DOI: https://doi.org/10.22516/25007440.692

Review article

Diagnostic methods of portal hypertension

Octavio Muñoz,[1*] José Ferrusquía-Acosta,[2] Laura M. Serna-Patiño,[3] Andrés Cárdenas.[4]

OPEN ACCESS

Citation:
Muñoz O, Ferrusquía-Acosta J, Serna-Patiño LM, Cárdenas A. Diagnostic methods of portal hypertension. Rev Colomb Gastroenterol. 2021;36(2):218-226. https://doi.org/10.22516/25007440.692

[1] Internal Medicine, Hepatology and Liver Transplantation, Hospital Pablo Tobón Uribe, Universidad de Antioquia. Medellín, Colombia.
[2] Unitat d'Hemodinàmica Hepàtica. Institut Clínic de Digestives i Metabòliques (ICMDM), Hospital Clínic de Barcelona. Barcelona, Spain.
[3] Hospitalization Unit, Hospital Pablo Tobón Uribe. Medellín, Colombia.
[4] GI/LiverUnit, ICMDM, Hospital Clínic de Barcelona. Associate Professor, Universidad de Barcelona. Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS) and Center for Research in Liver and Digestive Network (CIBERehd), Spain. Barcelona, Spain.

***Correspondence:** Octavio Muñoz.
octavio.g.munoz@gmail.com

Received: 28/10/20
Accepted: 28/04/21

Abstract

Portal hypertension is characterized by an increase in the portal pressure gradient, which is defined as the difference between the portal venous pressure and the pressure within the inferior vena cava. Such a pressure depends on venous flow and vascular resistance. In patients with cirrhosis, both variables are altered, initially due to fibrosis-dependent structural injury and regeneration nodules, and subsequently by vascular dynamic changes that cause intrahepatic vasoconstriction and splanchnic vasodilation, which explains the systemic manifestations of cirrhosis. The importance of portal hypertension lies in the frequency and severity of associated complications, especially variceal hemorrhage, but also ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy. The objective of this article is to carry out an updated review on the use of invasive and non-invasive diagnostic tests available for the study of portal hypertension and their application in clinical practice.

Keywords

Portal hypertension; Portal system; Hepatic cirrosis.

INTRODUCTION

Portal hypertension is a syndrome characterized by an increase in the portal pressure gradient (PPG), defined as the difference in pressure between the portal vein and the inferior vena cava. Normal PPG values range from 1 to 5 mm Hg, while values ≥ 6 mm Hg indicate portal hypertension[1,2]. Cirrhosis is the most common cause of portal hypertension and accounts for 90 % of cases in the United States and Europe. Less than 10% of cases have a non-cirrhotic origin. The most relevant disorders in this group include vascular diseases such as portal thrombosis, Budd-Chiari syndrome, portosinusoidal vascular liver disease, right heart failure, schistosomiasis, among others[3].

Measurement of the hepatic venous pressure gradient (HVPG) is considered the gold standard for diagnosis[4]. However, the presence of clinical manifestations in patients with risk factors may be sufficient to make the diagnosis[5]. Portal hypertension is clinically relevant when the HVPG exceeds the critical level of 10 mm Hg. At this point changes occur in the extrahepatic vascular beds that lead to the formation of portosystemic collateral pathways and splanchnic

vasodilatation, which contribute to the progressive increase of portal pressure and, finally, to its clinical expression (development of esophageal varices, ascites, encephalopathy and hepatocarcinoma).[6] This disorder is silent in the early stages, when HVPG is still in the range of 6-9 mm Hg.

The relevance of portal hypertension lies in the frequency and severity of associated complications. Its main form of presentation is variceal hemorrhage[7], which also includes entities such as hypertensive gastropathy, spontaneous bacterial peritonitis, hepatorenal and hepatopulmonary syndrome, hepatic encephalopathy, among others, all of them associated with increased mortality and the need for liver transplantation in patients with cirrhosis[8]. The severity of portal hypertension is directly related to the likelihood of developing this type of complication and is an independent prognostic indicator[9]. For example, an HVPG > 12 mm Hg increases the risk of esophageal variceal bleeding. Increased mortality has been observed when there is an increase in HVPG above 16 mm Hg and in variceal bleeding, and a HVPG > 20 mm Hg predicts the possibility of failure to control bleeding and decreases survival at 1 year (**Figure 1**)[1,10]. When cirrhosis is diagnosed, esophageal varices occur in 40% of compensated patients and 60 % of patients with ascites; additionally, up to 30 % to 50 % of patients with acute bleeding may die within 6 weeks[11,12]. Thus, achieving reductions in portal pressure decreases the frequency of decompensation and improves survival.

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION

Portal pressure, as in any other vascular bed, is the product of venous flow times vascular resistance; in fact, the development of portal hypertension in chronic liver diseases is the result of the supraphysiological elevation of both parameters[13].

Increased portal flow and hyperdynamic circulation

Patients with portal hypertension present with a peripheral vasodilatation phenomenon, which is dependent on an imbalance in vasodilator synthesis due to endothelial dysfunction in the hepatic microvasculature —such as prostaglandins, nitric oxide and glucagon— and an increase in the production of vasoconstrictors (endothelin, norepinephrine, thromboxane A_2, angiotensin II), all of which is related to the dynamic component of liver resistance[14,15]. The increase in portal pressure sends signals to the splanchnic system to promote vasodilatation and increase portal flow (nitric oxide is recognized as one of the main mediators of splanchnic vasodilatation and angiogenesis). Another consequence of the splanchnic vasodilation is the shunting of cardiac output from the systemic circulation to the mesentery, which results in systemic hypotension and relative renal hypoperfusion[16]. This decrease in central blood volume leads to activation of compensating mechanisms such as the renin-angiotensin-aldosterone system, the sym-

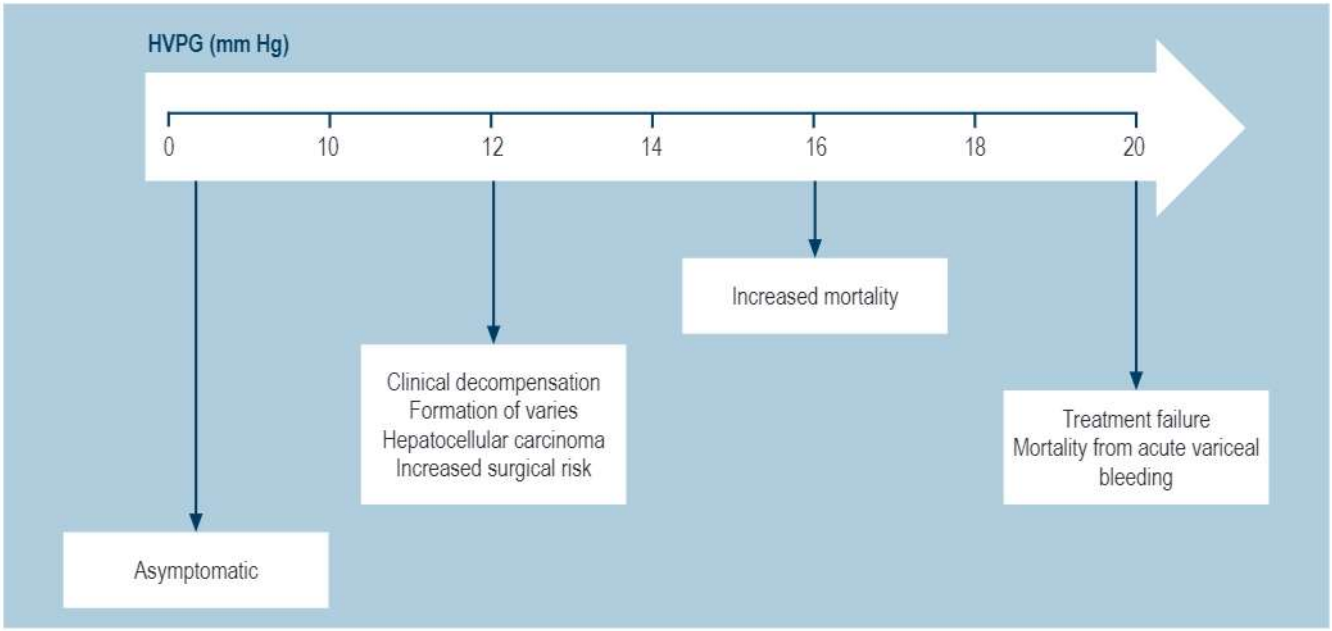

Figure 1. Risks associated with increased hepatic venous pressure gradients.

pathetic nervous system and vasopressin, which lead to sodium and water retention, increasing plasma volume[17]. Hyperdynamic circulation driven by the activation of the β-adrenergic system is another form of compensatory response to systemic hypotension.

Increase in vascular resistance

The liver is a low resistance system and its microcirculation is unusual in that the ratio of pre- and post-sinusoidal resistance is 49:1, unlike other tissues such as skeletal muscles, whose ratio is 4:1. The hepatic endothelium, which is discontinuous, uses this characteristic as a protective mechanism[17]. Sites of increased resistance may be prehepatic, hepatic or posthepatic, and portal hypertension syndromes have been classified in this way. Traditionally, these phenomena have been explained by mechanical involvement of portal venous flow and distortion of vascular anatomy caused by thrombosis, fibrosis, and nodules.

These mechanisms explain, in part, pre- and posthepatic involvement, but in intrahepaticinvolvement, and especially in the case of cirrhosis, the sinusoidal endothelial cells become dysfunctional, thus acquiring a vasoconstrictor phenotype. This resulting imbalance promotes contraction of hepatic stellate cells, myofibroblasts and vascular smooth muscle cells, resulting in increased hepatic vascular tone and portal pressure[8]. As a consequence of the activation of stellate cells, there is a profound alteration of the sinusoidal structure, characterized by the loss of its fenestrations, which impairs the natural dispersion of the hydrostatic pressures in normal sinusoids[18].

In summary, the formation of scar tissue and regenerative nodules that occurs in patients with cirrhosis (structural changes) leads to an increase in intrahepatic vascular resistance and, consequently, portal pressure. These structural changes can be seen in the early stages of portal hypertension related to cirrhosis, followed by compensatory splanchnic vasodilatation, which in turn results in an increase in portal blood flow, further worsening portal pressure (**Figure 2**)[19,20].

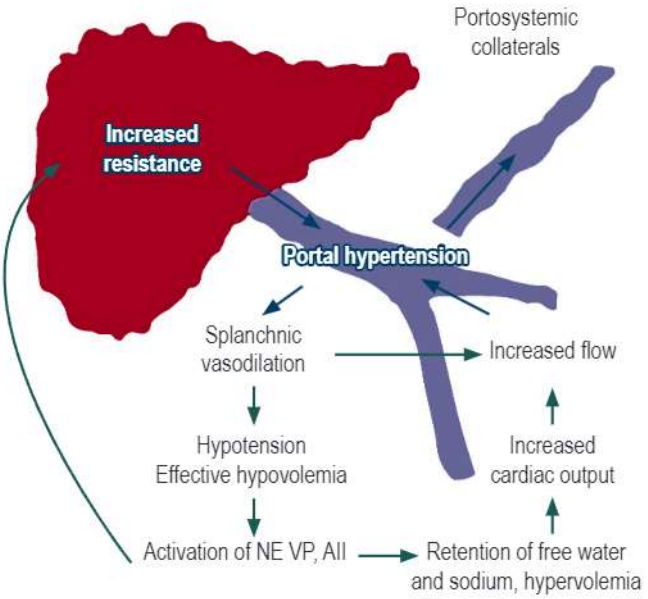

Figure 2. Pathophysiology of portal hypertension. AII: Angiotentesin; NE: Norepinephrine; VP: Vasopressin.

DIAGNOSIS OF PORTAL HYPERTENSION

Although the definitive diagnosis of portal hypertension requires the use of invasive methods, an accurate diagnosis could be made based on the presence of complications associated with portal hypertension and the exclusion of other potential causes. Because cirrhosis is the leading cause of portal hypertension, invasive assessment of portal blood pressure is rarely needed in conventional clinical practice for diagnostic purposes. However, invasive measurements are useful for assessing the severity of portal hypertension, for prognostic purposes, or when the initial diagnosis is uncertain[21].

Patients with portal hypertension usually present with general signs and symptoms of chronic liver disease, manifested by jaundice, ascites, spider nevus, palmar erythema, testicular atrophy, gynecomastia, parotid hypertrophy, and muscle atrophy. Additionally, they may present with signs of hepatic encephalopathy that may be as subtle as lack of concentration and irritability, or as serious as stupor or coma.

The portal system has collaterals that intercommunicate with the systemic circulation in an attempt to decompress it. These collateral venous systems are part of portal hypertension syndrome. The most clinically important collaterals are esophageal and gastric venous dilatations, since they can bleed acutely[22]. The umbilical vein, originating from the left portal vein, may be dilated by intrahepatic causes that are manifested by venous dilatations in the anterior abdominal wall. In the rectum, venous systems of collateral bypass of the inferior mesenteric vein may be seen as rectal varices or hemorrhoidal dilations, which are nonspecific. Retroperitoneal collateral circulation cannot be clinically evaluated, and the presence of dorsal venous dilatations is rare and is most often associated with obstruction of the inferior vena cava. Although splenomegaly is common in portal hypertension syndromes, there is no proportionality between spleen size and pressure in the portal system[20].

INVASIVE METHODS FOR EVALUATING PORTAL HYPERTENSION

Hepatic venous pressure gradient

On the one hand, the hepatic venous pressure gradient has been proven to be a safe, accurate and reproducible technique to quantitatively estimate portal pressure, in addition to being useful for assessing response to pharmacological therapy; it may have prognostic significance in patients with cirrhosis. Due to its scarce availability, routine use in clinical practice is limited to specialized centers. The procedure involves inserting a catheter through the internal jugular, ulnar, cubital, or femoral vein, with fluoroscopic guidance, which is advanced into one of the suprahepatic veins. Once the position is reached, the balloon is inflated to occlude the vein and measure wedged hepatic venous pressure (WHVP). On the other hand, free hepatic venous pressure (FHVP) is measured at a distance of 2-3 cm from the hepatic vein orifice. The difference between these 2 pressures is equal to HVPG[23]. The normal value of HVPG ranges from 2 to 5 mm Hg, and if it is above 5 mm Hg, it is defined as *portal hypertension*. Clinically significant portal hypertension is diagnosed when HVPG is ≥ 10 mm Hg. In patients with portal hypertension of unknown cause, an increase in HVPG due to increased WHVP indicates elevated sinusoidal pressure, which is most often associated with cirrhosis. A normal HVPG value, with normal WHVP and FHVP, is typical of presinusoidal portal hypertension, whereas, in posthepatic portal hypertension, there is an increase in WHVP and FHVP[22].

Pharmacological or mechanical reduction of HVPG using a transjugular intrahepatic portosystemic shunt (TIPS) reduces the development of decompensation and improves survival[24]. Vasoactive drugs, especially nonselective β-blockers, and nitrates, reduce HVPG in patients with cirrhosis. A good hemodynamic response is defined as a reduction in HVPG < 12 mm Hg or a decrease of at least 20 % with respect to the baseline value, indicating an improvement with the treatment of liver disease[25]. When the reduction goal is reached, the risk of variceal bleeding, ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome is drastically reduced, and this improves survival. Failure to achieve these reduction goals is the strongest independent predictor of variceal bleeding or rebleeding[24,26].

Despite being considered an invasive procedure, it is a very safe and well-tolerated technique for patients. Most complications are associated with venous puncture and are, therefore, limited to the puncture site (pain, hematoma, seroma).

Endoscopic assessment

Upper GI tract endoscopy is an important tool in the evaluation of portal hypertension and has been classically recommended to all patients with cirrhosis as a screening tool to document the presence of varicose veins (27). Identifying and treating patients with high-risk varices improves clinical outcomes. It is estimated that 30 % of patients with compensated cirrhosis and 60 % of patients with decompensated cirrhosis have varicose veins at diagnosis. Each episode of variceal bleeding is associated with a 20% increase in mortality, plus a 70% risk of developing recurrence of bleeding within a year after presenting the initial event[3].

Endoscopy has other advantages: it evaluates the presence and characteristics of gastroesophageal varices, classifies them by size —small (< 5 mm) or large (> 5 mm)—, and reports on the appearance of the variceal wall (red patches and cherry red spots in the variceal wall), which, together with the Child-Pugh classification, constitute a prognostic index of bleeding (**Figure 3**). One of the most complete systems is the Japanese system, which evaluates 6 characteristics: location, shape/size, color, red patches, evidence of bleeding, and mucosal characteristics[27]. Endoscopic changes are not only limited to the esophagus, but it is also common to find vascular changes in the stomach due to the presence of gastric varices and hypertensive gastropathy[28]. Gastric varices are less prevalent than esophageal varices and are the etiology of 5 %-10 % of cases of gastrointestinal bleeding in patients with cirrhosis. Hypertensive portal gastropathy is another common finding in patients with cirrhosis, with prevalences ranging from 11 % to 80 %, while gastric antral vascular ectasia may occur in 30 % of patients with portal hypertension[1,27]. The colonic mucosa also has vascular changes in patients with portal hypertension, characterized by hemorrhoids, anorectal varices and colopathy due to the tortuous and irregular capillaries associated with lamina propria edema and chronic inflammatory signs. Moreover, with the use of capsule endoscopy, vascular alterations in the small intestine have been identified, which define the term portal *hypertensive enteropathy*[29].

Endoscopic ultrasound (EUS)

EUS allows for the early detection of changes in collateral circulation in patients with portal hypertension. It also allows evaluating the intrinsic drainage of the esophagus, which is seen as visible varicose veins in traditional endoscopy, as well as identifying extrinsic veins along the gastroesophageal junction, including periesophageal and

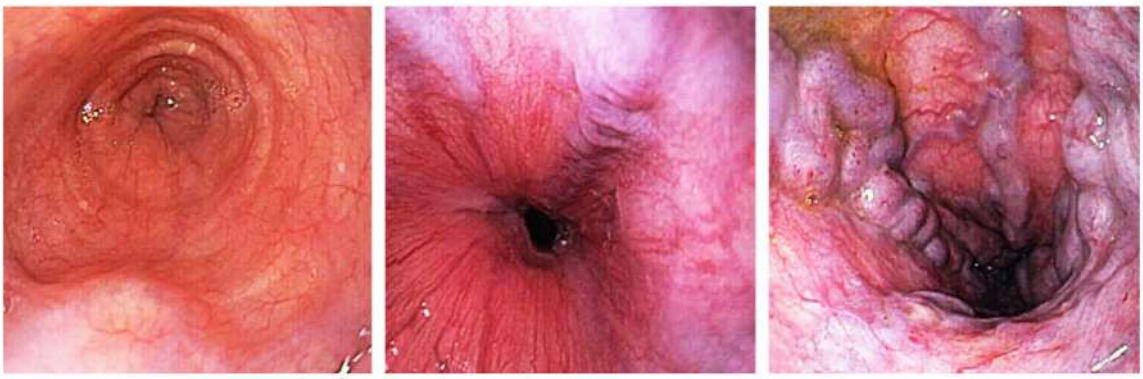

Figure 3. Classification of esophageal varices.

paraesophageal varices[30]. Thus, this method allows the visualization of esophageal and gastric varices, venous collaterals, the portal system, the azygos vein, and the thoracic duct[31,32]. Additionally, this system allows the assessment of perforating esophageal veins and has shown that patients with large paraesophageal varices have a higher risk of recurrence and bleeding after therapy[33].

The advantage of EUS over traditional endoscopy is its capacity to identify esophageal varices at increased risk of bleeding. Endosonography allows measuring the size of varices and visualizing red spots that may look like saccular aneurysm projections on the surface of the variceal surface, representing focal wall weakness with increased risk of rupture. Studies have demonstrated the accuracy of EUS to determine the radius of the varices and wall thickness, which may be useful as a minimally invasive way to predict intravariceal pressure. Varicose wall stress is directly proportional to varicose vein pressure and radius and inversely proportional to varicose vein wall thickness, while the risk of rupture is directly related to wall stress. Despite all these advantages, its use in clinical practice is not common[31].

NONINVASIVE METHODS FOR EVALUATING PORTAL HYPERTENSION

Risks arising from invasive procedures, the use of sedation or anesthesia, and the possibility of adverse effects or complications have created the need to investigate the use of noninvasive tests for the study of portal hypertension.

Serological markers and laboratory tests

Platelet count is used worldwide as an indirect sign of portal hypertension. Moderate thrombocytopenia occurs in 10%-15% of patients with liver cirrhosis, and a count < 150 000 cells has a positive predictive value of only 15.1 % for identifying medium and large esophageal varices[34]. Furthermore, changes in platelet count in patients with chronic liver disease are not directly related to the hepatic venous pressure gradient and are affected by splenic sequestration, bone marrow suppression, and depressed thrombopoietin levels[35]. When using the platelet count to spleen diameter ratio with a cutoff point < 909, performance to rule out the presence of significant portal hypertension is improved[36]. Laboratory tests such as albumin, bilirubin, international normalized index (INR) or its combination in the Child-Pugh score correlate with HVPG and the prevalence and grade of esophageal varices in patients with cirrhosis[1].

There are other indirect markers of liver fibrosis that have been associated with the degree of portal hypertension, including alanine-aminotransferase/aspartate-aminotransferase (ALT/AST), AST to platelet ratio index, FIB-4 index, and the Forns Index, and Lok Score. Despite its usefulness in assessing fibrosis, their diagnostic performance in the case of portal hypertension is low[37]. More recently, other direct biomarkers such as laminin, hyaluronic acid, type III procollagen, von Willebrand factor, and soluble CD163 have been tried, but the results are inconsistent and their clinical utility remains uncertain[38].

Abdominal ultrasound

Many researchers have made efforts to diagnose portal hypertension using Doppler ultrasound since it is safe, inexpensive, and can assess indirect signs of liver disease. Doppler ultrasound studies are useful for assessing portal vein patency, determining direction, and measuring blood flow through portal and splanchnic beds, as well as allowing the visualization of morphologic abnormalities associated with portal

hypertension such as dilation of the portal venous system, splenomegaly and presence of portosystemic collaterals[39]. The hemodynamic parameters studied include splanchnic flow diameters and velocity, variation of vascular caliber with respiration, portal venous congestion index, pulse rate, and portal vascular resistance[27]. As in other areas of diagnostic medicine, EUS has the disadvantage of subjectivity because it is an operator-dependent test; moreover, diagnostic accuracy depends on technical factors and intra-observer and inter-observer variability is high[40].

Computed tomography (CT) and magnetic resonance imaging (MRI)

Liver architecture, perfusion, and blood flow in the splenic artery determined by MRI have been shown to correlate with portal pressure. A study in patients with cirrhosis found that hepatic longitudinal relaxation time and splenic artery velocity correlated significantly with HVPG[4]. With these methods, portal vasculature can be visualized and assessed in a qualitative manner with great accuracy. Increased image definition, three-dimensional reconstruction techniques and multidetector CT scanners have allowed more accurate assessment of the portal system and its collaterals in order to define their patency and signs of portal hypertension. In CT, collateral vessels and varicose veins are commonly seen in the esophagus, hepatogastric ligament, and splenic hilum; additionally, the umbilical vein can be seen recanalized[41].

Magnetic resonance imaging allows the quantification of portal vein and azygos vein flow as indirect signs for portal hypertension assessment and, as in CT, initial findings take into account portal vein dilatation and, subsequently, the definition of portosystemic collaterals[42]. Although these imaging techniques allow the identification of specific signs of portal hypertension (collateral circulation), they do not quantitatively assess portal hypertension and are therefore unable to evaluate its dynamic changes.

The usefulness of these 2 imaging techniques is representative for patients requiring a detailed assessment of the portal venous system, such as the assessment of the extent of thrombosis, detection of portal cholangiopathy in patients with portal cavernomas, mapping collateral circulation in patients with ectopic variceal hemorrhage, or for the placement of TIPS in complex patients, especially those with Budd-Chiari syndrome.

Elastography

In recent years, the assessment of liver disease has improved substantially after the introduction of elastography. The possibility of estimating liver fibrosis and, indirectly, the severity of portal hypertension with the measurement of liver stiffness has changed patient management[43]. The rationale behind the use of liver stiffness measurement as an expression of portal hypertension is based on the fact that liver stiffness depends on the amount of collagen and, thus, on the structural component of portal pressure. The best correlation between HVPG and liver stiffness measurement occurs when HVPG values are between 5 and 12 mm Hg. However, as portal hypertension becomes more severe, the correlation between liver stiffness and HVPG is lost; in these cases, the measurement of spleen stiffness appears to be a more reliable marker of portal hypertension, as well as a predictor of liver decompensation[4]. The Baveno VI consensus suggests that a fibroscan value of 20-25 kPa, alone or in combination with platelet count and spleen size, is sufficient to confirm the presence of significant portal hypertension in patients with cirrhosis. It further recommends that screening endoscopy can be postponed in patients with less than 20 kPa and more than 150 000 platelets due to the low probability of having high-risk esophageal varices[44]. With these criteria, 21% of digestive endoscopies can be avoided and only less than 5% of patients with high-risk esophageal varices would be lost. Validation of these criteria has shown that the severity of portal hypertension can be misclassified in 2% of the population[45]. Spleen elastography has also been used, although portal hypertension is related to spleen stiffness, when portal venous pressure gradient is > 12 mm Hg, and is not directly related to reported kPa grade and, therefore, its clinical use to predict the presence of esophageal varices is not recommended[46].

Given that, independently, non-invasive markers have some limitations, as well as their use in clinical practice, so the combination of different tests can provide more accurate information, for which mathematical models that integrate elastography, platelet count and spleen diameter have been proposed, and in some cohorts of patients it has allowed better selection of those who require endoscopic study, which reduces the number of invasive procedures by up to 65%[47].

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