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REVIEW ARTICLE

Invasive and non-invasive assessment of portal hypertension

Jonathan Chung-Fai Leung[1] · Thomson Chi-Wang Loong[1] · James Pang[1] · Jeremy Lok Wei[1] · Vincent Wai-Sun Wong[1,2]

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Abstract Portal hypertension is the central driver of complications in patients with chronic liver diseases and cirrhosis. The diagnosis of portal hypertension has important prognostic and clinical implications. In particular, screening for varices in patients with portal hypertension can effectively reduce the morbidity and mortality of variceal bleeding. In this article, we review the invasive and non-invasive methods to assess portal hypertension. Hepatic venous pressure gradient remains the gold standard to measure portal pressure but is invasive and seldom performed outside expert centers and research settings. In recent years, a number of non-invasive tests of fibrosis have shown good correlation with liver histology. They also show promise in identifying patients with portal hypertension and large varices. As a result, the latest Baveno VI consensus guidelines endorse the use of liver stiffness measurement by transient elastography and platelet count as initial assessment to select patients for varices screening. On the other hand, the performance of non-invasive tests in assessing the response to non-selective beta-blockers or transjugular intrahepatic portosystemic shunting is either suboptimal or unclear.

Keywords Hepatic venous pressure gradient · Transient elastography · Liver stiffness measurement · Magnetic resonance elastography · Baveno VI criteria · Variceal bleeding

List of abbreviations

ALT	Alanine aminotransferase
APRI	AST-to-platelet ratio index
AST	Aspartate aminotransferase
AUROC	Area under the receiver-operating characteristics curve
CT	Computed tomography
FHVP	Free hepatic vein pressure
HCC	Hepatocellular carcinoma
HVPG	Hepatic vein pressure gradient
IVCP	Inferior vena cava pressures
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
TIPSS	Transjugular intrahepatic porto-systemic shunt
WHVP	Wedged hepatic vein pressure

Introduction

Portal hypertension is the central driver of complications in patients with chronic liver diseases and cirrhosis. While some manifestations of portal hypertension (e.g., ascites) are clinically apparent, others are more silent. For example, patients with varices remain asymptomatic until variceal bleeding develops. It is therefore important to identify patients with portal hypertension and offer endoscopic screening before bleeding occurs. Apart from cirrhotic complications, portal hypertension is strongly associated with mortality in patients with different liver conditions [1, 2].

While cirrhosis is the main cause of portal hypertension, the latter can arise in non-cirrhotic patients, a condition referred to as non-cirrhotic portal hypertension [3]. In

✉ Vincent Wai-Sun Wong
wongv@cuhk.edu.hk

[1] Department of Medicine and Therapeutics, 9/F, Clinical Sciences Building, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong, China

[2] State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, China

addition, not every cirrhotic patient would have portal hypertension. Among cirrhotic patients, the thickness of fibrous septa and the degree of hepatic architectural distortion affect the portal pressure and clinical outcomes. In this article, we focus on portal hypertension as a result of cirrhosis. We describe the gold standard of assessing portal hypertension and review the role of non-invasive tests of fibrosis in the setting of portal hypertension.

Clinical and radiological features of portal hypertension

Splenomegaly and the associated hypersplenism are features of portal hypertension. A splenic craniocaudal length of >13 cm indicates splenomegaly. However, splenomegaly is a non-specific sign of portal hypertension. Using color Doppler ultrasound, the presence of small reflective channels within the splenic parenchyma may suggest that splenomegaly is caused by portal hypertension rather than from other causes [4]. Another specific radiological finding is Gamna-Gandy bodies, which can be detected on MRI as tiny hypointense foci in the spleen, but are present in only 6–12% of portal hypertensive patients [5].

A recent study showed that the splenic arterial resistive index (SARI), which measures a change in splenic hemodynamics, is highly correlated with the HVPG, especially in patients without splenomegaly ($r = 0.830$) [6]. This test can possibly serve as a non-invasive method for diagnosing clinically significant portal hypertension in patients without an enlarged spleen.

The umbilical vein is often reopened in patients with portal hypertension, acting as a portosystemic shunt between the left portal vein and superficial epigastric veins. In fact, it is the most specific ultrasonographic sign of portal hypertension. Recanalization of the umbilical vein is detected in 26% of portal hypertensive patients by percutaneous transhepatic portography [7], but this invasive procedure has been largely replaced by ultrasonography. The presence of a recanalized umbilical vein can be recognized as a central sonolucent region of the falciform ligament on ultrasound, known as a 'bull's-eye' appearance [8]. It is present in 34% of patients detected by ultrasonography [9]. It has been suggested that the lumen of the umbilical vein should be more than 3 mm in diameter and extend for a considerable length away from the left portal vein for the diagnosis of portal hypertension [10]. Nevertheless, one study showed that the recanalised umbilical vein seen on ultrasound is in fact a paraumbilical vein by histological analysis on liver specimens [11]. While the actual recanalized structure is still a matter of debate, the presence of an enlarged vein in the falciform ligament on ultrasound should serve as a highly reliable sign of portal hypertension.

A dynamic CT scan performed with a bolus of contrast material can accurately detect most portosystemic collaterals in patients with portal hypertension [12]. It is superior to other modalities such as angiography, ultrasound and endoscopy in detecting varices, e.g., paraumbilical and abdominal wall varices, but its sensitivity is relatively low in detecting esophageal varices [12]. To this end, the PillCam ESO capsule endoscopy can detect esophageal varices and portal hypertensive gastropathy with a sensitivity and specificity of 80–90% [13, 14]. The high cost of capsule endoscopy makes it a less attractive option than the transient elastography-based assessment as recommended by the Baveno VI consensus guidelines.

Recently, the multiparametric MRI has been developed as a one-stop examination for hepatic steatosis, inflammation, fibrosis and iron content based on T1 and T2* imaging [15]. In a small prospective series, the liver inflammation fibrosis (LIF) score was associated with adverse clinical outcomes [16]. The same technique, when applied to the spleen, also correlated with the hepatic venous pressure gradient (HVPG).

Another recent multi-center study evaluated the use of shear-wave elastography of the liver and spleen in diagnosing patients with clinically significant portal hypertension [17]. Using a rule-in algorithm with both liver and spleen shear-wave elastography, the sensitivity and specificity in diagnosing clinically significant portal hypertension were 89.2 and 91.4%, respectively. This algorithm could save a proportion of patients from undergoing invasive HVPG measurements.

Hepatic venous pressure gradient

Measuring the HVPG is the gold standard for determining the portal pressure [18]. It is an invasive procedure that can diagnose portal hypertension with other clinical applications. Although the HVPG measures the portal pressure indirectly, it is highly consistent with direct measurements obtained through less invasive means [19–21]. The interpretation of HVPG readings is also highly reproducible [22].

The procedure

Under sedation and local anesthesia, a balloon-tipped catheter is passed through the right internal jugular vein (or femoral vein or antecubital vein) and into the hepatic vein under fluoroscopic guidance [18]. The HVPG is the free hepatic vein pressure (FHVP) subtracted from the wedged hepatic vein pressure (WHVP). The FHVP is measured in the hepatic vein 2–4 cm from the opening into the inferior vena cava. The inferior vena cava pressure (IVCP) is also measured below the diaphragm. Although FHVP and IVCP

are almost identical, the FHVP can be falsely elevated by 1–3 mmHg by inadequate placement of the catheter, hence underestimating the HVPG; a difference of less than 2 mmHg is considered acceptable. Some surgeons always prefer using IVCP to FHVP.

The WHVP is measured in the hepatic vein after balloon occlusion. Compared to a straight-end catheter, a balloon occludes a greater area of hepatic veins, thereby improving the reliability and reproducibility of measurements [23]. Contrast dye injected into the hepatic vein confirms the occlusion by the absence of reflux.

The pulse rate, blood pressure and oxygen saturation are monitored during the procedure. Complications are minimal: major complications include bleeding, hematoma or arterial-venous fistula formation at the puncture site, which can be reduced by ultrasound guidance. Passing the catheter through the right atrium might cause self-limiting arrhythmias. Patients allergic to contrast dyes can use carbon dioxide as a contrast agent. Those with severe thrombocytopenia or prolonged prothombin time should consider platelet or fresh frozen plasma transfusion before the procedure.

Interpretation of results

The WHVP is equivalent to the sinusoidal pressure, which is roughly equivalent to portal pressure. The FHVP serves as a reference zero; when subtracted from the WHVP, the HVPG gives an accurate depiction of the portal pressure. HVPG of 6–9 mmHg indicates preclinical portal hypertension, and a HVPG $\geq$10 mmHg is diagnostic of significant portal hypertension. However, in prehepatic or intrahepatic presinusoidal hypertension, the WHVP cannot reflect the raised portal pressure as any blood that flows to the hepatic veins travels via unaffected sinusoids, which have large capacity and low resistance. Therefore, these patients have normal WHVP and HVPG (Fig. 1).

Applications of HVPG

The HVPG independently predicts mortality among patients with cirrhosis [24, 25]. The 1-year mortality rate is 1.9% among those with HVPG $\leq$17 mmHg versus 16.2% in patients with HVPG >17 mmHg [25]. However, when combined with the Model for End-Stage Liver Disease (MELD) score, it does not significantly improve the stratification [24].

A reduction of baseline HVPG to $\leq$12 mmHg or by $\geq$20% by beta-blockers significantly reduces the risk of variceal bleeding and mortality [26, 27]. Furthermore, patients with an acute response to intravenous propranolol, i.e. reduction of HVPG to $\leq$12 mmHg or by $\geq$10% within 20 min, are less likely to have a first episode of variceal bleeding in the next 2 years (4 vs. 46%, $p < 0.001$). These

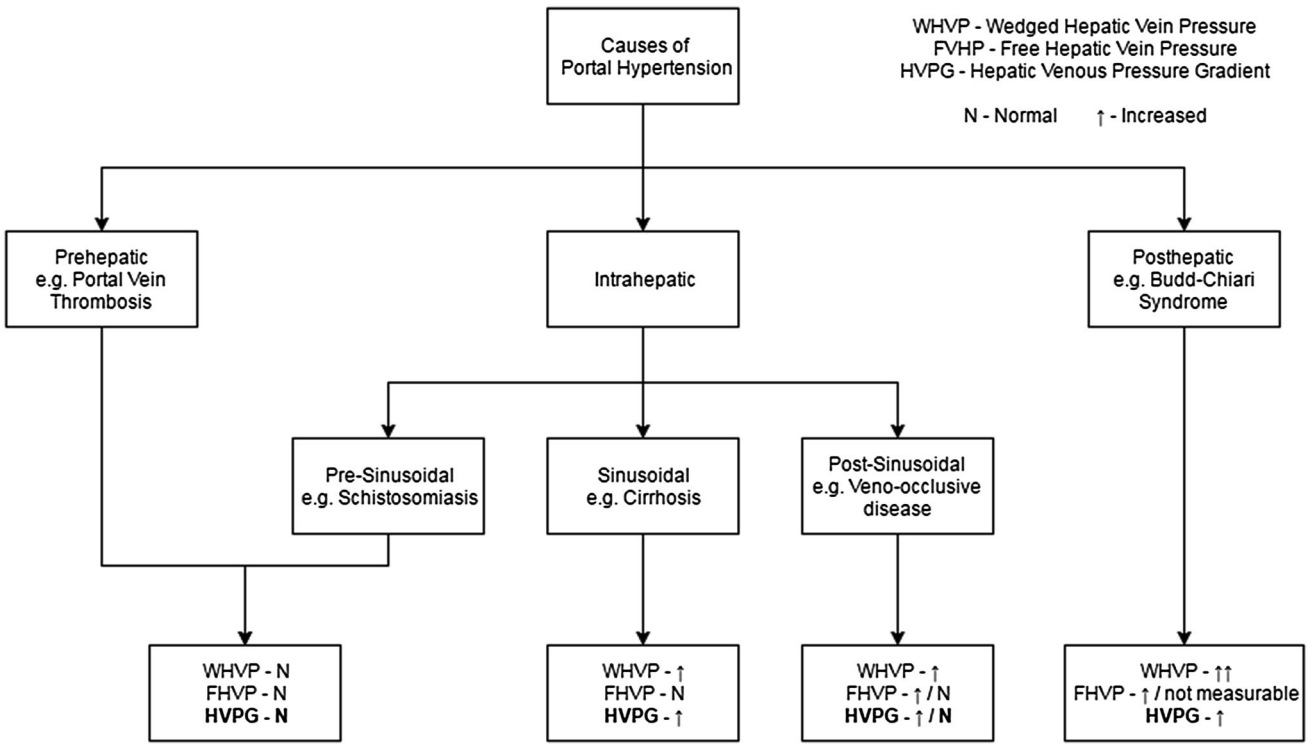

Fig. 1 Assessment of portal hypertension by hepatic vein pressures

patients are also likely to be chronic responders to the beta-blocker treatment [27].

The HVPG can also be used to monitor the response to transjugular intrahepatic porto-systemic shunt (TIPSS). After TIPSS, the HVPG should be maintained at 5–12 mmHg to reduce the risk of ascites and post-TIPSS encephalopathy [28]. Compared to traditional parameters, the HVPG better predicts the post-operative course after hepatectomy in patients with hepatocellular carcinoma. Those with a preoperative HVPG $\geq$10 mmHg are at greater risk of hepatic decompensation and mortality after hepatectomy [29].

Despite these applications, HVPG measurement is invasive and has to be carried out in facilities with fluoroscopy and expertise. It is therefore seldom performed outside a research setting except in some expert centers.

Serum markers for portal hypertension

Serum tests may also serve as surrogate non-invasive markers of portal hypertension. For instance, osteopontin, von Willebrand factor and the VITRO score have been evaluated in the context of portal hypertension.

Osteopontin is associated with pathological conditions including inflammation, angiogenesis and fibrosis [30]. In one study comprising 157 liver cirrhosis patients [31], osteopontin was showed to distinguish clinically significant portal hypertension (CSPH) (HVPG >10 mmHg) at 75% sensitivity and 63% specificity, and has an AUROC of 0.763 using a cut-off value of 80 ng/mL. The study also described the prognostic value of osteopontin as similar to HVPG.

Von Willebrand factor was also proposed to be a clinically significant non-invasive predictor of CSPH [32]. Using a cut-off value of $\geq$241%, the AUROC for detection of CSPH in compensated patients was 0.85, with the mortality prediction similar to the MELD score.

Recently, researchers have proposed using a new score, the VITRO score (Von Willebrand Factor Antigen/Thrombocyte Ratio), as a possible marker for detecting CSPH [33]. The AUROC was found to be 0.86, which was higher than that of the von Willebrand factor, and the APRI and ELF score, but lower than that of transient elastography.

Non-invasive tests of liver fibrosis

Serum tests

Despite histological examination being the gold standard of liver fibrosis assessment, the liver biopsy procedure carries notable drawbacks. Variable sampling error [34] and potential complications, including severe hemorrhage or even death [35], are known limitations of liver biopsy. The demand for non-invasive assessments of liver fibrosis has become increasingly relevant. The lookout for feasible methods that allow frequent testing and regular monitoring of liver fibrosis is also becoming the new trend. Among different non-invasive techniques, serum-based tests offer one of the alternative approaches which is cost–effective and widely available [36]. They are also extensively discussed in most recent guidelines of the European Association for the Study of the Liver [37].

An ideal fibrosis biomarker should be liver-specific, not influenced by alterations in liver, renal, or reticulo-endothelial function, measure one or more of the processes related to fibrosis, and easy to perform [38]. Serum biomarkers for liver fibrosis can be divided into Class I and Class II. Class I markers aim to directly measure the activity of fibrogenesis or fibrinolysis, while class II markers aim to measure surrogate parameters that correlate with fibrosis [39]. There has been no consensus in giving preference to markers from one of the classes. Class I or II markers may be used individually, but are very commonly used in combination, especially in commercialized tests.

Generic and proprietary serum tests of liver fibrosis

While most of the serum tests are widely available, some have been patented and commercialized. These became 'proprietary' tests as compared to the unpatented 'generic' tests. When using generic tests, results can often instantly be calculated from its required biomarker(s), and can be carried out by any laboratory. On the other hand, proprietary tests often require blood samples to be sent to respective corporations, and payments are required. The formulae of proprietary tests are also protected or undisclosed.

This article reviews 13 popular serum tests of liver fibrosis, including 8 generic tests and 5 proprietary tests (Table 1). Selected generic tests include platelet count, aspartate aminotransferase (AST)-to-platetlet ratio index (APRI), FIB-4, AST/alanine aminotransferase (ALT) ratio, hyaluronic acid, Lok index, Forns' index and Fibroindex. Selected proprietary tests include FibroMeter (Echosens, Paris, France), FibroTest/FibroSure (BioPredictive, Paris, France/LabCorp, Burlington, NC, USA), Hepascore (PathWest, University of Western Australia, Australia), FibroSpect (Prometheus, San Diego, CA, USA) and Enhanced Liver Fibrosis (Siemens Healthineers, Erlangen, Germany). Different studies often evaluated the same serum test using different cutoff thresholds (Table 2). Some studies aimed to detect F2-4 disease, and some aimed to detect F3-4 disease. While positive and negative predictive values are dependent on the disease prevalence; sensitivity and specificity are affected by the chosen cutoff

Table 1 Examples of serum tests of liver fibrosis

	Components
Generic tests	
Platelet count	Platelet count
AST-to-platetlet ratio index (APRI)	Platelet count, AST
FIB-4	Platelet count, AST, ALT, age
AST/ALT ratio	AST, ALT
Hyaluronic acid	Hyaluronic acid
Lok index	Platelet count, AST, ALT, INR
Forns' index	Platelet count, GGT, age, cholesterol
Fibroindex	Platelet count, AST, gamma globulin
Proprietary tests	
FibroMeter (Echosens, Paris, France)	α2-macroglobulin, ALT, AST, GGT, urea, prothrombin index, platelet count
FibroTest/FibroSure (BioPredictive, Paris, France/LabCorp, Burlington, NC, USA)	α2-macroglobulin, GGT, total bilirubin, haptoglobin, apolipoprotein A1
Hepascore (PathWest, University of Western Australia, Australia)	α2-macroglobulin, hyaluronic acid, GGT, total bilirubin, age, sex
FibroSpect (Prometheus, San Diego, CA, USA)	α2-macroglobulin, hyaluronic acid, tissue inhibitor of metalloproteinase-1
Enhanced Liver Fibrosis (ELF) (Siemens Healthineers, Erlangen, Germany)	Hyaluronic acid, tissue inhibitor of metalloproteinase-1, amino-terminal propeptide of type III collagen

ALT alanine aminotransferase, *AST* aspartate aminotransferase

value; the area under the receiver-operating characteristics curve (AUROC) provides better information on the accuracy of a dichotomous diagnostic test [40].

Some of the commonly used generic serum tests, such as APRI, have been more extensively studied. A meta-analysis evaluating APRI has included over 8000 patients from 40 studies [41]. The mean AUROC of APRI in detecting F2-4 disease was 0.77. Hyaluronic acid was suggested as the most validated single marker that most accurately predicts advanced fibrosis compared to other individual biomarkers [42]. It is a biomarker commonly included in many of the proprietary composite tests. It is a component of the extracellular matrix. It increases during collagen synthesis as a result of inflammation and decreased sinusoidal endothelial function, which reduces endothelial absorption and destruction of hyaluronic acid [43]. A Japanese study has reported the AUROC of hyaluronic acid to be 0.87 in detecting F2-4 disease and 0.89 in detecting F3-4 disease [43]. It was also suggested to use the high negative predictive value (98–100%) of hyaluronic acid at a high cut-off value to exclude advance fibrosis [44]. Another popular biomarker used in proprietary formulae is α2-macroglobulin. It is a wide-spectrum proteinase inhibitor which inhibits the catabolism of matrix proteins during fibrosis [45].

FibroTest (Biopredictive), also known as Fibrosure in the USA (LabCorp), was the first proprietary test calculated from combining several generic parameters [46]. It is one of the most extensively investigated proprietary serum tests of liver fibrosis [47]. Its AUROC has been reported by three studies [48–50], ranging from 0.69 to 0.81 in detecting F2-4 disease, and from 0.72 to 0.84 in detecting F3-4 disease. FibroMeter is another popular proprietary serum test of liver fibrosis, which has been claimed to surpass the accuracy of its peers [48, 51, 52]. In two studies, its AUROC was reported to range from 0.84 to 0.85 in detecting F2-4 disease and from 0.85 to 0.91 in detecting F3-4 disease [48, 49].

Assessment of varices

Many studies have been carried out in search of predictive markers related to varices [53–55]. A number of serum tests of liver fibrosis have been correlated with esophageal varices, variceal bleeding or mortality. There is considerable interest in developing accurate screening tests to detect or predict variceal complications [56], as more may benefit from primary prophylaxis and may reduce complications or healthcare burden from frequent endoscopy. A large retrospective cohort study has reported that platelet count, APRI, AST/ALT ratio and Lok index were useful in predicting the presence of varices prior to endoscopy, in differentiating patients with and without varices, and in predicting the likelihood of variceal bleeding [57].

Another study also provided cutoff values in seven generic serum tests to potentially predict the presence of large varices [58]. It also evaluated their AUROCs in the prediction, which range from 0.55 to 0.71. FibroTest has

Table 2 Performance of serum tests of fibrosis

Author	Etiology	*n*	Test (s)	Cutoff	Fibrosis stage detection	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Generic tests										
Pohl [103]	Chronic hepatitis C	211	AST/ALT ratio	1	F3-4		47.1	81.6	43.2	83.8
			Platelet count	150,000/mm^3	F3-4		41.2	99.1	93.1	85.0
Lin [41]	Hepatitis C (± human immunodeficiency virus)	8739 (from 40 studies)	APRI	0.7	F2-4	0.77	77	72	70	79
Vallet-Pichard [104]	Chronic hepatitis C	592	FIB-4	3.25	F3-4	0.85	37.6	98.2	82.1	
Suzuki [43]	NAFLD	79	Hyaluronic acid		F2-4	0.87				
				46.1 ng/ml	F3-4	0.89	85.0	79.7	51.1	95.5
Sirli [105]	Chronic hepatitis C	150	Forn's index	4.57	F2-4	0.748	71.6	68.5	95	24
			Lok index	0.17	F2-4	0.701	57.5	81.2	96.2	18.6
			Platelet count	176,000/mm^3	F2-4	0.732	37.3	100	100	16
			APRI	0.52	F2-4	0.766	70	81	97	24.5
			FIB-4	2.1365	F2-4	0.686	35.8	100	100	15.7
Koda [106]	Chronic hepatitis C	120	APRI	0.85	F2-4	0.82	31.6	91.7	79.2	57.2
			Forn's index	8.7	F2-4	0.84	21.7	98.3	92.9	55.7
			Fibroindex	2.25	F2-4	0.86	30.0	96.7	90.0	58.0
Proprietary tests										
Calès [48]	Chronic hepatitis C	1056	FibroMeter		F3-4	0.885	80.5	84.1	86.3	77.6
			FibroTest		F3-4	0.837				
			Hepascore		F3-4	0.834				
Leroy [49]	Chronic hepatitis B	255	FibroTest	0.48	F3-4	0.82	74	79	50	90
				0.38	F2-4	0.77	65	78	70	73
			FibroMeter	0.69	F3-4	0.85	66	88	60	90
				0.47	F2-4	0.84	73	80	77	77
			Hepascore	0.42	F3-4	0.82	75	71	95	90
				0.32	F2-4	0.75	71	69	69	71
	Chronic hepatitis C	255	FibroTest	0.52	F3-4	0.84	80	82	55	94
				0.40	F2-4	0.81	66	82	78	73
			FibroMeter	0.72	F3-4	0.91	90	85	60	97
				0.64	F2-4	0.85	66	89	84	74
			Hepascore	0.47	F3-4	0.86	79	85	53	95
				0.34	F2-4	0.77	74	64	69	69
Zaman [107]	Chronic hepatitis C	108	FIBROSpect II	42	F2-4	0.826	71.8	73.9	60.9	82.3
Friedrich-Rust [50]	Mixed	74	FibroTest	0.32	F2-4	0.69	57	60	74	42
				0.59	F3-4	0.72	39	88	71	67
			Enhanced Liver Fibrosis	9.78	F2-4	0.78	78	80	88	65
				10.22	F3-4	0.79	74	70	64	79

also been evaluated as a possible non-invasive aid in the detection of large esophageal varices [59], and the study suggested that using a high threshold may rule out the presence of large esophageal varices. Some serum tests have been correlated as prognostic markers of mortality, including FibroTest and APRI [60, 61].

However, there are also studies pointing out the low predictive values of using individual serum markers, such as APRI, to sufficiently predict varices itself. Another study evaluating four class I serum markers, including hyaluronic acid, has suggested their correlation in predicting the presence of varices, but they are not reliable enough for assessing the risk of variceal bleeding [62].

In portal hypertensive patients, non-selective beta-blockers and TIPSS are common treatments [63]. The discovery of non-invasive tests which can monitor changes induced by these treatments of portal hypertension can provide useful prognostic information. While the serum markers discussed here were initially for detecting liver fibrosis and not portal pressure, FibroTest was reported as having significant correlation with HVPG values [60]. Another study quoted the AUROC of FibroTest in detecting severe portal hypertension as 0.79 [64].

Non-invasive measurements of liver stiffness

The non-invasive measurements of liver stiffness or elasticity include transient elastography, shear-wave elastography, acoustic radiation force impulse and magnetic resonance elastography [65]. The first three are ultrasound-based, while magnetic resonance elastography (MRE) utilizes magnetic resonance imaging (MRI). It is possible to examine the liver parenchyma and perform HCC surveillance in the same session with the latter three techniques; transient elastography is only equipped with M mode ultrasound and cannot be used for structural examination. MRE has the advantage of examining the entire liver and not being affected by obesity. It is also more accurate in delineating milder degrees of liver fibrosis. However, existing data suggest that the ultrasound-based measurements are probably as good as MRE in detecting cirrhosis, with all techniques typically having AUROCs of over 0.90 [66–69]. The availability and cost are the major hurdles preventing broader application of MRE.

Liver stiffness or elasticity measurement is affected by high alanine aminotransferase level [70], congestive heart failure [71], biliary obstruction [72], food intake [73], amyloidosis [74], extreme body size [75], and, to a lesser extent, hepatic steatosis [76, 77]. Although most studies on the confounders of liver stiffness measurement were performed using transient elastography, the physical property likely applies to the other techniques as well. Caution should be exercised when interpreting liver stiffness values in such patients.

Liver stiffness has been correlated with HVPG. In a cross-sectional study of 150 patients undergoing liver biopsy, HVPG and transient elastography, liver stiffness had an AUROC of 0.95 in detecting significant portal hypertension (HVPG $\geq$10 mmHg) with an optimal cutoff of 21 kPa [78]. Likewise, patients with portal hypertension have increased splenic vein pressure, splenomegaly and high spleen stiffness [79, 80]. Nevertheless, transient elastography measures a core of tissue that is 4 cm in length and is not designed for measuring spleen stiffness, particularly in patients without splenomegaly. To this end, acoustic radiation force impulse has also been used to measure spleen stiffness, which correlated with the presence of esophageal varices [81]. This technique captures small regions of interest and can handle spleens of different sizes.

Other than correlation with HVPG, multiple studies have confirmed that liver and/or spleen stiffness can be used to predict the presence of all varices or large varices [82–86]. Importantly, liver stiffness is correlated with subsequent variceal bleeding and other complications of portal hypertension [87]. Based on these observations, the latest Baveno VI consensus guidelines recommend the use of liver stiffness and platelet count to select cirrhotic patients for varices screening [88]. For patients with liver stiffness <20 kPa and normal platelet count, the risk of having large varices or variceal bleeding is minimal, and the non-invasive tests may be repeated annually (Fig. 2) [89]. Otherwise, upper gastrointestinal endoscopy should be performed for formal screening.

Two related questions deserve further discussion. First, large varices and/or variceal bleeding may be treated with non-selective beta-blockers and TIPSS. While the HVPG response to these treatments can be used to predict who will develop variceal bleeding, few centers can provide HVPG monitoring. It is thus of interest to see if elastography may serve this purpose. Theoretically, a reduction in portal blood flow should result in decreased liver and

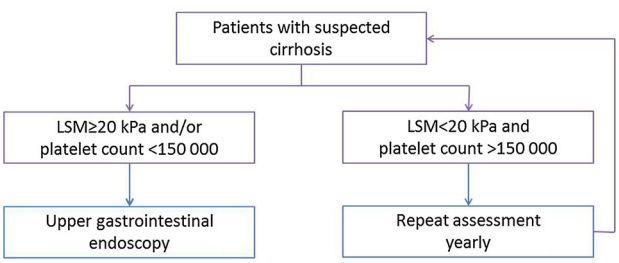

Fig. 2 Baveno VI consensus on the selection of patients for varices screening based on liver stiffness measurement and platelet count. *LSM* liver stiffness measurement

spleen stiffness. However, liver stiffness is not expected to normalize because neither non-selective beta-blockers nor TIPSS affect liver fibrosis. In a small study of 10 patients, the spleen stiffness by acoustic radiation force impulse decreased from 3.65 to 3.27 m/s after TIPSS, but there was no significant change in liver stiffness [90].

Another question is whether annual examination according to the Baveno VI consensus is needed in patients whose liver disease is quiescent [88]. This question has become highly relevant now that we can suppress hepatitis B virus with antiviral drugs and cure chronic hepatitis C virus infection with direct-acting antivirals in almost all patients. Successful treatment of chronic viral hepatitis can prevent disease progression and reverse cirrhosis in the majority of patients [91–93]. Incident varices and variceal bleeding are also rare in patients on long-term antiviral therapy for chronic hepatitis B [94]. Therefore, it is likely that patients with quiescent liver diseases may not require further liver stiffness measurement once the value drops below a certain threshold. The notion should be explored in prospective studies.

Investigations for the cause of portal hypertension

Cirrhosis is the end result of all causes of chronic liver disease and is the most common cause of portal hypertension. It is important to identify the underlying cause of liver injury, not only to direct management decisions but also because it may have other implications such as family screening in cases of hereditary hemochromatosis and Wilson's Disease. The etiology of cirrhosis can usually be made from patient history and serological testing.

Radiological assessment

Cirrhosis can lead to hemodynamic changes such as blood flow velocity in the portal and systemic circulation. Altered portal blood flow direction, velocity, stigmata of portal hypertension (e.g., splenomegaly,) portal vein thrombosis and evidence of portosystemic shunting can be detected using ultrasonography. Hemodynamic changes can directly influence the severity of portal hypertension. It may be detected by Doppler ultrasound even in those with normal B-mode findings and before the appearance of varices and splenomegaly [95]. A portal blood flow velocity of <15 cm/s had a sensitivity and specificity of 88 and 96%, respectively, for the detection of portal hypertension [96]. In addition, computed tomography (CT) and MRI can provide a detailed mapping of the portal venous system prior to TIPSS procedure and to detect radiological signs of portal hypertension.

Portal venography has been the standard method of mapping collateral vessels for many years and involved puncture of a branch artery which feeds the gastrointestinal system, such as the celiac, mesenteric, or splenic artery [97]. Because of the invasive nature of the procedure, venography is now generally performed using CT or MRI (with contrast enhancement), which has a high resolution and allows 3D-reconstruction of the portal venous system.

Carbon dioxide has been found in some studies to be better than iodinated-contrast for wedged hepatic venography and for visualizing the portal vein before TIPSS [98]. In cirrhotic patients, visualization of the portal vein and branches by carbon dioxide-occluded venography was achieved in 85% of patients versus 35% with iodinated-contrast venography.

Non-cirrhotic portal hypertension

Non-cirrhotic portal hypertension is usually caused by diseases that lead to changes in the hepatic vasculature, with preserved hepatic synthetic function and near-normal HVPG [99]. The etiology of portal hypertension is generally classified by the site of resistance to blood flow: pre-hepatic, hepatic, and post-hepatic. Hepatic causes can be further divided into pre-sinusoidal, sinusoidal and post-sinusoidal (Table 3).

Portal vein thrombosis can be classified as acute or chronic, and partially or completely occlusive. The most common causes of portal vein thrombosis are secondary including cirrhosis, hypercoagulable states (e.g., antiphospholipid syndrome, malignancy), abdominal trauma, surgery or infection.

Parasitic infestations such as schistosomiasis can cause extensive periportal fibrosis but retained hepatic function [100]. It is one of the leading causes of non-cirrhotic portal hypertension, particularly in low-income countries in southeast Asia and central Africa. Diagnosis can be made by demonstration of eggs in urine, feces, or tissue biopsies.

Acquired forms of prothrombotic states, e.g., hematological malignancies and myeloproliferative disorders, can be the underlying cause of venous occlusion. In a recent meta-analysis, the prevalence of V617F mutation of Janus kinase 2, which is associated with various myeloproliferative disorders, can be found in 27.7% of patients with portal vein thrombosis [101].

Idiopathic non-cirrhotic portal hypertension is rare in western countries and occurs mainly in India and Japan [102]. Proposed etiologies include childhood infections and prothrombotic states.

Conclusions

The diagnosis of portal hypertension in patients with chronic liver disease has important prognostic and management implications. HVPG, while invasive, will remain an important research tool for the pathophysiology of

Table 3 Causes of non-cirrhotic portal hypertension

Pre-hepatic
Portal vein thrombosis
Splanchnic vein thrombosis
Storage diseases: Gaucher's Disease
Lymphoma, myeloproliferative disorders
Hepatic
Pre-sinusoidal
Sarcoidosis
Schistosomiasis
Primary biliary cholangitis
Primary sclerosing cholangitis
Splanchnic arterio-venous fistula
Congenital hepatic fibrosis
Idiopathic non-cirrhotic portal hypertension
Toxins: arsenic, copper, vinyl chloride
Sinusoidal
Drugs: e.g., methotrexate, amiodarone
Infiltrative diseases: Amyloidosis, sarcoidosis
Vitamin A intoxication
Post-sinusoidal:
Veno-occlusive disease
Budd Chiari Syndrome
Post-hepatic
Inferior vena cava obstruction
Constrictive pericarditis
Right-sided cardiac failure

portal hypertension and may be used in specific situations at expert centers. The Baveno VI criteria based on liver stiffness measurement and platelet count are robust and may be applied clinically to select patients for varices screening. Further studies are required to determine the best method to monitor response to treatment in patients with portal hypertension.

Compliance with ethical standards

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Conflict of interest Vincent Wong has served as an advisory board member for Perspectum Diagnostics and a speaker for Echosens. The other authors report no conflict of interest.

Ethical approval Not applicable because this is a review article.

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