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Spleen ultrasound elastography: state of the art and future directions – a systematic review

G. GIBIINO, M. GARCOVICH, M.E. AINORA, M.A. ZOCCO

Department of Internal Medicine, Gastroenterology and Hepatology, A. Gemelli Hospital – IRCCS, Catholic University of Rome, Rome, Italy

Abstract. – OBJECTIVE: An early and accurate diagnosis of clinically significant portal hypertension is mandatory for a correct prediction and management of the complications usually observed in patients affected by chronic liver disease (CLD). Spleen stiffness measurement is arising as a promising non-invasive technique, giving a reliable measure of haemodynamic changes occurring during cirrhosis progression, but contrasting data are available to date.

MATERIALS AND METHODS: A systematic review was performed including the several studies dealing with the spleen stiffness measurement in the evaluation of portal hypertension in adult patients affected by hepatic or extra-hepatic portal hypertension (PH). Results were organized in technical classification from the first one-dimensional device (TE) to the latest ultrasound elastographic techniques (pSWE and 2D-SWE).

RESULTS: We evaluated a total of nearly twenty studies dealing with all available elastographic techniques that were usually compared with HVPG, which is the gold standard for diagnosing the presence of PH. Spleen stiffness showed overall a good diagnostic accuracy to diagnose clinically significant PH in CLD, in some cases even with reliable cut-off values for severe PH.

CONCLUSIONS: Spleen ultrasound elastography could be an accurate non-invasive tool for assessing the presence of portal hypertension. However, the different techniques available to date and the various cut-off values suggested might still limit the impact on clinical practice.

Key Words:
Clinically significant portal hypertension, Spleen stiffness, Cirrhosis, Esophageal varices, Liver stiffness measurement, Ultrasound elastography.

Introduction

Portal hypertension (PH) is a clinical syndrome characterized by an increase in the venous pressure gradient across the liver, often observed during the progression of chronic liver disease (CLD)[1]. Globally more than 1.75 million deaths are attributed to CLDs, being an important source of health and economic burdens. In the United States, nearly 150,000 people are diagnosed with CLDs annually (of which 20% are diagnosed with cirrhosis), and 36,000 patients die for complications of decompensated cirrhosis and/or hepatocellular cancer[2,3]. In the Western world, 90% of PH is a consequence of advanced CLD, but it can be caused by several conditions affecting the extrahepatic district, classified as pre- or post-hepatic disease. PH can remain asymptomatic for many years but can be suggested by imaging and laboratory findings predicting the disease progression. Splenomegaly is commonly the first consequence of PH and most recent evidence confirmed some tissue modifications in this condition[4], leading to hypersplenism and thrombocytopenia. As widely known, PH is characterized by the risk of severe complications, such as upper digestive bleeding from gastrointestinal varices, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy.

The Consensus Baveno VI identified some non-invasive measures that clinicians should adopt to have an early identification of at-risk patients[5]. Liver biopsy, hepatic venous pressure gradient (HVPG) measure and upper endoscopy are the gold standard methods in the assessment of PH in CLD[6]. Despite their accuracy, they are invasive, expensive and require dedicated specialists. Using laboratory and clincal score can be useful in daily practice but are often limited to short-term prognosis, as Wang et al[7] recently showed. The development of ultrasound (US) elastography allowed the possibility to assess liver disease and its complications through non-invasive means.

Elastography techniques are based on the principle that all tissues have intrinsic elastic properties which can be measured by creating a distortion in the tissue and then evaluating its response.

Corresponding Author: Giulia Gibiino, MD; e-mail: giulia.gibiino@gmail.com

US-based elastography refers to the techniques that employ ultrasound to detect the velocity of the microdisplacement (share waves) induced in the tissue. Following this principle, elastography is used in liver disease to detect changes in the mechanical properties of the liver, giving a revolutionary change in the non-invasive approach to the detection of liver fibrosis and portal disorders[8]. Transient Elastography (TE) was the first elastography technique introduced in Europe in 2003[9] and it is now available in more than seventy countries. It requires the use of a dedicated device that was originally developed for the liver stiffness assessment, while its use to target organs other than the liver might need a preliminary standard US guidance, leading to higher costs and lower feasibility. Therefore, in the last years new methods that are built into high-end ultrasound devices have been developed, with focus high-intensity short-duration acoustic pulses to generate the tissue displacement either at one point (point shear wave elastography, pSWE) or in larger, distinct portions of the insonated area (two-dimensional shear wave elastography, 2D-SWE)[10]. These techniques allow the real-time visualization of the region of interest, enabling a semi-quantitative assessment of elasticity by colour-coding, and a quantitative measurement expressed either in m/s or kPa. Among all the pSWE techniques available, Virtual Touch Quantification (VTQ) by Acoustic Radiation Force Impulse (ARFI) imaging (Siemens Acuson S2000 Ultrasound System, Siemens Healthcare, Erlangen, Germany) is the most validated for the liver fibrosis and, considering the 2D-SWE techniques, Supersonic Shear Wave Elastography (SSI; Aixplorer, Supersonic Imagine, France) is close to full validation[11].

Spleen stiffness is believed to be a direct reflection of PH, while liver stiffness measurements (LSM) can be influenced by several hepatic changes beyond fibrosis, giving an indirect measure of PH[12]. It has been postulated that spleen stiffness measurement (SMM) by ultrasound elastography can be an accurate non-invasive surrogate for PH, giving a reliable measure of haemodynamic changes occurring during cirrhosis progression and avoiding limitations attributed to LSM[13]. Furthermore, it has been suggested that SSM might act as an indirect mark for the presence of oesophageal varices (EV), especially in case of high risk of bleeding.

We performed a systematic review of the several studies concerning the SMM in the evaluation of PH, focusing on a technical classification from the first one-dimensional device (TE) to the latest ultrasound elastographic techniques (pSWE and 2D-SWE).

Materials and Methods

Search Strategy and Inclusion Criteria

We performed a literature search to identify published study articles that examined SSM to determine PH in adult patients affected by CLD and other diseases leading to this condition. The online literature search was carried out using Pubmed Medline, the Cochrane Library and Embase for the studies published until April 30, 2018 using the following search terms: "spleen", "elastography", "spleen stiffness"," portal hypertension", "chronic liver disease", and "extra-hepatic portal hypertension". Then, a manual search of the reference lists of primary studies was performed to locate any other studies.

The inclusion criteria for primary studies were as follows: (1) adult study population (> 18 years); (2) studies that evaluated the accuracy of spleen stiffness performed using TE, p-SWE or 2D-SWE techniques for the prediction of PH in patients with CLD or affected by extra-hepatic disorders; (2) studies that measured portal pressure using the HVPG (PH defined as ≥6 mmHg, CSPH ≥10 mmHg, and severe PH ≥12 mmHg); (3) studies reporting cut-off values based on Receiver Operating Characteristic (ROC), sensitivity, and specificity for the diagnosis of PH, significant PH, and severe PH.

Additional studies including healthy volunteers were also considered to analyse further advantages and limitations of this technique. Only studies written in English were included in our review. The investigation was approved by the local Ethics Committee.

Results

Transient Elastography and Spleen Stiffnes

In the setting of PH and liver cirrhosis, TE examination of liver stiffness acquired a critical role in screening patients who can safely avoid endoscopy, according to Baveno VI[5]. Indeed, patients with a liver stiffness <20 kPa and with a platelet count >150,000 have a very low risk of having varices requiring treatment and can avoid screening endoscopy (recommendation 1b, grade A). An interesting issue is now developing on the use of

spleen stiffness as well. Performing TE on the spleen requires a dedicated device (FibroScan® Echosens, Paris, France) and a preliminary scanning with a standard US equipment to locate the organ. The applicability of TE is limited to about 70% of the cases since it is technically strictly dependent on the presence of increased spleen size to fit in the acquisition window. Moreover, measurements with TE can reach a maximum value of 75 kPa. The studies reviewed on this topic are reported in Table I.

Stefanescu et al[14] first published an extensive report using TE to measure spleen stiffness and demonstrated that SSM is a useful tool for grading CLD. Notably, they compared its performance in diagnosing the presence of EV in liver cirrhosis patients with other validated non-invasive approaches. The authors defined a cut-off value of 46.4 kPa with a good Area under Receiver Operating Characteristic (AUROC), predictive for the presence of EV. These findings were then confirmed by a consecutive research in a study cohort of HCV-related cirrhosis, supporting the use of SSM in association with LSM for a more accurate measure of PH with a strong correlation with HVPG values[15]. On the contrary, it has been reported that spleen elastography offers no advantage in comparison to standard liver elastography in the prediction of clinically significant or severe PH in a study conducted by Zykus et al[16] Nevertheless, they identified that liver stiffness <11.4 kPa could rule out and >21.9 kPa rule in clinically significant PH. Liver stiffness <12.1 kPa could rule out and >35 kPa rule in severe PH. Promising results have arisen from consecutive studies performed to assess the use of SSM to predict EV[17] and cut-off values were even generated to differentiate the presence of large varices *vs.* small ones (56 kPa *vs.* 49 kPa, p=0. 001) and bleeders *vs.* non-bleeders subjects (58 kPa *vs.* 50.2 kPa, p=0.001)[18].

The concomitant use of non-selective beta-blockers (NSBB) and the possible regression of liver fibrosis during antiviral therapy are still debated as possible influencers of the spleen stiffness value. In fact, a cohort of HBV-chronic liver disease was recently studied to verify the performance of LSM and SSM to predict EV. The diagnostic performance of SSM was not as high as expected from the previous studies, but patients included were at an early stage of liver cirrhosis and consequently, splenomegaly was present in 22.2% of the whole cohort. Furthermore, the authors observed that all patients had received antiviral therapy for a mean duration of 57±18 months, which could have led to the regression of liver fibrosis. Looking at the secondary endpoint, they showed that the use of NSBB did not affect the diagnostic accuracy of SSM[19].

A specific contribution was given by another study exploring the role of TE and SSM for PH due to extrahepatic portal vein obstruction. Sixty-five patients underwent liver stiffness and spleen stiffness measurement showing higher levels of SSM for patients with a history of bleeding compared with control subjects. In patients with a history of bleeding, a spleen stiffness cut-off of 42.8 kPa yielded sensitivity and specificity of 88% and 94% in the prediction of haemorrhage, respectively[20].

Moreover, a retrospective analysis reported the influence of transjugular intrahepatic portosystemic shunt (TIPS) on SSM in twenty-four patients with measurements occurring one day before (D-1), one day after (D+1), and 28 days after TIPS (D+28) placement. Looking at the results, TIPS implantation resulted in a statistically significant decrease of spleen stiffness, with mean values 67.1 ± 17.3 kPa at D-1, 44.7 ± 18.5 kPa at D+1, and 35.6 ± 17.0 kPa at D+28 ($p < 0.001$), while liver stiffness decreased without statistical significance. Although they did not reach a significant cut-off value, they supported a possible role of SSM in monitoring proper TIPS function[21].

Despite the growing evidence on the utility of performing TE for SSM, it is not applicable in patients with ascites or obesity (especially in patients with a BMI >30 kg/m^2) and, as mentioned above, it strictly depends on spleen size and the possible maximum value is 75 kPa. For this reason, Calvaruso et al[22] enrolled 112 patients with compensated cirrhosis to undergo standard SSM with TE; all SSM were analysed using a modified software version, not commercially available, that allows measurement of stiffness between 1.5 and 150 kPa. This led to a cut-off value of 50 kPa of modified SSM for predicting EV and a cut-off of 54 kPa for predicting grade 2 or grade 3 EV.

Point-Shear Wave Elastography and Spleen Stiffness

Among the different commercially available p-SWE devices, Virtual Touch Quantification (VTQ) by Acoustic Radiation Force Impulse (ARFI) imaging (Siemens Acuson S2000 Ultrasound System, Siemens Healthcare, Erlangen, Germany) has been the most tested and discussed in the measurement of spleen stiffness.

Table I. Studies reporting SSM with transient elastography.

Author	Study type	Study population	BMI	Spleen diameter (cm, mean)	End-point	AUROC	Cut-off	Sensitivity	Specificity	Success rate <60% (No. of subjects)	Comments
Stefanescu et al[12]	Prospective, cross-sectional	191 (HCV, chronic and cirrhosis)	24.7 in chronic HCV 26.36 in cirrhosis	10.9 in chronic HCV 14.11 in cirrhosis	EV	0.781	46.4 kPa	83.6%	71.4%	28	SSM measured with the transducer in the left intercostal spaces, not on the usual posterior axillary line
Colecchia et al[13]	Prospective, longitudinal cohort study	113 (HCV)	25	13.75	CSPH EV	0.966 0.941	40 kPa to rule-out 52.8 kPa to rule-in 41.3 kPa to rule-out 55 kPa to rule-in	98.5% 76.9% 98.1% 71.7%	74.3% 97.1% 66.0%	13	
Zykus et al[14]	Prospective, cross-sectional	107 (mixed aetiologies)	26.7 (±4.2)	n.a. (not applicable)	CSPH	0.846	47.6 kPa 50.7 kPa as cut-off of SSM for severe PH with the same accuracy	77.3%	79.2%	8	In case of not typical elastography picture using TE device, exact point for spleen stiffness measurement was found by standard US
Fraquelli et al[14]	Prospective, cross-sectional	244 (132 CLD, 48 myelo-prolif disorders, 64 healthy subjects)	23 23.6 21	>12	F ≥ 2 F = 4 EV	0.75 0.84 0.9	36 kPa for F ≥ 2 46 kPa for F = 4 <48 kPa rule-out EV	65% 93% 100%	98% 75% 60%	22	A study including myeloproliferative disorders and healthy subjects

Continued

Table I (Continued). Studies reporting SSM with transient elastography.

Author	Study type	Study population	BMI	Spleen diameter (cm, mean)	End-point	AUROC	Cut-off	Sensitivity	Specificity	Success rate <60% (No. of subjects)	Comments
Sharma et al[16]	Prospective, cross-sectional	200 (mixed aetiologies)	24.6	14.9	EV	0.898	40.8 kPa	94%	76%	26	Significant correlation of liver stiffness to spleen diameter platelet ratio score (LSPS) with SS, LS, HVPG, and Platelet count/spleen diameter ratio (PSR)
Wong et al[17]	Prospective, cross-sectional	176 (HBV)	24.4	11.3	EV	0.685	18.9 kPa to rule-out 54.9 kPa rule-in	91.4% 37.1%	36.1% 91.8%	28	
Sharma et al[18]	Prospective, cross-sectional	115 (65 with EHPVO, 50 controls)	n.a.	18 10	Variceal bleeding	n.a.	42.8 kPa	88%	94%	10	
Calvarusoet al[20]	Prospective, cross-sectional	112, HCV	27	14.1 in EV– 15.0 in EV+	EV	0.701 0.82 (mSSM)	50 kPa 54 kPa	65% 80%	61% 70%	16	SS measurements analysed by a software version that allow measurement of stiffness between 1.5 and 150 kPa

Notes: SSM, spleen stiffness measurement; BMI, Body Mass Index; AUROC, Area under Receiver Operating Characteristic; EV, esophageal varices; PH, portal hypertension; CSPH, clinically significant portal hypertension; n.a., not applicable; TE, transient elastography; CLD, chronic liver disease; LSPS, liver stiffness to spleen diameter platelet ratio score; HVPG, hepatic venous pressure gradient measurement; PSR, platelet count/spleen diameter ratio; EHPVO, extra hepatic portal venous obstruction. mSSM, modified spleen stiffness measurement.

Studies included are reported in Table II. Applicability of p-SWE in SSM is much higher as compared to TE, with a feasibility of 95%. The first study reporting its use in the assessment of CLD was conducted by Bota et al[23], who enrolled 54 cirrhotic subjects and showed that SSM evaluated by ARFI had a very good predictive value for the presence of cirrhosis (AUROC 0.91, accuracy 87.1%) with an optimal SS cut-off value of 2.51 m/s, but could not predict the presence or severity of EV and also the risk of variceal bleeding. Then, the same group introduced the combination of LSM and SSM, as well as the presence of ascites to increase the value of ARFI elastography for predicting significant EV[24]. Interesting results stemmed from another study performed in 125 subjects, including 30 with PH, 70 with CLD without PH, and 25 healthy controls. ARFI elastography of the spleen was successfully performed and the authors observed that the stiffness of the spleen was much higher than that of the liver and increased with age. The authors concluded that the PH and especially the spleen size were not well reflected by the measurement of spleen stiffness and therefore, SSM did not offer a reliable tool for diagnosing PH[25]. The controversial influence of ascites on SSM value was confirmed by another study[26]: among thirty-three hepatitis C patients with chronic hepatitis or liver cirrhosis, the median spleen shear-wave velocity using ARFI was 3.6 m/s in the presence of ascites and 2.90 m/s in the absence of ascites with a significant difference comparing the two groups (p<0.05); despite the correlation with decompensated disease, the spleen stiffness did not differ between the groups with and without EV. A considerable contribution on the accuracy of ARFI for the detection of complications in cirrhotic patients was given by Vermehren et al[27], who enrolled 166 patients for ARFI-imaging of the liver and the spleen, TE of the liver and Fibrotest, a serum fibrosis test (BioPredictive, Paris, France). The study population was tested to assess the possibility to predict the complications of cirrhosis using these non-invasive techniques. The diagnostic accuracy of ARFI imaging of the liver and spleen for the non-invasive detection of large EV and hepatocellular carcinoma was not significantly different from TE and Fibrotest. Also, AUROC values were similar for the two techniques in the prediction of liver-related complications. Nevertheless, ARFI was performed in all patients, while TE failed to achieve the 18% of the enrolled patients, due to the presence of ascites. Furthermore, SSM by ARFI better predicted the presence of large EV and hepatocellular carcinoma compared to LSM by ARFI.

Encouraging results concerning the use of ARFI for the definition of EV risk were described by Kim et al[28]. SSM was significantly correlated with the presence, severity and bleeding risk of EV, with an optimal cut-off value of 3.40 m/s for high-risk varices or variceal haemorrhage. A similar cut-off value of 3.1 m/s was then generated in a comparable study population[29,30], and SSM was considered an accurate predicting tool for HVPG >10 mmHg and HVPG ≥12 mmHg with EV[31]. The spleen stiffness measured by ARFI proved to be a reliable measurement with better diagnostic performance as compared to LSM in a study recently conducted by Takuma et al[32]. In this work, sixty-two patients with liver cirrhosis underwent HVPG, LSM and SSM, and gastrointestinal endoscopy. The authors showed that SSM and LSM measured by ARFI were linearly correlated with HVPG, with a correlation significantly higher between HVPG and SSM as compared to LSM. Spleen stiffness was the most accurate predictor for the identification of clinically significant PH, severe PH, EV, and high-risk EV (with stiffness values that were significantly higher than those of LSM). A spleen stiffness cut-off value of 3.51 m/s was identified as a good threshold for the prophylactic treatment of EV. As reported in another recent study[33], ARFI spleen values can also reflect the modification of portal pressure induced by TIPS placement with a significant decrease after TIPS (pre-TIPS 3.7 m/s *vs.* post-TIPS 3. 1 m/s; $p < 0.001$) and are directly correlated to portal atrial gradient.

As regards other p-SWE techniques, a recent Italian study included fifty-four cirrhotic patients with low-grade EVs or without EVs undergoing standard abdominal US simultaneously with p-SWE of the liver and spleen using the Elast-PQ technique (Philips Healthcare, Bothell, WA, USA) to investigate EV predictors. Liver stiffness had the highest accuracy in predicting the presence of EVs (AUROC = 0.913); SSM had the lowest accuracy (AUROC = 0.675); platelet count and spleen diameter had intermediate accuracy (AUROC = 0.731 and 0.729, respectively). According to this data, the SSM did not have an advantage over LSM in predicting low-grade EVs and cannot be proposed as a useful tool in the diagnostic process of cirrhotic patients who require esophago-gastro-duodenoscopy screening[34].

Table II. Studies reporting SSM with p-shear wave elastography.

Author	Study type	Study population	BMI	Spleen diameter (cm, mean)	End-point	AUROC	Cut-off	Sensitivity	Specificity	Success rate <60% (No. of subjects)	Comments
Bota et al[21]	Prospective, cross-sectional	82 (mixed)	n.a	n.a	Presence of cirrhosis EV	0.91	2.51 m/s	85.2%	95.8%	4	No predictive value of SSM for the presence of EV and a history of variceal bleeding
Bota et al[22]	Prospective, cross-sectional	145 (mixed)	26.7	n.a	EV	0.578	2.55 m/s	28.9%	49.5%	3	Low accuracy (56.5%), improved by the use of a suggested formula which includes LSM, SSM and ascites
Rifai et al[23]	Prospective, cross-sectional	125 (mixed)	25	14.3	CSPH	0.68	3.29 m/s	47%	73%	1	
Mori et al[24]	Prospective, cross-sectional	33 (HCV)	n.a.	n.a.	EV	0.800	3.34 m/s	73.3%	77.8%	0	
Vehrmeren et al[25]	Prospective, cross-sectional	166 (mixed)	26	n.a.	Prediction of complications related to cirrhosis	0.58 for EV and HCC	3.04 m/s for grade 2 or 3 EV 2.87 m/s for HCC	35% 87%	83% 31%	0	
Kim et al[26]	Prospective, cross-sectional	125 (mixed)	n.a.	12.10	Presence of EV Grade of EV Previous EV bleeding	0.785 0.762 0.813	3.16 m/s 3.40 m/s 3.40 m/s	87% 78.9% 94.3%	60.4% 63% 61.1%	0	

Continued

Table II (Continued). Studies reporting SSM with p-shear wave elastography.

Author	Study type	Study population	BMI	Spleen diameter (cm, mean)	End-point	AUROC	Cut-off	Sensitivity	Specificity	Success rate <60% (No. of subjects)	Comments
Takuma et al[27]	Prospective, cross-sectional	340 (cirrhosis)	23.5	11.4	EV	0.933	3.18 m/s	98 %	60%	0	
		16 (healthy controls)			High-risk EV	0.930	3.3 m/s	98 %	62%		
Rizzo et al[28]	Prospective, cross-sectional	54 (HCV) 63 (healthy controls)	n.a	n.a	EV	0.96	3.1 m/s	96%	88%	0	
Attia et al[29]	Prospective, cross-sectional	78 (mixed aetiologies)	n.a.	14.1	HVPG ≥ 10 mmHg	0.968	2.32 m/s	96%	89%	0	
					HVPG ≥ 12 mmHg	0.945	2.53 m/s	94%	89%		
					HVPG ≥ 10 mmHg + EVs	0.899	2.55 m/s	95%	90%		
					HVPG ≥ 12 mmHg + EVs	0.931	2.71 m/s	95%	92%		
Takuma et al[30]	Prospective, cross-sectional	62 (mixed aetiologies)	23.4	11.2	CSPH	0.943	3.10 m/s	97%	57%	2	
					Severe PH	0.963	3.15 m/s	82%	61%		
					EV	0.937	3.36 m/s	95%	77%		
					High-risk EV	0.955	3.51 m/s	93%	84%		
Lucchina et al[32]	Prospective, cross-sectional	54 (mixed aetiologies)	n.a.	12.26 (EV-) 14.36 (EV+)	Presence of EV	0.675	23.84 kPa	73.81%	59.52%	12	ElastPQ was used for SSM

Notes: SSM, spleen stiffness measurement; BMI, Body Mass Index; AUROC, Area under Receiver Operating Characteristic; n.a., not applicable; EV, esophageal varices; LSM, liver stiffness measurement; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient measurement.

2-Dimensional Shear Wave Elastography and Spleen Stiffness

Liver stiffness assessment by 2D-SWE has already been introduced as a promising and accurate tool to predict the various stages of liver fibrosis and to diagnose PH in patients with CLD[35]. Encouraging results for spleen stiffness as a surrogate marker of PH when compared to HVPG are emerging, although the specific role of SSM performed with this latest technique is still controversial. All the studies evaluated in this field were performed using Aixplorer US system (SSI, SuperSonic Imagine S.A., Aix-en-Provence, France), shown in Figure 1, and reported in table III. In 2015, Procopet et al[36] published the first report assessing the applicability and diagnostic performance of 2D-SWE performed on spleen in the assessment of clinically significant PH. They enrolled 88 patients with long-lasting CLD or compensated and decompensated cirrhosis, in which HVPG was indicated before starting NSBB or before the TIPS insertion. Liver stiffness was measured by 2D-SWE and by TE, while spleen stiffness was measured only by 2D-SWE. SSM was feasible only in 60% of the study population, a lower discriminative ability as compared to LSM[36]. Another study observed that the diagnostic performance of LSM by using 2D-SWE was significantly better than SSM for the diagnosis of clinically significant PH (AUROC of 0.87 *vs.* 0.64, p=0.003). They enrolled seventy-nine patients with cirrhosis undergoing SWE and TE at the time of the HVPG measurement. The technical success rate of SWE was significantly better than that of TE for both LS and SS, being respectively 97% and 97% *vs.* 44% and 42%. They also considered two composite scores such as the spleen-diameter-to-platelet-ratio score (LSPS) Kim et al[37] and the PH score, a specific formula developed by Berzigotti et al[38]. While the clinically significant PH was accurately assessed by evaluating LSM, it was not to possible to discriminate patients with or without high-risk EV by means of LSM, SSM, LSPS, and PH risk score (both with 2D-SWE and TE)[39].

A wide population of 401 cirrhotic patients was then evaluated by Cassinotto et al[40], who reported a failure rate of SSM of 29.2% compared with 6.2% for LSM using 2D-SWE. Both liver and spleen stiffness showed a correlation with the severity of cirrhosis, considering the Child-Pugh score and the presence of liver-related complications, but no cut-off value for the spleen was mentioned.

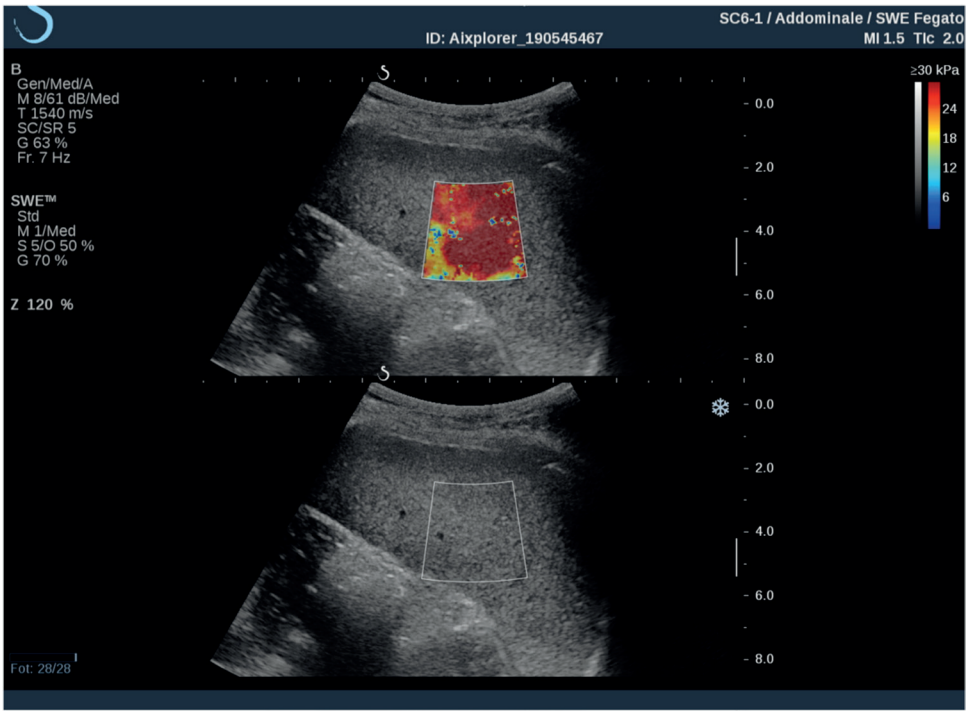

Figure 1. This figure shows spleen stiffness assessed by using 2D-SWE (Supersonic, Aixplorer). A ROI is positioned in the middle of the splenic parenchyma.

Table III. Studies reporting SSM with p-shear wave elastography.

Author	Study type	Study population	BMI	Spleen diameter (cm, mean)	End-point	AUROC	Cut-off	Sensitivity	Specificity	Success rate <60% (No. of subjects)	Comments
Procopet et al[34]	Prospective, cross-sectional	88, (mixed aetiologies) 9 controls	n.a.	13.3	CSPH	0.725	22.7 kPa to rule-out 40 kPa to rule-in	> 90%	> 90%	30	
Elkrief et al[37]	Prospective, cross-sectional	78	26	13.0	CSPH	0.64	34.7 kPa	40%	100%	2	
Cassinotto et al[38]	Prospective, Cross-sectional	401	27.1	n.a.	EV	0.75	25.6 kPa	94%	36%	117	
Jansen et al[39]	Prospective, Cross-sectional	158	n.a.	13.2 ± 2.9	HVPG ≥ 5 mmHg HVPG ≥ 10 mmHg HVPG ≥ 12 mmHg	0.84	24.0 kPa 26.3 kPa 28.5 kPa	79%	84%	46	For the first time accurate spleen stiffness cut-offs with SWE are described to assess different stages of PH

Notes: SSM, spleen stiffness measurement; BMI, Body Mass Index; AUROC, Area under Receiver Operating Characteristic; CSPH, clinically significant portal hypertension; n.a., not applicable; HVPG, hepatic venous pressure gradient measurement.

On the other hand, SSM was the only independent variable significantly associated with EVs or high-risk EVs at multiple regression analysis, with cut-off value identified of ≤ 25.6 kPa to rule-out high-risk EVs[40].

An additional prospective multicenter study[41] proved an almost equal association and predictive power of 2D-SWE with HVPG values. The authors enrolled 158 cirrhotic patients showing that 2D-SWE of the spleen could rule in and rule out clinically significant PH with a diagnostic accuracy similar to LSM. The best cut-off value for SSM was 26.3 kPa, corresponding to clinically significant PH (> 10 mmHg) and, in addition, promising cut-offs were also identified for HVPG > 5 mmHg and > 12 mmHg (24.0 kPa and 28.5 kPa, respectively).

Spleen Ultrasound in Healthy Volunteers – Lights and Shadows of the Spleen Stiffness Measurements

Looking beyond the variety of literature on spleen stiffness measurement in patients affected by CLD, many efforts have been recorded to study the values of this technique also in healthy subjects. In 2010 thirty-five young healthy volunteers underwent p-SWE with VTQ tissue quantification to assess the normal values of shear-wave speed in healthy abdominal organs[42]. Results revealed lower values in the pancreatic parenchyma in comparison with the liver and kidney, whereas the spleen was characterized as the "toughest" abdominal organ with mean values of 2.44 m/s. A following study[43] assessed the mean value of spleen stiffness measured by 2D-SWE in healthy patients and its dependence on age, sex, and spleen dimensions, and evaluated the repeatability of this method in fifty-nine healthy volunteers without any clinical evidence of CLD, PH, haematological disorders, and without any pathological ultrasonographic spleen results. A mean value of 16.6 ± 2.5 kPa was identified as a reference standard for the following studies in several diseases. No correlation was shown between SSM and sex, age of patients or spleen size. More interesting data emerged during the study on the misinterpretation of liver and spleen stiffness using 2D-SWE and TE after a moderate or high caloric meal, respectively a 250 ml liquid meal containing 625 kcal on the first day and another liquid meal of twice the caloric and volumetric size (500 ml and 1,250 kcal) on day two. Baseline and post-meal measurements included liver stiffness and spleen stiffness with 2D-SWE and TE, controlled attenuation parameter (CAP), portal vein diameter and portal venous blood flow at 20, 40, 60, 120, and 180 min after meal ingestion. Overall, remarking the importance of a correct fasting period, the meal-related increase in liver stiffness was only moderately affected by the size of the meal, while spleen stiffness was unaffected by the meal size[44].

Discussion

Chronic liver disease complicated by PH is considered part of a remodeling process involving passive congestion, enhanced angiogenesis, and fibrogenesis that may alter the extra-hepatic hemodynamic condition and the spleen stiffness[13,45]. We evaluated a total of nearly twenty studies dealing with all available elastographic techniques that were usually compared with HVPG, which is the gold standard for diagnosing the presence of PH. Another target of these studies is the potential use of such techniques for predicting the presence of EV and the risk of gastroesophageal bleeding. Song et al[46] reported the first meta-analysis discussing SSM for the diagnosis of CSPH. A good accuracy was suggested for predicting CSPH with summary sensitivity and specificity of 0.88 (95% CI 0.7-0.96) and 0.84 (95%CI 0.72-0.92), respectively. A source of heterogeneity was the application of the ARFI technique, which showed higher sensitivity and lower specificity compared to non-ARFI group. Similar results were reported in case of severe PH, with sensitivity and specificity values of 0.92 and 0.79, respectively; however, there was no study correlating an exact HVPG value with a specific SSM value to define the group of patients likely to have CSPH and candidate to invasive examination.

A systematic review of 12 studies[47] supported the possibility to adopt SSM as a non-invasive surrogate for screening endoscopy in newly diagnosed cirrhosis, since the diagnostic performance of SSM was significantly better than that of LSM. The diagnostic odds ratios for detecting the presence of any EV or large EVs were 7.5 and 8.8 for LSM, while comparable values for SS were 19.3 and 12.6. In the same way, another meta-analysis[48] postulated that the accuracy of spleen stiffness was superior to liver stiffness for predicting EV in CLD. The authors indicated a summary sensitivity of 0.88 and a summary specificity of 0.78. They also established a cut-off value of ≥ 47 kPa for the prediction of EV. This study promoted the superiority of SS for predicting the

presence of EV better than LS, on both sensitivity and specificity, while the diagnostic accuracy of both was limited in predicting severe EV. Studies focused on CLD are however characterized by a wide heterogeneity, first of all, comparing the results between compensated or decompensated disease and different underlying etiologies. The epidemiology of chronic viral hepatitis is quickly changing with the advent of the new antiviral agents, while non-alcoholic fatty liver disease and obesity are now writing the future history of CLD. In this context, the evaluation of spleen stiffness could become a valid support to help therapeutic decisions and to follow-up patients, but data on specific populations are still lacking[49]. In addition, Marasco et al[50] suggest also a possible role for SSM evaluated by transient elastography in predicting the late recurrence of hepatocellular carcinoma, as shown in 175 patients evaluated in terms of recurrence after 24 months from liver resection.

Despite the huge literature considering the study of liver and also spleen stiffness in CLD, the possibility to perform spleen elastography could be an instrument to study the whole portal system in several other conditions[13].

Conclusions

Spleen stiffness showed overall a good diagnostic accuracy to diagnose clinically significant PH in CLD, in some cases even with reliable cut-off values for severe PH. The use of SSM has also been proposed by several studies as a promising non-invasive tool to predict the presence of EV and therefore to possibly avoid screening endoscopy in these patients. However, the different techniques available and the different cut-off values assessed to date might limit the impact on clinical practice and more high-quality prospective studies are warranted[51].

Conflict of Interests

The Authors declared that they have no conflict of interests.

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