CLINICAL—LIVER

Measurement of Spleen Stiffness by Acoustic Radiation Force Impulse Imaging Identifies Cirrhotic Patients With Esophageal Varices

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BACKGROUND & AIMS: We evaluated whether spleen stiffness (SS), measured by acoustic radiation force impulse imaging, can identify patients who have esophageal varices (EVs); those without EVs would not require endoscopic examination. **METHODS:** In a prospective study, we measured SS and liver stiffness (LS) in 340 patients with cirrhosis undergoing endoscopic screening for EVs and 16 healthy volunteers (controls) at the Kurashiki Central Hospital in Okayama, Japan. The diagnostic accuracy of SS for the presence of EVs was compared with that of other noninvasive parameters (LS, spleen diameter, and platelet count). Optimal cutoff values of SS were chosen to confidently rule out the presence of varices. **RESULTS:** Patients with cirrhosis had significantly higher SS and LS values than controls ($P < .0001$ and $P < .0001$, respectively). Levels of SS were higher among patients with EVs (n = 132) than controls, and values were highest among patients with high-risk EVs (n = 87). SS had the greatest diagnostic accuracy for the identification of patients with EVs or high-risk EVs compared with other noninvasive parameters, independent of the etiology of cirrhosis. An SS cutoff value of 3.18 m/s identified patients with EVs with a 98.4% negative predictive value, 98.5% sensitivity, 75.0% accuracy, and 0.025 negative likelihood ratio. An SS cutoff value of 3.30 m/s identified patients with high-risk EVs with a 99.4% negative predictive value, 98.9% sensitivity, 72.1% accuracy, and 0.018 negative likelihood ratio. SS values less than 3.3 m/s ruled out the presence of high-risk varices in patients with compensated or decompensated cirrhosis. SS could not be measured in 16 patients (4.5%). **CONCLUSIONS: Measurements of SS can be used to identify patients with cirrhosis with EVs or high-risk EVs. A cutoff SS was identified that could rule out the presence of varices and could be used as an initial noninvasive screening test; UMIN Clinical Trials Registry number, UMIN 000004363.**

Keywords: Diagnostic Tool; Prognostic Factor; Prediction; Liver Disease.

Esophageal varices (EVs) resulting from portal hypertension are a serious complication of cirrhosis. The estimated prevalence of EVs in patients with cirrhosis has been reported to be 50%,[1] and the mortality rate of variceal bleeding ranges from 20% to 35%.[2] There is an ongoing effort to develop effective prophylactic treatments for esophageal variceal bleeding, not only to improve patients' prognosis but also to reduce the costs of hospitalization. American and European guidelines for the primary prophylaxis of esophageal variceal bleeding have also been established,[3,4] and screening endoscopy for EVs is recommended for all patients with cirrhosis. However, a general program of routine endoscopic screening of these patients may be financially onerous.

Therefore, noninvasive measures for diagnosing EVs in cirrhotic patients before performing an invasive screening endoscopy are needed to decrease the number of patients treated with unnecessary β-blockers and to avoid unneeded endoscopic examinations of low-risk patients with cirrhosis. The platelet count/spleen diameter ratio (PSR) with a cutoff value of 909 was determined by Giannini et al to have the highest sensitivity (100%) and specificity (93%) for the diagnosis of EVs.[5] However, recent studies have reported that a PSR with a cutoff value of 909 is not sufficiently accurate for the prediction of EVs.[6,7] Among imaging methods, ultrasound-based transient elastography (TE)[8] is a new technique for rapid and noninvasive measurement of tissue stiffness. It has been largely ac-

Abbreviations used in this paper: ARFI, acoustic radiation force impulse; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; EVs, esophageal varices; HVPG, hepatic venous pressure gradient; ICC, intraclass correlation coefficient; IQR, interquartile range; +LR, positive likelihood ratio; −LR, negative likelihood ratio; LS, liver stiffness; NEVs, no esophageal varices; NPV, negative predictive value; PPV, positive predictive value; PSR, platelet count/spleen diameter ratio; ROC, receiver operating characteristic; RTE, real-time tissue elastography; SS, spleen stiffness; TE, transient elastography.

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cepted that liver stiffness (LS) is reflective of the degree of fibrosis and also predictive of EVs.[9,10] Measurements of LS by TE have been considered a useful but not excellent method for predicting EVs.[10] Recently, Colecchia et al[11] reported that measuring spleen stiffness (SS) using TE was another feasible method for predicting EVs in patients with hepatitis C virus–induced cirrhosis.

Acoustic radiation force impulse (ARFI) imaging[12] has been proposed as a new alternative method to assess tissue elasticity. ARFI imaging, which can be integrated with real-time B-mode imaging, is an ultrasound-based technique in which shear wave velocity is evaluated to assess the elastic properties of target tissues.[12] Promising results on the accuracy of ARFI technology for noninvasive assessment of liver fibrosis have been reported.[13,14] TE has some limitations. Measurement of LS by TE is difficult in patients who are obese or who have narrow intercostal spaces and is impossible in patients with ascites.[15] Furthermore, TE is affected by the operator's experience, because measurement by TE is based on M- and A-mode imaging. However, ARFI can be performed under clear observation of the actual measuring site by B-mode imaging and can be used even in obese patients and in patients with ascites.[16] Therefore, an important clinical advantage of this new device is that a success rate of ARFI measurements is higher than that for TE.[17,18]

The aims of our study were to use ARFI imaging to determine SS values in healthy subjects and in patients with cirrhosis and also to evaluate SS values determined by ARFI imaging as predictors of the presence and severity of EVs. Furthermore, to rule out patients with EVs and high-risk EVs, we assessed the validity of this diagnostic tool in subsets of patients with different degrees of liver impairment and different etiologies of liver disease.

Patients and Methods

Patients

We prospectively collected data on 1423 consecutive patients referred to our institution for the staging of liver disease between September 2010 and August 2011. Among them, 461 patients with a diagnosis of cirrhosis were enrolled in the study. Cirrhosis was diagnosed based on results of histologic examination of liver tissue (115 patients; 24.9%) or combined physical, laboratory, and radiologic findings,[19,20] including a nodular surface, a coarse texture, and an enlarged caudate lobe of the liver on ultrasonography, computed tomography, or magnetic resonance imaging. Exclusion criteria were as follows: active alcohol abuse (less than 6 months of alcohol abstinence) (n = 10), portal thrombosis (n = 3), history of treatments for portal hypertension (splenectomy, partial splenic embolization, transjugular intrahepatic portosystemic shunt, balloon-occluded retrograde transvenous obliteration, β-blocker therapy, or endoscopic therapies) (n = 53), and previous digestive tract hemorrhage (n = 36) because of the high risk of variceal bleeding. Thus, these patients were considered to be candidates for periodic endoscopy, meaning that there was no additional benefit to examining SS to avoid endoscopic examination. Among the 359 patients satisfying the inclusion criteria, 3 patients (0.8%) had unsuccessful measurements of LS because of exceeded evaluable depth by severe ascites and 16 patients (4.5%) had unsuccessful measurements of SS because the spleen was poorly visualized as a result of obesity or gastrointestinal gas.

Therefore, 340 patients were included in this study. Sixteen healthy volunteers consisting of hospital workers were also included as controls in the analysis. Inclusion criteria for the controls were age 20 years or older, no history of chronic liver disease, normal serum liver enzyme levels, and normal findings on abdominal ultrasonography.

The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board. Written informed consent was obtained from all study patients. All authors had access to the study data and reviewed and approved the final manuscript. Measurements of ARFI for each patient were performed using a Siemens Acuson S2000 ultrasound system by one of 2 experienced sonographers (J.T. and A.S., with 10 and 15 years of experience, respectively) who were blinded to the clinical data throughout the study. After an overnight fast, each patient was placed in the supine position and underwent ARFI on B-mode imaging. A region of interest (fixed-dimension 1 × 0.5–cm box; maximum evaluable depth, 5.5 cm) in the liver and spleen parenchyma, free of large blood vessels, was selected. LS was measured in the right lobe of the liver, 1 cm below the liver capsule, using the intercostal approach. SS was measured 1 cm below the spleen capsule using the intercostal approach. ARFI shear wave velocity was measured in meters per second. According to previous reports,[13,14,21] more than 5 successful measurements should be performed for each patient. Thus, 5 valid measurements were performed in the liver and in the spleen of each patient and median values were calculated because ARFI has a memory capability. Similar to TE, LS or SS failure was defined as zero valid shots, and unreliable measurements were defined as an interquartile range (IQR) to median value ratio greater than 30% or a success rate less than 60%.[13,15] Any LS or SS value that satisfied the previously described conditions was considered an unsuccessful measurement and was excluded from further analysis.

The maximum spleen bipolar diameter was estimated using ultrasound scanning and was expressed in millimeters. PSR[5] was calculated for all patients. Clinical and laboratory parameters were measured in each patient on the day of ultrasonography, which included ARFI imaging.

After the ultrasonographic examinations, all patients were also evaluated by screening upper digestive endoscopy, and the presence and degree of EVs was determined by one of 2 experienced endoscopists (A.D. and I.S., with 7 and 10 years of experience, respectively) who were blinded to clinical, laboratory, and ultrasonographic data. EVs were classified based on the criteria for describing endoscopic findings of esophagogastric varices in Japan.[22] Briefly, the severity of EVs was classified as follows: (1) F_1, straight and small-caliber varices; (2) F_2, beady varices; and (3) F_3, tumor-shaped varices. Red color indicates a high risk of variceal bleeding. "EVs in danger of rupture" (high-risk EVs) were defined as F_2 to F_3 EVs or F_1 EVs with red color signs or Child–Pugh class C according to the Baveno V criteria.[4] Low-risk EVs were defined as F_1 EVs without red color signs or Child–Pugh class C.

Patients were divided into 2 groups according to the presence/absence of EVs (EVs/no EVs [NEVs]). Complete evaluation for each patient (ultrasonographic plus endoscopic) was performed within 3 months. To evaluate interobserver and intraobserver agreements on the ultrasonographic examinations, ultrasonographic examinations of 30 cirrhotic patients who were not included in our study were independently performed by the