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BRIEF REPORT

Outstanding feasibility of spleen stiffness measurement by 100-Hz vibration-controlled transient elastography

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Key words
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Author contribution: Xiaofeng Zhang drafted the manuscript. Haiyu Wang participated in revising the manuscript. Damei Zhou, JiaoyuTai, and Qiaoping Wu operated the device to measure spleen stiffness and liver stiffness. Jinjun Chen supervised the study and secured finical support. All the other authors collected the data.

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Introduction

Spleen stiffness measurement (SSM) using ultrasound-based elastography has emerged as a valid, non-invasive tool to assess portal hypertension.[1] In patients with hepatitis C-virus-related cirrhosis, spleen stiffness (SS) was found to be positively correlated with hepatic venous pressure gradient (HVPG),[2] which is capable of predicting the occurrence of clinical decompensation in compensated cirrhotic patients combined with model for end-stage liver disease (MELD) score.[3] Among the existing ultrasound-based elastography techniques, vibration-controlled transient elastrography (VCTE) (FibroScan, Echosens, Paris, France) is the most commonly used and validated. For liver stiffness measurement (LSM), VCTE operates with a 50-Hz shear wave and the results range from 1.5 to 75 kPa. Owing to the fact that normal spleen is stiffer than the normal liver,[4] VCTE settings were recently adapted to specifically address SSM (frequency of the shear wave, ultrasound pulse repetition frequency, measurement depths, output range) and introduced on the FibroScan 630 Expert machine, equipped with dedicated modules for liver (LSM@50 Hz) and spleen (SSM@100 Hz). Data on the dedicated SSM device is very scarce at present. We performed a prospective, observational study to investigate the feasibility of this spleen-dedicated stiffness measurement device in subjects with and without chronic liver disease.

Patients and methods

Study population. This is a prospective observational study conducted at the liver clinic of Nanfang Hospital. Subjects willing to undergo LSM and SSM were prospectively and consecutively enrolled from July 2021 to September 2021 (Clinical trial No. NCT 04820166). The inclusion criteria were as follows: (i) subjects aged between 18 and 85 years, and (ii) willing to undergo LSM and SSM. The exclusion criteria were as follows: the presence of (i) non-cirrhotic portal hypertension; (ii) decompensated cirrhosis; (iii) splenectomy; (iv) splenic embolization; (v) hepatocellular carcinoma; and (vi) extra-hepatic malignancy. This study was conducted in compliance with the Declaration of Helsinki and approved by the hospital ethics committee (NFEC-202009-K6).

Healthy volunteers with no previous history of liver or hematological disease and with alcohol intake within the recommended limits were also enrolled.

Study assessment and definitions. Liver stiffness and spleen stiffness were assessed using the FibroScan 630 apparatus with "M" probe, under the condition of fasting for at least 3 hours. Results were expressed in kilopascals (kPa). All examinations were performed by experienced operators who had conducted more than 1000 liver procedures with FibroScan and undergone a certified training session specifically for SSM with FibroScan 630 with an Echosens consultant prior to its use in the clinical setting. When measuring spleen stiffness, the spleen was first located by a built-in ultrasonic probe.

A successful LSM or SSM was defined by at least 10 individual valid measures obtained in a patient.[4] Reliability of the LSM was determined by IQR/med: "very reliable" (<0.1); "reliable" (0.1–0.3, or >0.3 with LSM median <7.1 kPa); and "poorly reliable" (>0.3 with LSM ≥7.1 kPa).[5] The reliability of SSM was described with IQR/med in an exploratory manner. Using a cut-off of <7 kPa, LSM performed well in ruling out compensated advanced chronic liver disease (cACLD) and LSM > 15 kPa to confirm cACLD in chronic liver disease.[6,7] Healthy volunteers were defined as those without overt chronic and acute liver disease, after excluding the presence of systemic disease, cardiac diseases including congestive heart failure, anti-HCV and/or HBsAg, autoimmune hepatitis, alcohol consumption, and non-alcoholic steatohepatitis (NAFLD), and those with serum alanine aminotransferase higher than upper limit of normal (>40 U/L).

Endoscopic findings were recorded in a standard format, and esophageal varices were graded according to international guidelines.[8]

Results

Overall, 2026 subjects were consecutively screened, and 1832 subjects were eligible for this study. Patients with splenectomy ($n = 7$), splenic embolization ($n = 6$), decompensated liver disease ($n = 127$), non-cirrhotic portal hypertension ($n = 6$), hepatocellular carcinoma ($n = 39$), or extra-hepatic malignancy ($n = 9$) were excluded from further analyses. In the end, 315 healthy volunteers and 1517 patients with liver disease were included for analysis (Fig. 1).

In this study, 20 cases failed for LSM (13 were without any valid measurement and 7 had less than 10 individual valid measures) with a LSM success rate at 98.9% (1812/1832); overall, 50 subjects failed in the measurement of spleen stiffness (40 were without valid measurement and 10 had less than 10 individual valid measures) with a SSM success rate at 97.3% (1782/1832). One patient failed in both LSM and SSM. The success rate of SSM was 100% in healthy volunteers ($n = 315$) and 96.7% in patients with chronic liver disease ($n = 1517$). For the latter with successful LSM ($n = 1497$), the success rate of SSM was 96.6% (967/1001) in patients with LSM < 7 kPa, 96.2% (354/368) in those with LSM 7–15 kPa, and 99.2% (127/128) in those with LSM >15 kPa. The cause of failure of SSM included too short of anteroposterior spleen diameter ($n = 6$), narrow intercostal spaces ($n = 10$), or obesity ($n = 34$, body mass index 23.41 ± 3.58 kg/m^2). Finally, 1763 subjects had both successful LSM and SSM.

Of these 1763 subjects, the proportion of very reliable, reliable, and poorly reliable LSM were 35.1% ($n = 618$), 64.8% ($n = 1143$), and 0.1% ($n = 2$), respectively. In the 315 healthy

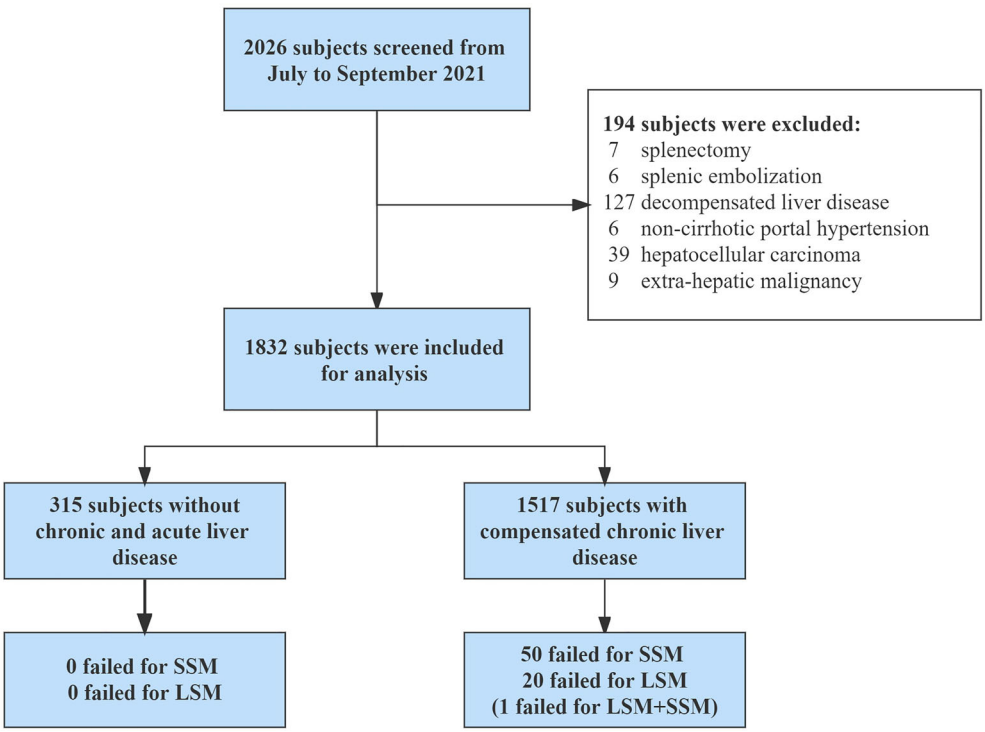

Figure 1 Flowchart of subjects enrollment. LSM, liver stiffness measurement; SSM, spleen stiffness measurement.

Table 1 Characteristics of subjects with successful spleen stiffness and liver stiffness measurement

Subjects' characteristics ($n = 1763$)	
Patients with chronic liver disease ($n = 1448$)	
Age, years	40.1 ± 11.0
Male, *n* (%)	1076 (74.3)
Etiology of liver disease, *n* (%)	
Hepatitis B	948 (65.5)
Hepatitis C	18 (1.2)
Alcohol	34 (2.4)
Non-alcoholic fatty liver disease	333 (23.0)
Miscellaneous	14 (1.0)
Others	55 (3.8)
Cryptogenic	46 (3.2)
Body mass index, kg/m^2	23.8 ± 3.7
Liver stiffness, kPa	7.9 ± 6.9
Liver stiffness, *n* (%)	
<7 kPa	967 (66.8)
7–15 kPa	354 (24.4)
>15 kPa	127 (8.8)
Controlled attenuation parameter, dB/m	234.6 ± 56.9
Spleen stiffness, kPa	22.0 ± 10.4
Spleen stiffness, IQR/med (%)	18.0 ± 10.6
Healthy volunteers ($n = 315$)	
Age, years	38.9 ± 18.2
Male, *n* (%)	156 (49.5)
Body mass index, kg/m^2	21.8 ± 2.8
Liver stiffness, kPa	4.7 ± 1.1
Controlled attenuation parameter, dB/m	201 ± 32
Spleen stiffness, kPa	17.1 ± 4.7
Spleen stiffness, IQR/med (%)	20.0 ± 11.0

IQR/med, ratio of interquartile range to median.

volunteers, the median LSM was 4.7 ± 1.1 kPa with IQR/med 14 ± 6%, and the median controlled attenuation parameter was 201 ± 32 dB/m. As for SSM, the median was 17.1 ± 4.7 kPa with IQR/med 20 ± 11% (Table 1).

For patients with chronic liver disease ($n = 1448$), the main etiologies were hepatitis B virus infection ($n = 948$, 65.5%), followed by NAFLD ($n = 333$, 23.0%) (Table 1). Patients with chronic liver disease with LSM < 7 kPa ($n = 967$) had significantly lower SSM (18.6 ± 5.9 kPa) than patients with LSM > 15 kPa ($n = 127$, 39.9 ± 15.1 kPa, $P < 0.001$; Fig. 2a). The SSM of patients with LSM 7–15 kPa was in the middle (25.1 ± 10.6 kPa) and significantly different from the two other groups ($P < 0.001$, Fig. 2a). Interestingly, IQR/med for SSM was significantly lower in patients with LSM > 15 kPa than those with LSM < 7 kPa (15 ± 8% *vs* 19 ± 11%, $P = 0.001$; Fig. 2b).

Furthermore, 692 patients had undergone abdominal ultrasound or computed tomography, thus allowing assessment of the presence of splenomegaly. Patients with splenomegaly ($n = 119$) had higher SSM than those without (37.8 ± 18.3 kPa *vs* 21.4 ± 9.2 kPa, $P < 0.001$; Fig. 2c) and significantly lower IQR/med for SSM (14 ± 8% *vs* 19 ± 11%, $P < 0.001$; Fig. 2d). As expected, patients with splenomegaly had higher LSM than those without (16.1 ± 11.2 kPa *vs* 7.8 ± 6.3 kPa, $P < 0.001$).

We further performed a subgroup analysis among 177 patients with chronic liver disease who underwent examinations using a gastroduodenoscope and VCTE measurement and 14.7% (26/177) prevalence of high-risk varices (HRV). For the diagnosis of HRV, the area under the receiver operating characteristic (AUROC) of SSM@100 Hz was 0.88 (95% CI 0.78–0.96) and of LSM 0.80 (95% CI 0.69–0.89).

Discussion

Hepatic venous pressure gradient was found to be closely correlated with LSM in patients with cACLD; however, when HVPG exceeded 10–12 mmHg, the correlation decreased.[9,10] Compared with LSM, spleen stiffness measured by VCTE has a higher correlation with HVPG and HRV.[11] Recently, the Baveno VII faculty further emphasized the importance of SSM in clinical practice, which allows early identification and holds prognostic information of patients with chronic liver disease at risk of having clinically significant portal hypertension both at index investigation and follow-up.[12] It also suggested that the newly proposed SSM cut-offs using the spleen-dedicated VCTE (with a 100 Hz shear wave frequency) to confirm or rule out portal hypertension-related conditions needed further validation.[12] However, all the studies that have so far assessed SSM have been conducted with a standard FibroScan appliance with no spleen-dedicated module, which is now available and has higher accuracy than the liver-dedicated module. In these studies, SSM assessment (with the liver-dedicated module) was affected by a high failure rate of the examinations, ranging from 10 to 20%.[3,13,14] Hence, the general efficiency of this spleen-dedicated VCTE device (FibroScan 630) should be evaluated.

In our study, the overall success rate of this novel dedicated SSM was found to be obviously higher than our previously published data (95.9%) using liver-dedicated VCTE on the spleen (with FibroScan 502).[15] In addition to patients with significant liver disease, we also first tested the feasibility of this device in healthy volunteers without acute or chronic liver disease (success rate of 100%) and in chronic liver disease patients with LSM < 7 kPa who were unlikely to have portal hypertension (success rate of 96.6%). Our data implied that this dedicated SSM would also be applicable for portal hypertension screening in patients with relatively mild liver disease who had normal spleen size. The major reason for SSM failure with this new device was obesity in compensated patients, which might be solved by the development of dedicated SSM using the FibroScan XL probe. Accordingly, our study endorsed that this novel spleen-dedicated stiffness measurement device is easy to operate and has a very high success rate, making it a potential tool for portal hypertension screening from community health care to referral liver center.

LSM cutoff at LSM < 7 kPa performed well in ruling out and LSM > 15 kPa in confirming cACLD in chronic liver disease.[6,7] In patients with compensated chronic liver disease, SSM is significantly higher in the group with LSM >15 kPa (highly suggestive of cACLD) than the group with LSM < 7 kPa (assumed without cACLD). Obviously, subjects without liver disease had a much lower SSM. Similarly, patients with

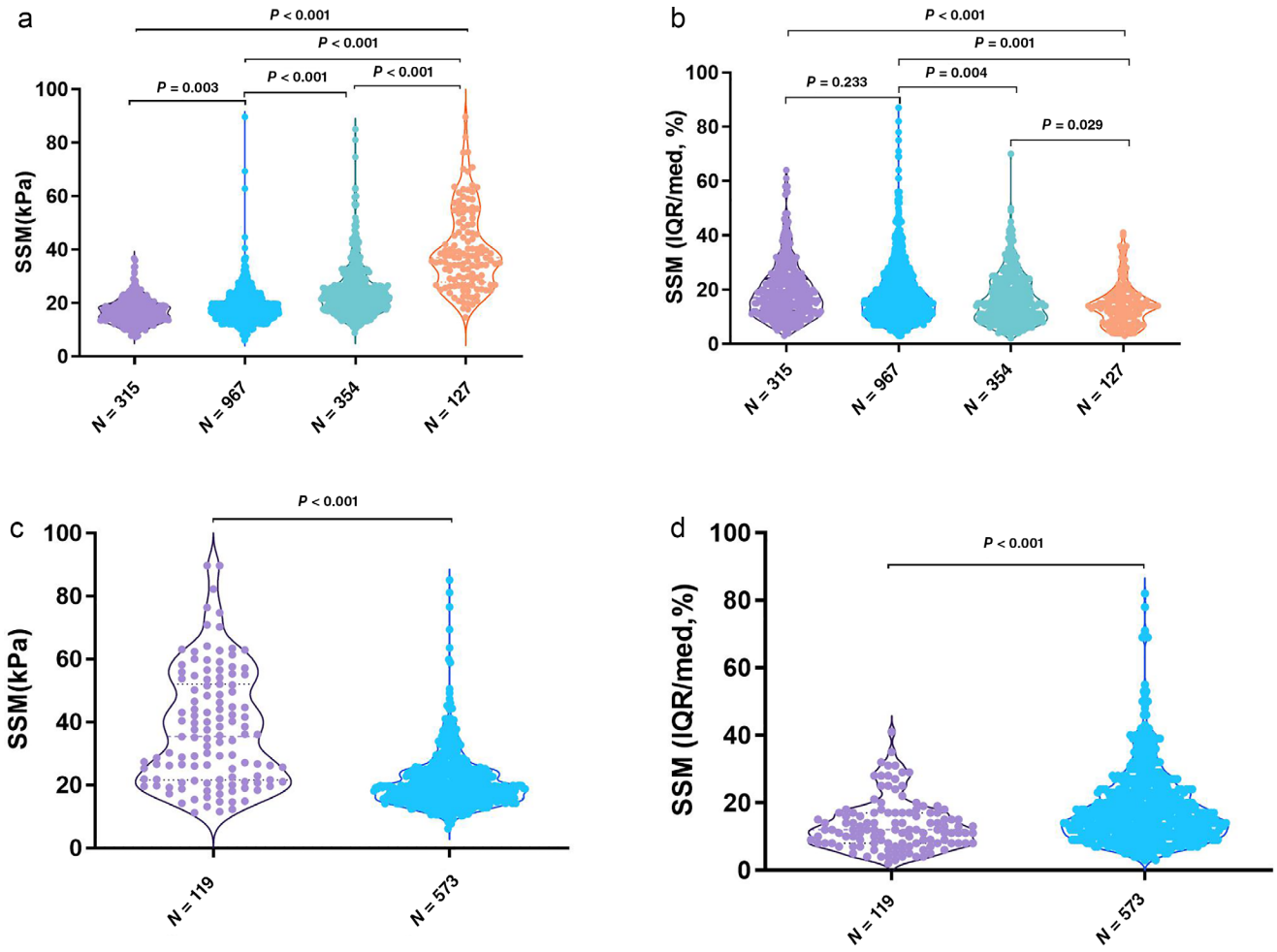

Figure 2 (a) Spleen stiffness distributions stratified with liver stiffness. (b) spleen stiffness measurement ratio of interquartile range to median (SSM IQR/med) distributions stratified with liver stiffness. (c) Spleen stiffness distributions stratified with splenomegaly. (d) SSM IQR/med distributions stratified with splenomegaly. ▭, healthy subjects; ▭, LSM < 7 kPa; ▭, LSM 7–15 kPa; ▭, LSM > kPa; ▭, splenomegaly; ▭, without splenomegaly.

splenomegaly, which indicates potential portal hypertension in patients with chronic liver disease, had higher SSM than those without. These data suggest that spleen stiffness is correlated with liver stiffness, which reflects the liver fibrosis stage. Whether SSM is able to reflect the severity of liver disease warrants further observation.

IQR/med is commonly used to assess the reliability of LSM. In this study, the IQR/med of SSM seemed to be associated with the liver fibrosis stage indicated by LSM. IQR/med for SSM was significantly lower in patients with LSM > 15 kPa than in those with LSM < 7 kPa. In line with this, patients with splenomegaly had lower IQR/med for SSM than those without. Our preliminary data suggest that SSM in patients with more advanced liver disease, including those with LSM > 15 kPa or those with splenomegaly, seemed to be more reliable.

In conclusion, our study suggests that this novel spleen-dedicated FibroScan has a high success rate, is easy to operate, and makes it possible to extensively screen liver-related complications. The reliability of SSM in patients with relatively mild liver disease still needs further investigation.

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Ethics statement

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the hospital ethics committee.

Data availability statement. Data pertaining to this work are available from the corresponding author on reasonable request and approval from Prof. Jinjun Chen.

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