analyses.

Multivariate regression analysis identified V_{PV}, S_{PV}, liver stiffness, and visible GEV as independent indicators for discriminating absence, presence, and degree of GEV (Table 4). The area under the ROC curve (AUC) was 0.70 for V_{PV}, 0.64 for S_{PV}, and 0.69 for liver stiffness. Visible GEV showed 14% sensitivity and 98% specificity. In a subgroup analysis that excluded 32 patients with collateral pathways, the diagnostic performances of V_{PV} and liver stiffness were slightly improved (Table 5); the AUC was 0.73 for V_{PV} and 0.71 for liver stiffness.

Multivariate analysis for discriminating severe from absent to mild GEV

Multivariate analysis demonstrated V_{PV}, S_{PV}, and visible GEV, but not liver stiffness, as independent indicators for discriminating severe from absent to mild GEV (Table 4). The AUC was 0.72 for V_{PV} and 0.64 for S_{PV}. Visible GEV showed 30% sensitivity and 98% specificity. In the subgroup analysis, the diagnostic performances of V_{PV} and S_{PV} did not change (Table 5). Figure 4 shows MR

Table 3. Comparison of clinical characteristics and measured parameters among the 3 groups with no, mild, and severe gastroesophageal varices (GEV)

Variables	No GEV n = 85	Mild GEV n = 62	Severe GEV n = 48	P-value
Age (years)	70 ± 10	69 ± 9	71 ± 8	0.72
Male : Female	58 : 27	34 : 28	27 : 21	0.19
Body weight (kg)	59 ± 11	57 ± 12	57 ± 18	0.45
Child-Pugh A/B/C	67/18/0	47/13/2	27/20/1	0.03
PC-MRI				
V _{PV} (cm/s)	10 ± 3.0	8.1 ± 2.1	7.1 ± 2.0	<0.001
S _{PV} (mm ²)	127 ± 34	146 ± 54	163 ± 58	0.001
Q _{PV} (mL/s)	722 ± 260	718 ± 325	690 ± 331	0.63
V _{SMV} (cm/s)	7.0 ± 2.0	6.1 ± 1.9	6.5 ± 3.4	0.24
S _{SMV} (mm ²)	80 ± 32	98 ± 46	88 ± 37	0.11
Q _{SMV} (mL/s)	314 ± 132	373 ± 239	327 ± 180	0.72
MRE				
Liver stiffness (kPa)	4.2 ± 1.6	5.4 ± 2.0	5.7 ± 1.6	<0.001
APRI	1.8 ± 2.0	1.6 ± 1.5	2.4 ± 1.3	<0.001
Visual analysis				<0.001
Visible GEV positive	1	1	14	
Visible GEV negative	84	60	33	

Values are expressed as mean ± standard deviation. APRI, aspartate aminotransferase (AST) platelet ratio index ([AST level/32]/[platelet counts/10⁶] × 100); PV, portal vein; Q, flow volume; S, cross-sectional area; SMV, superior mesenteric vein; V, mean velocity.

Table 4. Multivariate analyses for discrimination of presence or absence of gastroesophageal varices (GEV) and severe from absent to mild GEV

Variate	Discrimination of presence of GEV from no GEV			Discrimination of severe GEV from no to mild GEV		
	OR	95%CI	P-value	OR	95%CI	P-value
V _{PV}	0.72	0.61–0.84	<0.001	0.69	0.56–0.83	0.001
Liver stiffness*	1.43	1.15–1.82	0.001	1.20	0.95–1.53	0.11
S _{PV}	11.7	1.4–123	0.03	1.00	0.99–1.01	0.09
APRI	0.37	0.03–3.6	0.39	1.18	0.90–1.51	0.41
Child-Pugh grade (B or C)	1.22	0.50–3.05	0.43	2.53	0.95–6.92	0.07
Visual analysis	19.7	2.7–435	0.001	60.1	11.6–543	<0.001

APRI, aspartate aminotransferase (AST) platelet ratio index ($[\text{AST level}/32]/[\text{platelet counts}/10^6] \times 100$); CI, confidence interval; OR, Odds Ratio; PV, portal vein; S, cross-sectional area; V, mean velocity. * Liver stiffness was calculated by magnetic resonance (MR) elastography.

Table 5. Subgroup analyses of patients without visible collateral pathways for discrimination of presence or absence of gastroesophageal varices (GEV) and severe GEV from absent to mild GEV

Variate	Discrimination of presence and absence of GEV			Discrimination of severe GEV from no to mild GEV		
	OR	95%CI	p-Value	OR	95%CI	p-Value
V _{PV}	0.75	0.61–0.89	0.001	0.73	0.56–0.91	0.005
Liver stiffness	1.56	1.19–2.08	<0.001	1.09	0.78–1.49	0.920
S _{PV}	1.02	1.00–1.03	0.002	1.01	1.00–1.02	0.016
APRI	0.91	0.67–1.18	0.492	1.31	0.97–1.74	0.763
Child-Pugh grade (B or C)	0.59	0.18–1.78	0.512	1.62	0.48–5.43	0.557
Visual analysis	28.9	4.16–614	0.001	62.9	11.4–611	<0.001

APRI, aspartate aminotransferase (AST) platelet ratio index ($[\text{AST level}/32]/[\text{platelet counts}/10^6] \times 100$); CI, confidence interval; OR, Odds Ratio; PV, portal vein; S, cross-sectional area; V, mean velocity.

elastograms, liver stiffness, and V_{PV} of representative cases from the 3 GEV groups (Fig. 4a, absent GEV; 4b, mild GEV; 4c, severe GEV).

Discussion

In this study, we sought to develop a noninvasive predictor of GEV using functional MR imaging. Some reports have suggested that PV flow volume calculated by PC-MRI or by Doppler ultrasound is not a useful predictor of advanced GEV,^{27,29} and our data confirmed this. PV flow volume did not differ significantly between patients with CLD and controls. S_{PV} increased in proportion to the portal pressure in patients with GEV. As a result, measuring V_{PV} is more reliable than calculating PV flow volume for predicting GEV or portal hypertension, as shown in our analysis. We also demonstrated liver stiffness measured by MRE as a significant indicator for discriminating patients with and without GEV. However, though liver stiffness and

APRI are valid markers of hepatic fibrosis, they were not useful predictors of clinically important or severe GEV. These results suggest that hepatic fibrosis develops before portal pressure increases.

In the subgroup analysis that excluded patients with collateral pathways of the portal venous system, the diagnostic performance of V_{PV} and liver stiffness were slightly improved. This result suggests that confounding factors of collateral pathway development negatively affect the diagnostic performance of these functional parameters.

Visibility of GEV on routine dynamic contrast-enhanced MR imaging showed high specificity (98%) and low sensitivity (14 to 30%) for predicting presence of GEV in this study; on routine MR imaging, only advanced dilated GEV was visibly identifiable. One previous report demonstrated moderate sensitivity (60–90%) and excellent specificity (70–100%) of computed tomography (CT) and MR imaging for detecting varices.³⁰ The different diagnostic criteria for varices of the previous

Fig. 4. Magnetic resonance (MR) elastogram, liver stiffness, and mean velocity of portal vein (V_{PV}) in representative cases of gastroesophageal varices (GEV), (a) absent, (b) mild, and (c) severe. (a) In a case without GEV, liver stiffness is not elevated and V_{PV} is not decreased. (b) In a mild case of GEV, liver stiffness is elevated and V_{PV} is mildly decreased. (c) In a severe case of GEV, liver stiffness is elevated and V_{PV} is significantly decreased.

report and ours may account for this discrepancy in sensitivity. Another more accurate morphological assessment of the portal venous system, such as 3D contrast-enhanced MR portography,³¹ is also reported. However, we believe functional quantitative parameters may be more subjective than qualitative morphological assessment.

Previous Doppler ultrasound-based studies have found no significant difference in V_{PV} among variceal grades (e.g., small vs. large varices or F1 vs. F2 vs. F3 varices).^{29,32} We speculate this discrepant finding is due to the different precision of the 2 measurement modalities. Doppler ultrasound can measure flow in the PV and may be cheaper and more widely available than PC-MRI. However, flow measurement is more valid by PC-MRI than ultrasonography, which yields more variable and overestimated results.³³

The decreased V_{PV} in patients with GEV is thought to result from the constant rather than pul-

satile flow of the venous system because the pressure gradient between the PV and the sinusoids of the liver is considered a driving force of PV flow. If sinusoidal pressure increases as hepatic fibrosis develops, the pressure gradient and V_{PV} will decrease. Thus, we propose a decrease in V_{PV} as a direct indicator of portal hypertension. Evaluating chronic pulmonary arterial hypertension (PAH) using breath-hold 2D cine PC-MRI applied to the pulmonary artery, Sanz and colleagues showed average pulmonary artery velocity to be the most useful parameter in predicting chronic PAH.⁸ We speculate that a similar relationship exists between portal hypertension and V_{PV} .

Our study has some limitations. First, we did not assess the predictability of GEV bleeding, the most important clinical outcome. Further longitudinal evaluation is warranted; we hope functional MR imaging parameters may be more useful than morphological assessments in predicting future GEV

bleeding and clinical prognosis in patients with CLD. Second, it seemed we could eliminate the confounding effects of increased mesenteric venous flow from eating by having patients fast for at least 3 hours; the robustness of PV flow measurement on only one slice at a specific time point should be considered. Recently developed time-resolved 3- or 4-dimensional PC-MRI may soon resolve this problem.^{34–36} The retrospective design also limited our study. We expect a prospective study with longitudinal observations would strengthen the conclusions of our study.

In conclusion, PV flow parameters measured by PC-MRI of the portal venous system and liver stiffness measured by MRE can be useful for identifying GEV in patients with CLD.

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