The Value of Liver and Spleen Stiffness for Evaluation of Portal Hypertension in Compensated Cirrhosis

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Patients with compensated advanced chronic liver disease who develop clinically significant portal hypertension (CSPH) are at high risk for hepatic decompensation and mortality if left untreated. Liver biopsy and hepatic venous pressure gradient (HVPG) measurements are the current gold standard procedures for determining fibrosis severity and diagnosing CSPH, respectively; however, both are invasive, limiting their use in clinical practice and larger trials of novel agents. As such, there is an unmet clinical need for reliable, validated, noninvasive measures to detect CSPH and to further assess portal hypertension (PH) severity. Alterations in the biomechanical properties of the liver or spleen in patients with cirrhosis can be quantified by tissue elastography, which examines the elastic behavior of tissue after a force has been applied. A variety of methods are available, including magnetic resonance elastography, shear-wave elastography, and the most thoroughly investigated measure, vibration-controlled transient elastography. Liver stiffness (LS) and spleen stiffness (SS) measurements offer valuable alternatives to detect and monitor CSPH. Both LS and SS correlate well with HVPG, with thresholds of LS >20-25 kPa and SS >40-45 kPa indicating a high likelihood of CSPH. Because SS is a direct and dynamic surrogate of portal pressure, it has the potential to monitor PH severity and assess PH improvement as a surrogate marker for clinical outcomes. Importantly, SS seems to be superior to LS for monitoring treatment response in clinical trials focusing on reducing PH. (*Hepatology Communications* 2022;6:950-964).

Liver cirrhosis is a consequence of chronic liver disease, with viral hepatitis B (HBV) and hepatitis C (HCV), alcohol-related liver disease (ALD), and nonalcoholic steatohepatitis (NASH) representing the most common etiologies.[1] The Global Burden of Disease study indicates that the prevalence of cirrhosis has almost doubled during the past 3 decades, with more than 122 million cases of cirrhosis documented in 2017.[1] With the use of effective antiviral therapy, HBV and HCV are in decline yet still represent the leading causes of cirrhosis burden worldwide.[1] However, NASH is increasing in prevalence[2] and is soon expected to overtake viral hepatitis to become the leading cause of cirrhosis, hospitalization, and need for liver transplantation.[1,3] Cirrhosis is clinically classified into two distinct prognostic stages, compensated and decompensated cirrhosis, based on the absence or presence of clinically evident decompensation events that include variceal hemorrhage (VH), hepatic encephalopathy (HE),

Abbreviations: 2D-SWE, two-dimensional shear-wave elastography; ACLD, advanced chronic liver disease; APRI, aminotransferase/platelet ratio index; AST, aspartate aminotransferase; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; ELF, enhanced liver fibrosis; EV, esophageal varices; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; ICG-r15, indocyanine green 15-minute retention; LS, liver stiffness; MELD, Model for End-Stage Liver Disease; MR, magnetic resonance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NSBB, nonselective β-blocker; PH, portal hypertension; pSWE, point shear-wave elastography; SS, spleen stiffness; TE, transient elastography; TIPS, transjugular intrahepatic portosystemic shunt; VCTE, vibration-controlled transient elastography; VH, variceal hemorrhage; VNT, varices needing treatment; vWF-Ag, von Willebrand factor antigen.

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and ascites, the most common first decompensation event.[4] The compensated stage of cirrhosis is also termed, more comprehensively, compensated advanced chronic liver disease (cACLD) to account for the fact that the transition from advanced fibrosis to cirrhosis is difficult to identify. Importantly, cACLD is further subdivided into two prognostic substages of mild portal hypertension (PH) and clinically significant portal hypertension (CSPH).[4,5] While patients with CSPH may already show varices at endoscopy, many remain otherwise asymptomatic.[4,5] Patients may remain in the cACLD stage for decades (median survival >12 years)[4,5]; however, CSPH is the main driver of decompensation.[6] The decompensated stage is clinically evident by the occurrence of complications related to CSPH and has a much shorter median survival of about 2 years.[4,5]

Mild PH is a hemodynamic abnormality defined by a hepatic venous pressure gradient (HVPG) of 6-9 mmHg.[4,7] PH in cirrhosis results from increased vascular resistance caused by structural changes to liver parenchyma (due to collagen deposition, inflammation, nodule formation, and vascular remodeling/occlusion) and increased intrahepatic vascular tone caused by vasoconstriction (driven by decreased vasodilator availability and increased vasoconstrictor production).[4,8,9]

CSPH is defined by an HVPG of ≥10 mmHg and is present in around 60% of patients with cACLD and in all patients with decompensated cirrhosis.[4,10] CSPH is independently associated with an increased risk of decompensation events, including the development of varices and hepatocellular carcinoma (HCC).[4,7,8,11] The risk of developing clinical liver events/decompensation within 2-4 years increases by 11% with each 1 mmHg increase over 10 mmHg in HVPG.[6,12] Furthermore, reducing HVPG by 20% and/or to <10 mmHg greatly reduces the decompensation risk.[12] The mortality rate among patients with cirrhosis increases with the development of complications. One-year mortality is 5.4% in patients with compensated cirrhosis but up to 20.2% in patients with decompensated cirrhosis,[13] while 1-year mortality in patients with compensated cirrhosis without CSPH is 3.4% and increases to 7.3% in patients with CSPH.[13]

Reducing portal pressure in cirrhosis results in better outcomes,[14] and guidelines for the management of cACLD of any etiology focus on prevention of CSPH and decompensation.[4,7] In patients with compensated cirrhosis, guidelines recommend preventing CSPH by eliminating the underlying cause of liver disease (i.e., etiological therapy) and treating comorbidities that contribute to decompensation or are a consequence of liver disease, such as obesity, diabetes, pulmonary, renal, and cardiovascular disease, to help prevent complications and reduce PH.[4,7] However, while removing the cause of cirrhosis might improve portal pressure, it is a slow process and patients may continue to be at risk of decompensation.[14]

The mainstay of cirrhosis treatment over the last 35 years has been nonselective β-blockers (NSBBs), which act by reducing portal venous inflow.[14] Initially developed to prevent bleeding (and rebleeding) from varices,[7] a recent randomized, double-blind, placebo-controlled, multicenter trial showed that long-term treatment with

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β-blockers could increase decompensation-free survival in patients with compensated cirrhosis and CSPH, mainly by reducing the incidence of ascites.[15] In a meta-analysis of 15 studies with a total of 1,113 patients with cirrhosis, good hemodynamic response to NSBBs was associated with a lower risk of cirrhosis complications and death or transplantation.[16]

For patients who have progressed to decompensated cirrhosis, guidelines recommend treatment to prevent rebleeding of varices and ascites.[4,7,17,18] Assessment of PH can help to identify those patients at high risk of progression.[7] There is a need for better therapies to lower portal pressure in cirrhosis, and recent clinical trials of several novel drugs, mainly targeting intrahepatic mechanisms, have shown promise.[14] In phase III clinical trials of cirrhosis, the US Food and Drug Administration currently advocates a composite endpoint based on the occurrence of clinical outcomes (complications of ascites, VH, HE, worsening of Model for End-Stage Liver Disease [MELD] score, liver transplantation, or all-cause death).[19] The European Medicines Agency (EMA) supports the composite endpoint of all-cause death and decompensation events but acknowledges the challenge of defining appropriate endpoints in patients with existing cirrhotic disease.[20] For patients with nondecompensated disease, the EMA suggests reversal of cirrhosis ("improvement of liver cirrhosis to noncirrhotic liver disease [1 or more point improvement in fibrosis stage]") supported by descriptive data on decompensation events, liver transplantation, and death in addition to secondary outcomes derived from noninvasive disease markers, such as biomarkers, imaging data, or determination of liver stiffness (LS), that are the focus of this review.[20]

Invasive Assessments of Established Prognostic Relevance in cACLD

HVPG

The gold standard for assessing PH is HVPG, which represents the gradient between the pressure in the hepatic sinusoidal capillary network and the free hepatic venous (systemic) pressure. HVPG is measured by retrograde insertion of a balloon-tipped central vein catheter into a main hepatic vein (Fig. 1).[7,9,21,22]

Guidelines encourage use of HVPG measurements in clinical trials,[7] and a decrease in HVPG is recommended as the main goal in phase II proof-of-concept studies in PH.[14] If PH-associated endpoints are well defined,[7] decompensating events are recommended as the main primary endpoint in phase III trials; however, where a low rate of events is expected, HVPG response assessment would be needed as a surrogate marker.[7,14]

While a decrease in HVPG following treatment with NSBBs (targeting hyperdynamic circulation and splanchnic vasodilation) has been linked to improved outcomes,[16] the association between HVPG change and clinical benefit in developmental therapies for PH may be different and needs to be established.[14] For example, a decrease in HVPG by etiologic therapies for HCV (targeting mainly intrahepatic vascular resistance, the sinusoidal PH) only translates to improved outcomes in patients before PH has developed.[23]

LIVER BIOPSY

Liver biopsy is another assessment of cACLD used in the setting of (suspected) cirrhosis, mostly only to differentiate between severe alcoholic hepatitis and decompensated alcoholic cirrhosis[24] and to confirm a diagnosis and investigate the possible cause.[25] The livers of patients with CSPH in cACLD are modified compared with those with mild PH and develop thick fibrous septa and smaller nodules.[4] A biopsy may be carried out from a percutaneous or a transjugular route, and while both approaches provide comparable samples, the transjugular route has the advantage that it allows concomitant HVPG measurement.[25-27] Compared with biopsy, HVPG measurement is better at predicting the likelihood of developing complications of cirrhosis[4,7]; however, both techniques are unsuitable for routine measurements to determine disease progression as both are invasive, and HVPG is not widely available due to high costs and is restricted to highly specialized centers with extensive experience.[8,11,28] Furthermore, a vasoactive drug may produce rapid, dynamic changes, and repeated measurements in a trial may be required over a number of days. Guidelines, therefore, recommend that research should focus on validation of noninvasive predictors of decompensation for clinical trials.[7] Some noninvasive techniques have been demonstrated to be of diagnostic value regarding the prediction of risk of CSPH and/or decompensation (Fig. 2).

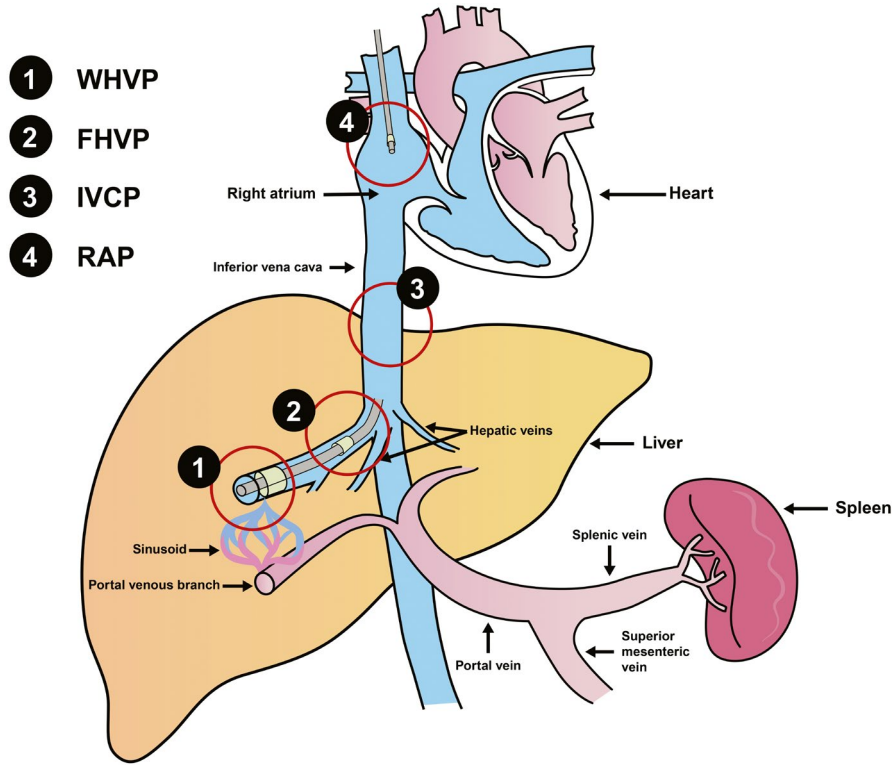

FIG. 1. Measurement of HVPG. HVPG is measured by retrograde insertion of a balloon-tipped central vein catheter into a main hepatic vein. HVPG represents the difference between the occluded hepatic sinusoidal capillary network (wedged hepatic venous) pressure and the free hepatic venous (systemic) pressure. Abbreviations: FHVP, free hepatic venous pressure; IVCP, inferior vena cava pressure; RAP, right atrium pressure; WHVP, wedged hepatic venous pressure.

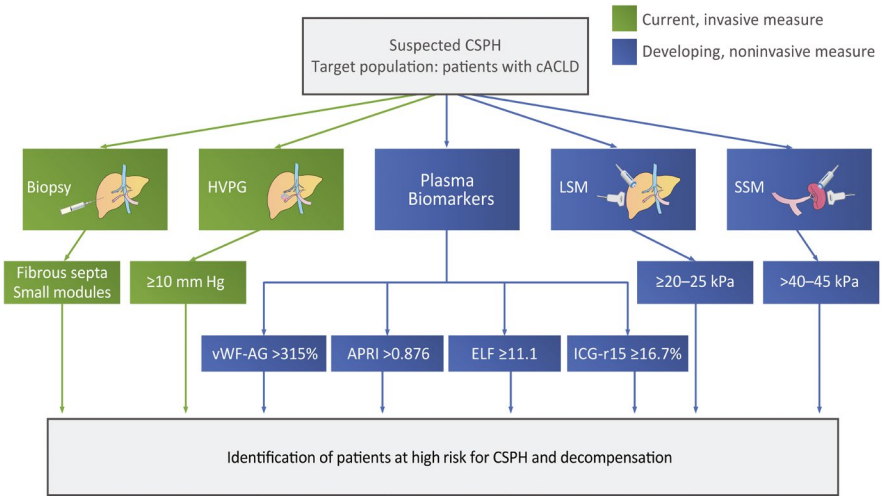

FIG. 2. Techniques for identifying CSPH. Multiple screening techniques can be used to identify patients at high risk for progression to decompensated cirrhosis, with various cut-off values to signify the presence of CSPH. Abbreviations: LSM, liver stiffness measurement; SSM, spleen stiffness measurement.

Noninvasive Assessments of Portal Hypertension of Prognostic Relevance in cACLD

A selection of currently used noninvasive assessments of PH are shown in Table 1. Serum levels of degraded extracellular matrix (ECM) products correlate with HVPG and may be regarded as direct biomarkers of PH.[29] Platelet counts represent an indirect biomarker of PH, and may be combined with imaging findings (such as spleen diameter) to suggest PH.[30] Von Willebrand factor antigen (vWF-Ag) is elevated in patients with liver cirrhosis, correlates with HVPG, is predictive of CSPH, and a value >315% is associated with greater mortality in patients with compensated and decompensated disease.[31,32] More recently, the vWF-Ag/thrombocyte ratio (VITRO) score, initially derived as a marker of liver fibrosis and cirrhosis in patients with chronic HCV,[33] has been shown to correlate with HVPG and CSPH in patients with cACLD[34] and is a predictor of transplant-free mortality and decompensation.[35] In patients with liver disease, FibroTest values correlate with HVPG and the presence and severity of PH, although this association is weaker in patients with cirrhosis.[36]

Several blood-based indirect fibrosis makers have been investigated in relation to PH. The aspartate aminotransferase (AST)/platelet ratio index (APRI) shows moderate correlation with HVPG, with scores of 0.876 and ≥1.09 predicting HVPG ≥12 mmHg in two independent studies.[37,38] The Lok index (derived from AST/alanine aminotransferase ratio, prothrombin and international normalized ratio, and platelet count) and fibrosis-4 (FIB-4) are independently associated with all-cause death in patients with decompensated disease.[39] The Lok index has been independently associated with the degree of PH and is predictive of CSPH and esophageal varices (EV).[40,41] FIB-4 has been associated with the presence of cirrhosis in patients with cACLD.[41] The enhanced liver fibrosis (ELF) score, a combined measurement of serum markers of fibrogenesis and ECM remodeling which was originally developed to detect liver fibrosis, correlates well with HVPG up to values of ≤20 mmHg, and an ELF score ≥11.1 identifies patients at high risk of CSPH.[30,42] The indocyanine green 15-minute retention (ICG-r15) test is a quantitative assessment of liver function that can identify CSPH (ICG-r15 ≥16.7%), rule out the presence of EV (ICG-r15 >10%),

TABLE 1. NONINVASIVE ASSESSMENTS OF PORTAL HYPERTENSION

Feature	Method	Studies
Portal venous congestion	LS	Various (see below)
	SS	Various (see below)
	Extracellular matrix protein levels (PRO-C3, ELM, C6M)	Leeming et al.[29]
	Platelet count (indirect marker)	Berzigotti et al.[30]
Vasculature	Plasma vWF-Ag	La Mura et al.[32]
		Ferlitsch et al.[31]
Liver fibrosis	LS	Various (see below)
	APRI	Verma et al.[37]
		Kirnake et al.[38]
	Lok index	Lissotti et al.[40]
		Cho et al.[39]
		Procopet et al.[41]
	Fib-4	Cho et al.[39]
		Procopet et al.[41]
	FibroTest	Thabut et al.[36]
	ELF test	Berzigotti et al.[30]
		Simbrunner et al.[42]
Hepatic function	ICG retention	Lisotti et al.[40,43]

Abbreviations: C6M, matrix metalloprotease degraded type VI collagen; ELM, elastin; PRO-C3, procollagen type III.

and predict decompensation events (ICG-r15 ≥23%) in patients with cACLD.[40,43] Studies have investigated the association between computed tomography and HVPG/CSPH in patients with HCC, HBV-included advanced chronic liver disease (ACLD), and cACLD.[44-47] However, a recent review questioned the validity of the findings, highlighting small sample sizes and the inclusion of large proportions of patients with Child-Turcotte-Pugh stage B/C.[48] Alterations to the biomechanical properties of the liver or spleen in cirrhosis can be measured by elastography techniques, which are based on the elastic behavior of tissue after a force has been applied by ultrasound or magnetic resonance (MR).[7,8,49]

LIVER STIFFNESS

The main determinant of liver tissue elasticity (also known as LS) is the presence of fibrosis due to collagen deposition, which reflects the main mechanical ("static") component of hepatic resistance.[8,50] Initial studies of LS measured with vibration-controlled transient elastography (VCTE) in patients with HCV-related cirrhosis indicated that cut-off values of 13.6 and 17.6 kPa are predictive of HVPG values of ≥10 and ≥12 mmHg, respectively.[50] Subsequent studies have shown reasonable correlation of VCTE with CSPH and HVPG, with a threshold of >20-25 kPa[51,52]; although, it should be noted that in ranges of HVPG values ≥12 mmHg when complications, such as ascites, develop, this correlation becomes weaker.[50] Recent guidelines support the noninvasive diagnosis of CSPH by VCTE >20-25 kPa, at least in virus-related cirrhosis.[7] Similarly, VCTE >20-25 kPa should be used for CSPH risk stratification in cACLD, ideally in combination with platelet count and spleen size.[4,53] However, for the assessment of PH severity beyond ruling CSPH in or out, current clinical practice guidelines do not suggest that HVPG can be replace by noninvasive methods and that HVPG remains the only validated tool.[53] A meta-analysis of 18 studies concluded that VCTE is able to differentiate between patients with and without CSPH with high accuracy,[54] whereas another meta-analysis of 11 studies assessing the diagnostic performance of VCTE in assessing CSPH concluded that results of VCTE correlated well with HVPG and proposed cut-off values of 13.6-18 kPa for maximum sensitivity.[55] In a 2-year study of 41 patients with chronic liver disease, an LS of ≥21 kPa and an HVPG of ≥10 mmHg were equally effective for predicting decompensation events,[56] and a study of 78 patients with chronic liver disease demonstrated that LS, measured by point shear-wave elastography (pSWE), could identify an HVPG of ≥10 mmHg and ≥12 mmHg with high diagnostic performance.[57] The Anticipate study including 518 patients with cACLD concluded that VCTE and LS to spleen/platelet score (LSPS) reliably identifies patients at high risk of CSPH, with LSPS providing the highest level of discrimination.[58] In a study of patients with cACLD secondary to nonalcoholic fatty liver disease (NAFLD), an LS of 21.8 kPa identified esophageal varices with high accuracy and has been proposed as a threshold that may obviate the need for a diagnostic esophagogastroduodenoscopy[59] in line with existing recommendations (<20 kPa) for patients with cACLD of viral origin.[7] A summary of the heterogeneity of cut-off values for LS that have been proposed to identify HVPG ≥10 and ≥12 mmHg and other clinically relevant outcomes related to PH, such as presence of EVs or varices needing treatment (VNT), are listed in Table 2. Ultimately, it is evident that a wide range of published cut-off values for ruling in and ruling out cACLD and CSPH result from heterogeneous patient characteristics with variable pretest and posttest probabilities of the condition of interest. Thus, the Baveno VI consensus guidelines recommend the following use of "easy-to-remember" LS measurement cut-off values for daily clinical use: (i) at LS <10 kPa, rule out cACLD if no other clinical signs, (ii) an LS >15 kPa is highly suggestive of cACLD, and (iii) at LS ≥20-25 kPa, rule in CSPH in patients with virus-related cACLD.[7] Importantly, these cut-off values have been mostly validated in patients with hepatitis C,[60] and although supporting evidence has been created in patients with cholestatic liver disease,[61] historically these cut-off values did not perform as well in patients with NASH due to the close association with obesity.[62] High body mass index (BMI), particularly ≥30 kg/m^2, is independently associated with higher LS measurements, affecting the interpretation of LS cut-off values when using the standard probe.[63] However, development of the XL probe has enabled the use of standard cut-off values in patients with obesity.[64]

SPLEEN STIFFNESS

Since the splenic blood flow drains via the splenic vein into the portal venous system, spleen stiffness (SS) not only reflects static hepatic resistance due to liver

TABLE 2. LS CUT-OFF VALUES

Study	Etiology	Modality	HVPG ≥10 mmHg	HVPG ≥12 mmHg	Other
Vizzutti et al.[50]	HCV	VCTE	13.6 kPa	17.6 kPa	EV: 17.6 kPa
	n = 61				
Bureau et al.[105]	CLD	VCTE	21 kPa		EV: 21.1 kPa
	n = 150				
Lemoine et al.[106]	HCV	VCTE	20.5 kPa		
	n = 44				
	ALD	VCTE	34.9 kPa		
	n = 48				
Sanchez-Conde et al.[107]	HIV-HCV	VCTE	14.0 kPa	23.0 kPa	
	n = 100				
Robic et al.[56]	CLD	VCTE			Low-risk CD: ≤21.1 kPa
	n = 100				High-risk CD: >21.1 kPa
Colecchia et al.[28]	HCV	VCTE	24.2 kPa	25.0 kPa	EV: 25.0 kPa
	n = 100				
Reiberger et al.[108]	HCV	VCTE	18.0 kPa	20.0 kPa	Mild PH (≥6 mmHg): 8.0 kPa
	n = 390				
	ALD	VCTE	19.0 kPa	23.0 kPa	Mild PH (≥6 mmHg): 10.0 kPa
	n = 227				
Llop et al.[109]	HCC	VCTE	21 kPa		
	n = 97				
Hong et al.[110]	cACLD	VCTE	21.95 kPa	24.25 kPa	
	n = 59				
Sharma et al.[111]	cACLD	VCTE			EV: 27.3 kPa
	n = 174				
Augustin et al.[52]	CLD	VCTE	25 kPa		
	n = 250				
Salzl et al.[83]	cACLD	VCTE	16.8 kPa		EV: 27.9 kPa
	n = 88	pSWE	2.58 m/second		EV: 2.74 m/second
Attia et al.[57]	CLD	pSWE	2.17 m/second		
	n = 78				
Elkrief et al.[84]	cACLD	VCTE	65.3 kPa		
	n = 79	SWE	24.5 kPa		
Kim et al.[112]	cACLD	SWE	15.2 kPa	21.6 kPa	
	n = 115				
Procopet et al.[86]	CLD	VCTE	13.6 kPa		
	n = 202	SWE	15.4 kPa		
Schwabl et al.[113]	CLD	VCTE	16.1 kPa		Cirrhosis: 14.5 kPa
	n = 226				
Jansen et al.[90]	ACLD	SWE	16.0 kPa		Rule out CSPH: LSM <16 kPa and SS <26.6 kPa
	n = 158				Rule in CSPH: LSM ≥16 kPa or SS ≥26.6 kPa
Jansen et al.[114]	cACLD	SWE	24.6 kPa	28.5 kPa	Rule out CSPH: LSM 16.0 kPa
	n = 158				Rule in CSPH: LSM >29.5 kPa or SSM >27.9 kPa
Wong et al.[64]	NAFLD	VCTE			Rule out cACLD: <10 kPa
	n = 548				Rule in cACLD: ≥15 kPa
Galizzi et al.[59]	cACLD-NAFLD	VCTE			Any EV: 21.8 kPa
	n = 21				VNT: 21.8 kPa

TABLE 2. *Continued*

Study	Etiology	Modality	HVPG ≥10 mmHg	HVPG ≥12 mmHg	Other
Souhami et al.[115]	HCC n = 140	VCTE	21.0 kPa		
Stefanescu et al.[71]	cACLD n = 127	SWE	11.3 kPa		
Thiele et al.[85]	ACLD n = 328	2D-SWE			Rule out CSPH: <14 kPa
Trebicka et al.[87]	ACLD n = 1,827	2D-SWE			High risk of decompensation or death: ≥20 kPa and MELD ≥10

Abbreviations: ALD, alcohol-related liver disease; CD, clinical decomposition; CLD, chronic liver disease; HIV, human immunodeficiency virus.

fibrosis (that is captured by LS) but may also capture dynamic (pre)sinusoidal vasoconstriction and congestion of the portal blood inflow (a potential surrogate of PH-associated splanchnic hypoperfusion) and PH-induced splenic fibrosis.[65-68] SS is impacted by an increase in PH, which leads to splenic congestion, but also induces architectural changes in the splenic arteries and veins and fibrosis.[66] Thus, SS measurement is a valuable surrogate of PH (and initially an SS value of 56 kPa was reported to be associated with CSPH), and SS correlates well with HVPG irrespective of the etiology.[28,69,70] However, as evidence has accumulated, it appears that lower thresholds of ≤41-46 kPa are able to rule out the presence of CSPH and high-risk varices.[28,71-73] In a meta-analysis of nine studies, SS measured by ultrasound-based elastography showed good correlation with HVPG, detecting CSPH with a sensitivity and specificity of 0.88 and 0.92, respectively, and severe PH with a sensitivity and specificity of 0.92 and 0.79, respectively.[70] A study of 100 patients with HCV also demonstrated that SS, measured by transient elastography (TE), correlated strongly with the whole range of HVPG values >5 mmHg, suggesting that the increase in SS is closely tied with the progression of PH from early to late stages of cirrhosis.[28] SS has been combined with MELD score to provide an accurate predictor of decompensation in patients with HCV and is at least as accurate as HVPG.[69] In patients with HCV-related ACLD, SS is a direct surrogate of persisting PH following HCV therapy with direct-acting antivirals.[11] Studies of healthy volunteers and patients with various etiologies of chronic liver disease indicate that SS, as measured by MR elastography, correlates with platelet count, spleen volume, and splenomegaly and that an SS of ≥10.5 kPa is associated with esophageal varices.[74] SS as determined by pSWE has also been shown to be predictive of the development of esophageal varices,[75] and in a study of 78 patients with chronic liver disease it was able to identify an HVPG of ≥10 mmHg and ≥12 mmHg with high diagnostic performance.[57] The different cut-off values of SS that have been proposed to predict HVPG ≥10 and ≥12 mmHg and other clinically relevant outcomes related to PH, such as the detection of high-risk EV, are summarized in Table 3.

LIVER STIFFNESS VERSUS SPLEEN STIFFNESS

Data show that SS may be a superior marker of PH to LS in patients with cirrhosis with viral etiologies, and an increasing body of evidence suggests this may also be the case for other etiologies.[11,28,69,76,77] For example, in a meta-analysis of 16 studies of chronic liver disease, SS detected esophageal varices (one of the most serious consequences of PH[78] that is independently predicted by HVPG[10]) with a superior sensitivity and specificity (0.88 and 0.78, respectively) to LS (0.83 and 0.66, respectively).[77] Furthermore, in studies of virus-related compensated cirrhosis, SS was better than LS and similar to HVPG in predicting a first clinical decompensation event.[28,69] A recent study also showed that compared with LS, SS measurement was a direct surrogate of PH in patients after cure from HCV and may be useful for monitoring response and stratifying risk following therapy.[11] This may be explained by the fact that SS measurements are less influenced by liver necroinflammation than LS measurements.[11] In addition, SS might be

TABLE 3. SS CUT-OFF VALUES

Study	Etiology	Modality	HVPG ≥ 10 mmHg	HVPG ≥ 12 mmHg	Other
Talwalkar et al.[74]	CLD n = 38	MRE			EV: 10.5 kPa
Colecchia et al.[28]	HCV n = 100	VCTE	52.8 kPa	55.0 kPa	EV: 55.0 kPa
Sharma et al.[111]	cACLD n = 174	VCTE			EV: 40.8 kPa
Colecchia et al.[69]	HCV n = 92	VCTE			Low risk of CD: <54.0 kPa High risk of CD: >54.0 kPa
Elkrief et al.[84]	cACLD n = 79	VCTE SWE	56.3 kPa 34.7 kPa		
Kim et al.[116]	cACLD n = 125	pSWE			EV: 3.16 m/second
Jansen et al.[90]	ACLD n = 158	SWE			CSPH: ≥26.6 kPa and LS <16 kPa
Jansen et al.[114]	cACLD n = 158	SWE	26.3 kPa	28.5 kPa	
Colecchia et al.[72]	cACLD n = 498	VCTE			Rule out VNT: ≤46 kPa
Fierbinteanu-Braticevici et al.[75]	cACLD n = 135	pSWE			Any EV: 3m/second VNT: 3.5 m/second
Marasco et al.[117]	CLD after HCC n = 157	VCTE			Late HCC recurrence: >70 kPa
Marasco et al.[81]	ACLD with HRV n = 20	VCTE			No NSBB: 61.5 kPa With NSBB: 35.8 kPa
Stefanescu et al.[118]	ACLD n = 260	Spleen-TE	34.16 kPa	44.95 kPa	HRV: 41.3 kPa
Cho et al.[119]	cACLD n = 270	SWE			Rule out HRV: ≤27.3 kPa
Wang et al.[104]	HBV, cACLD n = 341	VCTE			Rule out HRV: ≤46 kPa
Dajti et al.[73]	ACLD				Low-risk VNT: ≤46 kPa
Dajti et al.[120]	HCV-related ACLD n = 140	VCTE			High-risk HCC: >42 kPa

Abbreviations: CD, clinical decomposition; HRV, high-risk varices; MRE, magnetic resonance elastography.

a more dynamic marker, reflecting "acute" changes in HVPG that are not detected by LS (e.g., a decrease in portal pressure occurring immediately after and within 30 minutes of transjugular intrahepatic portosystemic shunt [TIPS][79]) or changes in HVPG that occur mainly due to pharmacologic inhibition of hyperdynamic circulation/splanchnic blood flow.[80] For example, in a single-cohort, proof-of-concept study in patients with CSPH in cirrhosis and high-risk varices, a change in SS predicted a hemodynamic response (≥20% decrease in HVPG or an HVPG <12 mmHg) to the NSBB carvedilol whereas LS and HVPG did not.[76] Another study investigated changes in SS measured by TE in 20 patients with cirrhosis and high-risk varices undergoing sequential HVPG measurement before and during NSBB therapy.[81] The authors found that SS significantly correlated with changes in HVPG following NSBB therapy (r = 0.784; P<0.0001) while LS measured by TE did not (r = 0.107, P = 0.655).[81] Importantly, a ≥10% decrease in SS was an excellent predictor of HVPG response to NSBBs (area under the receiver

operator characteristic curve, 0.973; 95% confidence interval, 0.912-1.000) and was associated with a sensitivity of 100% and specificity of 60%.[81] However, due to the limited sample sizes and uncontrolled designs, additional validation studies of SS are required.[82]

American Association for the Study of Liver Diseases practice guidelines (2016) state that newer sonoelastography techniques, such as pSWE, can facilitate SS measurements and compared with TE have similar or greater accuracy in predicting CSPH.[4,83,84] Two-dimensional shear-wave elastography (2D-SWE) can be applied to LS and SS, with an LS cut-off value of 14 kPa able to rule out the presence of CSPH in patients with cACLD.[85] LS by 2D-SWE is superior to SS by 2D-SWE, correlates strongly with VCTE, and can accurately diagnose CSPH if suitable reliability criteria are fulfilled.[86] A large international study used a 2D-SWE LS cut-off value of ≥20 kPa combined with a MELD score of ≥10 (the M10LS20 algorithm) to stratify the risk of decompensation and mortality in patients with compensated or decompensated cirrhosis.[86] This algorithm was validated by both TE and pSWE measurements and can identify patients requiring intensified care and early treatment.[86] However, although these techniques show promise, the heterogeneity of cut-off values observed and the limited number of studies mean their use cannot yet be routinely recommended in clinical practice guidelines.[53]

LS and SS can be used in combination to identify high-risk patients and rule out the presence of CSPH. A randomized, controlled trial showed the potential noninferiority of combined LS and SS measurements compared with universal endoscopic screening for detecting clinically significant varices in patients with cirrhosis.[88] A prospective follow-up study showed that patients undergoing this screening technique were at low risk for incident VH and that the use of this technique reduced the need for endoscopic screening by up to 50%.[89] Another study developed an algorithm to identify patients with CSPH by using sequential LS and SS measurements by SWE, with cut-off values of LS ≥16.0 kPa or LS <16.0 kPa and SS ≥26.6 kPa showing a sensitivity of 98.6%.[90] As LS is the most validated noninvasive test for PH, clinical practice guidelines only currently recommend SS as an additional measure that can improve risk stratification for high-risk varices and CSPH.[53]

DETERMINANTS AND CONFOUNDERS OF TISSUE STIFFNESS

In addition to accuracy, reliability and repeatability of measurements are important factors in assessing the performance of sonoelastography techniques. The ability to achieve consistent and reproducible measurements depends on several critical factors, and multiple confounders affect both LS and SS measurements and can lead to false-positive diagnoses of fibrosis and CSPH.

First, the ability to achieve consistent and reproducible results can depend on the experience of the operator, with a greater impact on SS than LS.[91] Although operator experience is more relevant with pSWE and 2D-SWE than with VCTE, inexperience also decreases the reliability of LS measured by VCTE.[92]

Second, obesity (mostly due to a higher skin-to-liver capsule distance) impacts LS results. In a 5-year study of 13,369 VCTE-based LS examinations in 7,261 patients, almost one in five measurements were unreliable due to the impact of body weight and increased waist circumference, making its application limited in patients affected by obesity.[92] Importantly, a VCTE probe specifically designed for patients with obesity (i.e., the XL probe) has been developed,[91] allowing for LS measurements at a greater depth. This XL probe yields accurate VCTE measurements in patients with obesity that are similar to measurements obtained with a standard probe in patients without obesity.[64] This allows the same VCTE cut-off values to be used for cACLD diagnosis in patients with higher BMI.[64]

Third, venous congestions of the liver (i.e., due to heart failure) also increase LS up to values that clearly fall in the "cirrhotic" range, thereby precluding fibrosis staging in patients with heart failure (such as in Fontan-associated liver failure).[93,94]

Fourth, mechanical cholestasis increases LS,[95] with bile duct obstruction leading to increased pressure, edema, swelling, and inflammation that could lead to incorrect patient classification.[96]

Fifth, postprandial increases in portal venous perfusions impact LS results,[97,98] with 10%-16% of patients with cirrhosis misclassified with CSPH after the consumption of a moderate- or high-calorie meal.[99] SS was also significantly (P <0.001) increased

from baseline after food intake by 17%-19%.[99] These elevated measurements can persist for 3 hours after a meal, leading to recommendations of at least a >3-hour fasting period before LS or SS measurements.[99]

Sixth, local and systemic inflammation increases LS, likely due to inflammatory cell infiltrations and hepatocellular swelling.[100,101] Inflammation-dependent LS cut-off values have been developed based on increased AST levels to improve fibrosis staging and could be used to identify patients at high risk irrespective of inflammation.[101] However, the effect of inflammation on SS is less clear, with studies suggesting SS measurements may be less biased by inflammation than LS,[102] but aminotransferase levels can still be a significant confounding factor.[103] One study looked at the effect of inflammation on LS and SS in patients receiving TIPS for PH.[79] This study found that, in patients with higher levels of inflammatory markers, LS increased after TIPS despite the decrease in portal pressure observed; this effect was not seen in SS.[79]

SS measurements using the conventional TE probe are difficult, with a higher failure rate for SS than LS.[91] In a prospective study of 341 patients with HBV, reliable SS could not be obtained in 4.1% of patients (14/341) due to factors relating to obesity, ascites, or invalid SS measurements.[104] Similarly, in patients with compensated disease (cACLD without ascites), SS failed in 5.2% of patients (26/498).[72] Specific training has been shown to improve the repeatability of SS measurements.[91] More recently, a novel spleen-dedicated stiffness measurement TE probe has been developed that has further improved the screening for high-risk esophageal varices.[71]

To compensate for the potential pitfall of false-positive results, it is recommended to repeat VCTE LS measurements on at least 2 different days under fasting conditions and not use LS for fibrosis staging in patients presenting with venous congestion, mechanical cholestasis, pronounced inflammation, and high levels of transaminases.[7]

Conclusions

Patients with compensated cirrhosis (i.e., cACLD) who develop CSPH are at high risk for progression to decompensated cirrhosis and have increased mortality if left untreated. With limited treatment options available, there is an unmet clinical need to develop effective therapies to lower portal pressure in cirrhosis. Clinical trials for novel therapies require validated outcome measures that are easily repeatable. Current procedures for determining PH severity in cACLD, such as HVPG and biopsy, are invasive, expensive, and restricted to specialist centers, which limit their repeatability and use both in clinical practice and in larger trials. Noninvasive measurements of LS and SS correlate well with HVPG and offer valuable alternatives to monitor CSPH. Because SS is a direct and dynamic surrogate of PH that has the potential to assess an improvement in PH as a surrogate marker for clinical outcomes, SS may be a superior tool to LS for monitoring therapy response in clinical trials.

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