Spleen Stiffness

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Rationale for the Use of Spleen Stiffness for Portal Hypertension

Splenomegaly is a hallmark of portal hypertension. Once portal pressure increases, whatever the cause, passive congestion of the spleen occurs, leading to its increase in size and stiffness. In addition, splanchnic arterial vasodilation leads to increased splenic arterial flow, further aggravating this phenomenon. From a microscopical point of view, splenic lymphoid tissue activation, angiogenesis, and fibrogenesis occur. Altogether, this leads to an increase in the stiffness of the organ [1].

Using spleen stiffness measurement (SSM) as a marker of portal hypertension in cACLD potentially overcomes two of the main limitations of liver stiffness measurement (LSM), since SSM a) is devoid of the confounding effect of liver congestion, inflammation, infiltration, or cholestasis and b) takes into account the flow-related component of portal hypertension, not mirrored by LSM [2].

After the initial papers published by Stefanescu et al. [3] and Colecchia et al. [4] showing that, using transient elastography (standard 50 Hz probe, FibroScan, Echosens, France), spleen stiffness measurement (SSM) correlates with the size of esophageal varices and with HVPG, there has been an increasing interest in the use of this novel parameter in patients with cACLD. Up to now, about 50 studies presented data on SSM measured either by ultrasound elastography (transient elastography, TE; point shear wave elastography, pSWE; 2D shear wave elastography, 2D-SWE) or by magnetic resonance elastography (MRE) as a marker of portal

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R. de Franchis (ed.), *Portal Hypertension VII*,
https://doi.org/10.1007/978-3-031-08552-9_12

Table 12.1 Studies reporting on SSM according to the measurement technique. Small studies with less than 30 cases were not included

Study	Year	Method used	N included and etiology	Failure rate	Endpoint	AUROC for the selected endpoint	Chosen cutoff for the selected endpoint	Sensitivity	Specificity
SSM by TE									
Stefanescu et al. [3]	2011	TE	174, mixed	14.4%	EV	0.781	46.4 kPa	83.6%	71.4%
Colecchia et al. [5]	2012	TE	113, HCV, compensated	11.5%	CSPH	0.966	40.0 kPa (rule out)	98.5%	74.3%
							52.8 kPa (rule in)	76.9%	97.1%
					EV	0.941	41.3 kPa (rule out)	98.1%	66.0%
							55.0 kPa (rule in)	71.7%	95.7%
Sharma et al. [32]	2013	TE	200, mixed	13%	EV	0.898	40.8 kPa	94%	76%
Calvaruso et al. [10]	2013	TE (modified range)	112, HCV, compensated	14.3%	EV	0.701	50.0 kPa	65%	61%
					LEV	0.820	54.0 kPa	80%	70%
Zykus et al. [33]	2015	TE	107, mixed, most compensated	7.5%	CSPH	0.846	47.6 kPa	77.3%	79.2%
Stefanescu et al. [34]	2015	TE	136, mixed	N/A	HRV	0.742	53 kPa	89%	54%
Wong et al. [35]	2016	TE	176, HBV	15.9%	EV	0.685	21.4 kPa (rule out)	90.3%	43.4%
							50.5 kPa (rule in)	45.2%	90.3%

Colecchia et al. [8]	2018	TE	498 (derivation cohort 258, 85% HCV; internal validation cohort 240, 40% HCV); external validation cohort 115, mixed	26 (4.5%)	HRV	0.847	46.0 (rule out)	97.8%	43.8%
Arribas Anta et al. [36]	2019	TE	66, mixed	9.1%	EV	0.800	48 kPa	87%	69%
Stefanescu et al. [9]	2020	TE (spleen-dedicated, 100 Hz)	260, mixed	7.5% (vs. 24% for 50 Hz)	CSPH	0.811	34.15 kPa	N/A	N/A
					EV	0.728	33.3 kPa (rule out)	90.3%	33.7%
							70 kPa (rule in)	29.1%	90.5%
					HRV	0.756	41.3 kPa (rule out)	91.3%	40.8%
							79.9 kPa (rule in)	26.1%	90.1%
Wang et al. [11]	2021	TE	341, HBV cirrhosis with viral suppression	4.1%	HRV	N/A	46 kPa	95.7%	65.3%
SSM by pSWE									
Rifai et al. [37]	2011	pSWE (VTQ)	100, mixed	22%	CSPH	0.680	3.29 m/s	47%	73%
Bota et al. [38]	2012	pSWE (VTQ)	145, mixed	2.1%	LEV	0.578	2.55 m/s	96.7%	21.0%
Ye et al. [39]	2012	pSWE (VTQ)	204, HBV	N/A	EV LEV	0.830 0.839	3.16 m/s 3.39 m/s	84.1% 78.9%	81% 78.3%

(continued)

Table 12.1 (continued)

Study	Year	Method used	N included and etiology	Failure rate	Endpoint	AUROC for the selected endpoint	Chosen cutoff for the selected endpoint	Sensitivity	Specificity
Vermehren et al. [40]	2012	pSWE (VTQ)	166, mixed	0%	LEV	0.580	3.04 m/s	90%	25%
Takuma et al. [41]	2013	pSWE (VTQ)	340, mixed	4.5%	EV HRV	0.937 (viral) 0.923 (others) 0.930 (all)	3.18 m/s 3.24 m/s 3.30 m/s	98.9% 97.7% 98.9%	59.9% 65.2% 62.9%
Rizzo et al. [42]	2014	pSWE (VTQ)	54, HCV	N/A	EV	0.959	3.10 m/s 2.32 m/s	96.4%	88.5%
Attia et al. [43]	2015	pSWE (VTQ)	78, mixed, some decompensated, 90% CSPH, 76% EV	0%	CSPH	0.968		96%	89%
Kim et al. [44]	2015	pSWE (VTQ)	132, mixed	4.5%	EV LEV	0.785 0.786	3.16 m/s 3.40 m/s	87.0% 78.9%	60.4% 63.0%
Park et al. [45]	2016	pSWE (ElastPQ)	366, viral and alcohol	24%	EV	0.859	29.9 kPa	85.1 kPa	79.1 kPa
Takuma et al. [46]	2016	pSWE (VTQ)	62, mixed, most compensated	3.2%	CSPH HVPG ≥12 EV LEV	0.943 0.963 0.937 0.955	3.10 m/s 3.15 m/s 3.36 m/s 3.51 m/s	97.1% 96.6% 95.8% 93.8%	57.7% 61.3% 77.8% 84.1%

Fierbinteanu-Braticevici et al. [47]	2019	pSWE (VTQ)	135, mixed	0%	EV HRV	0.776 0.972	2.5 m/s (rule out) 3.5 m/s (rule in) 3.2 m/s (rule out) 3.8 m/s (rule in)	92% 47% 97% 55%	22% 96% 69% 98%
Peagu et al. [48]	2019	pSWE (VTQ)	178, viral	N/A	EV LEV	0.872 0.969	2.89 m/s 3.30 m/s	91.4% 96.4%	67.7% 88.5%
Darweesh et al. [49]	2019	pSWE (VTQ)	200, HCV	1%	EV	0.760	3.25 m/s	85%	58%
Giuffrè et al. [50]	2020	pSWE (ElastPQ)	210, mixed, compensated	4.5%	EV	0.95	31 kPa (rule out) 69 kPa (rule in)	100% 14%	60% 100%
SSM by 2D-SWE									
Elkrief et al. [51]	2015	2D-SWE (SSI) TE	79, mixed, most decompensated, 89% CSPH, 69% child-Pugh B-C	3% 58%	CSPH	0.640	34.7 kPa	40%	100%
					LEV CSPH LEV	0.580 0.630 0.650	32.3 kPa 56.3 kPa 73.5 kPa	48% 73% 54%	71% 67% 78%
Procopet et al. [7]	2015	2D-SWE (SSI)	55, mixed, most compensated	34%	CSPH	0.725	22.7 kPa (rule out)	90%	N/A
							40 kPa (rule in)	N/A	90%

(continued)

Table 12.1 (continued)

Study	Year	Method used	N included and etiology	Failure rate	Endpoint	AUROC for the selected endpoint	Chosen cutoff for the selected endpoint	Sensitivity	Specificity
Cassinotto et al. [12]	2015	2D-SWE (SSI)	401, mixed, some decompensated	29.2%	EV	0.80	N/A	N/A	N/A
					HRV	0.78 (all)	N/A	N/A	N/A
						0.75 (compensated)	25.6 kPa (with NPV >90%)	94%	36%
Grgurevic et al. [19]	2015	2D-SWE (SSI)	126, mixed	29.4%	EV	0.790	30.3 kPa	79.6%	75.8%
Jansen et al. [52]	2017	2D-SWE (SSI)	158, mixed, some decompensated	18.8%	CSPH	0.840	26.3 kPa 21.7 kPa (rule out) 35.6 kPa (rule in)	79.7% 91.9% 51.4%	84.2% 50% 92%
Zhu et al. [53]	2019	2D-SWE (SSI)	104, HBV, most compensated	24.6%	CSPH	0.810	23.2 kPa (rule out)	>90%	N/A
							34.2 kPa (rule in)	N/A	>90%
Karagiannakis et al. [14]	2019	2D-SWE (SSI)	64, mixed, compensated	9.8%	HRV	0.792 (all) 0.854 (excluding cholestatic LD)	33.7 kPa (rule out) 35.8 kPa (rule out)	91.7% 88.9%	60.0% 72.4%
Cho et al. [54]	2020	2D-SWE	274, mixed, compensated	N/R	HRV	0.844	≤27.3 kPa (rule out)	98.1%	35.9%
SSM by MRE									
Danielsen et al. [55]	2021	2D-MRE	52, mixed etiologies, some decompensated	Not reported	HVPG HVPG ≥12	Correlation 0.94 0.810 (0.64–0.97)	10.5 kPa	80%	79%

hypertension or varices using HVPG measurement or endoscopy as gold standards. The studies with a larger sample size are summarized in Table 12.1.

A recent systematic review and meta-analysis of 32 studies using any of the above-mentioned techniques in 3952 patients concluded that spleen stiffness had a summary area under the ROC curve (sAUROC) of over 0.90, with a sensitivity of 0.85 and specificity of 0.86 for detecting CSPH. As for high-risk varices (HRV), the sAUROC was 0.83 with a sensitivity of 0.87 and specificity of 0.66. The performance of SSM was superior in Asian subjects, who had a lower body mass index.

SSM Using Transient Elastography

Ten large ($n > 100$) studies on SSM using TE have been published so far. Over 80% of study patients had a viral etiology of liver disease (untreated HCV or HBV, or HBV on viral suppression). SSM was measured using the standard liver probe with 50 Hz frequency in all studies except one. Reproducibility has been proven excellent [5–7]. Due to technical requirements not being met in small spleens, SSM had a high failure rate up to 15%–27%, which constitutes a major limitation of the method. When ultrasound was used to locate the spleen, applicability improved significantly [5, 8]. Similarly, the failure rate of SSM using a novel, spleen-dedicated probe with 100 Hz frequency improved to 7.5% [9].

Since the spleen is stiffer than the liver, with normal values up to 21 kPa, a ceiling effect at 75 kPa was occurring with the standard probe in patients with ACLD, as proven by the use of a modified software able to provide a range up to 150 kPa [10]. The novel spleen-dedicated probe provides values up to 100 kPa [9].

In the published studies using HVPG as a gold standard, SSM correlated with the HVPG with a similar or even closer correlation coefficient than LSM. The best cutoff value to rule out and rule in CSPH has not yet been set. From the analysis of the existing data, mainly in patients with cACLD due to HBV or HCV and using the standard 50 Hz probe, it seems that SSM < 21–30 kPa can rule out CSPH with a sensitivity >90%, while SSM above 50 kPa could rule in CSPH with a specificity >90%. Validation in other etiologies and large prospective series is needed.

As for ruling out and ruling in HRV, the available data suggest that SSM below 40 kPa (standard probe) rules out HRV with a sensitivity >90% (Tables 12.1 and 12.2). In two independent studies which proposed [8] or applied [11] a slightly higher SSM cutoff value (46 kPa), SSM alone or used in combination with the Baveno VI criteria increased the rate of spared endoscopies in comparison to the Baveno criteria, while maintaining the rate of missed varices requiring treatment below 5% (Table 12.2). In the only study published so far, using a spleen specific 100 Hz TE probe allowed improving the results obtained by the standard 50 Hz probe in terms of spared endoscopies [9].

Table 12.2 Performance of SSM combined to the Baveno VI criteria or with LSM alone

Study	Year	Method used	N included and etiology	N (%) HRV	Chosen SSM cutoff to spare endoscopy	% Spared endoscopies and missed HRV using Baveno VI	% spared endoscopies and missed HRV using SSM	% spared endoscopies and missed HRV using Baveno VI + SSM
Wong et al. [56]	2018	TE-randomized open label-controlled trial	548 (274 per arm), 85% viral hepatitis (>>HBV)	11 (4%) in the NITs arm, 5.8% in the standard of care arm	41.3 kPa + LSM < 12.5 kPa	N/A	N/A	N/A LSSM (LSM + SSM) strategy spared 41.8% endoscopies
Stefanescu et al. [9]	2020	TE (standard 50 Hz) TE (spleen-dedicated, 100 Hz)	260, mixed	69 (26.5%)	40.1 kPa 41.3 kPa	8.1%; 0 8.1%; 0	18.4%; 4.7% 30.8%; 4.7%	26.5%; 4.7 38.1%; 4.7
Colecchia et al. [8]	2018	TE	Derivation cohort 258, 85% HCV Internal validation cohort 240, 40% HCV External validation cohort 115	54 (20.9%) 46 (19%) 28 (13%)	46 kPa	21.7%; 2.2% 16.5%; 0	35.8%; 2.2% 30.4%; 0	43.8%; 4.3% 37.4%; 0
Wang et al. [11]	2021	TE	341, HBV cirrhosis with viral suppression	70 (20.5%)	46 kPa	37.0%; 0	52.1%; 0	61.6%; 4.3%
Cho et al. [54]	2020	2D-SWE	274, mixed, compensated	54 (19.7%)	27.3 kPa	18.6% (LSM <16 kPa + Plt > 150 G/L); 0	28.8%; 1.9%	36.1%; 1.9%

SSM Using Other Ultrasound Elastography Methods

The applicability of pSWE and 2D-SWE is affected by similar factors, including the absence of splenomegaly, obesity, movements caused by heart beating and ascites [12]. Even though several studies are available with both methods (Table 12.1), there is a considerable heterogeneity in the type of included patients, and several studies included decompensated ACLD patients.

With these limitations, the analysis of the data suggests that using pSWE (Virtual Touch Siemens; pSWE by other devices has too limited data) SSM values <2.5 m/s could be used to rule out CSPH and HRV, while values >3.5 m/s might suggest EV (see Table 12.1). In a prospective study using pSWE (Virtual Touch Siemens) in patients with cACLD mostly due to HBV, SSM predicted variceal bleeding with an AUROC of 0.911 [13]. The best cutoff value discriminating patients developing variceal bleeding from those who did not (with an incidence of 7.3% over 32 months of follow-up) was 3.48 m/s.

As for 2D-SWE (Supersonic Imagine; 2D-SWE by other devices has too limited data), values of SSM < 21–25 kPa could be used to rule out CSPH (cutoff value closer to TE), while values <35 kPa could be used to rule out HRV (see Table 12.1). Karagiannakis et al. [14] showed that SSM by this method might help sparing a larger proportion of endoscopies than the Baveno VI criteria, without missing more HRV.

SSM Using Magnetic Resonance Elastography

SSM by MRE has been evaluated in eight studies, most of which included a very small number of patients. Data regarding the prediction of varices and HRV are in line with those provided by ultrasound elastography methods, but a direct comparison of the accuracy of these methods is not possible yet [15]. Availability and cost limit the routine use of MRE to measure SSM in cACLD.

SSM for the Prediction of Liver-Related Events, Mortality, and Response to Therapy

SSM predicted the first clinical decompensation and mortality in five studies [4, 16–19] and predicted HCC recurrence in one study [20]. The best cutoff value predicting decompensation using TE was 54 kPa. In patients with HCV cirrhosis experiencing sustained virological response, SSM decreases significantly [21, 22], and SSM was an independent predictor of liver-related events (decompensation [23] and HCC [24]). Two studies (one using pSWE [25] and one with TE [26]) showed that SSM might predict the hemodynamic response to NSBB in patients started on primary prophylaxis. SSM decreases after TIPS, suggesting that it parallels the decrease in portal pressure [27–31].

Summary

The data summarized in this chapter show that SSM can be considered as a marker of portal hypertension and should be included as a complementary noninvasive test in the armamentarium of hepatologists to assess CSPH and varices in addition to the Baveno VI criteria. In patients with cACLD due to viral causes, SSM used in combination with the Baveno VI criteria seems to allow to safely expand the rate of spared endoscopies. However, SSM applicability remains an issue, and evidence is not strong enough to recommend cutoff values to rule out/rule in varices requiring treatment by techniques other than TE. In addition, data in patients with cACLD due to non-viral causes are scarce, and it is still difficult to draw solid conclusions in this context. Furthermore, whether the use of the novel TE spleen-specific probe allows better risk stratification remains to be ascertained in future studies.

References

1. Mejias M, Garcia-Pras E, Gallego J, Mendez R, Bosch J, Fernandez M. Relevance of the mTOR signaling pathway in the pathophysiology of splenomegaly in rats with chronic portal hypertension. J Hepatol. 2010;52:529–39.
2. Tseng Y, Li F, Wang J, Chen S, Jiang W, Shen X, et al. Spleen and liver stiffness for noninvasive assessment of portal hypertension in cirrhotic patients with large esophageal varices. J Clin Ultrasound. 2018;46:442–9.
3. Stefanescu H, Grigorescu M, Lupsor M, Procopet B, Maniu A, Badea R. Spleen stiffness measurement using Fibroscan for the noninvasive assessment of esophageal varices in liver cirrhosis patients. J Gastroenterol Hepatol. 2011;26:164–70.
4. Colecchia A, Colli A, Casazza G, Mandolesi D, Schiumerini R, Reggiani LB, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. J Hepatol. 2014;60:1158–64.
5. Colecchia A, Montrone L, Scaioli E, Bacchi-Reggiani ML, Colli A, Casazza G, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology. 2012;143:646–54.
6. Balakrishnan M, Souza F, Muñoz C, Augustin S, Loo N, Deng Y, et al. Liver and spleen stiffness measurements by point shear wave elastography via acoustic radiation force impulse: intraobserver and interobserver variability and predictors of variability in a US population. J Ultrasound Med. 2016;35:2373–80.
7. Procopet B, Berzigotti A, Abraldes JG, Turon F, Hernandez-Gea V, García-Pagán JC, et al. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. J Hepatol. 2015;62:1068–75.
8. Colecchia A, Ravaioli F, Marasco G, Colli A, Dajti E, Di Biase AR, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. J Hepatol. 2018;69:308–17.
9. Stefanescu H, Marasco G, Cales P, Fraquelli M, Rosselli M, Ganne-Carrie N, et al. A novel spleen-dedicated stiffness measurement by FibroScan(R) improves the screening of high-risk oesophageal varices. Liver Int. 2020;40:175–85.
10. Calvaruso V, Bronte F, Conte E, Simone F, Craxì A, Di Marco V. Modified spleen stiffness measurement by transient elastography is associated with presence of large oesophageal varices in patients with compensated hepatitis C virus cirrhosis. J Viral Hepat. 2013;20:867–74.
11. Wang H, Wen B, Chang X, Wu Q, Wen W, Zhou F, et al. Baveno VI criteria and spleen stiffness measurement rule out high-risk varices in virally suppressed HBV-related cirrhosis. J Hepatol. 2021;74:584–92.

12. Cassinotto C, Charrie A, Mouries A, Lapuyade B, Hiriart JB, Vergniol J, et al. Liver and spleen elastography using supersonic shear imaging for the non-invasive diagnosis of cirrhosis severity and oesophageal varices. Dig Liver Dis. 2015;47:695–701.
13. Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Takabatake H, et al. Prediction of oesophageal variceal bleeding by measuring spleen stiffness in patients with liver cirrhosis. Gut. 2016;65:354–5.
14. Karagiannakis DS, Voulgaris T, Koureta E, Chloupi E, Papatheodoridis GV, Vlachogiannakos J. Role of spleen stiffness measurement by 2D-shear wave elastography in ruling out the presence of high-risk varices in cirrhotic patients. Dig Dis Sci. 2019;64:2653–60.
15. Singh R, Wilson MP, Katlariwala P, Murad MH, McInnes MDF, Low G. Accuracy of liver and spleen stiffness on magnetic resonance elastography for detecting portal hypertension: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2021;32(2):237–45.
16. Meister P, Dechêne A, Büchter M, Kälsch J, Gerken G, Canbay A, et al. Spleen stiffness differentiates between acute and chronic liver damage and predicts hepatic decompensation. J Clin Gastroenterol. 2019;53(6):457–63.
17. Takuma Y, Morimoto Y, Takabatake H, Toshikuni N, Tomokuni J, Sahara A, et al. Measurement of spleen stiffness with acoustic radiation force impulse imaging predicts mortality and hepatic decompensation in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2017;15:1782–1790.e1784.
18. Zhang Y, Mao DF, Zhang MW, Fan XX. Clinical value of liver and spleen shear wave velocity in predicting the prognosis of patients with portal hypertension. World J Gastroenterol. 2017;23:8044–52.
19. Grgurević I, Bokun T, Mustapić S, Trkulja V, Heinzl R, Banić M, et al. Real-time two-dimensional shear wave ultrasound elastography of the liver is a reliable predictor of clinical outcomes and the presence of esophageal varices in patients with compensated liver cirrhosis. Croat Med J. 2015;56:470–81.
20. Marasco G, Colecchia A, Colli A, Ravaioli F, Casazza G, Bacchi Reggiani ML, et al. Role of liver and spleen stiffness in predicting the recurrence of hepatocellular carcinoma after resection. J Hepatol. 2019;70:440–8.
21. Ravaioli F, Colecchia A, Dajti E, Marasco G, Alemanni LV, Tame M, et al. Spleen stiffness mirrors changes in portal hypertension after successful interferon-free therapy in chronic-hepatitis C virus patients. World J Hepatol. 2018;10:731–42.
22. Pons M, Santos B, Simon-Talero M, Ventura-Cots M, Riveiro-Barciela M, Esteban R, et al. Rapid liver and spleen stiffness improvement in compensated advanced chronic liver disease patients treated with oral antivirals. Ther Adv Gastroenterol. 2017;10:619–29.
23. Dajti E, Ravaioli F, Colecchia A, Marasco G, Bacchi Reggiani ML, Colli A, et al. Spleen stiffness measurements predict the risk of hepatic decompensation after direct-acting antivirals in HCV cirrhotic patients. Ultraschall Med. 2020; https://doi.org/10.1055/a-1205-0367.
24. Dajti E, Marasco G, Ravaioli F, Colecchia L, Ferrarese A, Festi D, et al. Risk of hepatocellular carcinoma after HCV eradication: determining the role of portal hypertension by measuring spleen stiffness. JHEP Rep. 2021;3:100289.
25. Kim HY, So YH, Kim W, Ahn DW, Jung YJ, Woo H, et al. Non-invasive response prediction in prophylactic carvedilol therapy for cirrhotic patients with esophageal varices. J Hepatol. 2019;70:412–22.
26. Marasco G, Dajti E, Ravaioli F, Alemanni LV, Capuano F, Gjini K, et al. Spleen stiffness measurement for assessing the response to beta-blockers therapy for high-risk esophageal varices patients. Hepatol Int. 2020;14:850–7.
27. Ran HT, Ye XP, Zheng YY, Zhang DZ, Wang ZG, Chen J, et al. Spleen stiffness and splenoportal venous flow: assessment before and after transjugular intrahepatic portosystemic shunt placement. J Ultrasound Med. 2013;32:221–8.
28. Gao J, Zheng X, Zheng YY, Zuo GQ, Ran HT, Auh YH, et al. Shear wave elastography of the spleen for monitoring transjugular intrahepatic portosystemic shunt function: a pilot study. J Ultrasound Med. 2016;35:951–8.

29. De Santis A, Nardelli S, Bassanelli C, Lupo M, Iegri C, Di Ciesco CA, et al. Modification of splenic stiffness on acoustic radiation force impulse parallels the variation of portal pressure induced by transjugular intrahepatic portosystemic shunt. J Gastroenterol Hepatol. 2018;33:704–9.
30. Buechter M, Manka P, Theysohn JM, Reinboldt M, Canbay A, Kahraman A. Spleen stiffness is positively correlated with HVPG and decreases significantly after TIPS implantation. Dig Liver Dis. 2018;50:54–60.
31. Attia D, Rodt T, Marquardt S, Hinrichs J, Meyer BC, Gebel M, et al. Shear wave elastography prior to transjugular intrahepatic portosystemic shunt may predict the decrease in hepatic vein pressure gradient. Abdom Radiol (NY). 2019;44:1127–34.
32. Sharma P, Kirnake V, Tyagi P, Bansal N, Singla V, Kumar A, et al. Spleen stiffness in patients with cirrhosis in predicting esophageal varices. Am J Gastroenterol. 2013;108:1101–7.
33. Zykus R, Jonaitis L, Petrenkienė V, Pranculis A, Kupčinskas L. Liver and spleen transient elastography predicts portal hypertension in patients with chronic liver disease: a prospective cohort study. BMC Gastroenterol. 2015;15:183.
34. Stefanescu H, Radu C, Procopet B, Lupsor-Platon M, Habic A, Tantau M, et al. Non-invasive ménage à trois for the prediction of high-risk varices: stepwise algorithm using lok score, liver and spleen stiffness. Liver Int. 2015;35:317–25.
35. Wong GL, Kwok R, Chan HL, Tang SP, Lee E, Lam TC, et al. Measuring spleen stiffness to predict varices in chronic hepatitis B cirrhotic patients with or without receiving non-selective beta-blockers. J Dig Dis. 2016;17:538–46.
36. Arribas Anta J, Garcia Gonzalez M, Torres Guerrero ME, Garrido Gomez E, Rodriguez de Santiago E, Lopez Duran S, et al. Prediction of the presence of esophageal varices using spleen stiffness measurement by transient elastography in cirrhotic patients. Acta Gastroenterol Belg. 2018;81:496–501.
37. Rifai K, Cornberg J, Bahr M, Mederacke I, Potthoff A, Wedemeyer H, et al. ARFI elastography of the spleen is inferior to liver elastography for the detection of portal hypertension. Ultraschall Med. 2011;32(Suppl 2):E24–30.
38. Bota S, Sporea I, Sirli R, Focsa M, Popescu A, Danila M, et al. Can ARFI elastography predict the presence of significant esophageal varices in newly diagnosed cirrhotic patients? Ann Hepatol. 2012;11:519–25.
39. Ye XP, Ran HT, Cheng J, Zhu YF, Zhang DZ, Zhang P, et al. Liver and spleen stiffness measured by acoustic radiation force impulse elastography for noninvasive assessment of liver fibrosis and esophageal varices in patients with chronic hepatitis B. J Ultrasound Med. 2012;31:1245–53.
40. Vermehren J, Polta A, Zimmermann O, Herrmann E, Poynard T, Hofmann WP, et al. Comparison of acoustic radiation force impulse imaging with transient elastography for the detection of complications in patients with cirrhosis. Liver Int. 2012;32:852–8.
41. Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Toshikuni N, et al. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. Gastroenterology. 2013;144:92–101. e102
42. Rizzo L, Attanasio M, Pinzone MR, Berretta M, Malaguarnera M, Morra A, et al. A new sampling method for spleen stiffness measurement based on quantitative acoustic radiation force impulse elastography for noninvasive assessment of esophageal varices in newly diagnosed HCV-related cirrhosis. Biomed Res Int. 2014;2014:365982.
43. Attia D, Schoenemeier B, Rodt T, Negm AA, Lenzen H, Lankisch TO, et al. Evaluation of liver and spleen stiffness with acoustic radiation force impulse quantification elastography for diagnosing clinically significant portal hypertension. Ultraschall Med. 2015;36:603–10.
44. Kim HY, Jin EH, Kim W, Lee JY, Woo H, Oh S, et al. The role of spleen stiffness in determining the severity and bleeding risk of esophageal varices in cirrhotic patients. Medicine. 2015;94:e1031.
45. Park J, Kwon H, Cho J, Oh J, Lee S, Han S, et al. Is the spleen stiffness value acquired using acoustic radiation force impulse (ARFI) technology predictive of the presence of esophageal varices in patients with cirrhosis of various etiologies? Med Ultrason. 2016;18:11–7.

46. Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Takabatake H, et al. Portal hypertension in patients with liver cirrhosis: diagnostic accuracy of spleen stiffness. Radiology. 2016;279:609–19.
47. Fierbinteanu-Braticevici C, Tribus L, Peagu R, Petrisor A, Baicus C, Cretoiu D, et al. Spleen stiffness as predictor of esophageal varices in cirrhosis of different etiologies. Sci Rep. 2019;9:16190.
48. Peagu R, Sararu R, Necula A, Moldoveanu A, Petrisor A, Fierbinteanu-Braticevici C. The role of spleen stiffness using ARFI in predicting esophageal varices in patients with hepatitis B and C virus-related cirrhosis. Rom J Intern Med. 2019;57:334–40.
49. Darweesh SK, Yosry A, Salah M, Zayed N, Khairy A, Awad A, et al. Acoustic radiation forced impulse-based splenic prediction model using data mining for the noninvasive prediction of esophageal varices in hepatitis C virus advanced fibrosis. Eur J Gastroenterol Hepatol. 2019;31:1533–9.
50. Giuffre M, Macor D, Masutti F, Abazia C, Tine F, Bedogni G, et al. Spleen Stiffness Probability Index (SSPI): a simple and accurate method to detect esophageal varices in patients with compensated liver cirrhosis. Ann Hepatol. 2020;19:53–61.
51. Elkrief L, Rautou PE, Ronot M, Lambert S, Dioguardi Burgio M, Francoz C, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology. 2015;275:589–98.
52. Jansen C, Bogs C, Verlinden W, Thiele M, Möller P, Görtzen J, et al. Shear-wave elastography of the liver and spleen identifies clinically significant portal hypertension: a prospective multicentre study. Liver Int. 2017;37:396–405.
53. Zhu YL, Ding H, Fu TT, Peng SY, Chen SY, Luo JJ, et al. Portal hypertension in hepatitis B-related cirrhosis: diagnostic accuracy of liver and spleen stiffness by 2-D shear-wave elastography. Hepatol Res. 2019;49(5):540–9.
54. Cho YS, Kim Y, Sohn JH. Application of supersonic shear imaging to the Baveno VI criteria and a combination model with spleen stiffness measurement to rule out high-risk varices in compensated advanced chronic liver disease. Ultraschall Med. 2020; https://doi.org/10.1055/a-1168-6271.
55. Danielsen KV, Hove JD, Nabilou P, Yin M, Chen J, Zhao M, et al. Using MR elastography to assess portal hypertension and response to beta-blockers in patients with cirrhosis. Liver Int. 2021;41:2149–58.
56. Wong GLH, Kwok R, Hui AJ, Tse YK, Ho KT, Lo AOS, et al. A new screening strategy for varices by liver and spleen stiffness measurement (LSSM) in cirrhotic patients: a randomized trial. Liver Int. 2018;38:636–44.