European Radiology (2019) 29:6611–6619
https://doi.org/10.1007/s00330-019-06230-8

MAGNETIC RESONANCE

Prediction of esophageal varices by liver and spleen MR elastography

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Received: 24 October 2018 / Revised: 5 April 2019 / Accepted: 8 April 2019 / Published online: 30 April 2019

Abstract

Objectives We aimed to assess the diagnostic performance of MR elastography (MRE) in predicting esophageal varices (EVs) in patients with chronic liver disease.

Methods We prospectively performed liver (LSM) and spleen stiffness measurements (SSM) using MRE and endoscopic screening for EVs to determine if patients with hepatocellular carcinoma were eligible for resection. We investigated whether LSM, SSM, and other non-invasive preoperative parameters were associated with the presence of EVs. In order to predict EVs, 211 patients were divided into training ($n = 140$) and test ($n = 71$) groups. A nomogram was built using independent factors based on logistic regression analysis in the training group and its accuracy was validated using an independent cohort.

Results Forty-six patients (21.8%) were diagnosed as having EVs (mild, $n = 36$; severe, $n = 10$). According to multiple regression analysis, LSM (odds ratio, 2.362; 95% confidence interval [CI], 1.341–4.923; $p = 0.001$) and SSM (1.489; 1.095–2.235; $p = 0.010$) were independent predictors of EVs in the training group. The nomogram showed good discrimination, with a C-index of 0.942 (95% CI, 0.892–0.974) through internal validation, and good calibration. Application of the nomogram in the test group still gave good discrimination (C-index, 0.948; 95% CI, 0.868–0.995).

Conclusions The combination of LSM and SSM using MRE is an accurate tool to identify patients at risk for EVs.

Key Points

- *Performance of MR elastography can estimate the presence of esophageal varices non-invasively.*
- *Liver and spleen stiffness measurements are independent predictors for esophageal varices.*
- *The nomogram using a combination of liver and spleen stiffness measurements allows for the risk of esophageal varices.*

Keywords Esophageal varices · Liver · MR elastography · Spleen

Abbreviations

APRI	Aspartate aminotransferase-to-platelet ratio index
AST	Aspartate aminotransferase
AUC	Area under the curve
CI	Confidence interval
C-index	Concordance index
CLD	Chronic liver disease
EVs	Esophageal varices
HCC	Hepatocellular carcinoma
ICGR15	Indocyanine green clearance rate at 15 min
LSM	Liver stiffness measurement
MRE	MR elastography
OR	Odds ratio
ROC	Receiver operating characteristic
SSM	Spleen stiffness measurement

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Introduction

Presence of EVs is an established risk factor in patients with chronic liver disease (CLD), as bleeding can be fatal [1]. The estimated prevalence of EVs in patients with chronic hepatitis and liver cirrhosis is 25% and 50%, respectively, while the mortality rate of variceal bleeding ranges from 20 to 35% [1, 2].

Screening endoscopy for EVs is recommended in all patients with liver cirrhosis [3]. However, endoscopy is an invasive and unpleasant procedure that sometimes requires sedation and carries rare but serious complications [4, 5]. Moreover, a general program of routine endoscopic screening in such patients is costly [6]. Non-invasive methods, such as elastography, are useful to identify patients at high risk for EVs.

There is growing evidence that non-invasive imaging-based methods such as transient elastography (TE) and MR elastography (MRE) are safe and reliable options for evaluating not only liver fibrosis but also portal hypertension, in patients with CLD [3, 7–9]. Liver stiffness measurement (LSM) using TE or MRE is independently associated with decompensated liver disease [10]. Splenomegaly also plays an important role in the pathophysiology of portal hypertension by increasing splanchnic inflow [11]. Splenomegaly also plays an important role in the pathophysiology of portal hypertension by increasing splanchnic inflow [4, 12]. However, previous studies have not focused on the appropriate diagnostic value of both LSM and SSM using MRE for predicting EVs in patients with CLD [12].

Therefore, in this study, we aimed to assess the diagnostic performance of LSM and SSM using MRE in determining the presence of EVs in consecutive patients with CLD.

Materials and methods

Patients

Patients with hepatocellular carcinoma (HCC) who were scheduled for liver resection in the Department of Digestive Surgery at Nihon University School of Medicine between 2014 and 2017 were included in this prospective study. In all, 211 consecutive patients underwent upper gastrointestinal endoscopy and MRE after diagnosis of HCC (Fig. 1). Eight patients were excluded because of suboptimal MRE image quality owing to failure to generate a satisfactory mechanical wave through the abdomen. Patients with advanced HCC (Vp $\geq$ 2 and Vv $\geq$ 2 based on the General Rules for the Clinical and Pathological Study of Primary Liver Cancer) were also excluded [13]. All study participants provided written, informed consent, and this study was approved by the Institutional Review Board of Nihon University (protocol number: RK-141209-4). All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

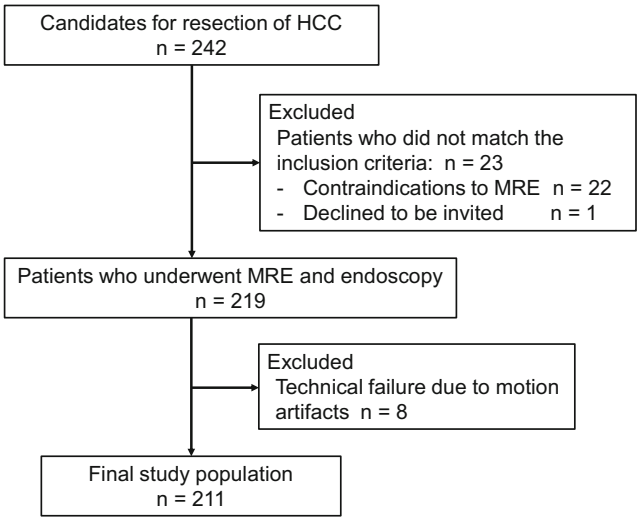

Fig. 1 Flowchart of the study population. HCC, hepatocellular carcinoma; MRE, magnetic resonance elastography

Clinical, hematologic, and biochemical parameters

Routine clinical, hematological, and biochemical parameters were measured and upper gastrointestinal endoscopy was performed within 4 weeks of MRE scanning. LSM and SSM by MRE were determined before treatment of EVs. The aspartate aminotransferase (AST)-to-platelet ratio index (APRI) was included as a biochemical and hematologic marker of liver fibrosis (APRI = AST level / [upper limit of normal] × 100 / platelet count [10^9/L]) [14, 15]. The longitudinal diameter of the spleen was measured by ultrasonography. The degree of fibrosis of resected specimens was histologically determined in accordance with the New Inuyama Classification by two pathologists with more than 5 years of experience in the field of liver pathology.

Definition of EVs

Upper gastrointestinal endoscopy was performed as described previously [1]. Briefly, endoscopy was performed by two operators with expertise in the assessment of patients before surgery. Staging of EVs was classified as none (no veins above the esophageal mucosal surface; F0), small (minimally elevated veins above the esophageal mucosal surface; F1), medium (tortuous veins occupying less than one-third of the esophageal lumen; F2), or large (those occupying more than one-third of the esophageal lumen; F3) according to the General Rules for Recording Endoscopic Findings of Esophagogastric Varices (The Japan Society for Portal Hypertension) based on Beppu's classification [16, 17]. Mild EVs were defined as F1 EVs without red-color signs, which did not require preoperative treatment. On the other hand, severe EVs were defined as those requiring interventional treatment, such as endoscopic variceal ligation, before surgery

(F2/F3 EVs or F1 EVs with red-color signs). In the case of discrepancy between the two operators, final reports based on their consensus opinion were adopted.

Liver and spleen stiffness measurements

MRE was performed using a 3.0-T MR unit (Discovery 750 W; GE Healthcare) with a 32-channel system (maximum gradient strength, 44 mT/m; peak slew rate, 200 T/m/s) and a 32-channel phased-array coil in all patients within 1 month prior to surgical treatment. For MRE acquisition, low-frequency (60 Hz) mechanical shear waves with wave amplitude of 70% were applied to the liver with a proprietary passive driver placed over the right upper quadrant of the abdominal wall. During mechanical vibration, synchronous motion-encoding bipolar gradient spin-echo diffusion-weighted imaging was performed (TR/TE = 800/58.9 ms; matrix = 64 × 64; flip angle = 90°; acquisition time = 22 s/4 slices; FOV = 42 cm; bandwidth = 250 kHz; number of excitations = 2) under breath-holding conditions. After MRE scanning, axial wave and elastogram map images were generated automatically to evaluate quantitative liver stiffness in kilopascals (kPa) using commercially available software (MR Touch; GE Healthcare) [18, 19]. One radiologist with 10 years of experience, blinded to the histopathologic results and all clinical data, measured liver stiffness by placing regions of interest on the right lobe of the liver on the elastogram map using an average of four hepatic slice locations. A single region of

Table 1 Patient characteristics

Characteristic	All patients (n = 211)	Training group (n = 140)	Test group (n = 71)	p
Age, year	69 (42–86)	69 (42–86)	70 (46–86)	0.331
Male, n (%)	169 (80.1)	110 (78.6)	59 (83.1)	0.472*
Background liver disease, n (%)				
NAFLD	28 (13.3)	20 (14.3)	8 (11.3)	–
Hepatitis B virus infection	55 (26.0)	34 (24.3)	21 (29.6)	–
Hepatitis C virus infection	83 (39.3)	58 (41.4)	25 (35.32)	–
Alcoholic liver disease	42 (19.9)	27 (19.3)	15 (21.1)	–
Wilson disease	1 (0.5)	1 (0.7)	0 (0)	–
Unknown	2 (1.0)	0 (0.0)	2 (2.8)	–
Body mass index, kg/m^2	23.4 (15.7–37.2)	23.4 (15.7–37.2)	23.5 (17.4–35.8)	0.759
Hematocrit, %	39.7 (19.7–52.8)	40.6 (24.6–52.8)	38.9 (19.7–48.3)	0.028
Platelet count, 10^9/L	157 (38–385)	154 (38–331)	164 (64–385)	0.138
Aspartate aminotransferase, U/L	34 (10–279)	35 (14–279)	31 (10–178)	0.317
Total bilirubin, mg/dL	0.69 (0.20–1.56)	0.68 (0.20–1.56)	0.69 (0.24–1.49)	0.549
Albumin, g/L	3.9 (2.3–4.8)	3.9 (2.3–4.8)	3.9 (2.6–4.8)	0.846
PT-INR	1.02 (0.82–1.54)	1.01 (0.88–1.54)	1.04 (0.82–1.33)	0.322
Cholinesterase, U/L	233 (58–521)	227 (58–521)	243 (92–414)	0.299
Ammonia, μg/dL	39 (12–101)	38 (12–101)	40 (17–101)	0.520
Hyaluronic acid, ng/mL	102 (9–762)	116 (12–649)	97 (9–762)	0.196
ICGR15, %	13.4 (1.9–61.0)	13.4 (4.3–47.4)	14.1 (1.9–61.0)	0.948
Child-Pugh classification B≤, n (%)	10 (4.7)	9 (6.4)	1 (1.4)	0.170*
LSM value, kPa	4.2 (1.1–12.0)	4.3 (2.0–12.0)	3.9 (1.2–10.9)	0.288
SSM value, kPa	8.7 (2.8–18.4)	8.6 (2.8–18.4)	9.2 (4.7–14.4)	0.178
Spleen size, mm	105 (72–186)	105 (72–186)	105 (70–160)	0.986
APRI	0.75 (0.14–5.53)	0.77 (0.24–5.53)	0.71 (0.14–4.96)	0.156
Esophageal varices, n (%)	46 (21.8)	30 (21.4)	16 (22.5)	0.861*
Mild: Severe	36 (17.1):10 (4.7)	24 (17.1):6 (4.3)	12 (16.9):4 (5.6)	0.736*

Data were presented as median (range), if not specified

*p values were determined by using Fisher's exact test and other p values by the Mann-Whitney U test

NAFLD, non-alcoholic fatty liver disease; *PT-INR*, prothrombin time-International normalized ratio; *ICGR15*, indocyanine green clearance rate at 15 min; *LSM*, liver stiffness measurement; *SSM*, spleen stiffness measurement; *APRI*, asparate aminotransferase-to-platelet ratio index

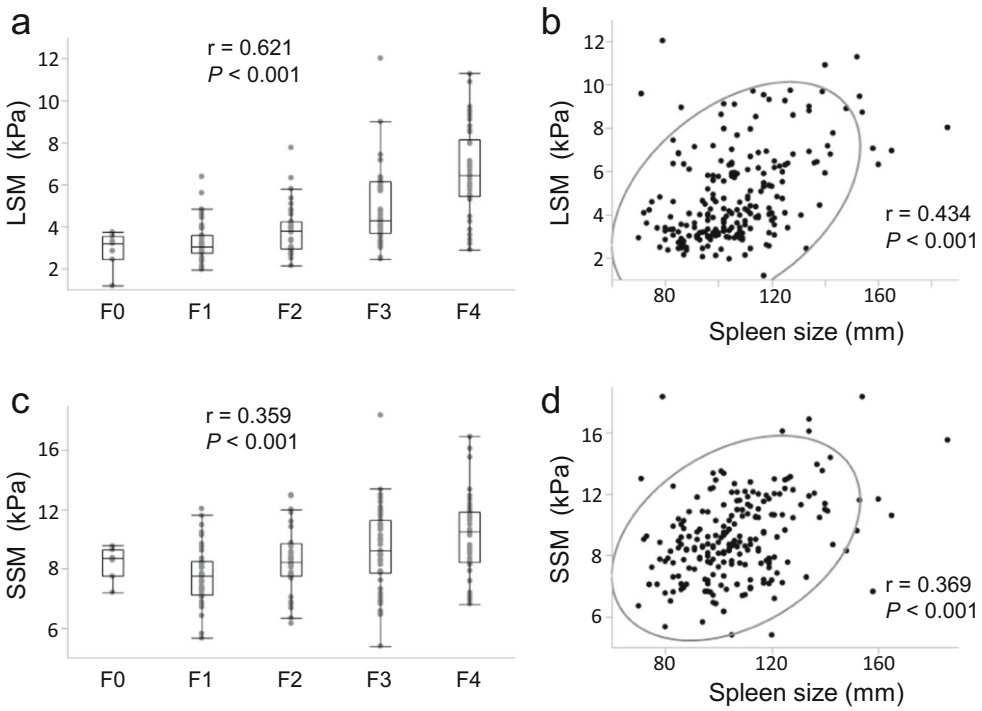

Fig. 2 Box plots of MRE and liver fibrosis, and scatter plots of MRE and spleen size. **a**, **b** LSM value was significantly correlated with liver fibrosis ($r = 0.621$, $p < 0.001$) and spleen size ($r = 0.434$, $p < 0.001$). **c**, **d** SSM value was also significantly correlated with liver fibrosis ($r = 0.359$, $p < 0.001$) and spleen size ($r = 0.369$, $p < 0.001$). The real line indicates the 95% confidence ellipsoid. LSM, liver stiffness measurement; MRE, magnetic resonance elastography; SSM, spleen stiffness measurement

interest of at least 150 mm^2 was drawn freehand avoiding larger vessels (> 3 mm in size), the edge of the liver, and wave reflection/interference artifacts, which automatically appeared as areas of crosshatching on the elastogram maps [20, 21]. In addition, regions of interest were measured more than 10 mm apart from the nodules if they were located in the right lobe of the liver to eliminate overlap with the nodules, in reference to the coronal image. Regions of interest were also placed on the spleen at three levels where the spleen showed a large area while avoiding the edge of the spleen and large vessels; this process was performed by the same radiologist [12, 22].

Statistical analysis

Continuous variables were presented as median and range. Data were compared using the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables, as required. The correlation coefficient was calculated using Spearman's rank test.

Independent factors for presence of EVs were determined using multiple logistic regression analysis, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Variables with *p* values < 0.10 in univariate analysis were entered into the multivariate model. Lastly, the prediction model was established by multiple logistic regression modeling based on these variables.

To provide the clinician with a quantitative tool to predict presence of EVs, we built a nomogram on the basis of multivariable logistic analysis in the training group [23, 24]. Calibration curves were plotted to assess the predictive accuracy of the nomogram, accompanied by the Hosmer-Lemeshow test [25, 26]. To quantify the discrimination performance of the nomogram, the concordance index (C-index) was also measured. The nomogram was subjected to bootstrapping validation (1000 bootstrap resamples) to calculate a relatively corrected C-index and

Table 2 Endoscopic findings in patients with esophageal varices ($n = 46$)

Esophageal varices	Training group ($n = 30$)		Test group ($n = 16$)	
	Mild ($n = 24$)	Severe ($n = 6$)	Mild ($n = 12$)	Severe ($n = 4$)
Form (F0/F1/F2/F3), *n*	0/24/0/0	0/0/4/2	0/12/0/0	0/1/3/0
Red color varices, *n*	0	3	0	4
Endoscopic treatment, *n*	0	6	0	4
Portal hypertensive gastropathy, *n*	3	2	1	2
Gastric varices, *n*	1	4	4	3
Gastric or duodenum ulceration, *n*	2	2	1	0

evaluate the relationship between predicted probabilities by the nomogram and observed rates [23, 24].

P values < 0.05 were considered statistically significant. Statistical analyses were performed using the JMP Pro 13.2.1 statistical software package (SAS Institute Inc, Cary) and a nomogram was built using R version 2.11.1 (R Foundation for Statistical Computing) with the "nomogram" function in the "rms" package [27]. The C-index was computed on R with the "rms" package and the "Hmisc" package.

Results

Patients and biochemical, clinical, and virological testing results

In total, 140 patients enrolled in the first two-thirds of the study period were selected for the training group and the remaining 71 patients in the last third were selected for the test group. The median age of the 211 patients (169 men [80.1%]) was 69 years (range, 42–86 years). In total, 138 patients (65.3%) had a viral hepatitis infection (hepatitis B, $n = 55$ [26.0%]; hepatitis C, $n = 83$ [39.3%]). Ten patients (4.7%) were assigned Child-Pugh classification B; no patient was assigned Child-Pugh classification C. There was no significant difference between the training group and the test group, except for the hematocrit value ($p = 0.028$) (Table 1).

Liver fibrosis and spleen size

LSM value was significantly correlated with liver fibrosis ($r = 0.621$, $p < 0.001$) and spleen size ($r = 0.434$, $p < 0.001$) on Spearman's rank test (Fig. 2a, b). We also found that SSM value was significantly correlated with liver fibrosis ($r = 0.359$, $p < 0.001$) and spleen size ($r = 0.369$, $p < 0.001$) (Fig. 2c, d).

Esophageal varices

Using screening endoscopy, 46 patients (21.8%) were diagnosed as having EVs. Among them, 10 (4.7%) were classified as having severe EVs and were treated preoperatively by endoscopic variceal ligation to prevent variceal bleeding (Table 2). Viral hepatitis infections were frequent and liver function and fibrosis markers were worse in patients with EVs than in those without EVs in the training group (Table 3). Representative endoscopic images and liver and spleen stiffness by MRE of each EV are shown in Fig. 3.

In univariate logistic regression analysis, viral hepatitis infections ($p = 0.013$), platelet count ($p < 0.001$), AST

Table 3 Data of patients with and without esophageal varices in the training group ($n = 140$)

	Absence of EVs ($n = 110$)	Presence of EVs ($n = 30$)	*p*
Age, year	69 (42–84)	68 (51–86)	0.550
Male, *n* (%)	89 (80.9)	21 (70.0)	0.214*
Body mass index, kg/m^2	23.7 (15.7–37.2)	22.5 (16.7–31.8)	0.126
Hepatitis virus infection, *n* (%)	66 (60.0)	25 (83.3)	0.018*
Platelet count, 10^9/L	168 (57–331)	98 (38–175)	< 0.001
Aspartate aminotransferase, U/L	32 (14–279)	58 (15–101)	0.003
Total bilirubin, mg/dL	0.67 (0.24–1.48)	0.80 (0.20–1.56)	0.164
Albumin, g/L	3.9 (2.3–4.8)	3.7 (2.4–4.4)	0.069
PT-INR	1.01 (0.88–1.36)	1.06 (0.94–1.54)	0.038
Hyaluronic acid, ng/mL	39 (12–553)	251 (27–649)	< 0.001
ICGR15	12.2 (4.3–47.4)	18.6 (7.4–34.4)	< 0.001
Child-Pugh classification B, *n* (%)	7 (6.4)	2 (6.7)	0.952*
LSM value, kPa	3.9 (2.0–8.9)	7.0 (4.6–12.0)	< 0.001
SSM value, kPa	8.2 (2.8–13.0)	11.9 (5.6–18.4)	< 0.001
Spleen size, mm	102 (72–148)	120 (79–186)	< 0.001
APRI	0.65 (0.24–4.89)	1.81 (0.36–5.53)	< 0.001

Data were presented as median (range), if not specified

**p* values were determined by using Fisher's exact test and other *p* values by the Mann-Whitney *U* test

EVs, esophageal varices; *PT-INR*, prothrombin time-international normalized ratio; *ICGR15*, indocyanine green clearance rate at 15 min; *LSM*, liver stiffness measurement; *SSM*, spleen stiffness measurement; *APRI*, asparate aminotransferase-to-platelet ratio index

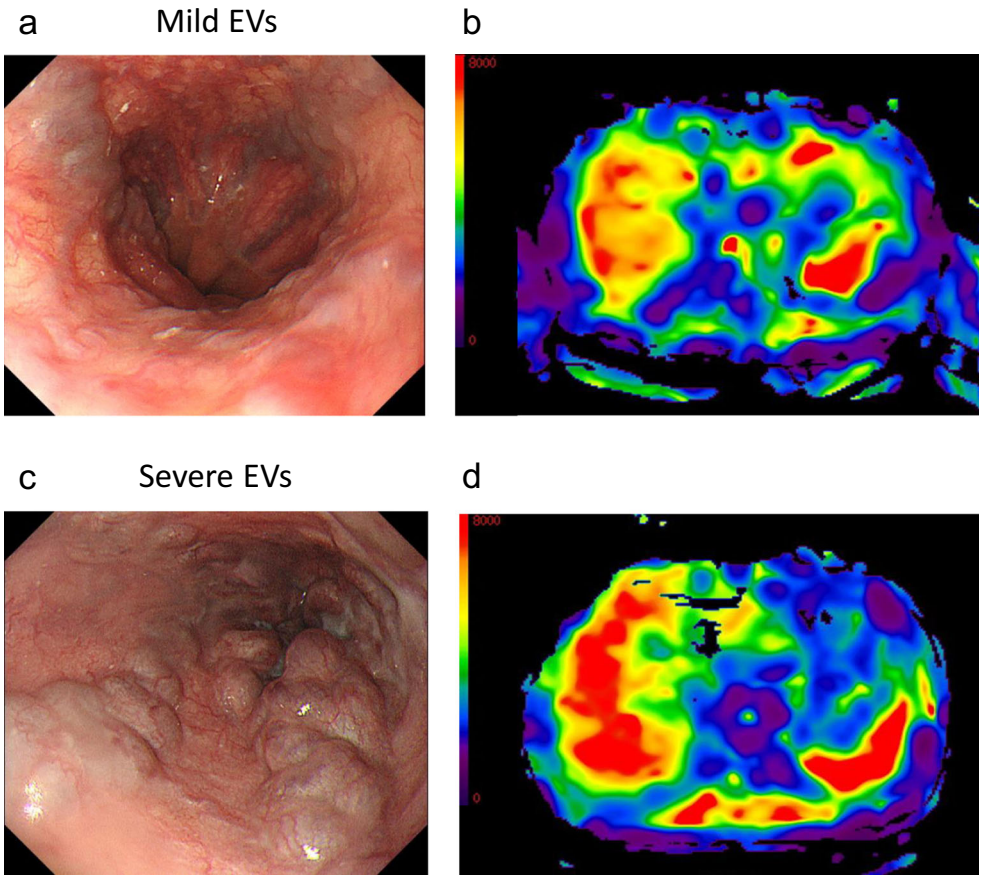

Fig. 3 Representative endoscopic images and liver and spleen stiffness by MRE of each EVs are shown. **a** Mild EVs, F1 EVs without red-color signs. **b** Magnetic resonance elastogram of mild EVs shows LSM to be 5.5 kPa and SSM to be 10.6 kPa. **c** Severe EVs, F3 EVs without red-color signs. **d** Magnetic resonance elastogram of severe EVs shows LSM to be 8.7 kPa and SSM to be 18.3 kPa. MRE, magnetic resonance elastography; EVs, esophageal varices; LSM, liver stiffness measurement; SSM, spleen stiffness measurement

($p = 0.049$), hyaluronic acid ($p < 0.001$), indocyanine green clearance rate at 15 min (ICGR15) ($p = 0.001$), LSM ($p < 0.001$), SSM ($p < 0.001$), and spleen size ($p < 0.001$) were significant predictors of EVs in the training group. Multiple logistic regression analysis showed that LSM (OR, 2.362; $p = 0.001$) and SSM (OR, 1.489; $p = 0.010$) were independent predictors of EVs in the training group (Table 4).

Table 4 Independent factors for esophageal varices in the training group ($n = 140$)

Variables	Univariate		Multivariate	
	OR (95%CI)	p*	OR (95%CI)	p*
Age	1.009 (0.962–1.056)	0.719		
Sex	0.551 (0.210–1.420)	0.210		
Body mass index	1.097 (0.987–1.230)	0.186		
Hepatitis virus infection	3.333 (1.273–10.46)	0.013	1.366 (0.256–8.354)	0.717
Platelet count	0.721 (0.624–0.813)	< 0.001	0.857 (0.709–1.006)	0.059
Aspartate aminotransferase	1.011 (1.000–1.023)	0.049	0.991 (0.959–1.013)	0.495
Hyaluronic acid	1.009 (1.006–1.013)	< 0.001	1.003 (0.997–1.009)	0.300
ICGR15	1.096 (1.037–1.163)	0.001	0.940 (0.825–1.047)	0.286
Child-Pugh classification	1.051 (0.151–4.642)	0.952		
LSM value	3.279 (2.245–5.414)	< 0.001	2.362 (1.341–4.923)	0.001
SSM value	1.783 (1.443–2.315)	< 0.001	1.489 (1.095–2.235)	0.010
Spleen size	1.059 (1.034–1.090)	< 0.001	1.004 (0.966–1.046)	0.834

*p values were determined by using logistic regression

OR, odds ratio; *95%CI*, 95% confidence interval; *ICGR15*, indocyanine green clearance rate at 15 min; *LSM*, liver stiffness measurement; *SSM*, spleen stiffness measurement

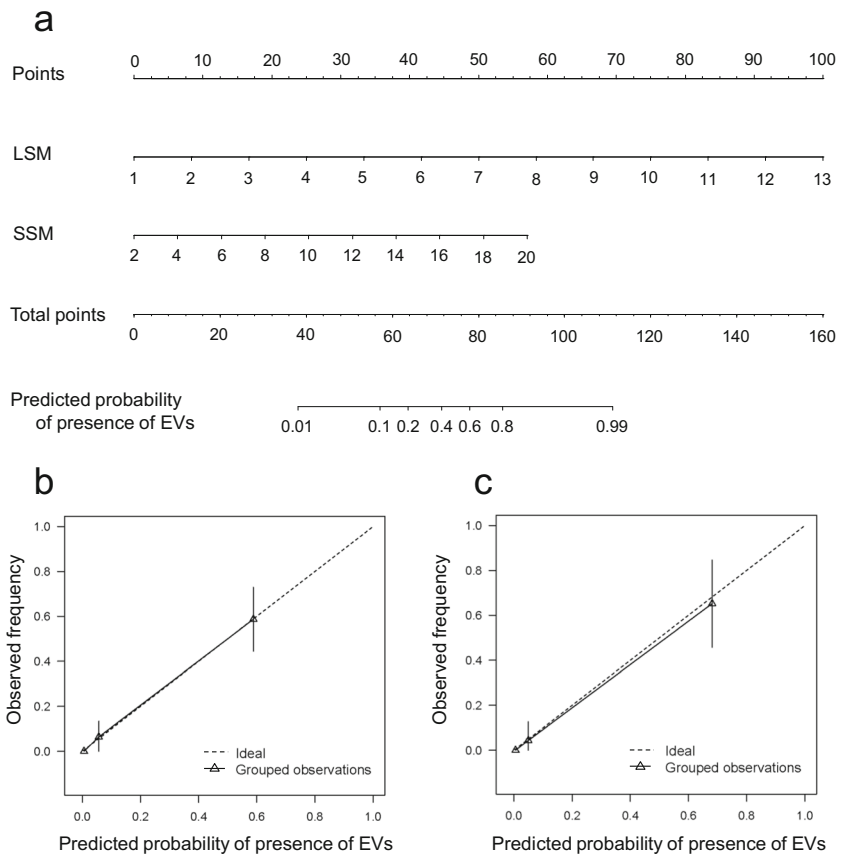

Fig. 4 Nomogram to predict EVs and nomogram calibration. **a** In the nomogram of the training group, the value of a patient's given parameter was plotted on the appropriate scale and vertical lines were drawn up to the points line (top line) to obtain the associated scores. After repeating this process for LSM value and SSM value, all scores were summed to obtain the total points. The total point score on the total points line (second from bottom) was plotted and a vertical line was drawn down to the bottom line. The corresponding value represents the predicted probability of EVs for the given patient. **b** Calibration curve of the nomogram in the training group. **c** Calibration curve of the nomogram in the test group. Calibration curves depict the calibration of each group in terms of the agreement between the predicted probability of EVs and observed frequency. The "ideal" line indicates the ideal nomogram reference line. The "grouped observations" line was calculated directly from the data set to represent the performance of the nomogram. EVs, esophageal varices; LSM, liver stiffness measurement; SSM, spleen stiffness measurement

Nomogram, calibration, and validation to predict esophageal varices

After multiple logistic regression analysis, LSM and SSM were selected as variables for the EV prediction model and to develop the nomogram using the training group (Fig. 4a). The calibration curve of the nomogram for the probability of EVs demonstrated good agreement between prediction and observation in the training group and the test group (Fig. 4b, c). The Hosmer-Lemeshow test yielded a non-significant statistical result for the training group ($p = 0.873$). The C-index for the prediction nomogram via bootstrapping validation was 0.942 (95% CI, 0.892–0.974) for the training group. As external validation, the C-index for the prediction nomogram was 0.948 (95% CI, 0.868–0.995) for the test group. Consequently, the nomogram established using LSM and SSM could accurately predict the presence of EVs in patients with CLD.

Discussion

Our study showed that the combined model of LSM and SSM was a promising method for assessing presence of EVs. In multivariate analysis, LSM and SSM using MRE were independent prognostic factors for presence of EVs. Based on this analysis, the present nomogram using a combination of LSM and SSM allows for identification of patients at risk for EVs.

Several researchers reported that LSM by MRE was a good predictor for the presence of EVs [8, 9]. LSM by MRE was reported to be a reliable parameter for predicting the presence of EVs (area under the curve [AUC], 0.859) and severe EVs (AUC, 0.810) in patients with liver cirrhosis, although other reports demonstrated that LSM alone is not sufficient to predict EVs [4]. SSM was recently recognized to correlate with portal hypertension and its complications, and thus SSM using

MRE has become a novel and non-invasive parameter that closely correlates with presence of EVs [7, 28]. SSM has been shown to be the best parameter for identifying patients with severe EVs (AUC, 0.93). However, both LSM (> 4.81 kPa) and SSM (> 7.60 kPa) values have shown better performance than spleen length in association with EVs [12]. In the present study, we built a nomogram as a prediction model for EVs by combining LSM and SSM values in the training group; these results were confirmed using the independent cohort. These results suggest that our nomogram is capable of better predicting the presence of EVs in CLD patients compared with previous reports.

In the current study, we showed that MRE, which can be done during liver MR, performed for the detection of tumor in CLD management was useful to identify patients at high risk for EVs. Possibility to predict EVs could also help reduce the cost and burden of screening endoscopy [4].

Patients with advanced CLD and liver cirrhosis can safely avoid screening endoscopy with a platelet count $> 150 \times 10^9$/L and LSM < 20 kPa by TE in the Baveno VI criteria [3]. However, the total number of avoided endoscopies using this rule is relatively low. On the other hand, the quantitative information such as the nomogram using MRE is useful in clinical practice. In addition, the advantage of MRE over TE is that this technique visualizes the entire liver and spleen and does not require an accurate acoustic window [28]. MRE shows appropriate reproducibility and better diagnostic accuracy than TE, especially in patients with obesity or moderate ascites. Therefore, MRE can avoid the sampling variability caused by the heterogeneity seen in advanced liver fibrosis [21].

APRI, platelet count, and other non-invasive fibrosis markers have also been reported to be excellent parameters for detecting EVs in patients with liver cirrhosis and portal hypertension [14, 29]. In addition, significant splenomegaly with low platelet count is considered a surrogate marker for portal hypertension [30]. Indeed, the diameter of the spleen is easily measured using ultrasonography at the patient's bedside. However, these non-invasive markers and spleen size were not independently associated with presence of EVs in the present study.

As previously reported, LSM using MRE could be an excellent marker for evaluating liver fibrosis as well as predicting major complications due to blood loss during liver resection [19, 28]. Furthermore, liver fibrosis grade was accurately and reproducibly determined using three clinical variables: LSM, ICGR15, and platelet count [31]. This prediction model of liver fibrosis is available to determine the management of patients with CLD. In addition to these variables, we demonstrated that LSM and SSM using MRE could be useful surrogate markers for the presence of EVs.

This study has several limitations. First, severe EVs were uncommon in this study (approximately 5% overall) because the patient cohort was limited to candidates for liver resection [32]. Consequently, this study included few severe liver fibrosis (grade) and portal hypertension cases. Second, we did not measure hepatic venous pressure gradient in any patient although this method is considered the gold standard to evaluate portal hypertension in patients with cirrhosis [33]. Hence, the diagnostic accuracy of other non-invasive tests could not be compared with hepatic venous pressure gradient in this study. Finally, this study was performed in a relatively small cohort and the data should warrant prospective evaluation in a larger cohort, with comparative analysis including new technologies for evaluating LSM and SSM.

In conclusion, LSM and SSM using MRE could identify patients at risk for EVs. The present predictive score based on LSM and SSM could clearly and accurately predict the probability of EVs. Consequently, physicians can recognize the presence of EVs in patients with CLD, make better-informed decisions, and provide appropriate prophylactic treatment using the nomogram proposed in this study.

Acknowledgements This research was supported by Japan Agency for Medical Research and Development (AMED) under Grant Number 18hk0102049s0301 and a grant-in-aid of the 106th Annual Congress of JSS Memorial Surgical Research Fund, Tokyo, Japan.

Funding This research was supported by Japan Agency for Medical Research and Development (AMED) under Grant Number 18hk0102049s0301 and a grant-in-aid of the 106th Annual Congress of JSS Memorial Surgical Research Fund, Tokyo, Japan.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Tadatoshi Takayama, Department of Digestive Surgery, Nihon University School of Medicine.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- diagnostic or prognostic study
- performed at one institution

References

1. Yamazaki S, Takayama T, Nakamura M et al (2014) Prophylactic impact of endoscopic treatment for esophageal varices in liver resection: a prospective study. J Gastroenterol 49:917–922

2. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver D, Practice Parameters Committee of the American College of Gastroenterology (2007) Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 46:922–938
3. de Franchis R, Baveno VI Faculty (2015) Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 63:743–752
4. Morisaka H, Motosugi U, Ichikawa S, Sano K, Ichikawa T, Enomoto N (2015) Association of splenic MR elastographic findings with gastroesophageal varices in patients with chronic liver disease. J Magn Reson Imaging 41:117–124
5. Berzigotti A, Seijo S, Arena U et al (2013) Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 144:102–111 e1
6. Stefanescu H, Radu C, Procopet B et al (2015) Non-invasive menage a trois for the prediction of high-risk varices: stepwise algorithm using lok score, liver and spleen stiffness. Liver Int 35: 317–325
7. Ronot M, Lambert S, Elkrief L et al (2014) Assessment of portal hypertension and high-risk oesophageal varices with liver and spleen three-dimensional multifrequency MR elastography in liver cirrhosis. Eur Radiol 24:1394–1402
8. Morisaka H, Motosugi U, Ichikawa T et al (2013) MR-based measurements of portal vein flow and liver stiffness for predicting gastroesophageal varices. Magn Reson Med Sci 12:77–86
9. Sun HY, Lee JM, Han JK, Choi BI (2014) Usefulness of MR elastography for predicting esophageal varices in cirrhotic patients. J Magn Reson Imaging 39:559–566
10. Asrani SK, Talwalkar JA, Kamath PS et al (2014) Role of magnetic resonance elastography in compensated and decompensated liver disease. J Hepatol 60:934–939
11. Bolognesi M, Merkel C, Sacerdoti D, Nava V, Gatta (2002) Role of spleen enlargement in cirrhosis with portal hypertension. Dig Liver Dis 34:144–150
12. Shin SU, Lee JM, Yu MH et al (2014) Prediction of esophageal varices in patients with cirrhosis: usefulness of three-dimensional MR elastography with echo-planar imaging technique. Radiology 272:143–153
13. The Liver Cancer Study Group of Japan (2015) The general rules for the clinical and pathological study of primary liver cancer, 6th edn, revised version. Kanehara & Co., Ltd, Tokyo
14. Wai CT, Greenson JK, Fontana RJ et al (2003) A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 38:518–526
15. Lin ZH, Xin YN, Dong QJ et al (2011) Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 53:726–736
16. Beppu K, Inokuchi K, Koyanagi N et al (1981) Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc 27:213–218
17. Tajiri T, Yoshida H, Obara K et al (2010) General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc 22:1–9
18. Huwart L, Sempoux C, Vicaut E et al (2008) Magnetic resonance elastography for the noninvasive staging of liver fibrosis. Gastroenterology 135:32–40
19. Abe H, Midorikawa Y, Mitsuka Y et al (2017) Predicting postoperative outcomes of liver resection by magnetic resonance elastography. Surgery 162:248–255
20. Venkatesh SK, Wang G, Lim SG, Wee A (2014) Magnetic resonance elastography for the detection and staging of liver fibrosis in chronic hepatitis B. Eur Radiol 24:70–78
21. Ichikawa S, Motosugi U, Morisaka H et al (2015) Comparison of the diagnostic accuracies of magnetic resonance elastography and transient elastography for hepatic fibrosis. Magn Reson Imaging 33:26–30
22. Dyvorne HA, Jajamovich GH, Besa C, Cooper N, Taouli B (2015) Simultaneous measurement of hepatic and splenic stiffness using MR elastography: preliminary experience. Abdom Imaging 40: 803–809
23. Huang YQ, Liang CH, He L et al (2016) Development and validation of a radiomics nomogram for preoperative prediction of lymph node metastasis in colorectal cancer. J Clin Oncol 34:2157–2164
24. Sugihara T, Yasunaga H, Horiguchi H et al (2013) A nomogram predicting severe adverse events after ureteroscopic lithotripsy: 12 372 patients in a Japanese national series. BJU Int 111:459–466
25. Paul P, Pennell ML, Lemeshow S (2013) Standardizing the power of the Hosmer-Lemeshow goodness of fit test in large data sets. Stat Med 32:67–80
26. Harrell FE Jr, Lee KL, Mark DB (1996) Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361–387
27. R Development Core Team (2011) R: A language and environment for statistical computing. Available via http://www.R-project.org/. Accessed 10 Jan 2012
28. Abe H, Midorikawa Y, Okada M, Takayama T (2018) Clinical application of magnetic resonance elastography in chronic liver disease. Hepatol Res 48:780–787
29. Singh S, Muir AJ, Dieterich DT, Falck-Ytter YT (2017) American Gastroenterological Association Institute technical review on the role of elastography in chronic liver diseases. Gastroenterology 152:1544–1577
30. Forner A, Llovet JM, Bruix J (2012) Hepatocellular carcinoma. Lancet 379:1245–1255
31. Mitsuka Y, Midorikawa Y, Abe H et al (2017) A prediction model for the grade of liver fibrosis using magnetic resonance elastography. BMC Gastroenterol 17:133
32. Santambrogio R, Kluger MD, Costa M et al (2013) Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? HPB (Oxford) 15:78–84
33. Groszmann RJ, Wongcharatrawee S (2004) The hepatic venous pressure gradient: anything worth doing should be done right. Hepatology 39:280–282