REVIEW

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Ultrasonography for Noninvasive Assessment of Portal Hypertension

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Portal hypertension is a major pathophysiology in patients with cirrhosis. Portal pressure is the gold standard to evaluate the severity of portal hypertension, and radiological intervention is the only procedure for pressure measurement. Ultrasound (US) is a simple and noninvasive imaging modality available worldwide. B-mode imaging allows broad applications for patients to detect and characterize chronic liver diseases and focal hepatic lesions. The Doppler technique offers real-time observation of blood flow with qualitative and quantitative assessments, and the application of microbubble-based contrast agents has improved the detectability of peripheral blood flow. In addition, elastography for the liver and spleen covers a wider field beyond the original purpose of fibrosis assessment. These developments enhance the practical use of US in the evaluation of portal hemodynamic abnormalities. This article reviews the recent progress of US in the assessment of portal hypertension. **(Gut Liver 2017;11:464-473)**

Key Words: Ultrasonography, Doppler; Contrast media; Liver; Hypertension, portal

INTRODUCTION

Because of the close relationship with disease severity, portal hemodynamics is the key pathophysiology in cirrhosis.[1-3] The development of collateral vessels represents a portal abnormality, which results in gastroesophageal varices, ectopic varices, and hepatic encephalopathy; these are the major manifestations in cirrhosis.[4-6] A proper management may be the key issue in clinical practice because the complications caused by portal hypertension affect the prognosis and quality of life of cirrhosis patients.[7,8]

The severity of portal hypertension is determined by the portal pressure.[7,9] Performing interventional radiology (IVR) may be the only procedure to obtain the hepatic venous pressure gradient (HVPG), a surrogate marker for directly measured portal pressure. However, because of its invasiveness under radiation exposure, noninvasive markers available for repeated use during the long-term clinical course may be preferable.[1,10]

Because of simple and less-invasive evaluations, ultrasound (US) may be the most frequently used imaging procedure in the practical management of patients with chronic liver disease.[4,5] Doppler mode enables real-time observation of blood flow under physiological conditions, and contrast-enhanced US with microbubble contrast agents allows detailed assessment of peripheral blood flow. In addition, elastography for liver and spleen shows broad application beyond the original purpose of fibrosis assessment. Clearly, such advancement is supported by the development of digital technologies and diffusion of information. With this background, this review article describes the recent progress of using US in the noninvasive assessment of portal hypertension.

B-MODE US

Recent developments in digital technology have introduced various imaging modes, color/power Doppler, harmonic imaging for contrast enhancement, three-dimensional visualization, and fusion imaging.[1,4,11] However, fundamental tissue images are available only using B-mode sonography. The role of this simple technique for portal hypertension is to characterize cirrhosis, measure vessel diameter and spleen size, and identify the ascites and abnormal collateral route.[12-14] However, because they are indirect findings to suspect the presence of portal hypertension, benefits of B-mode US on the prediction of portal pressure and the assessment of the severity of portal hypertension are limited.

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DOPPLER US

With the advantage of real-time observation of blood flow under physiological conditions, studies using Doppler US have been performed for evaluating the severity of liver disease and portal hypertension (Fig. 1).[1,4,6,15-18] Indeed, portal hemodynamics are predictive markers of outcomes in cirrhosis, lower velocity (<12.8 cm/s) in the portal trunk in compensated cirrhosis for decompensation, and reverse portal flow in decompensated cirrhosis for poor prognosis (Table 1).[19] However, a major issue is the prediction of HVPG, which is a standard maker for the severity of portal hypertension. According to a Korean study, patients with a damping index (minimum velocity/maximum velocity of the hepatic vein waveform) >0.6 are significantly more likely to have severe portal hypertension (SPH; HVPG >12 mm Hg), with 76% sensitivity and 82% specificity, suggesting an effective parameter to predict the grade of portal hypertension (Table 1).[20] In another study, in 66 patients with hepatitis C virus infection, there were significant correlations between HVPG and intraparenchymal splenic artery resistance index (SA-RI) (r=0.50, p<0.0001), superior mesenteric artery-pulsatility index (SMA-PI) (r=−0,48, p<0.0001), and right interlobar renal artery resistance index (RRA-RI) (r=0.51, p<0.0001) (Table 1).[21] However, dividing patients according to the presence or absence of SPH, correlations between HVPG and intraparenchymal SA-RI (r=0.70, p<0.0001), SMA-PI (r=−0.49, p=0.02), and RRA-RI (r=0.66, p=0.0002) were observed only in patients with HVPG <12 mm Hg. The HVPG but not Doppler parameters correlated with the presence of esophageal varices (EV; p<0.0001). Indeed, the negative aspect of the Doppler US may be enhanced in late years because of less statistical power for the prediction of clinically significant portal hypertension (CSPH; HVPG >10 mm Hg) and EV.[22] The effect of Doppler US to predict the severity of portal hypertension may still be debated due to the lack of a definitive parameter.

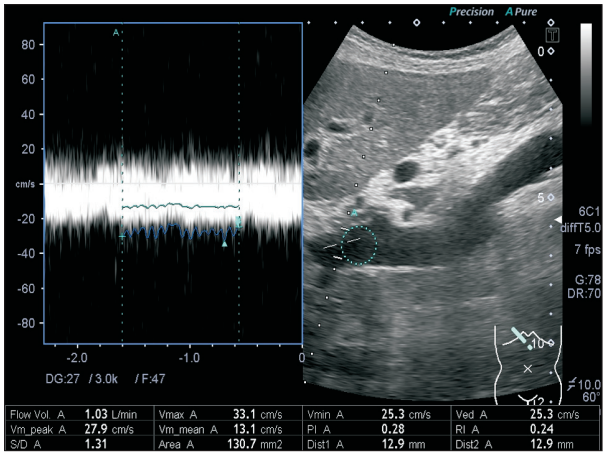

Fig. 1. Pulsed Doppler image for portal trunk (68-year-old male, non-B, non-C cirrhosis). The portal trunk was demonstrated as a longitudinal view and sample volume was used with the optimal width to include the vessel. Time-averaged mean flow velocity was obtained from the waveform of the Doppler signal with the beam-vessel angle, which was 60 degrees or smaller. Flow volume was calculated by multiplying mean flow velocity by automatic cross-section of the vessel every 60 seconds.

CONTRAST-ENHANCED US

1. Contrast-enhanced US and portal hypertension

With its simplicity and safety, contrast-enhanced US has become popular for assessing liver disease.[23-26] Currently, it is applied in the wide range of liver diseases to differentiate diffuse liver diseases and assess the severity of portal hypertension, in addition to the management of focal hepatic lesions.[4-11]

The interval time between vessels is a representative parameter for microbubble hemodynamics and shows close correlation with portal pressure, between free portal pressure and hepatic vein–hepatic artery interval time (r=−0.804, p=0.009) or the portal vein–hepatic artery interval time (r=0.506, p=0.036).[27] More recent studies have demonstrated original parameters for portal pressure; the first study proposed "regional hepatic perfusion" using SonoVue, which correlated with HVPG (r=0.279, p=0.041) and hyperdynamic syndrome markers.[28] The other study has shown that the portal vein/hepatic artery time-intensity curve

Table 1. Diagnostic Ability of Doppler Parameters

Study	Patients, no.	Etiology	Parameter	Cutoff value	Diagnosis	Se/Sp/PPV/NPV	AUROC
Kondo *et al*.[19]	236	Mix	Velocity	12.8 cm/s	Decompensation	68/75/68/75	0.7395
			Flow direction	Reverse	Prognosis	21.8/99.3/70.6/60.6	-
Kim *et al*.[20]	76	Mix	Damping index*	0.6	SPH	75.9/81.8/91.1/58.1	0.860
Vizzutti *et al*.[21]	66	HCV	SA-RI	0.6	SPH	84.6/70.4/80/76	0.82
			SMA-PI	2.7	SPH	85.7/65.2/79/75	0.78
			RRA-RI	0.65	SPH	79.5/59.3/74/66	0.78

Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under the receiver operating curve; SPH, severe portal hypertension (hepatic venous pressure gradient >12 mm Hg); HCV, hepatitis C virus; SA-RI, intraparenchymal splenic artery resistance index; SMA-PI, superior mesenteric artery-pulsatility index; RRA-RI, right interlobar renal artery resistance index.
*Damping index=minimum velocity/maximum velocity of the hepatic vein waveform.

ratio, portal vein/hepatic artery strength ratio, and portal vein/hepatic artery wash-in perfusion slope ratio have close correlation with portal pressure.[29]

2. Diagnostic ability for portal hypertension

Three studies reported the actual diagnostic value of contrast parameters for the severity of portal hypertension (Table 2). The first two studies, both from South Korea, used hepatic transit time as a contrast parameter. A study by Kim *et al*.[30] reported that the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratios (PLR), negative likelihood ratios (NLR), and area under the receiver operating curve (AUROC) of transit time from the venous access to the hepatic vein (hepatic vein arrival time, HVAT) using SonoVue (cutoff value, 14 seconds) were 92.7%, 86.7%, 90.5%, 89.7%, 6.95, 0.08, and 0.973, respectively, on the prediction of CSPH in compensated cirrhosis. The next study compared the two parameters using SonoVue, HVAT, and intrahepatic transit time in 53 cirrhosis patients. Both showed significant differences between patients <12 mm Hg and those ≥12 mm Hg; however, the diagnostic abilities were higher in the latter (sensitivity, 85.3%; specificity, 91.2%; AUROC, 0.94) than in the former (sensitivity, 58.1%; specificity, 62.8%; AUROC, 0.72).[31] The last study focused on the splenic circulation (i.e., the traveling time of microbubbles from splenic artery to splenic vein).[32] The AUROC was 0.76 for CSPH with best cutoff value of 13.5 seconds and 0.76 for SPH with best cutoff value of 14.5 seconds.

3. Subharmonic imaging

The subharmonic mode is a novel technique using a characteristic property of microbubble. An early study in canines reported the possibility of a subharmonic aided pressure estimation (SHAPE) in the estimation of portal pressure.[33] The same group examined the clinical effect of the technique in human subjects and found a good overall agreement (r=0.82) between the SHAPE gradient (the portal and hepatic veins) and HVPG.[34] The diagnostic abilities of the SHAPE were 89% sensitivity and 88% specificity for patients with CSPH and 100% sensitivity and 81% specificity for patients with SPH. These data suggest the potential of this novel parameter as a noninvasive marker for the severity of portal hypertension.

ELASTOGRAPHY

1. Transient elastography for liver stiffness

Although the original application of transient elastography (TE) was assessing the fibrosis grade in the liver, recent studies have expanded the use of TE to evaluate potential liver function, severity of portal hypertension, and risk of cancer development.[1,10,35]

A significant relationship between the HVPG and liver stiffness (LS) by TE has been reported,[36] and its actual diagnostic ability may be acceptable because the AUROC is ≥0.8,[37-43] except for two studies showing an AUROC of 0.76 and 0.78 (Ta-

Table 2. Comparison of Diagnostic Abilities in Contrast Parameters for Grading Portal Hypertension

Contrast agent	Patients, no.	Parameter (cutoff value)	Reliability*	Grade of PH	Se/Sp/PPV/NPV/Ac/PLR/NLR	AUROC	Study
Sonovue	71	HVAT (14 s)	3.7%–3.9%, 2.7%–3.2%	CSPH	93/87/91/90/-/6.95/0.08	0.973	Kim *et al*.[30]
	35 (v†)		κ=0.87			0.953	
SonoVue	53	HVAT (19 s)	0.938 (ICC)	SPH	56/89/95/35/63/-/-, R1‡	0.72	Jeong *et al*.[31]
					(50/89/94/32/58/-/-, R2‡)	0.71	
		ITT (6 s)	0.860 (ICC)	SPH	91/89/97/73/91/-/-, R1‡	0.94	
					(85/78/94/58/84/-/-, R2‡)	0.90	
Sonazoid	91	SA-SV§ (13.5 s)	4.9% (IOV)	CSPH	71/68/69/70/-/-/-	0.76	Shimada *et al*.[32]
		SA-SV (14.5 s)		SPH	60/80/75/67/-/-/-	0.76	

The three studies show the diagnostic abilities of contrast parameters based on dynamic microbubbles for clinically significant portal hypertension (CSPH) and/or severe portal hypertension (SPH). The first study reported that hepatic vein arrival time (HVAT) showed area under the receiver operating curve (AUROC) 0.975/0.953 to diagnose CSPH; the second study compared two contrast parameters, HVAT and intrahepatic transit time (ITT) to diagnose SPH and found that ITT showed higher ability with AUROC 0.90/0.94. The third study proposed splenic circulation time using Sonazoid, and the AUROC for CSPH/SPH was 0.76.

PH, portal hypertension; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; Ac, accuracy; PLR, positive likelihood ratio; NLR, negative likelihood ratio; CSPH, clinically significant portal hypertension (hepatic venous pressure gradient ≥10 mm Hg); ICC, intraclass correlation coefficient; SPH, severe portal hypertension (hepatic venous pressure gradient ≥12 mm Hg); SA-SV, splenic artery-splenic vein; IOV, interobserver variability.

*Reliability was presented by interobserver/intraobserver variability, κ-value, or ICC, 3.7% and 3.9% for day-to-day intraobserver variability in the HVAT measurement, 2.7% and 3.2% for IOV of the drawing and interpretation of the time-intensity curve. κ=0.87, IOV. ICC for the interpretation, 0.938 (95% confidence interval, 0.894–0.964) for HVAT and 0.860 (0.769–0.917) for ITT. 4.9% for IOV; †Validation set; ‡R1, reader 1 and R2, reader 2; §The interval time from the contrast onset in the splenic artery to the time to reach the maximum intensity level in the splenic vein.

Table 3. Comparison of Diagnostic Abilities of Elastography for Grading Portal Hypertension

Equipment	Patient no.	Parameter (cutoff value)	Grade of PH	Se/Sp/PPV/NPV/Ac/PLR/NLR	AUROC	Study
TE	61 (HCV)	LS (13.6 kPa)	CSPH	97/92/97/92/-/13.7/0.02	0.99	Vizzutti *et al*.[37]
		LS (17.6 kPa)	SPH	94/81/86/91/-/4.9/0.08	0.92	
TE	44 (HCV)	LS (20.5 kPa)	CSPH	63/70/88/35/-/-/-	0.76	Lemoine *et al*.[44]
	48 (alcohol)	LS (34.9 kPa)	CSPH	90/88/97/64/-/-/-	0.94	
TE	150	LS (21 kPa)	CSPH	90/93/93/91/-/-/-	0.945	Bureau *et al*.[38]
TE	38 (HIV-HCV)	LS (14 kPa)	CSPH	93/50/84/71/-/3.5/0.6	0.80	Sánchez-Conde *et al*.[39]
		LS (23 kPa)	SPH	83/67/79/71/-/2.5/0.5	0.80	
TE	95	LS (29 kPa)	CSPH	72/100/100/56/-/0.3	0.90	Kitson *et al*.[40]
TE	97 (C-P A, HCC)	LS (13.6 kPa)	CSPH	91/57/59/90/-/2.13/0.16	-	Llop *et al*.[36]
		LS (21 kPa)	CSPH	53/91/81/74/-/6.24/0.51	-	
TE	79	LS (65.3 kPa)	CSPH	52/100/100/21/57/-/-	0.78	Elkrief *et al*.[41]
RT-SWE		LS (24.5 kPa)	CSPH	81/88/98/35/82/-/-	0.87	Elkrief *et al*.[41]
RT-SWE	92	LS (15.2 kPa)	CSPH	86/80/96/52/85/-/-	0.819	Kim *et al*.[42]
		LS (21.6 kPa)	SPH	83/81/92/66/83/-/-	0.867	
TE	124 (HCV)	LS (8.74 kPa)	HVPG >6 mm Hg	90/81/-/-/ 85/-/-	0.93	Carrión *et al*.[43]

Table 3 summarizes the diagnostic abilities of elastography for grading portal hypertension. Transient elastography (TE) showed area under the receiver operating curve (AUROC) 0.76–0.99 for clinically significant portal hypertension (CSPH) and 0.80/0.92 for severe portal hypertension (SPH), and real-time share wave elastography (RT-SWE) showed AUROC 0.819/0.87 for CSPH and 0.867 for SPH.
PH, portal hypertension; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; Ac, accuracy; PLR, positive likelihood ratio; NLR, negative likelihood ratio; HCV, hepatitis C virus; LS, liver stiffness; CSPH, clinically significant portal hypertension (hepatic venous pressure gradient [HVPG] ≥10 mm Hg); SPH, severe portal hypertension (HVPG ≥12 mm Hg); HIV, human immunodeficiency virus; C-P A, Child-Pugh A.

ble 3).[41,44] The accuracy of LS for SPH was significantly higher than that of Plt (platelet count)/Spl (spleen diameter) (AUROC: LS, 0.919 vs Plt/Spl, 0.828; p=0.038).[45] However, some studies suggested that the linkage between LS and HVPG was dominant in mild or moderate grade portal hypertension, presented by HVPG <10–12 mm Hg, and not in the severe grade in hepatitis C virus-related cirrhosis patients.[37,44] The reasons for the poor correlation in advanced portal hypertension may be the presence of extrahepatic changes in the portal hemodynamics and the influence of various factors, such as cholestasis and inflammation, on the LS value.[46]

The diagnostic ability by LS for EV was summarized in Table 4; even for large EV, the AUROC remains 0.75 to 0.87.[38,47,48] These poor abilities are supported by a recent meta-analysis study: 87% sensitivity and 53% specificity for EV and 86% sensitivity and 59% specificity for large EV.[49] Because of this insufficient ability, particularly poor specificity, replacement of endoscopy by TE alone may not be presently encouraged.

Recently, two studies focused on the other practical use of LS value, that is, the prediction of complications caused by portal hypertension. According to the study by Kitson *et al*.,[40] although LS >29 kPa was effective to identify CSPH, the prediction of complications related to portal hypertension showed 100% sensitivity with only 40% specificity. Meanwhile, the optimal cutoff value of 34.5 kPa provided 75.0% sensitivity, 69.4% specificity, 52.5% PPV, 86.2% NPV, PLR 2.5, and NLR 0.36 for the prediction of complications. Furthermore, a study in 100 patients (mean follow-up period, 491 days) with chronic liver disease has shown that LS is as effective as HVPG in predicting clinical decompensation and complications caused by portal hypertension.[50]

Although the waveform patterns in the hepatic vein show a close relationship with the severity of liver disease, the underlying mechanism for various patterns had been undetermined. A study by Sekimoto *et al*.[51] reported the linkage between waveform patterns and LS, which may be a major pathogenesis to determine the waveform patterns in the hepatic vein.

2. TE combined with other factors

The addition of other factors may increase the diagnostic performance of TE. The AUROC of LS and Liver stiffness, spleen size, and platelet count (LS×spleen size/platelet count) for CSPH was 0.883 and 0.918 in the training set and 0.901 and 0.906 in the validation set, respectively.[52] Another study also reported that combining LS with platelet count improved diagnostic accuracy in the exclusion of CSPH; an LS >29.0 kPa predicted CSPH with 71.9% sensitivity, 100% specificity, 100% PPV, and 56.0% NPV. An LS <25.0 kPa in those with platelet count $>150\times10^9$/L excluded CSPH with 91.7% sensitivity, 100% specificity, 100% PPV, and 90% NPV.[40]

As for the diagnosis of gastroesophageal varices, a combined model with LS and platelet count was more accurate for exclud-

ing the presence of high-risk gastroesophageal varices than either alone (training cohort AUROC: 0.87 [0.77–0.96] vs 0.78 [0.65–0.92] for LS and 0.71 [0.52–0.90] for platelets) with the combination of LS ≤25 kPa and platelets ≥100 having an NPV of 100% in both the training and validation cohorts.[53] However, a more recent study performed in 219 alcoholic cirrhosis patients showed that none of the noninvasive tests, including aspartate aminotransferase-to-platelet ratio index, FIB-4, Forns index, Lok index, (platelet count)^2/(monocyte fraction [%]×segmented neutrophil fraction [%]), and platelet count to spleen diameter ratio showed reliable performance (AUROCs of all investigated tests <0.70).[54] According to the study by Procopet *et al*.,[55] the use of artificial neural networks integrating different noninvasive tests did not increase the diagnostic accuracy of LS alone, which was the best way to assess the presence of cirrhosis, portal hypertension, and EV. Thus, the combined effect depends on the parameters, and further investigation may be required to seek better markers, particularly for the diagnosis and grading of EV.

3. Reliability in the TE measurement

It is generally believed that LS values obtained by TE are considered reliable with the traditional criteria, valid measurements of 10 times or more, a success rate >60%,[56,57] and a quotient of interquartile range per median (IQR/M) <0.30.[58] However, LS data are affected by several factors: sex,[59] levels of aminotransferases,[60,61] histological inflammation,[62,63] extrahepatic cholestasis,[64,65] liver steatosis,[39,66,67] body mass index,[68,69] fasting state,[70,71] and central venous pressure.[72] Therefore, further improvement of reliability is clearly required in TE measurement, and indeed, some studies have indicated problems in the traditional criteria and suggested room for improvement.[69,73-75]

Boursier *et al*.[76] proposed new reliability criteria: "very reliable'' (IQR/M≤0.10), ''reliable'' (0.10<IQR/M≤0.30, or IQR/M>0.30 with LS median<7.1 kPa), and ''poorly reliable'' (IQR/M>0.30 with LS median≥7.1 kPa). A more recent study compared traditional and new TE quality criteria (very reliable by IQR/M<0.1, and reliable by IQR<0.3 or >0.3, if TE<7.1 kPa)

Table 4. Diagnostic Ability of Elastography for Esophageal Varices

Study	Patient no.	Etiology	Prevalence of EV (%)	AUROC	Accuracy	Cutoff	Se/Sp/PPV/NPV	Endpoint
Liver stiffness by TE								
Vizzutti *et al*.[37]	61	HCV	63.7	0.76	90	17.6	90/43/77/66	Any EV
Kazemi *et al*.[47]	165	Mix	41.2	0.84	-	13.9	95/43/57/91	Any EV
				0.83	-	19	91/60/48/95	Large EV
Bureau *et al*.[38]	150	Mix	72	0.85	NA	21.1	84/71/-/-	Any EV
		Mix	48	0.76	NA	29.3	81/61/-/-	Large EV
Castéra *et al*.[48]	298	HCV	36	0.84	-	21.5	76/78/68/84	Any EV
			19	0.87	-	30.5	77/85/56/94	Large EV
Pritchett *et al*.[77]	211	Mix	62.6 (mild)	0.74	-	19.5	76/66/82/56	Any EV
			37.4, large	0.76	-	19.8	91/56/55/91	Large (vs small)
Nguyen-Khac *et al*.[78]	183	Mix	22.4, large	0.75	-	48	73.2/73.2/44.1/90.4	Large EV
Malik *et al*.[79]	124	Mix	50.8 (in cirrhosis)	0.85	NA	20	-/-/80/75	Any EV
Liver stiffness by ARFI								
Morishita *et al*.[80]	135	HCV	51.1	0.89	-	2.05 m/s	83/76/78/81	Any EV
			33.7	0.868	-	2.39 m/s	81/82/69/89	Large EV
Spleen stiffness								
Sharma *et al*.[81]	174	Mix	71	0.898	86	40.8 kPa	94/76/91/84	Any EV
				0.819	-	54.5 kPa	76/73/-/-	Bleeder
Colecchia *et al*.[45]	100	HCV	53	0.941				Any EV
Spleen stiffness by ARFI								
Takuma *et al*.[82]	340	Mix	38.8	0.933	75	3.18	98.5/60.1/61/98.4	Any EV
				0.93	72.1	3.3	98.9/62.9/47.8/99.4	Large EV

The diagnostic ability of liver/spleen stiffness measurement for esophageal varices (EV) is summarized. Liver stiffness measurement showed area under the receiver operating curve (AUROC) 0.74–0.89 for a presence of EV and 0.75–0.87 for large varices. Spleen stiffness measurement showed AUROC 0.898–0.941 to detect a presence of EV, which was greater than that based on liver stiffness measurement.
Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; TE, transient elastography; HCV, hepatitis C virus; NA, not available; ARFI, acoustic radiation force impulse imaging.

regarding their diagnostic accuracy for cirrhosis and portal hypertension[83] and found that the latter increases the number of patients with accurate measurements without affecting diagnostic performance for detecting cirrhosis and portal hypertension.

4. Acoustic radiation force impulse and share wave elastography

Acoustic radiation force impulse (ARFI) and share wave elastography (SWE) are modalities using US-based impulse instead of mechanical impulse for TE. An early study reported an increase of share wave velocity in parallel with the increase of the splenic index (ρ=0.409, p<0.01) and splenoportal index (ρ=0.451, p<0.01).[84]

In the study by Morishita *et al*.,[80] AUROC values for the presence of EV and high-risk EVs by ARFI were 0.890 and 0.868, respectively, which had the highest diagnostic performance among factors, including serum fibrosis markers (Table 4). The diagnostic accuracy of LS by ARFI was comparable to TE and Fibrotest for the detection of complications in patients with cirrhosis.[85] As for the portal pressure, data obtained by SWE (SuperSonic) showed significant correlation with the HVPG and feasibility to estimate the change in HVPG due to the medication by non-selective β-blocker in patients with portal hypertension.[86]

Another issue is the lack of reliability criteria for the measurement of real-time SWE. A recent study demonstrated that standard deviation/median ≤10 and/or depth <5.6 cm are considered reliable criteria in the assessment of CSPH.[87]

5. Spleen stiffness

Spleen is another target of elasticity measurement, and investigators have shown the benefits of spleen stiffness (SS) measurement. Two studies reported significant correlations between SS and HVPG, with SS (r=0.433, p=0.001), but not with LS (r=0.178, p=0.20) by Sharma *et al*.[81] and with SS (r=0.885, p=0.0001) and LS (r=0.836, p=0.0001).[45] In fact, SS appears to provide better diagnostic performances for detecting EV compared to other noninvasive markers (Table 4).

Prospective comparison of SS and LS by using SWE and TE for detection of portal hypertension in cirrhosis was conducted by Elkrief *et al*.[41] In patients with advanced cirrhosis who are undergoing HVPG measurements, LS measurements obtained by using SWE have a higher technical success rate and a better diagnostic value than TE for CSPH. A more recent study has shown that SS can noninvasively assess changes in portal pressure after liver transplantation and decreases significantly when portal hypertension resolves.[88]

As expected, a combination of LS with SS may be effective to predict the severity of portal hypertension; the accuracy to predict significant EV was 69.6% to 70.8% using the formula with both LS and SS "–0.572+0.041×LS (m/s)+0.122×SS (m/s)+0.325×ascites (1, absent; 2, present)."[89]

CHALLENGES AND FUTURE DIRECTIONS

Strength/advantage and weakness/disadvantage of various US-based techniques are summarized in Table 5. Against their apparent benefits, there are still some limitations in each modality.

Table 5. Summary of Ultrasound-Based Techniques

	Application	Strength/advantage	Weakness/disadvantage
Ultrasound			
B-mode	First line approach	Simple and noninvasive	Available only anatomical information
Doppler (pulsed, color, power)	Flow direction and velocity measurement	Real-time observation	Poor detection of slow blood flow Reduced frame rate
Contrast	Second line approach Focal hepatic lesions (detection, characterization, therapeutic support) Diffuse liver disease (characterization, grading fibrosis and portal hypertension)	Increased detectability of blood flow Kupffer imaging (Sonazoid)	Invasiveness (agent injection) Possible adverse events Limited availability of agents Cost
Transient elastography	Grading fibrosis and portal hypertension Evaluation of complication	Simple and noninvasive	No grey-scale image Low technical success in patients with ascites
Share wave elastography	Grading fibrosis and portal hypertension Evaluation of complication	Simple and noninvasive Available grey-scale image Technical success in patients with ascites	Small number of research

Unfortunately, the diagnostic ability of Doppler parameters for portal hypertension is unsatisfactory, making the clinical application limited, and therefore alternative parameters are required with a hard/software development.

As for the contrast-enhanced US, the major problem is the limited availability of contrast agents and still, there is no available agents in some countries. Next is that because the dynamics and metabolism of *in vivo* microbubble have not been fully examined, the interpretation of contrast findings needs further investigation.

An establishment of reliability criteria and an improved assessment for patients with unreliable data should be considered in the field of elastography.

And finally, noninvasive diagnosis of EV is facing poor diagnostic performance. There are still challenges in the research field, suggesting our future directions for the improvement of diagnostic ability by achieving the international study with large patient population.

CONCLUSIONS

The present review article clearly demonstrates various benefits of US in the assessment of portal hypertension. Because of a close relationship with impaired portal hemodynamics, Doppler measurement data are useful to understand the underlying pathogenesis in the portal system. However, as the currently available parameters are not definitive indicator for HVPG, continuous efforts are required to determine the appropriate Doppler markers.

As for contrast-enhanced US, quantitative evaluation of microbubble behavior allows comprehensive assessment of portal hemodynamics, resulting in the efficient prediction of severity of portal hypertension.

Elastography may have an advantage of simplicity and reproducibility over Doppler/contrast mode and shows improved diagnostic ability to estimate the severity of portal hypertension. Moreover, recent studies suggest that multiple factor-based combined parameters are superior to a single modality-based parameter in the diagnostic performance.

It is expected that further development of technology (hardware and software) would make the role of US dominant in the current IVR-based diagnosis and grading of portal hypertension.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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