

# Approaches to the Diagnosis of Portal Hypertension: Non-Invasive or Invasive Tests?

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**Abstract:** Portal hypertension is the main driver of complications in patients with advanced chronic liver disease (ACLD) and is defined by values of hepatic venous pressure gradient measurement (HVPG) >5 mmHg. Values of HVPG  $\geq$ 10 mmHg determine the presence of clinically significant portal hypertension (CSPH), the main predictor of the risk of variceal bleeding, hepatic decompensation, and mortality. However, its measurement is invasive and requires high expertise, so its routine use outside third level centers or clinical trials is limited. In the last decades, several non-invasive tests (NITs) have been developed and validated for the diagnosis of portal hypertension. Among these, liver (LSM) and spleen stiffness measurement (SSM) are the most promising tools available, as they have been proven accurate to predict CSPH, high-risk esophageal varices, decompensation, and mortality in patients with ACLD. In the last Baveno VI Consensus proceedings, LSM evaluation was recommended for the first time for diagnosis of CSPH (LSM >20-25 kPa) and the screening of patients with a low probability of having high-risk varices (LSM <20 kPa and platelet count >150.000/mm<sup>3</sup>). In this review, we aimed to summarize the growing evidence supporting the use of non-invasive tests for the evaluation of portal hypertension in patients with chronic liver disease.

**Keywords:** liver stiffness, spleen stiffness, portal hypertension, hepatic venous pressure gradient, liver cirrhosis

## Introduction

Liver cirrhosis is a major cause of morbidity and mortality worldwide and is associated with increasing health burden and costs.<sup>1</sup> It is a very heterogeneous and dynamic condition, and at least two distinct stages should be recognized: compensated and decompensated cirrhosis.<sup>2</sup> Decompensation includes the development of clinical events such as ascites, variceal bleeding, hepatic encephalopathy, or hepato-renal syndrome, and it is associated with a significant decrease in patient survival.<sup>3</sup> Cirrhosis in the compensated phase, on the other hand, is associated with an up to 80% 5-year survival rate; it can be further classified according to the degree of portal hypertension, as evaluated by its gold standard,<sup>4</sup> the hepatic venous pressure gradient (HVPG), in compensated cirrhosis without portal hypertension (HVPG <5 mmHg), with mild portal hypertension (HVPG >5 mmHg, but <10 mmHg), or clinically significant portal hypertension (CSPH, and HVPG  $\geq$ 10).<sup>5</sup> The development of CSPH is an important hallmark in the natural history of liver cirrhosis and is associated with an increased risk of gastroesophageal varices, hepatic decompensation, hepatocellular carcinoma (HCC), and mortality.<sup>5</sup>

In this view, early identification of patients with compensated cirrhosis and risk stratification according to the severity of portal hypertension is of extreme

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importance for the hepatologist. In the last years, several non-invasive tests have been developed and validated for these purposes, with liver (LSM) and spleen stiffness measurement (SSM) being the most promising tools available.<sup>6</sup> In the present paper, we aim to summarize the pros and cons and the evidence supporting the use of both invasive and non-invasive tests (NITs) in the diagnosis of portal hypertension.

## Part I – Invasive Evaluation of Portal Hypertension: The Hepatic Venous Pressure Gradient

It is widely recognized that patients with compensated advanced chronic liver disease (ACLD) may progress to decompensation at a rate of about 5–7% per year.<sup>7</sup> The leading cause of decompensation is the development of portal hypertension and its complications such as variceal bleeding, hepatic encephalopathy, and ascites, thus impacting on overall patient mortality rate.<sup>8</sup>

The gold standard method used for the evaluation of portal hypertension is the measurement of HVPG, which has been widely validated also as a prognostic factor.<sup>9</sup> Portal hypertension is defined by HVPG values > 5 mmHg; HVPG  $\geq$ 10 mmHg is associated with clinically significant portal hypertension (CSPH), which is an at-risk condition for decompensation, esophageal varices, and HCC development.<sup>4,5,10</sup> Severe PH is defined by HVPG > 12 mmHg, whereas very severe PH by HVPG >16 mmHg; these conditions are both associated with a higher risk of variceal bleeding and mortality.<sup>4</sup> Briefly, through venous access, a catheter is introduced into the right brachial vein or the right internal jugular vein until a branch of the hepatic veins is reached, usually the median or the right vein. Afterward, a balloon is inflated occluding all the vessels below, and then the measurement of wedged hepatic vein pressure is performed.<sup>11</sup> Subsequently, after deflating the balloon at the tip of the catheter, the free hepatic vein pressure is measured.<sup>4,11</sup>

Non-selective beta-blockers (NSBB) represent the most common therapeutic choice for the primary and secondary prophylaxis of variceal bleeding.<sup>2</sup> HVPG measurement is also employed for the prediction of acute and chronic hemodynamic response to NSBB therapy for high-risk varices (HRV).<sup>4</sup> According to the Baveno VI consensus, the response to NSBB is defined as the reduction of HVPG  $\geq$ 10% or  $\leq$ 12 mmHg after treatment.<sup>12</sup> Moreover, HVPG may be used to assess the hemodynamic response

to NSBB to guide therapy for the prevention of variceal bleeding recurrence.<sup>13</sup>

Besides, recently, the PREDESCI trial<sup>14</sup> showed that NSBB could significantly improve decompensation-free survival in patients with compensated cirrhosis and HVPG  $\geq$ 10 mmHg, with criteria similar to those adopted for assessing hemodynamic response for HRV, since these patients were those who most benefited from NSBB. Regarding HVPG prospective evaluations, one of the main applications is related to the evaluation of patency and therapeutic effectiveness after transjugular intrahepatic portosystemic shunt (TIPS) placement, which is indicated in patients with decompensated portal hypertension.<sup>15</sup>

Interestingly, dynamic HVPG changes have been prospectively reported in other settings, such as in patients with hepatitis C virus (HCV)-associated cirrhosis treated with the new direct-acting antiviral agents (DAAs), showing that sustained virologic response (SVR) was associated with a significant reduction of HVPG when compared with that assessed before treatment, thus mirroring both hemodynamic and fibrotic changes occurring after treatment.<sup>16</sup> Also, the portal hypertension degree influences the natural history of chronic liver diseases, leading to HCC.<sup>10</sup> Previously, an HVPG value >10mmHg has been identified as independently associated with HCC occurrence.<sup>10,17,18</sup>

Finally, HVPG value has been associated with outcomes in patients with cirrhosis undergoing elective extrahepatic surgery, allowing an accurate patients risk stratification thus improving post-surgical outcomes.<sup>19</sup> However, HVPG use is limited by its invasiveness and is available only in highly specialized centers; thus, in the last decade, several attempts have been made to find the ideal NIT able to replace HVPG.

## Part II – Non-Invasive Evaluation of Portal Hypertension

The last decade has seen several efforts to develop tests that can replace invasive methods for the assessment of portal hypertension in patients with ACLD. Patients were routinely subjected to liver biopsies in order to establish the severity of fibrosis, and HVPG measurement is still considered the gold standard in portal hypertension evaluation.<sup>4</sup> However, as mentioned above, these methods are invasive, not widely available, and risky for patients. Such limitations have led to the development and validation of new alternative NITs which have revolutionized the clinical approach to ACLD patients. The increasing need

for NITs in patients with liver cirrhosis has also been recently highlighted by the guidelines of the European Society for the Study of the Liver (EASL).<sup>20</sup>

Novel elastographic techniques have got increasing attention through the years and today play a well-recognized role in liver disease assessment, as stated also by the last Baveno VI Consensus Workshop.<sup>2</sup> Among ultrasound-based elastographic techniques, transient elastography (TE) is the first and the most validated method for LSM evaluation.<sup>21</sup> Liver stiffness represents a surrogate marker of liver fibrosis; therefore, it is useful in diagnosing ACLD and its complications (Table 1). Being liver fibrosis a fundamental determinant of hepatic resistance to the portal blood flow,<sup>6</sup> LSM application has been consequently extended to portal hypertension assessment and the prediction of esophageal varices (EV) with good results; in fact, LSM represents today a valuable non-invasive alternative to HVPG in clinical practice. One of the first pieces of evidence was produced by Carrión et al in 2006 in HCV-patients undergoing liver transplantation;<sup>22</sup> LSM by TE technique showed a close correlation with HVPG and good accuracy (AUC=0.93) in diagnosing portal hypertension (defined as HVPG > 6 mmHg). It was followed by several studies aimed at establishing the optimal LS cut-off for portal hypertension diagnosis, obtaining controversial results. A recent meta-analysis still confirmed the good correlation between LSM and HVPG ( $r = 0.783$ ).<sup>23</sup>

However, Vizzutti et al reported that, while the correlation between LSM and HVPG values less than 10–12 mmHg was excellent ( $r = 0.81$ – $0.91$ ), it appeared to be poorer for higher HVPG values, with a non-optimal linear regression analysis ( $r^2=0.35$  for HVPG > 10 mmHg,  $r^2=0.17$  if > 12 mmHg).<sup>24</sup> A possible explanation is that in an early phase portal hypertension is mainly linked to fibrotic modifications of liver parenchyma, but at later stages, it is determined by many hemodynamic changes driven, such as neoangiogenesis, hyperdynamic circulation, portosystemic collateral development, and splanchnic vasodilation,<sup>6</sup> and these modifications are not captured by an indirect surrogate of portal hypertension, such as LSM.

More recently, increasing attention has been driven to the evaluation of SSM by elastosonography. It is today clear that splenomegaly does not simply reflect spleen congestion in ACLD patients, but it is determined also by structural changes and tissue hyperplasia due to fibrogenesis, angiogenesis, activation of lymphoid compartment.<sup>25–27</sup> Consensually, SSM proved to have a strong correlation with the whole range of HVPG values, as shown in the

seminal paper by Colecchia et al:<sup>28</sup> SSM provided the strongest correlation with HVPG ( $r = 0.885$ ), as compared to LSM. A recent meta-analysis confirmed the good correlation between SSM and HVPG.<sup>29</sup> Therefore, SSM is considered today as a direct surrogate of portal hypertension that captures all of its physiopathological components, from early to the late cirrhotic stages. From a technical point of view, SSM values are obtained using the same probe used to perform LS, with the patient in a supine position with maximal abduction of the left arm and the probe positioned in an intercostal space where the spleen was correctly visualized by ultrasound. Since no specific reliability criteria have been developed for SSM, the same as those for LSM are generally applied; besides, SSM is not considered reliable if the splenic parenchymal thickness is <4 cm under the probe. The main limit of SSM is its feasibility since the rate of technical failure reported in current literature is highly variable (0–60%). However, in expert centers, this rate is usually <10%.<sup>30,31</sup> Moreover, new devices including build-in ultrasound for spleen detection<sup>32</sup> or fusion-methods,<sup>33</sup> have been developed to improve SSM feasibility and accuracy in the prediction of portal hypertension.

Besides elastography techniques, several serum biomarkers and radiological scores have been developed to non-invasively detect liver fibrosis<sup>34</sup> and portal hypertension.<sup>35–43</sup> For instance, the aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) and Fibrosis (FIB-4) Score showed an AUROC of was 0.728 and 0.710, respectively, for the prediction of large varices in a meta-analysis.<sup>44</sup> Several studies evaluated also more direct surrogates of portal hypertension, such as von Willebrand factor<sup>39,40</sup> or indocyanine green clearance<sup>45,46</sup> showing more promising results. However, the modest correlation with HVPG<sup>47</sup> and overall suboptimal performance of the above-mentioned readily available serum biomarkers, as well as the limited evidence and availability of other more direct biomarkers, hampers the routine use of such NITs for the detection of portal hypertension and its complications in everyday clinical practice.<sup>40</sup>

## Liver and Spleen Stiffness for the Diagnosis of Clinically Significant Portal Hypertension

The identification of CSPH is fundamental in ACLD since it allows to identify the patients who are at increased risk of gastroesophageal varices, decompensation, HCC, and mortality.<sup>5</sup> With the introduction of LSM in clinical practice, many attempts have been made to establish the best

**Table I** Performance of Liver and Spleen Stiffness in the Diagnosis of CSPH and Gastroesophageal Varices

Author, Year	Study Design	Nr. Patients	Technique	Parameter	Outcome	AUROC	Cut-Offs (Rule-Out or Rule-In)	Performance
Carrion, 2006 <sup>22</sup>	Prospective	129, HCV	TE	LSM	PH	0.930	8.74 kPa	Sens 100% Spec 60.8%
Vizzutti, 2007 <sup>24</sup>	Retrospective	61, HCV	TE	LSM	CSPH	0.990	13.6 kPa	Sens 97%, Spec 92%
Reiberger, 2012 <sup>48</sup>	Retrospective	502, mixed	TE	LSM	CSPH	0.871	18 kPa	Sens 82.2% Spec 83.4%
Salz, 2014 <sup>49</sup>	Prospective	88, mixed	p-SWE	LSM	CSPH	0.855	2.58 m/s	Sens 71.4% Spec 87.5%
					EV	0.743	2.74 m/s	Sens 62.5% Spec 89.5%
Procopet, 2015 <sup>50</sup>	Prospective	88, mixed	2D-SWE	LSM	CSPH	0.858	17 kPa	Sens 80.8% Spec 82.1%
Maurice, 2016 <sup>66</sup>	Retrospective	310, mixed	TE	LSM	CSPH	0.746	<20 kPa and PLT >150.000	33% spared EGDS
Bae, 2018 <sup>78</sup>	Retrospective	1035, mixed	TE	LSM	HRV	N/A	<20 kPa and PLT >150.000	21% spared EGDS
Augustin, 2018 <sup>72</sup>	Retrospective	925, Mixed	TE	LSM	HRV	N/A	<20 kPa and PLT >150.000	21% spared EGDS
							<25 kPa and PLT >110.000	40% spared EGDS
Moctezuma-Velazquez, 2018 <sup>70</sup>	Retrospective	227, PBC or PSC	TE	LSM	HRV	N/A	<20 kPa and PLT >150.000	36.1% spared EGDS
Petta, 2018 <sup>65</sup>	Retrospective	790, NAFLD	TE	LSM	HRV	N/A	<20 kPa and PLT >150.000	33.3% spared EGDS
Berger, 2020 <sup>76</sup>	Retrospective	2368, mixed	TE	LSM	HRV	N/A	<20 kPa and PLT >150.000	24% spared EGDS
Hirooka, 2011 <sup>55</sup>	Prospective	60, mixed	RTE	LSM	CSPH	0.832	N/A	N/A
				SSM	CSPH	0.978	8.24 m/s	Sens 96%
Colecchia, 2012 <sup>28</sup>	Prospective	100, HCV	TE	LSM	CSPH	0.920	<16 kPa >24.2 kPa	Sens 96.2% Spec 97.9%
					EV	0.899	<16.4 kPa >25 kPa	Sens 95.4% Spec 97.1%
				SSM	CSPH	0.966	<40 kPa >52.8 kPa	Sens 98.5% Spec 97.1%
					EV	0.941	<41.3 kPa >55 kPa	Sens 98.1% Spec 95.7%
Takuma, 2013 <sup>54</sup>	Prospective	340, mixed	p-SWE	LSM	EV	0.746	1.87 m/s	Sens 99.2%
				SSM	EV	0.933	3.18 m/s	Sens 98.9%

(Continued)

Table I (Continued).

Author, Year	Study Design	Nr. Patients	Technique	Parameter	Outcome	AUROC	Cut-Offs (Rule-Out or Rule-In)	Performance
Takuma, 2016 <sup>52</sup>	Prospective	60, viral	p-SWE	LSM	CSPH	0.833	N/A	N/A
				SSM	CSPH	0.943	3.1 m/s	Sens 97.1%
Elkrief, 2017 <sup>58</sup>	Prospective	191, mixed	2D-SWE	LSM	CSPH	0.80	<16 kPa >38 kPa	Sens 95% Spec 52%
				SSM	CSPH	0.61	<26.6 kPa >27.9 kPa	
Colecchia, 2018 <sup>30</sup>	Retrospective, Prospective	613, mixed	TE	LSM	HRV	0.768	<20 kPa + >PLT 150.000	21.7% spared EGDS
				SSM	HRV	0.837	≤46 kPa	35.8% spared EGDS
				Baveno VI + SSM 46 kPa	HRV	N/A	Combined model	43.8% spared EGDS
Wang, 2020 <sup>31</sup>	Prospective	341, HBV	TE	LSM	HRV	N/A	<20 kPa + > PLT 150.000	37% spared EGDS
				SSM	HRV	N/A	≤46 kPa	52.8% spared EGDS
				Baveno VI + SSM 46 kPa	HRV	N/A	Combined model	61.6% spared EGDS

**Abbreviations:** 2D-SWE, two-dimensional shear wave elastography; AUROC, area under ROC curve; CSPH, clinically significant portal hypertension; HBV, hepatitis B virus; HCV, hepatitis C virus; HRV, high-risk varices; EGDS, esophagogastroduodenoscopy; EV, esophageal varices; LSM, liver stiffness measurement; N/A, not available; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PLT, platelet count; p-SWE, point-shear wave elastography; Sens, sensitivity; Spec, specificity; SSM, spleen stiffness measurement; TE, transient elastography.

LSM values to rule-in and rule-out CSPH.<sup>24,48–50</sup> In 2017, a meta-analysis confirmed the good performance of LS in predicting CSPH (AUC=0.921) for low cut-off values of 13.6–18 kPa.<sup>23</sup> Another meta-analysis highlighted that an LSM value <13.6 kPa assessed by TE resulted valuable to rule-out CSPH with high sensitivity (>90–95%), while the cutoff value > 22 kPa provided the overall best performance and appeared to accurately confirm CSPH (specificity > 90–95%).<sup>51</sup> The last Baveno VI Consensus Workshop of 2015 recommended the use of LSM in clinical practice, suggesting LSM values >15 kPa as highly suggestive of cACLD and ≥20–25 kPa as sufficient to rule-in CSPH, alone or combined to platelets count and spleen size in virus-related chronic liver disease.<sup>2</sup>

Being a direct surrogate of portal hypertension, SSM showed a strong correlation with the whole range of HVPG values.<sup>28</sup> Colecchia et al<sup>28</sup> proposed values of 40 kPa and 52.8 kPa to respectively rule-out (sensitivity 98.5%) and rule-in CSPH (specificity 97.1%). A recent meta-analysis reported for SSM by TE a good

performance in diagnosing CSPH (AUC = 0.92) and severe PH (AUC = 0.87), with elevated sensitivity (respectively 88% and 92%) and specificity (84% and 79%).<sup>29</sup>

Among other elastographic techniques, promising results have been observed as well. LSM and SSM evaluated by Acoustic Radiation Force Impulse (ARFI)<sup>52–55</sup> were able to diagnose HVPG ≥ 10 mmHg and HVPG ≥ 12 mmHg with similarly high diagnostic performance (LSM, AUC = 0.93 and 0.87, respectively; SSM, AUC = 0.97 and 0.95).<sup>56</sup> Promising results were found for LSM assessed by 2-dimensional shear wave elastography (2D-SWE)<sup>57,58</sup> or Magnetic Resonance Elastography (MRE) as well,<sup>59–61</sup> even if further evidence to better identify the optimal cutoffs for CSPH and the best application fields is needed.

## Liver and Spleen Stiffness for the Diagnosis of High-Risk Esophageal Varices

One of the most relevant applications of elastometry is the identification of patients with gastroesophageal varices.

Patients with ACLD require routine endoscopic surveillance in order to identify esophageal varices needing treatment (VNT), reduce upper digestive bleeding incidence and mortality. LSM is considered to have high sensitivity, but medium/low specificity in predicting esophageal varices (EV) in several studies.<sup>62–66</sup> A meta-analysis including about 3650 patients from 18 studies, showed that LSM has a sensitivity and a specificity of 87% and 53% for any varices, and 86% and 59% for VNT.<sup>67</sup>

Regarding SSM, Stefanescu et al<sup>68</sup> analysed its performance in chronic hepatitis patients; among cirrhotic group population, SSM resulted higher in those with EV (63.69 vs 47.48 kPa), with the best cut-off to detect EV of 52.5 kPa. In 2012, Colecchia et al<sup>28</sup> confirmed LSM and SSM as more accurate in predicting both CSPH and EV than other NITs; moreover, they proposed a new combined logistic model using together SSM and LSM to reduce indeterminate cases.

The last Baveno VI Consensus Workshop stated that in patients with ACLD, the prevalence of VNT in patients with LSM < 20 kPa and platelet count is >150×10<sup>9</sup>/L is low (< 5%), and endoscopic surveillance can be safely avoided in these patients.<sup>2</sup> Since the postulation of these criteria in 2015, many studies have validated their safety in clinical practice. In a recent meta-analysis by Stafylidou et al<sup>69</sup> including about 9000 patients from 30 studies, Baveno VI criteria proved to have a sensitivity of 0.97 and a specificity of 0.32 in predicting EV. Moreover, since Baveno VI criteria are originally to be applied only in patients with viral chronic liver disease, several efforts have been made for their validation in other etiologies (ie metabolic liver disease,<sup>65</sup> cholestatic liver disease,<sup>70</sup> after HCV-eradication<sup>71</sup>).

Nevertheless, the number of spared upper endoscopies by the application of Baveno VI criteria is relatively low (15–25%), so different attempts have been made to modify these criteria and increase the rate of spared endoscopies. Augustin et al proposed to use LSM cutoff of 25 kPa and PLT > 110 × 10<sup>9</sup>/L<sup>72</sup> (the Expanded Baveno VI), sparing up to 40–60% of upper endoscopies, as confirmed also by other authors.<sup>73–75</sup> However, a higher rate of missed EVs has been reported, often over the safe threshold of 5%.<sup>76–78</sup> This was confirmed also by a recent meta-analysis,<sup>69</sup> where the Expanded Baveno VI criteria showed superior specificity (51%) for HRV, but with an increased risk of missed HRVs (up to 10%).

More recently, a new combined model<sup>30</sup> including Baveno VI criteria and SSM (cut-off ≤ 46 kPa, assessed by TE), proved to be efficient in increasing the number of

spared endoscopies without raising the rate of missed HRV. In a large cohort of almost 500 patients, this algorithm allowed to safely increase the rate of spared endoscopies to 43.8% (2% of HRV missed), as compared to Baveno VI criteria alone (21.7%); the excellent performance was then confirmed in a prospective multicenter cohort. Importantly, this combined model has been recently validated in a large prospective cohort of virally suppressed HBV patients, producing excellent results in safely ruling-out HRV.<sup>31</sup> Similar performances were observed when combining Baveno VI criteria with SSM assessed with Supersonic Shear Imaging.<sup>79</sup>

In conclusion, non-invasive elastographic techniques are promising tools for EV prediction, and their combination will allow us to avoid unnecessary upper endoscopy in a considerable number of ACLD patients. However, which are the best criteria to apply in clinical practice is still a matter of debate, and this topic will be hopefully addressed during the upcoming Baveno VII consensus.

## Role of Elastography in the Prediction of Liver-Related Events and Response to Treatments

### Prediction of Hepatic Decompensation and Mortality

Liver and spleen stiffness correlate well with HVPG measurement and can identify patients with CSPH; therefore, it has been hypothesized that they can also predict other complications driven by portal hypertension.<sup>80</sup> A meta-analysis<sup>81</sup> has shown that an increase of 1 kPa in LSM is associated with an increased risk of hepatic decompensation [Relative risk (RR), 1.07; 95% CI, 1.03–1.11] and mortality (RR, 1.22; 95% CI, 1.05–1.43). The proposed cut-offs for the prediction of risk of hepatic decompensation usually are >20–25 kPa,<sup>82–85</sup> the cut-off to rule-in CSPH according to Baveno VI consensus.<sup>2</sup> Interestingly, the accuracy of LSM (0.837) for the prediction of any decompensation was not inferior to that of HVPG (0.815).<sup>82</sup> Since LSM cut-offs are influenced by liver etiology, numerous studies have demonstrated that LSM is an independent predictor of decompensation and other liver-related events also in large cohorts of non-alcoholic fatty liver disease (NAFLD),<sup>86,87</sup> primary biliary cholangitis,<sup>88,89</sup> primary sclerosing cholangitis<sup>90,91</sup> and other etiologies.<sup>92</sup>

SSM has also been validated as an accurate NIT able to stratify for the risk of decompensation and overall mortality in ACLD patients.<sup>93–96</sup> Colecchia et al<sup>93</sup> showed that

an SSM value of 54 kPa, evaluated by TE, could identify patients at lower risk of decompensation. Similarly, Takuma et al<sup>96</sup> showed that SSM >3.25 and >3.43 m/s, evaluated by p-SWE, accurately predicted decompensation and mortality, respectively. Recently, the 54 kPa SSM cut-off was validated to predict decompensation after HCV eradication with direct-acting antivirals.<sup>97</sup>

In conclusion, LSM and SSM are well-validated surrogates of portal hypertension and can be used in everyday clinical practice as prognostic markers, able to stratify for the risk of decompensation and liver-related events.

### Prediction of Outcomes in Patients with Hepatocellular Carcinoma

Studies with HVPG have shown that not only the degree of liver fibrosis but also that of portal hypertension can predict the risk of HCC development,<sup>10</sup> confirming that key features of portal hypertension, such as hyperdynamic circulation, liver hypoxia, and splanchnic neoangiogenesis, play an important role in liver carcinogenesis.<sup>98,99</sup> Similarly, LSM has been extensively shown as a valid NIT able to predict the risk of primary HCC,<sup>100</sup> in different etiologies of liver disease<sup>87,101–103</sup> and also after HCV eradication after DAA treatment.<sup>104</sup> Jung et al previously reported that LSM could also predict late recurrence after liver surgery<sup>105,106</sup> when liver disease severity is a major contributor to such complication.<sup>107</sup> More recently, SSM was found to be the only independent predictor of late recurrence in a proof-of-concept study,<sup>108</sup> confirming a major contribution of portal hypertension in liver carcinogenesis.

Portal hypertension is also a major determinant of morbidity and mortality in patients undergoing hepatic resection.<sup>109</sup> Since CSPH is not to be considered an absolute contraindication to liver surgery,<sup>110,111</sup> a correct stratification according to the severity of portal hypertension is mandatory in this context. LSM has been consistently shown to accurately predict the incidence of post-hepatectomy liver failure (PHLF)<sup>112–114</sup> or overall complications after hepatectomy,<sup>115</sup> interestingly, the accuracy of LSM was found not inferior to HVPG<sup>116</sup> and superior to ICG-r15,<sup>114</sup> for this outcome. More recently, SSM has been proposed as a more accurate predictor of PHLF development,<sup>117,118</sup> however, the number of patients included is limited and more studies are required.

### Prediction of Response to Non-Selective Beta-Blockers

As mentioned above, both acute and chronic HVPG response to NSBB has been shown to correlate with a lower risk of variceal bleeding and medical prophylaxis

failure.<sup>4</sup> A similar benefit in responders was recently shown also for the prevention of the first decompensation event, mainly ascites, in the PREDESCI trial.<sup>14</sup> With the broad administration of NSBB to all patients with CSPH, it would become even more timely and relevant to identify hemodynamical responders, the patients that truly benefit from this medical treatment, and to avoid exposure to significant adverse effects of NSBB, which are not uncommon, in non-responders. To date, no NIT has substituted HVPG in this context. Only recently a seminal paper by Kim et al<sup>119</sup> developed and validated a model including SSM, evaluated by p-SWE, that could predict for the first time hemodynamic response with excellent accuracy (AUROC=0.848). A recent pilot study<sup>11</sup> also demonstrated that  $\Delta$ SSM after NSBB initiation, as evaluated by TE, showed excellent correlation with  $\Delta$ HVPG ( $r=0.784$ ), and SSM reduction  $\geq 10\%$  predicted HVPG response with an AUROC of 0.973. These studies are truly preliminary, but SSM could be a very promising tool for the prediction of hemodynamic response and warrants further studies.

### Prediction of Outcomes in Patients with Transjugular Intrahepatic Portosystemic Shunts

Patients with TIPS represent another setting in which monitoring with NITs can provide clinically relevant information. Firstly, an increase in LSM has been shown to correlate with systemic inflammation and independently predict mortality in patients undergoing TIPS placement,<sup>120</sup> however, no or little correlation has been found between changes in LSM and portal pressure gradient before and after TIPS.<sup>121,122</sup> On the other hand,  $\Delta$ SSM significantly correlated with changes in portal pressure gradient after TIPS ( $r=0.56–0.87$ ),<sup>121–126</sup> and an SSM increase during follow-up can accurately predict TIPS dysfunction (AUROC=0.81–0.87),<sup>121,124,125,127</sup> suggesting that SSM could play a pivotal role in the non-invasive monitoring of TIPS patency and prediction of complications after its placement.

### Limits of Liver and Spleen Elastography in the Prediction of Portal Hypertension and Its Complications

The evidence supporting the use of elastography in the prediction of fibrosis and portal hypertension is substantial so that its role is now recognized in numerous guidelines and these techniques are used routinely in the evaluation of patients with chronic liver disease. However, the limits of the studies supporting this role should be acknowledged, in order to be addressed and overcome by future research. The

main limits of the above-mentioned papers are the retrospective nature and the inclusion of patients with mainly active viral hepatitis. Indeed, most of the studies were retrospective and lack of prospective validation in large multi-center cohorts. The selection of patients was not always adequate, as patients with previous decompensation were often included in these studies. Therefore, the prevalence of CSPH and high-risk varices was often higher than expected (ie 40–60% and 10–20%, respectively) and this clearly influenced the performance of the selected cut-offs of LSM and SSM. More importantly, most of the studies included patients either with active HCV infection or HBV infection. Despite some promising studies, it is uncertain to date whether the same cut-offs can be applied also in patients achieving SVR after DAA treatment or whether the performance of elastography is the same in this context. Moreover, NAFLD is quickly becoming the most prevalent cause of liver disease and indication to liver transplantation, so specific cut-offs for the prediction of CSPH, varices, and liver-related events are required for these patients. Cholestatic or autoimmune diseases, on the other hand, are far less frequent, and studies evaluating the predictive role for these outcomes in these specific etiologies are warranted. As for SSM, the substantial heterogeneity among the reported failure rates and the proposed cut-offs for add to the limitations of applicability of this method in everyday clinical practice.

### Part III – Conclusions

The HVPG measurement is the gold standard for the evaluation of portal hypertension; however, its measurement is invasive and requires expertise, so the use in everyday clinical practice and outside third level centers is limited. In the last decade, substantial evidence supports the use of NITs, such as liver stiffness, to define CSPH and guide surveillance for varices requiring treatment in patients with ACLD. SSM has also shown excellent results in the evaluation of portal hypertension; therefore, its measurement is encouraged in all patients with cirrhosis. Future studies are needed to explore and validate the use of LSM combined with other NITs, especially SSM, to optimize the accuracy of CSPH diagnosis and increase the number of safely spared screening endoscopies. The use of SSM to monitor response to NSBB or TIPS and to predict complications after such treatments is promising and should be further explored by future prospective studies.

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