Noninvasive Assessment of Portal Hypertension in Patients With Cirrhosis

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Severe portal hypertension is responsible for complications and death. Although measurement of the hepatic venous pressure gradient is the most accurate method for evaluating the presence and severity of portal hypertension, this technique is considered invasive and is not routinely performed in all centers. Several noninvasive techniques have been proposed to measure portal hypertension. Certain methods evaluate elements related to the pathogenesis of portal hypertension through the measurement of hyperkinetic syndrome, for example, or they investigate the development of hepatic fibrosis through the measurement of increased intrahepatic vascular resistance. Other methods evaluate the clinical consequences of portal hypertension, such as the presence of esophageal varices or the development of portosystemic shunts. Methods evaluating increased hepatic vascular resistance are fairly accurate and mainly involve the detection of hepatic fibrosis by serum markers and transient elastography. The radiological assessment of hyperkinetic syndrome probably has value but is still under investigation. The assessment of severe portal hypertension by the presence of varices may be performed with simple tools such as biological assays, computed tomography, and esophageal capsules. More sophisticated procedures seem promising but are still under development. Screening tools for large populations must be simple, whereas more complicated procedures could help in the follow-up of already diagnosed patients. Although most of these noninvasive methods effectively identify severe portal hypertension, methods for diagnosing moderate portal hypertension need to be developed; this shows that further investigation is needed in this field. (HEPATOLOGY 2011;53:683-694)

Portal hypertension is one of the main causes of severe complications and death in patients with cirrhosis. Thus, recommendations suggest that the presence and degree of portal hypertension be evaluated in all patients with cirrhosis and other chronic liver diseases.[1] The degree of portal hypertension can be correlated with the severity of cirrhosis, which is estimated by either the Child-Pugh score[2] or histological lesions.[3-5] As a result, an improvement in liver function is associated with decreases in portal hypertension[6] and its complications. However, although a reduction in the degree of portal hypertension results in a decrease in the risk of complications, there is no improvement in liver tests.

Portal hypertension is defined as an increase in the pressure in the portal vein and its territory. In normal, fasted subjects at rest and in the supine position, the portal pressure ranges from 7 to 12 mm Hg.[7] In these healthy subjects, the pressure gradient between the portal vein territory and the vena cava territory ranges from 1 to 4 mm Hg.[8] The direct measurement of the portal pressure is a very invasive technique that is no longer performed in patients with cirrhosis; the indirect, less invasive technique of measuring the hepatic venous pressure gradient (HVPG) is used. This indirect method can be performed in 10 minutes but can last more than 30 minutes when hepatic vein catheterization is difficult. It is also a very safe technique; in our experience with more than 13,000 procedures, only minor complications (mainly transient cardiac arrhythmias) have occurred (<1% of patients), and no deaths have been observed. Most of these HVPG

Abbreviations: AUROC, area under the receiver operating curve; CT, computed tomography; EV, esophageal varices; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; MRI, magnetic resonance imaging; NA, not available; PHT, portal hypertension.

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measurements have been performed in association with transjugular liver biopsy. The results provide information about the type and severity of portal hypertension and may also help us to diagnose cirrhosis, particularly when the HVPG is greater than 20 mm Hg.[7]

The HVPG is the difference between the wedged or occluded hepatic venous pressure and the free hepatic venous pressure.[7] Portal hypertension is considered moderate when the HVPG ranges from 5 to 10 mm Hg and severe when the HVPG is greater than 10 mm Hg. In patients with cirrhosis, although the HVPG is elevated, it differs greatly from one patient to another and ranges from 7 to 35 mm Hg.[7] The HVPG is a good reflection of portal pressure in patients with alcoholic or viral cirrhosis but is not in patients with noncirrhotic portal hypertension.[9-12] After the acute administration of a drug acting on the splanchnic circulation, the HVPG measurement does not necessarily provide a reliable estimation of the magnitude of the changes in the portal pressure.[10] In fact, changes in the HVPG depend not only on wedged and free hepatic venous pressure changes but also on variations in other factors such as the portal pressure, portal and hepatic artery blood flows, and intrahepatic vascular resistance. Patients with cirrhosis are at risk of developing complications from portal hypertension when the HVPG reaches 10 to 12 mm Hg.[13,14] Below these values, moderate portal hypertension may be present, but the risk of complications is low. Above these values, severe portal hypertension is known to be present, and although there is no correlation between the degree of the HVPG and the risk of complications,[13] an HVPG greater than 20 mm Hg has been associated with a higher mortality rate.[15] Over the last 30 years, significant progress has been made in understanding the pathophysiology of portal hypertension. At the same time, the natural history of portal hypertension and its complications still remains unclear; for example, the exact mechanism of the development of severe portal hypertension in patients with cirrhosis and moderate portal hypertension needs to be elucidated. Thus, the evaluation of moderate or severe portal hypertension must be studied in patients with cirrhosis. Determining the HVPG, which is the gold-standard method for measuring portal hypertension, is still a fairly invasive procedure. In this review, noninvasive techniques for evaluating the presence and degree of portal hypertension are reported and discussed. We have divided our review of these techniques into two sections: methods measuring elements related to the pathogenesis of portal hypertension and methods measuring the clinical complications resulting from portal hypertension (Table 1).

Table 1. Noninvasive Method for Evaluating Portal Hypertension

- Evaluation of the pathogenic factors of portal hypertension
  - Evaluation of hyperkinetic syndrome
    - Measurement of cardiac output
    - Measurement of splanchnic circulation
    - Evaluation of baroreflex sensitivity
    - Evaluation of portal blood flow
  - Evaluation of increased intrahepatic vascular resistance
    - Measurement of vasoconstriction and vascular injury
    - Evaluation of hepatic fibrosis
      - Assessment of biochemical parameters
      - Assessment of liver stiffness
  - Determination of liver failure
- Evaluation of clinical complications of portal hypertension
  - Evaluation of the presence of varices
    - Assessment by endoscopy
    - Assessment by biochemical parameters
    - Assessment by abdominal CT scan
    - Assessment by video capsule endoscopy
  - Measurement of variceal pressure
  - Spleen stiffness
  - Evaluation of modifications in the splanchnic circulation
    - Detection of portal vein enlargement and collaterals
    - Measurement of splenic pulsatility
    - Evaluation of hepatic vein waveforms

Noninvasive Assessment of Portal Hypertension Using Methods That Measure Elements Related to the Pathogenesis of Portal Hypertension

In patients with cirrhosis, portal hypertension depends on increased portal tributary blood flow or portal inflow and elevated intrahepatic vascular resistance.[16] Liver failure also has some effect on portal hypertension by mechanisms that have not been clarified.

Methods That Evaluate Hyperkinetic Syndrome

Measurement of the Cardiac Output. Splanchnic hyperkinetic syndrome is associated with increased cardiac output.[16] Cardiac output increases in patients with severe portal hypertension, and a relationship has been found between the HVPG and cardiac output in patients with cirrhosis.[17] Thus, in patients with cirrhosis, the cardiac index may be a good reflection of the presence and degree of portal hypertension. However, in the past, cardiac output was measured by the thermodilution method. This technique requires the introduction of a catheter into a pulmonary artery, which is invasive and is no longer recommended. A noninvasive method for measuring the cardiac index in patients with cirrhosis could provide a noninvasive assessment of portal hypertension, but further investigation is needed in this area.

Measurement of the Splanchnic Circulation. Portal hypertension can be evaluated by the estimation of the splanchnic circulation; this is achieved by the injection

of different markers to determine transit times. One study indirectly confirmed elevated blood flow in the portal territory and found a significant correlation between the splanchnic circulation times and the degree of portal hypertension measured by the HVPG.[18] However, with the development of imaging techniques for determining blood velocity, this type of technique is no longer used in patients.

Evaluation of the Baroreflex Sensitivity. Because autonomic dysfunction is associated with hyperkinetic syndrome, the baroreceptor sensitivity and the HVPG were measured in patients with cirrhosis.[19] The spontaneous baroreflex was determined by the sequence method. In this noninvasive study, the baroreceptor sensitivity was impaired in patients with more advanced cirrhosis, and the HVPG was significantly, independently, and inversely correlated with the baroreceptor sensitivity; this suggests that portal hypertension plays an important role in baroreceptor function disturbances. Although this technique cannot be used to evaluate portal hypertension in all patients with cirrhosis, it may help us to understand the mechanisms of development of portal hypertension and its complications.

Evaluation of the Portal Blood Flow. In patients with decompensated alcoholic cirrhosis for whom the HVPG was measured, the portal vein velocity was measured by Doppler ultrasound, and the portal vein flow was calculated.[20] The results showed a significant inverse correlation between Doppler measurements and HVPG values. However, a correlation between the portal vein velocity and the HVPG was not confirmed in a recent study.[21] Surprisingly, in these studies, neither hepatic artery resistance nor mesenteric artery resistance was correlated with the severity of portal hypertension. It should be noted that this method may not accurately characterize the portal blood flow because it measures only the peak velocity, whereas the flow is known to be parabolic. Furthermore, this method is operator-dependent and has poor reproducibility in obese patients. Thus, further studies are needed to confirm these results, and studies should be performed in patients with asymptomatic cirrhosis to determine the portal vein velocity or flow values that correspond to the presence of severe portal hypertension.

Methods That Evaluate Increased Intrahepatic Vascular Resistance

Methods That Measure Vasoconstriction and Vascular Injury. Different factors contribute to the increased vascular resistance of the liver in patients with cirrhosis.[22] One component is the hyperproduction of endogenous vasoconstrictors. For example, serum endothelin levels have been shown to be significantly correlated with HVPG values in patients with cirrhosis.[23] Thus, serum endothelin levels could be used to evaluate the degree of portal hypertension; however, further studies are needed to determine whether this dosage can be used in clinical practice.

Recently, peripheral circulating cells associated with vascular injury were evaluated in patients with cirrhosis.[24] The results showed that the circulating endothelial cell count or the ratio of circulating endothelial cells to the platelet count is potentially a new biomarker of portal hypertension, but further clinical investigations are needed to confirm these results.

Methods That Evaluate Hepatic Fibrosis. Increased hepatic vascular resistance in patients with cirrhosis is also influenced by the presence and extent of fibrosis.[4,5] In one recent study, the area of liver collagen, which is the major component of fibrous tissue, was measured by computer-assisted image analysis and was found to be significantly correlated with the HVPG in patients with cirrhosis.[5] Accordingly, an evaluation of the extent of hepatic fibrosis may provide information about the presence and severity of portal hypertension.

The noninvasive estimation of hepatic fibrosis has been a subject of extensive research in the last 10 years. However, only a few of these procedures have been evaluated for the noninvasive diagnosis of portal hypertension (Table 2). Only the methods that have evaluated the relationship between hepatic fibrosis and portal hypertension are reported in this review.

Assessment of the Biochemical Parameters. Different markers of hepatic fibrosis have been studied to assess portal hypertension. One group of markers comprises the constituents of developing basal lamina, such as glycoprotein and laminin, or the main constituents of loose connective tissue, such as glycosaminoglycan polymer, hyaluronic acid, and hyaluronan. The amino-terminal procollagen type III propeptide has also been studied. These different markers are found in the blood and have been correlated with the development of hepatic fibrosis.[25] Several studies have shown that serum laminin levels are significantly correlated with HVPG values in patients with hepatic fibrosis and in patients with cirrhosis.[26-28] However, the prediction of severe portal hypertension or esophageal varices by laminin levels was poor with a positive predictive value of 85% and a negative predictive value of 43%.[28] Similar correlations were found between the serum hyaluronic acid concentrations and the HVPG.[29] On the other hand, serum levels of the amino-terminal procollagen type III propeptide were poorly correlated with

Table 2. Performance of Simple, Noninvasive Tools in the Noninvasive Diagnosis of Portal Hypertension (Measured by HVPG) in Patients With Fibrosis or Cirrhosis

	Study	Patients (n)	Etiology of Disease	Prevalence of Pathological Condition (%)	AUROC	Accuracy (%)	Cutoff	Sensitivity (%)	Specificity (%)	HVPG Cutoff (mm Hg)	Successful Procedure (%)
Laminin and hyaluronate index	Kropf et al.[29]	45	Mix	NA	NA	82	NA	83	82	5	NA
		39	Alcohol only			88	NA	84	90		
FibroTest	Thabut et al.[31]	92	Mix	92	0.79	91	0.93	88	50	12	100
FibroScan	Vizzutti et al.[37]	47	HCV	57	0.99	95	13.4 kPa	97	92	10	90†
					0.92	90	17.6 kPa	94	81	12	
FibroScan	Lemoine et al.[39]	44	HCV	77	0.76	98	20.5 kPa	63	70	10	NA
		48	Alcohol	83	0.94	98	34.9 kPa	90	88		
FibroScan	Bureau et al.[38]	144*	Mix	51	0.95	92	21 kPa	90	93	10	96
FibroScan	Carrion et al.[41]	124	HCV	21	0.93	85	8.74 mm Hg	90	81	6	94

Abbreviations: AUROC, area under the receiver operating curve; HCV, hepatitis C virus; NA, not available.
*Only 89 patients had cirrhosis.
†For all patients.

the HVPG in patients with cirrhosis, but they were correlated with hepatic fibrosis.[27,30] The results for these different biochemical markers are important but suggest that these markers cannot be currently used to detect the presence of severe portal hypertension. At the same time, these studies were performed with small groups of patients, and new investigations with larger groups including patients with asymptomatic cirrhosis could help us to determine patients with severe portal hypertension as well as patients at risk of complications.

The second type of marker is FibroTest, a panel of biochemical markers of hepatic fibrosis that has been extensively validated. In one prospective study, 130 patients with or without cirrhosis were included to determine whether FibroTest could diagnose severe portal hypertension.[31] There was a significant correlation between FibroTest values and HVPG values, but this correlation was weaker in patients with cirrhosis. Although the FibroTest value was significantly higher in patients with severe portal hypertension, the area under the receiver operating characteristic curve for the diagnosis of severe portal hypertension was only 0.79. Thus, other studies are needed to confirm these results, especially in patients with nondecompensated cirrhosis.

Different noninvasive markers or combinations of markers have also provided good results for the evaluation of hepatic fibrosis. Studies on portal hypertension are ongoing.[32] These biochemical markers have the advantage of noninvasive and easily available blood tests and are, therefore, potentially interesting for screening. Moreover, FibroTest correlates with mortality in patients who are inactive hepatitis B virus carriers.[33] In particular, the prognostic value of FibroTest is higher than the prognostic value of the viral load or alanine aminotransferase. These biochemical markers must be validated in large samples for the diagnosis of portal hypertension to confirm the results obtained in pilot studies.

Assessment of Liver Stiffness by Transient Elastography. The third type of marker used to evaluate hepatic fibrosis and thus potentially portal hypertension is the measurement of liver stiffness by transient elastography.[34,35] Numerous studies have shown that this technique is an excellent tool for the detection of advanced fibrosis or cirrhosis, but the results for the prediction of different stages of moderate fibrosis are less conclusive. This technique has the advantage of being noninvasive, safe, reproducible, and rapid (it can be performed in less than 10 minutes). However, its interpretation has been recently questioned because liver stiffness measurements have been found to be impossible to interpret in nearly one of five cases. The main reasons are obesity and limited operator experience.[36]

Three recent studies have evaluated the relationship between the liver stiffness values and the HVPG in patients with viral or alcoholic cirrhosis, including patients with asymptomatic or compensated cirrhosis.[37-39] In these studies, the authors also evaluated whether liver stiffness measurements could predict severe portal hypertension with an HVPG above 10 to 12 mm Hg. A significant correlation was found between the liver stiffness and HVPG whatever the cause of cirrhosis was; the correlation was excellent in patients with HVPG values between 5 and 10 or 12 mm Hg and less strong in patients with an HVPG value above 10 or 12 mm Hg.[37] Moreover, in selected patients with variceal bleeding, liver stiffness did not diagnose patients with an HVPG above 20 mm Hg.[40] These results suggest that the extent of hepatic fibrosis plays a major role in the development of moderate portal hypertension and has less effect in patients with

severe portal hypertension. The receiver operating characteristic curve for the diagnosis of severe portal hypertension ranges from 0.76 to 0.92 with a cutoff of 13.6 to 34.9 kPa.[37,39] In addition, liver biopsy, transient elastography, and HVPG measurements have been performed in patients with recurrent hepatitis C after liver transplantation.[41,42] Both studies found a significant correlation between the two measurements with a 0.93 receiver operating characteristic curve for the prediction of severe portal hypertension, which was also correlated with the progression of recurrent liver disease. Although liver stiffness measurement is a new, noninvasive approach for assessing hepatic fibrosis, results also suggest that it may be useful for determining the presence and degree of portal hypertension and particularly for screening patients with severe portal hypertension at risk of developing esophageal varices and other complications. However, more studies are needed in large groups of patients to confirm these findings.

Assessment of Liver Stiffness by Magnetic Resonance Imaging (MRI). There are other, more complex noninvasive markers of hepatic fibrosis. For example, magnetic resonance elastography of the liver and spleen has recently been proposed.[43] This method involves evaluating the mechanical properties of soft tissue through the assessment of liver stiffness with MRI. In comparison with transient elastography, this technique has the advantage of evaluating the whole liver.[43] Its correlation with the HVPG has not been studied to date.

Determination of Liver Failure. Several investigations have demonstrated that the degree of portal hypertension is correlated with the severity of cirrhosis assessed by the Child-Pugh classification or the presence of ascites.[2,44] For example, low serum albumin levels and elevated prothrombin times are associated with the presence of severe portal hypertension but have not been correlated with the degree of portal hypertension.[45] In one study, patients with low serum albumin levels, which were associated with low platelet counts and large portal vein diameters, were more likely to have severe portal hypertension and varices.[46] However, liver tests are not accurate enough to evaluate the presence and severity of portal hypertension and thus cannot be used to assess portal hypertension.

Noninvasive Assessment of Portal Hypertension Using Methods That Evaluate the Clinical Complications of Portal Hypertension

The clinical diagnosis of severe portal hypertension by a physical examination is not difficult in patients with cirrhosis who have collateral circulation of the abdominal wall, ascites, and peripheral edema. Hepatic encephalopathy is rarely the first sign of portal hypertension. Splenomegaly is frequent but is not always present in patients with portal hypertension. The relationship between the portal pressure and the spleen size remains unclear.[47] The main result of splenomegaly is hypersplenism, which corresponds to a reduction in some blood elements and most frequently a low platelet count with normal bone marrow function. The presence of hepatopulmonary syndrome or portopulmonary syndrome may reveal severe portal hypertension.[48] Finally, an episode of gastrointestinal hemorrhaging may also reveal portal hypertension and cirrhosis.

There are two types of noninvasive methods that evaluate the clinical consequences of portal hypertension: techniques that evaluate the presence of varices and those that evaluate modifications in the splanchnic circulation and vessels (including hepatic veins).

Methods That Evaluate the Presence of Varices

In patients with cirrhosis, the presence of esophageal varices indicates severe portal hypertension. In the absence of varices, moderate or severe portal hypertension may be present.[13] No correlation exists between the degree of portal hypertension and the presence and size of varices above a certain HVPG level (10-12 mm Hg).[13,14] Several methods exist for detecting esophageal varices, the degree of portal hypertension, and the presence and size of varices.[7]

Assessment of Esophageal Varices by Endoscopy. At present, upper gastrointestinal endoscopy is the gold standard for determining the presence of varices.[49,50] This technique is uncomfortable and invasive for patients and is costly and time-consuming, Moreover, up to 50% of patients may not have developed varices 10 years after the diagnosis of cirrhosis. This proportion is likely to increase with the widespread use of noninvasive methods for detecting cirrhosis, which results in the detection of larger numbers of patients with compensated cirrhosis. Finally, it has been shown that there is interobserver variability as high as 30% for the detection of small esophageal varices.[50] Numerous alternatives to endoscopy have been studied for determining the presence of varices; these include biochemical methods, ultrasound, endoscopic sonography, computed tomography (CT) scanning parameters, and, more recently, video capsule endoscopy and spleen MRI. This section provides an overview of these noninvasive tools. The diagnostic performance of each test is generally described with the c index, sensitivity, specificity, and accuracy. However, several points should be

Table 3. Performance of Simple, Noninvasive Tools in the Noninvasive Diagnosis of EV in Patients With Cirrhosis

	Study	Patients (n)	Etiology of Disease	Prevalence of EV (%)	AUROC	Accuracy (%)	Cutoff	Sensitivity (%)	Specificity (%)	Endpoint
FibroTest	Thabut et al.[51]	99	Mix	72	0.77	92	0.85	85	53	Large EV
FibroScan	Vizzutti et al.[37]	61	HCV	63.7	0.76	90	17.6 kPa	90	43	Any EV
FibroScan	Kazemi et al.[52]	165	Mix	41.2	0.84	95	19 kPa	95	43	Any EV
					0.83	91	13.9 kPa			Large EV
FibroScan	Bureau et al.[38]	150	Mix	72	0.85	NA	21.1 kPa	84	71	Any EV
			Mix	48	0.76	NA	29.3 kPa	81	61	Large EV
FibroScan	Castera et al.[35]	70	HCV	36	0.84	73	21.5 kPa	76	78	Any EV
				19	0.87	79	30.5 kPa	77	85	Large EV

Abbreviations: AUROC, area under the receiver operating curve; EV, esophageal varices; HCV, hepatitis C virus; NA, not available.

kept in mind when we are comparing the different tools. First, the studied populations were heterogeneous for the etiology and severity of liver disease, whereas the target population for a screening tool should be patients with compensated cirrhosis. Moreover, because the prognostic value of small esophageal varices remains unknown, these diagnostic tools should be evaluated for the detection of medium to large varices. Second, because the purpose of a noninvasive diagnosis is to screen patients, high sensitivity should be the main issue. However, the sensitivity of different tests can be seriously compared only if robust cutoffs are determined with several validation studies for each test. Third, upper endoscopy (i.e., the gold standard for the diagnosis of esophageal varices) is not perfect, and this affects the performance of all diagnostic tests.

Assessment of Esophageal Varices by Biochemical Parameters. Fairly simple tests and procedures for determining the presence of varices include biochemical parameters and serum indexes, liver stiffness, and certain easily reproducible radiological parameters. Even if the diagnostic performance of these tests is only fair, from a screening perspective, they are inexpensive and easily available in comparison with the more complicated tests described later.

These simple screening tests are described in the following section and in Table 3. The sensitivity of biochemical and ultrasound parameters associated or not associated with clinical signs varied from 58% to 100% with a specificity range of 56% to 93%. The values of the receiver operating characteristic curve ranged from 0.59 to 0.98. However, the results differed widely from one study to another, and no correlation between these parameters and the degree of portal hypertension was examined; this indicates that further studies are needed.

FibroTest and FibroScan, which have already been discussed for the evaluation of the presence and extent of fibrosis, have been studied for the detection of esophageal varices.[51] In one retrospective study, FibroTest was evaluated for the determination of the presence of large esophageal varices (i.e., severe portal hypertension) in patients with cirrhosis.[51] The results confirmed the previous study, which showed that FibroTest has high discriminative power with an area under the receiver operating characteristic curve of 0.77. Further studies to validate these results are ongoing.

Discordant results were found for FibroScan: one study found a relationship between the presence of large esophageal varices and elevated liver stiffness values,[52] but two studies did not confirm these findings.[37,53] FibroScan has poor accuracy for predicting esophageal varices in patients with cirrhosis and at present cannot replace endoscopy for varices screening.

Recently, more complicated procedures have been investigated for the detection of esophageal varices; these include CT scanning, capsule endoscopy, and spleen stiffness. The results of different studies are summarized in Table 3.

Assessment of Esophageal Varices by Abdominal CT Scanning. Abdominal CT scanning has been evaluated as a screening tool for esophageal varices in three studies,[54-56] and the results are summarized in Table 4. Notably, the methodology was very good in all these studies: the CT scan images were reviewed by two radiologists in two studies,[54,55] and in one study,[56] five endoscopists analyzed the images. With different techniques (single versus multidetector), the results had a sensitivity ranging from 63% to 93% for the detection of all varices and a sensitivity ranging from 56% to 92% for the detection of large varices. The specificity ranged from 76% to 97% and from 84% to 92%, respectively. Although the interobserver agreement was good for radiologists, one study showed that the endoscopist's experience played a major role in detecting the presence and size of varices.[56] In that study, CT scanning was shown to be safe and to be much better tolerated and more cost-effective than endoscopic screening.

Table 4. Performance of Noninvasive Tools in the Noninvasive Diagnosis of EV in Patients With Cirrhosis

	Study	Patients (n)	Etiology of Disease	Prevalence of EV (%)	AUROC	Accuracy (%)	Cutoff	Sensitivity (%)	Specificity (%)	Endpoint	Interobserver Agreement on Scan/Capsule	Interobserver Agreement on Endoscopy
CT scanning	Kim et al.[54]	67	Mix	63	0.77-0.80	72-73	NA	64-69	76-88	Any EV	0.61	NA
				18			3 mm	92-92	Large EV			
Multidetector CT esophagography	Kim et al.[55]	90	Mix	59	0.93-0.96	90-93	NA	74-78†	70-89†	Large EV	0.76-0.80	0.83*
Multidetector CT scanning	Perri et al.[56]	101	Mix	78	NA	34-44†,‡	5 mm	75-85†,‡	62-75†,‡	Any EV Large EV	0.75§	0.36
Capsule PillCam ESO	Eisen et al.[57]	32	Mix	72	NA	100	NA	100	89	Any EV	NA	NA
Capsule PillCam ESO	Lapalus et al.[58]	21	Mix	75	NA	81	NA	81	100	Any EV	NA	NA
Capsule PillCam ESO	Pena et al.[59]	20	Mix	95	NA	68	NA	68	100	Any EV	NA	NA
Capsule PillCam ESO	de Franchis et al.[60]	288	Mix	63		94	NA	84	88	Any EV	0.62-0.92¶	NA
		288	Mix	27		88	25% of the frame	78	96	Large EV		
Capsule PillCam ESO	Lapalus et al.[61]	120	Mix	62	NA	NA	NA	77	86	Any EV	79	NA
			Mix	29	NA	85	NA	77	88	Large EV	90	
Spleen MRI	Talwalkar et al.[67]	17	Mix	41	NA	NA	10.5 kPa	100	NA	Any EV	NA	NA

Abbreviations: AUROC, area under the receiver operating curve; EV, esophageal varices; NA, not available.

*Two endoscopists with 11 and 13 years of experience.

†Two radiologists.

‡After agreement between endoscopists.

§Difference in the size of varices (defined as a 2-mm difference).

¶Centers with little experience versus centers with much experience.

Assessment of Esophageal Varices by Video Capsule Endoscopy. Video capsule endoscopy has been tested in five studies for the detection of varices in patients with portal hypertension.[57-61] The size of the study populations was low except in two studies.[60,61] This technique was compared to conventional upper endoscopy in all the studies. A significant correlation was found between capsule and standard endoscopy for the detection of varices. The sensitivity of capsule endoscopy ranged from 68% to 100% with a specificity ranging from 88% to 100%. For the detection of large varices, the sensitivity was 78% with a specificity of 96%.[60] In one large study, one patient who was determined to have large varices with capsule endoscopy but not with conventional endoscopy underwent a second endoscopic examination that confirmed the presence of large varices. This suggests that standard endoscopy may not be the gold standard for detecting esophageal varices. Patients in all these studies significantly preferred capsule endoscopy to standard endoscopy. Therefore, video capsule endoscopy appears to be a very promising tool for the detection of esophageal varices.

Variceal Pressure Measurement. The variceal pressure can be measured and reflects portal hypertension. This technique can be used in patients with large varices but cannot be used in patients with moderate portal hypertension or in patients with severe portal hypertension without varices. Two different techniques have been reported. Direct puncture of the variceal wall was first proposed, but this is invasive and has to be performed immediately before sclerotherapy because bleeding can occur.[62] Thus, this procedure is no longer used. The noninvasive measurement of variceal pressure by an endoscopic gauge has been shown to be well correlated with results obtained by direct variceal puncture.[63] The results have shown that noninvasive measurement has low interobserver variability and good reproducibility in the same patient under placebo conditions at 6 weeks to 1 year.[64] Variceal pressure is elevated in patients with cirrhosis but is lower than the portal pressure measured by the HVPG, and variceal pressure is not significantly correlated with the HVPG in patients with cirrhosis.[63] Moreover, hemodynamic changes induced by pharmacological treatment are not correlated with changes in variceal pressure.[65] However, the level of variceal pressure is a major predictive factor for the risk of a first variceal hemorrhage.[66] In practice, this noninvasive technique has been used only in certain prospective studies.

Spleen Stiffness. Finally, the investigators who developed the measurement of liver stiffness by magnetic resonance elastography studied the diagnosis of spleen stiffness (measured by MRI) for the detection of esophageal varices. Specificity was high in a pilot study and was better than the specificity of liver stiffness evaluated with the same technique.[67] However, its place as a screening tool must be investigated because this technique is available in only a few centers.

Methods Associated With Modifications in the Splanchnic Circulation

Some of the clinical consequences of portal hypertension are the development of portal and splanchnic vein enlargement and portosystemic collateral circulation and a reduction of the respiratory variation of the diameters of these vessels and changes in blood flows. Most of these abnormalities can be visualized with the noninvasive technique known as ultrasound color duplex Doppler. This method is, however, operator-dependent with high interobserver and intraobserver variability. Other imaging techniques, such as CT (including the helical mode) and MRI, provide excellent visualization of portal and splanchnic venous structures, particularly for the detection of portosystemic collaterals. They can be used to confirm an unclear diagnosis after an ultrasound examination.

Detection of Portal Vein Enlargement and Collaterals. Although the enlargement of the portal vein is a radiological sign of portal hypertension, studies have shown that with vessel diameters greater than 13 or 15 mm, the sensitivity of this sign is low.[68] Similar results were observed with superior and splenic veins in a large series of patients with cirrhosis.[69] The best discriminant finding for all these vessels was the reduction of expiration diameter measurements. The diameter of the portal vein was not correlated with the degree of portal hypertension.[19] Similar results were found with superior mesenteric and splenic veins.

Radiological detection of the collateral circulation is a sensitive and specific sign for the diagnosis of portal hypertension, and the presence of numerous portosystemic shunts has been significantly associated with a high HVPG.[70]

Splenic Pulsatility. To predict the degree of portal hypertension in patients with cirrhosis, splenic Doppler pulsatility and splanchnic parameters were measured and compared to HVPG values. The results led to a formula calculated with the splenic pulsatility index and portal blood flow that was correlated with the degree of portal hypertension.[69] Similar studies were performed in patients with hepatitis C virus–related chronic liver disease.[71] The findings of that study showed that the superior mesenteric artery pulsatility index and the intraparenchymal splenic and right interlobar artery resistance did not effectively predict severe portal hypertension.

Hepatic Vein Waveforms. Hepatic vein waveforms measured by Doppler ultrasonography have also been used in the noninvasive investigation of portal hypertension.[72] In patients with cirrhosis, biphasic or monophasic waveforms have been observed, whereas triphasic waveforms have been observed in healthy subjects. An assessment of the damping index allows the quantification of the extent of the abnormal hepatic vein waveform, and it has been shown that the damping index is significantly correlated with the grade of portal hypertension measured with the HVPG.[72] Patients with a damping index greater than 0.6 are significantly more likely to have severe portal hypertension; a receiver operating characteristic curve with a damping index of 0.6 showed a sensitivity of 76% and a specificity of 82%. These results suggest that the damping index of the hepatic vein waveform by Doppler ultrasonography might be a noninvasive tool for evaluating the presence and severity of portal hypertension, but further investigation is needed.

Perspectives

This review shows that no perfect noninvasive technique for assessing portal hypertension exists. Moreover, no noninvasive technique is reliable enough to avoid gastrointestinal endoscopy for the detection of varices. Some recent experimental approaches have shown a certain correlation with portal hypertension (e.g., novel three-dimensional, micro single-photon emission CT imaging enabling longitudinal follow-up of portosystemic shunting).[73] However, the performance in patients with cirrhosis has to be established. Certain recent studies have shown that proteomic approaches may detect hepatic fibrosis with good accuracy.[74] New studies in portal hypertension are necessary, but proteomics seems a promising track to follow. A new serum index combining already developed markers and other ones will probably be developed in the following years.

Noninvasive Diagnosis of Portal Hypertension in Clinical Practice

This review describes several noninvasive tools that could replace HVPG measurement for the evaluation of the presence and severity of portal hypertension. We have shown that most of these tools provide a fairly accurate estimation of the presence of severe portal hypertension but not of the presence of moderate portal hypertension in comparison with the HVPG. For the detection of esophageal varices, the only available noninvasive tools are CT scanning and esophageal capsules. These methods are still under evaluation, and they are fairly expensive and are more complicated than methods measuring hepatic fibrosis with serum markers or transient elastography.

Although HVPG measurement can be avoided in patients with the clinical complications of portal hypertension (i.e., severe portal hypertension), these patients do need gastrointestinal upper endoscopy. Thus, a satisfactory replacement for upper endoscopy must be found in the future to determine whether there is an indication for primary prophylaxis for variceal bleeding in these patients.

The management of patients without the clinical complications of portal hypertension (i.e., patients with compensated cirrhosis) is difficult because moderate or severe portal hypertension may be present. HVPG measurement may be useful for determining the severity of portal hypertension in these patients. At present, less than one-third of these patients have esophageal varices (severe portal hypertension) and require primary prophylaxis for variceal bleeding. With the early detection of cirrhosis by noninvasive methods, the proportion of patients with severe portal hypertension and esophageal varices (especially those with hepatitis C virus–related cirrhosis) will probably decrease even further.[50] We should try to avoid unnecessary upper endoscopy in the population of patients without the clinical complications of portal hypertension. Therefore, further studies are still needed to validate a simple HVPG index that can be repeated regularly and can delay the first gastrointestinal upper endoscopy procedure in this population. Figure 1 presents an algorithm for the detection of portal hypertension in these two categories of patients at present and in the future.

In conclusion, numerous noninvasive methods can be used to evaluate the presence and degree of portal hypertension in patients with cirrhosis, and the diagnostic performance is rather fair. Methods evaluating increased hepatic vascular resistance mainly include the detection of hepatic fibrosis by serum markers and transient elastography. The radiological assessment of hyperkinetic syndrome probably has value, but further studies are needed to confirm the results of preliminary investigations. The assessment of severe portal hypertension by the presence of varices may be performed with simple tools such as biological assays, CT scanning, and esophageal capsules. Screening tools for large populations must be simple and inexpensive, whereas more complicated procedures could help in the follow-up of already diagnosed patients. However, methods for evaluating moderate portal hypertension must still be established. Finally, further clinical and hemodynamic studies are needed to better understand

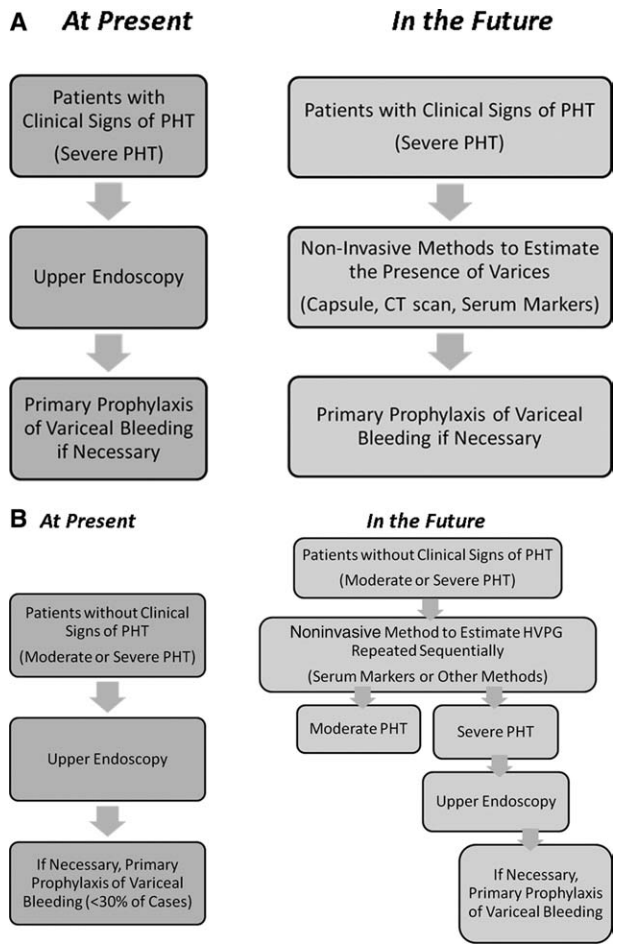

Fig. 1. Algorithm for detecting portal hypertension (PHT) in (A) patients with clinical signs of PHT and (B) patients without clinical signs of PHT.

the mechanisms responsible for portal hypertension and its complications.

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References

1. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005;43:167-176.
2. Braillon A, Calès P, Valla D, Gaudy D, Geoffroy P, Lebrec D. Influence of the degree of liver failure on systemic and splanchnic hemodynamics and on response to propranolol in patients with cirrhosis. Gut 1986; 27:1204-1209.
3. Krogsgaard K, Gluud C, Henriksen JH, Christoffersen P. Correlation between liver morphology and portal pressure in alcoholic liver disease. HEPATOLOGY 1984;4:699-703.
4. Nagula S, Jain D, Groszmann RJ, Garcia-Tsao G. Histological-hemodynamic correlation in cirrhosis. A histological classification of the severity of cirrhosis. J Hepatol 2006;44:111-117.
5. Calvaruso V, Burroughs AK, Standish R, Manousou P, Grillo F, Leandro G, et al. Computer-assisted image analysis of liver collagen: relationship to Ishak scoring and hepatic venous pressure gradient. HEPATOLOGY 2009;49:1236-1244.
6. Reynolds TB, Geller HM, Kuzma OT, Redeker AG. Spontaneous decrease in portal pressure with clinical improvement in cirrhosis. N Engl J Med 1960;263:734-739.
7. Lebrec D, Sogni P, Vilgrain V. Evaluation of patients with portal hypertension. Clin Gastroenterol 1997;11:221-241.
8. Gadano A, Hadengue A, Vachiery F, Moreau R, Sogni P, Soupison T, et al. Relationship between hepatic blood flow, liver tests, haemodynamic values and clinical characteristics in patients with chronic liver disease. J Gastroenterol Hepatol 1997;12:167-171.
9. Boyer TD, Triger DR, Horisawa M, Redeker AG, Reynolds TB. Direct transhepatic measurement of portal vein pressure using a thin needle. Comparison with wedged hepatic vein pressure. Gastroenterology 1977;72:584-589.
10. Valla D, Bercoff E, Menu Y, Lebrec D. Discrepancy between wedged hepatic venous pressure and portal venous pressure after acute propranolol administration in patients with alcoholic cirrhosis. Gastroenterology 1984;86:1400-1403.
11. Lin HC, Tsai YT, Chang TT, Lay CS, Lee SD, Lo KJ. Comparison between portal vein pressure and wedged hepatic vein pressure in hepatic B-related cirrhosis. J Hepatol 1989;9:326-330.
12. Sarin SK, Sethi KK, Nanda R. Measurement and correlation of wedged hepatic, intrahepatic, intrasplenic and intravariceal pressures in patients with cirrhosis and non-cirrhotic portal fibrosis. Gut 1987;28:260-266.
13. Lebrec D, de Fleury P, Rueff B, Nahum H, Benhamou JP. Portal hypertension, size of esophageal varices and risk of gastrointestinal bleeding in alcoholic cirrhosis. Gastroenterology 1980;79:1139-1144.
14. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. HEPATOLOGY 1985;5:419-424.
15. Monescillo A, Martinez-Lagares F, Ruiz-del-!Arbol L, Sierra A, Guevara C, Jimenez E, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. HEPATOLOGY 2004;40:793-801.
16. Blanchet L, Lebrec D. Changes in splanchnic blood flow in portal hypertensive rats. Eur J Clin Invest 1982;12:327-330.
17. Valla D, Poynard T, Bercoff E, Bataille C, Goldfarb G, Lebrec D. Systemic circulatory syndrome in patients with cirrhosis. Relationship with hepatocellular failure and portal hypertension. Gastroenterol Clin Biol 1984;8:321-324.
18. Friman L. Portal pressure correlated to visceral circulation times. Acta Radiol Diagn 1979;20:737-752.
19. Genovesi S, Prata DM, Pozzi M, Ratti L, Milanese M, Vincenti A, et al. Baroreceptor sensitivity and baroreceptor effectiveness index in cirrhosis: the relevance of hepatic venous pressure gradient. Liver Int 2010;30:232-239.
20. Taourel P, Blanc P, Dauzat M, Chabre M, Pradel J, Gallix B, et al. Doppler study of mesenteric, hepatic, and portal circulation in alcoholic cirrhosis: relationship between quantitative Doppler measurements and the severity of portal hypertension and hepatic failure. HEPATOLOGY 1999;28:932-936.
21. Choi YJ, Baik SK, Park DH, Kim MY, Kim HS, Lee DK, et al. Comparison of Doppler ultrasonography and the hepatic venous pressure gradient in assessing portal hypertension in liver cirrhosis. J Gastroenterol Hepatol 2003;18:424-429.
22. Rockey DC. Hepatic fibrosis, stellate cells, and portal hypertension. Clin Liver Dis 2006;10:459-479.
23. Hartleb M, Kirstetter P, Moreau R, Soupison T, Pussard E, Hadengue A, et al. Relations entre les concentrations plasmatiques d'endothéline et la sévérité de la cirrhose. Gastroentérol Clin Biol 1994;18:407-412.
24. Abdelmoneim SS, Talwalkar J, Sethi S, Kamath P, Fathalla MMF, Kipp BR, et al. A prospective pilot study of circulating endothelial cells as a potential new biomarker in portal hypertension. Liver Int 2009;29:191-196.
25. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005;115:209-218.

26. Gressner AM, Tittor W, Negwer A, Pick-Kober KH. Serum concentration of laminin and aminoterminal propeptide of type III procollagen in relation to the portal venous pressure of fibrotic liver diseases. Clin Chim Acta 1986;161:249-258.
27. Mal F, Hartmann DJ, Trinchet JC, Lacombe F, Ville G, Beaugrand M. Serum laminin and portal pressure in alcoholic cirrhosis. A study of 39 patients. Gastroenterol Clin Biol 1988;12:841-844.
28. Kondo M, Miszputen SJ, Leite-Mor MM, Parise ER. The predictive value of serum laminin for the risk of variceal bleeding related to portal pressure levels. Hepatogastroenterology 1995;42:542-545.
29. Kropf J, Gressner AM, Tittor W. Logistic-regression model for assessing portal hypertension by measuring hyaluronic acid (hyaluronan) and laminin in serum. Clin Chem 1991;37:30-35.
30. Gressner AM, Tittor W, Kropf J. Evaluation of serum aminoterminal procollagen type III propeptide as an index of portal hypertension and esophageal varices in chronic liver diseases. Clin Chim Acta 1988;174: 163-170.
31. Thabut D, Imbert-Bismut F, Cazals-Hatem D, Messous D, Muntenaus M, Valla DC, et al. Relationship between the FibroTest and portal hypertension in patients with liver disease. Aliment Pharmacol Ther 2007;26:359-368.
32. Calès P, Oberti F, Michalak S, Hubert-Fouchard I, Rousselet MC, Konaté A, et al. A novel panel of blood markers to assess the degree of liver fibrosis. HEPATOLOGY 2005;42:1373-1381.
33. Ngo Y, Benhamou Y, Thibault V, Ingiliz P, Munteanu M, Lebray P, et al. An accurate definition of the status of inactive hepatitis B virus carrier by a combination of biomarkers (FibroTest-ActiTest) and viral load. PLoS One 2008;3:e2573.
34. Friedrich-Rust M, Ong MF, Martens SJ, Sarrazin C, Bojunga J, Zeuzen S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960-974.
35. Castera L, Forms X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 2008;48:835-847.
36. Castera L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. HEPATOLOGY 2010;51:828-835.
37. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. HEPATOLOGY 2007;45:1290-1297.
38. Bureau C, Metivier S, Peron JM, Selves J, Robic MA, Gourraud PA, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. Aliment Pharmacol Ther 2008;27:1261-1268.
39. Lemoine M, Katsahian S, Ziol M, Nahon P, Ganne-Carrie N, Kazemi F, et al. Liver stiffness measurement as predictive tool of clinically significant portal hypertension in patients with compensated hepatitis C virus or alcohol-related cirrhosis. Aliment Pharmacol Ther 2008;28: 1102-1110.
40. Rudler M, Cluzel P, Massard J, Varaut A, Lebray P, Auguste M, et al. Transient elastography (FibroScan) and hepatic venous pressure gradient measurement in patients with cirrhosis and gastrointestinal haemorrhage related to portal hypertension [Abstract]. HEPATOLOGY 2008; 48(Suppl):324A.
41. Carrion JA, Navasa M, Bosch J, Bruguera, Gilabert R, Forms X. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Liver Transpl 2006;12:1791-1798.
42. Samonakis DN, Cholongitas E, Thalheimer U, Kalambokis G, Quaglia AP, Patch D, et al. Hepatic venous pressure gradient to assess fibrosis and its progression after liver transplantation for HCV cirrhosis. Liver Transpl 2007;13:1305-1311.
43. Yin M, Talwalkar JA, Glaser KJ, Manduca A, Grimm RC, Rossman PJ, et al. Assessment of hepatic fibrosis with magnetic resonance elastography. Clin Gastroenterol Hepatol 2007;5:1207-1213.
44. Kravetz D, Bildozola M, Argonz J, Romero G, Korula J, Munoz A, et al. Patients with ascites have higher variceal pressure and wall tension than patients without ascites. Am J Gastroenterol 2000;95:1770-1775.
45. Pilette C, Oberti F, Aubé C, Rousselet MC, Bedossa P, Gallois Y, et al. Non-invasive diagnosis of esophageal varices in chronic liver diseases. J Hepatol 1999;31:867-873.
46. Sarwar S, Khan AA, Butt AK, Shafquat F, Malik K, Ahmad I, et al. Non-endoscopic prediction of presence of esophageal varices in cirrhosis. J Coll Physicians Surg Pak 2005;15:528-531.
47. Simpson KJ, Finlayson NDC. Clinical evaluation of liver disease. Clin Gastroenterol 1995;9:639-659.
48. Hervé P, Lebrec D, Brenot F, Simonneau G, Humbert M, Sitbon O, et al. Pulmonary vascular disorders in portal hypertension. Eur Respir J 1998;11:1153-1166.
49. de Franchis R. Non-invasive (and minimally invasive) diagnosis of oesophageal varices. J Hepatol 2008;49:520-527.
50. Thabut D, Moreau R, Lebrec D. Screening for esophageal varices: endoscopy, other tools, or endoscopy and other tools? HEPATOLOGY 2008; 47:1434-1436.
51. Thabut D, Trabut JB, Massard J, Rudler M, Muntenau M, Messous D, et al. Non-invasive diagnosis of large oesophageal varices with Fibro Test in patients with cirrhosis: a preliminary retrospective study. Liver Int 2006;26:271-278.
52. Kazemi F, Kettaneh A, N'kontchou G, Pinto E, Ganne-Carrie N, Trinchet JC, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006;45:230-235.
53. Castera L, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol 2009;50:59-68.
54. Kim YJ, Raman SS, Yu NC, To'o KJ, Jutabha R, Lu DS. Esophageal varices in cirrhotic patients: evaluation with liver CT. AJR Am J Roentgenol 2007;188:139-144.
55. Kim SH, Kim YJ, Lee JM, Choi KD, Chung YJ, Han JK, et al. Esophageal varices in patients with cirrhosis: multidetector CT esophagography—comparison with endoscopy. Radiology 2007;242:759-768.
56. Perri R, Chioream MV, Fidler JL, Flercher JG, Talwalkar JA, Stadheim L, et al. A prospective evaluation of computerized tomographic scanning as a screening modality for esophageal varices. HEPATOLOGY 2008;47:1587-1594.
57. Eisen G, Eliakim R, Zaman A, Schwartz J, Faigel D, Rondonotti E, et al. The accuracy of PillCam ESO capsule endoscopy versus conventional upper endoscopy for the diagnosis of oesophageal varices: a prospective three-center pilot study. Endoscopy 2006;38:31-35.
58. Lapalus MG, Dumortier J, Fumex F, Roman S, Lot M, Prost B, et al. Oesophageal capsule endoscopy versus oesophagogastroduodenoscopy for evaluating portal hypertension. A prospective comparative study of performance and tolerance. Endoscopy 2006;38:36-41.
59. Pena LR, Cox T, Koch AG, Bosch A. Study comparing oesophageal capsule endoscopy versus EGD in the detection of varices. Dig Liver Dis 2008;40:216-223.
60. de Franchis R, Eisen GM, Laine L, Fernandez-Urien I, Herrerias JM, Brown RD, et al. Esophageal capsule endoscopy for screening and surveillance of esophageal varices in patients with portal hypertension. HEPATOLOGY 2008;47:1595-1603.
61. Lapalus MG, Ben Soussan E, Gaudric M, Saurin JC, D'Halluin PN, Favre O, et al. Esophageal capsule endoscopy vs. EGD for the evaluation of portal hypertension: a French prospective multicenter comparative study. Am J Gastroenterol 104:1112-1118.
62. Staritz M, Poralla T, Meyer zum Büschenfelde KH. Intravascular oesophageal variceal (IOVP) assessed by endoscopic fine needle puncture under basal conditions, Vasalva's manoeuvre and after glyceryltrinitrate application. Gut 1985;26:525-530.
63. Bosch J, Bordas JM, Rigau J, Viola C, Mastai R, Kravetz D, et al. Noninvasive measurement of the pressure of esophageal varices using an endoscopic gauge: comparison with measurements by variceal puncture in patients undergoing endoscopic sclerotherapy. HEPATOLOGY 1986;6:667-672.
64. Nevens F, Sprengers D, Feu F, Bosch J, Fevery J. Measurement of variceal pressure with an endoscopic pressure sensitive gauge: validation and effect of propranolol therapy in chronic conditions. J Hepatol 1996;24:66-73.

65. Feu F, Bordas JM, Luca A, Garcia-Pagan JC, Escorsell A, Bosch J, et al. Reduction of variceal pressure by propranolol: comparison of the effects on portal pressure and azygos blood flow in patients with cirrhosis. HEPATOLOGY 1993;18:1082-1089.
66. Nevens F, Bustami R, Scheys I, Lessaffre E, Fevery J. Variceal pressure is a factor predicting the risk of a first variceal bleeding: a prospective cohort study in cirrhotic patients. HEPATOLOGY 1998;27:15-19.
67. Talwalkar JA, Yin M, Venkatesh S, Rossman PJ, Grimm RC, Manduca A, et al. Feasibility of in vivo MR elastographic splenic stiffness measurements in the assessment of portal hypertension. AJR Am J Roentgenol 2009;193:122-127.
68. Bolondi L, Gandolfi L, Ariente V, Caletti GC, Corcionni E, Gasbarrini G, et al. Ultrasonography in the diagnosis of portal hypertension: diminished response of portal vessels to respiration. Radiology 1982;142:167-172.
69. Bolognesi M, Sacerdoti D, Merkel C, Bombonato G, Gatta A. Noninvasive grading of the severity of portal hypertension in cirrhotic patients by echo-Doppler. Ultrasound Med Biol 2001;27:901-907.
70. Vilgrain V, Lebrec D, Menu Y, Scherrer A, Nahum H. Comparison between ultrasonographic signs and the degree of portal hypertension in patients with cirrhosis. Gastrointest Radiol 1990;15:218-222.
71. Vizzutti F, Arena U, Rega L, Romanelli GR, Colagrande S, Cuofano S, et al. Performance of Doppler ultrasound in the prediction of severe portal hypertension in hepatitis C virus-related chronic liver disease. Liver Int 2007;27:1379-1388.
72. Kim MY, Baik SK, Park DH, Lim DW, Kim JW, Kim HS, et al. Damping index of Doppler hepatic vein waveform to assess the severity of portal hypertension and response to propranolol in liver cirrhosis: a prospective non randomized study. Liver Int 2007;27:1103-1110.
73. Van de Steenkiste C, Staelens S, Deleye S, de Vos F, Vandenberghe S, Geerts A, et al. Measurement of porto-systemic shunting in mice by novel three-dimensional micro-single photon emission computed tomography imaging enabling longitudinal follow-up. Liver Int 2010;30:1211-1220.
74. Cowan ML, Rahman TM, Krishna S. Proteomic approaches in the search for biomarkers of liver fibrosis. Trends Mol Med 2010;16:171-183.