

REVIEW

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The role of elastography in clinically significant portal hypertension

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HIGHLIGHTS

- In compensated cirrhosis, using non-invasive methods would exempt the patient from the need of an endoscopy.
- The Baveno VII presented the “rule of 5” for Vibration-Controlled Transient Elastography; liver stiffness measurement ≤ 15 kPa and platelets $>150.000/\text{mm}^3$ exclude clinically significant portal hypertension (CSPH), while when ≥ 25 kPa is highly suggestive of CSPH.
- Spleen stiffness measurement has been proposed as a more specific technique to predict the presence of CSPH.
- Elastography has gained prestige in the non-invasive evaluation of patients with advanced chronic liver disease by allowing prophylactic measures to be taken when suggesting the presence of CSPH.

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ABSTRACT – This is a narrative review that aims to discuss the importance of elastographic methods in the evaluation of clinically significant portal hypertension (CSPH) in cirrhotic patients, where the authors propose an algorithm for evaluating these patients. In compensated advanced chronic liver disease, the goal is to prevent the development of CSPH and, in those already with CSPH, prevent the appearance of gastroesophageal varices (GEV) and other complications of portal hypertension. In compensated cirrhosis, the prevalence of GEV is 30–40%, of which 10–20% are at risk of bleeding. Therefore, using non-invasive methods would exempt the patient from the need of an endoscopy. Hepatic Elastography is a non-invasive, safe, reproducible method, available through many techniques: Vibration-Controlled Transient Elastography (VCTE), Shear Wave Elastography (SWE) and Magnetic Resonance Elastography (MRE). The Baveno VII presented the “rule of 5” for VCTE: liver stiffness measurement (LSM) ≤ 15 kPa and platelets $>150.000/\text{mm}^3$ exclude CSPH, while an LSM ≥ 25 kPa is highly suggestive of CSPH. Also, the “rule of 4” for SWE has been proposed: patients with ≥ 17 kPa could be considered as having CSPH. At last, spleen stiffness measurement (SSM) has been proposed as a more specific technique to predict the presence of CSPH. In conclusion, elastography has gained prestige in the non-invasive evaluation of patients with advanced chronic liver disease by allowing prophylactic measures to be taken when suggesting the presence of CSPH.

Keywords – Portal hypertension; elastography; cirrhosis.

INTRODUCTION

When evaluating the burden of chronic liver disease⁽¹⁾, it is estimated that 1.5 billion patients are affected worldwide, with the most frequent causes being non-alcoholic fatty liver disease (NAFLD), hepatitis B and C viruses and alcoholic liver disease. Although the number is probably underestimated, chronic liver disease is responsible for 2.000.000 deaths per year worldwide. In Brazil, liver disease is considered the eighth most frequent cause of death⁽²⁾.

Until recently, the diagnosis of chronic liver disease was either histological, clinical, laboratory and echographic or endoscopic in the case of advanced disease. However, some tests are relatively invasive and impractical for the constant follow-up of these patients. This has raised interest in using non-invasive methods for assessing patients with compensated cirrhosis, but these were not usually adopted in clinical practice until very recently⁽³⁾. Consequently, elastography emerged as a robust and objective test for diagnosing or excluding severe fibrosis/cirrhosis and clinically significant portal hypertension (CSPH) in cirrhotic patients. Accordingly, the Baveno VI and Baveno VII consensus conference on portal hypertension suggested that liver stiffness measurement (LSM) can be used to identify patients having compensated advanced chronic liver disease (cACLD) and CSPH^(4,5).

This is a narrative review that aims to discuss the importance of elastographic methods in the evaluation of CSPH in cirrhotic patients, especially hepatic and splenic elastography, where the authors, in addition to reviewing the state of the art on the subject, propose an algorithm for evaluating these patients.

Classification of cirrhosis

Six stages of cirrhosis must be considered when classifying the disease⁽⁶⁾. In stage 0, there is compensated disease without CSPH. This stage is defined by a hepatic venous pressure gradient (HVPG) between 5 and 10 mmHg and reasonable response to the etiological treatment; in stage 1, the disease remains compensated, however with CSPH (HVPG ≥ 10 mmHg) and, therefore, with a higher risk of developing varicose veins, hepatocellular carcinoma and decompensation. In stage 2, the appearance of

gastroesophageal varices (GEV) becomes evident, and the 5-year mortality is about 10% if there is no decompensation. In stage 3, bleeding due to variceal rupture is already observed, with an estimated 5-year mortality of 20% if there is no decompensation of the liver disease. In stage 4, liver decompensation is present (bleeding not included, as it is more often related to the presence of ascites), with a 5-year mortality of 55–80%; in stage 5, there are further episodes of decompensation with a mortality up to 90% in 5 years. Finally, in stage 6, the patient has advanced decompensated cirrhosis (refractory ascites, infection, persistent hepatic encephalopathy (HE), jaundice and renal dysfunction), with a high mortality rate of 60 to 80% in 1 year.

Variceal veins are present in up to 40% of patients with compensated cirrhosis (Child A) and up to 85% in the decompensated (Child C)⁽⁷⁾. In a study carried out in our center evaluating a cohort of patients with chronic liver disease on an outpatient basis, digestive bleeding was the second most frequent complication at the presentation for these patients⁽⁸⁾. We emphasize that the recurrence of bleeding in one year could be up to 60% and that the actual mortality of each bleeding episode varies from 15 to 20%⁽⁷⁾.

Screening for gastroesophageal varices in cirrhosis

The screening criteria for GEV were based exclusively on performing an upper digestive endoscopy at the time of diagnosis of cirrhosis until a few years ago. In 2015, the Baveno VI consensus⁽⁴⁾ recommended that a measurement of less than 20 kPa when performing Fibrosan[®], associated with platelets count greater than 150.000/mm³, would exempt the patient from the need of an endoscopy. In the same year, the European Association for the Study of the Liver (EASL) guideline evaluating non-invasive tests in liver diseases⁽⁹⁾ considered that they should not replace endoscopy to detect the presence of varicose veins. Subsequently, many authors endorsed the position of Baveno VI^(3,10), including the guidance from the American Association for the Study of Liver Diseases (AASLD)⁽¹¹⁾ that reiterated the recommendation and suggested that when the possibility of high-risk bleeding varices (HRBV) is low, non-invasive tests could avoid the performance of a substantial num-

ber of endoscopies. However, international scientific societies, including the EASL⁽¹²⁾, emphasize that, because of the high risk of GEV in patients with decompensated disease, endoscopy should be performed annually in these patients.

Although we still consider endoscopy as an important screening tool in our center⁽¹³⁾, we have in mind that in compensated disease, the prevalence of GEV is 30–40%, of which only 10–20% are at risk of bleeding; therefore using non-invasive methods would be advantageous. Since the data are negative, the chance of HRBV is less than 5%, and up to 30% of endoscopies would be avoided⁽¹⁴⁾.

Changing paradigm in the assessment of patients with cirrhosis and portal hypertension

As we can observe in the classification of cirrhosis⁽⁶⁾, the prognosis of the disease begins to compromise the patient's survival more significantly from stage 3, when bleeding due to rupture of GEV happens. Still, it becomes more evident in stage 4 (first episode of decompensation), when mortality significantly increases. Thus, the premise should be to avoid bleeding and other complications in patients with cirrhosis, with CSPH being the leading cause of these complications.

In cACLD without CSPH, when elastography does not indicate CSPH (stage 0), the goal to be considered is to prevent the development of CSPH by treating or ruling out the cause of liver disease. In those already with CSPH (stage 1), the aim is to prevent the appearance of GEV and other complications of portal hypertension (ascites, HE). For this purpose, when yet to be performed, it is necessary to treat the cause of cirrhosis and adapt the patient's lifestyle. However, in many cases, even after successful treatment, CSPH could persist⁽¹⁵⁾, which leads us to infer that other measures are necessary since this seems to be the marker of hepatic decompensation episodes. In this way, the treatment with medications acting specifically by lowering portal pressure (NSBB) must be started⁽¹⁶⁾.

More recently, when the role of hyperdynamic circulation in cirrhosis and the response to NSBB were re-evaluated, it was shown that patients without CSPH have less hyperdynamic circulation and less reduction in portal hypertension with the use of NSBB when compared to those patients with CSPH⁽¹⁷⁾. Based on

this premise, the PREDESCI study⁽¹⁸⁾ was designed, which evaluated the role of NSBB in patients with CSPH. This randomized, prospective, controlled, multicenter, double-blind study was conducted in patients with compensated cirrhosis and CSPH. Patients who responded acutely to NSBB were then randomized into propranolol vs placebo and those who had not responded to carvedilol vs placebo. The group that used pharmacological therapy showed a better evolution, and the authors concluded that NSBB increase decompensation-free survival (exalting the role of lower incidence of ascites). This study was a milestone in the treatment of patients with cirrhosis. From then on, when faced with a patient with cACLD, the focus must be on the treatment of CSPH and no longer punctually on the treatment of GEV.

The main studies that promoted a change in medical management and those that established the cut-off values for the non-invasive evaluation of CSPH can be seen in TABLE 1.

The reduction in portal pressure improves the evolution of cirrhosis in the presence or absence of ascites, as demonstrated in a recent meta-analysis with more than 1100 patients⁽²⁰⁾. When evaluating primary prophylaxis, around half of the patients who responded to NSBB, in addition to having less bleeding due to variceal rupture, had fewer complications related to cirrhosis decompensation, less need for liver transplantation and lower mortality.

Despite the lack of head-to-head comparative studies between the two main NSBB available in our country (propranolol vs carvedilol), there is a greater tendency to use carvedilol, as it is believed to have a more significant role in lowering the HVPG⁽²¹⁾. The use of carvedilol increases the proportion of responders to 75% vs 50% of other conventional NSBB⁽²²⁾.

In a systematic review and meta-analysis evaluating four randomized controlled trials with 352 patients with compensated cirrhosis and CSPH (without previous bleeding), carvedilol decreased the risk of decompensation and patient mortality⁽²³⁾. These data were corroborated in a recent study in an American cohort after 3 years of follow-up evaluating cirrhotic Child-A patients with platelets between 30.000 and 150.000/mm³ and no previous history of decompensation⁽²⁴⁾.

The consensus of Baveno VII⁽⁵⁾, when taking a position regarding the prevention of the first decom-

TABLE 1. Summary of data from studies on the evaluation of portal hypertension in cirrhotic patients.

Author	Design/N	Aim/primary endpoint	Results/conclusion
Groszmann RJ, et al. ⁽¹⁹⁾	Prospective N=213 cirrhotic patients without varices receiving timolol (n=108) vs placebo (n=105)	Development of gastroesophageal varices or variceal hemorrhage	NSBB are ineffective in preventing varices/bleeding (39% treated vs 40% placebo; <i>P</i> =0.89) and are associated with adverse events
Villanueva C, et al. ⁽¹⁷⁾	Prospective, multicentric, cross-sectional study N=273 cirrhotic with PH (194 with CSPH and 79 with subclinical PH)	To characterize the hemodynamic profile of each stage of PH in compensated cirrhosis and the response to NSBB according to stage	Patients with subclinical PH have less hyperdynamic circulation and lower portal pressure reduction using NSBB compared to those with CSPH, suggesting that NSBB are more suitable to prevent decompensation of cirrhosis in patients with CSPH than in earlier stages
Villanueva C, et al. ⁽¹⁸⁾	Multicentric prospective, double-blind, RCT (PREDESCI). N=201 with compensated cirrhosis and CSPH without HRBV (100 received propranolol or carvedilol and 101 received placebo)	NSBB to prevent decompensation of cirrhosis with PH	Decompensation occurred in 16/100 (16%) patients in the NSBB group versus 27/101 (27%) patients in the placebo group (<i>P</i> =0.041). Long-term treatment with NSBB could increase decompensation-free survival in patients with compensated cirrhosis and CSPH
Albrades JC, et al. ⁽³⁾	Prospective, multicentric N=518 patients with cACLD	To develop noninvasive tests-based risk prediction models to provide a point-of-care risk assessment of cACLD patients	Platelets ≥ 150.000 and a LSM value of 20 kPa would have a predictive probability for HRBV of 5%, and 30% of the patients showed a predictive probability of HRBV below 5%
Pons M, et al. ⁽⁴³⁾	International cohort study N=836 compensated cirrhotic (358 HCV; 248 NASH; 203 alcohol abuse and 27 HBV)	To explore the prevalence of PH in the most common etiologies of patients with cACLD and develop classification rules based on LSM, that could be readily used to diagnose or exclude CSPH	LSM ≥ 25 kPa is sufficient to rule in CSPH in most etiologies, including non-obese with NASH, but not in obese patients with NASH. LSM ≤ 15 kPa plus platelets ≥ 150.000 ruled out CSPH in most etiologies
Rabiee A, et al. ⁽⁴⁵⁾	Validation study N=245 patients with compensated NASH cirrhosis	To validate the ANTICIPATE models using baseline data from a multicenter RCT; and to develop and validate a model using laboratory values (FIB4+)	The ANTICIPATE models performed well in predicting the presence of CSPH in NASH cirrhosis. A model using FIB-4 plus albumin (FIB4+) can be used to predict CSPH when VCTE is not available

NSBB: non-selective β -blockers; PH: portal hypertension; CSPH: clinical significant portal hypertension; RCT: randomized controlled trial; HRBV: high-risk bleeding varices; cACLD: compensated advanced chronic liver disease; LSM: liver stiffness measurement; HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis; HBV: hepatitis B virus; AUC: area under the curve; VCTE: vibration-controlled transient elastography.

compensation in patients with CSPH, suggests the use of NSBB, giving priority to carvedilol as it is more effective in reducing HVPG and in preventing decompensation, it decreases mortality, and it is better tolerated. It reiterates that patients with NSBB and cACLD do not need to undergo screening endoscopy and recommends endoscopic band ligation in those patients with HRBV with contraindication/intolerance to these drugs.

Thus, the new reality may be to focus more on CSPH and less on the presence of GEV. The treatment of the underlying disease and the use of NSBB are the therapies to be used for this purpose, and soon, the addition of new tools that could act at the level of portal pressure, such as statins, could complement the current therapeutic options.

Based on emerging data, the paradigm has shifted, focusing on treating CSPH rather than just HRBV and preventing any decompensation (variceal bleeding, ascites, or HE)⁽²⁵⁾. Thus, returning to the classification of cirrhosis⁽⁶⁾, we would already start clinically intervening in stage 1 (presence of CSPH without GEV) and no longer in stage 2. However, CSPH is defined by an HVPG ≥ 10 mmHg, and to confirm this diagnosis, we would have to perform an invasive procedure that is not available in all medical centers. This could lead to an impasse, but we believe that, over the years, the evidence has grown to endorse the role of non-invasive methods for diagnosing CSPH, even though the gold standard remains the HVPG. Among these methods, hepatic elastography has gained great prestige in literature.

Hepatic elastography

Hepatic elastography is a non-invasive, safe, reproducible method with good accuracy in evaluating liver fibrosis. The mechanical changes that occur in the liver as a result of liver fibrosis, promote an increase in the organ's resistance. Elastographic methods were the standard for assessing the biomechanical properties of tissue^(26,27). Thus, shear waves (SW) are generated when a directional force is applied to a tissue.

The ultrasound elastography consists of the LSM through the evaluation of the speed of the shear waves, which can be mechanically produced by an external stimulus as the vibration-controlled transient elastography - VCTE, used in the transient hepatic elastography - Fibroscan[®] or through ultrasonic pulses present in the shear wave methods like point shear wave (p-SW) and two-dimensional shear wave (2D-SW)⁽²⁸⁻³¹⁾. In the same way, magnetic resonance elastography (MRE) also uses external stimuli^(29,30). The first and most validated technique is the VCTE: a specific probe produces a vibratory wave into a right intercostal space over the liver area, which is transmitted to the liver. The result is expressed in kilopascals (kPa). In this method, the operator has little control over the evaluated area of interest, and the image is one-dimensional⁽³²⁾. Newer methods emerged, in which shear waves are produced by the acoustic impulse of the ultrasound beam directly into the liver, being called acoustic radiation force impulse (ARFI) techniques, generating shots in a single point (pSWE) or in larger portions of the area of interest to be evaluated (2D-SWE). All these latter techniques allow real-time visualization of the area of interest, with the result expressed in m/s or kPa^(26,33).

VCTE is a one-dimensional technique that uses elastic SW (50 Hz) and low-frequency ultrasound propagating through the skin and subcutaneous tissue to the liver, performed with the FibroScan[®] system (Echosens, France). The speed of the SW is directly related to the stiffness of the tissue⁽³⁴⁾, which means that the more resistant the tissue is, the faster the manipulation of vibrations. VCTE is easy to perform, reproducible, fast (takes 5–10 minutes) and can be performed at the bedside or in an outpatient setting. The results, expressed in kPa, and ranging from 1.5 to 75 kPa, are immediately available. It is a method with high intra and interobserver agreement. Howe-

ver, interobserver agreement becomes significantly lower in patients with a body mass index (BMI) ≥ 25 kg/m², with steatosis in $\geq 25\%$ of hepatocytes, hepatic fibrosis < 2 (METAVIR score), and in individuals with narrow intercostal spaces⁽³⁵⁾.

The p-SWE was the pioneer in the inclusion of a specific software coupled to the traditional ultrasound device to perform elastography. The B-mode projected image on the screen allows the visualization of the organ and the choice of the region of interest (ROI) to acquire the speed of the shear waves. Short-term acoustic pulses are emitted through the transducer, generating SW at the ROI chosen by the operator. Ultrasonographic images are used to guide the placement of the ROI, and measurement is feasible even if ascites is present⁽²⁶⁾. The result will be the median of 10 measures, and the reliability of the result is obtained with an interquartile range - IQR/median below 15%; the lower the IQR, the greater the reliability of the test result. The pSWE has excellent intra- and interoperator reproducibility for evaluating liver elastography in healthy individuals and patients with chronic liver disease⁽²⁶⁾.

The 2D-SWE follows the same principles described for p-SW but with the ability to produce quantitative SW images at a higher ROI and focus on multiple locations, sequentially detecting the time of arrival of the SW in multiple lateral areas of the liver parenchyma⁽²⁶⁾.

The MRE has been highlighted in the non-invasive evaluation of liver fibrosis. The detection and staging of liver fibrosis is the main clinical application of MRE, and it has been considered the most accurate non-invasive method for detecting and staging liver fibrosis, with excellent intra- and interobserver agreement⁽³⁶⁾. Compared to other methods, it is the only non-invasive technique capable of diagnosing mild liver fibrosis with reasonable accuracy⁽³⁷⁾.

Factors that may influence the performance of the methods

It must be emphasized that confounding bias, such as inflammation (aminotransferases above five times the upper limit of normal), liver congestion, mechanic cholestasis, heart failure, biliary obstruction, as well as food intake, should be excluded due to the misinterpretation of the results, mainly when using VCTE and SWE⁽³⁸⁾.

Although most studies used VCTE as a reference, studies using p-SWE or 2-D SWE almost always produced similar effects, suggesting that the same confounders must affect all techniques. For patients with falsely elevated liver elastography measurements due to alcoholic hepatitis, liver stiffness decreases after 1–4 weeks of abstinence. Other diseases that increase liver stiffness, independent of hepatic fibrosis, include amyloidosis, lymphomas, and extramedullary hematopoiesis^(26,28,39). Hepatic steatosis also causes attenuation of the ARFI pulse and may lead to greater variability in measurements⁽²⁶⁾.

Magnetic resonance imaging has been recognized for decades as an important imaging method for the liver. Although conventional anatomical images provide helpful diagnostic information, they have a limited role in diagnosing early-stage liver fibrosis and cACLD⁽⁴⁰⁾. Park et al. performed a prospective study comparing MRE vs VCTE's performance for fibrosis diagnosis in patients with NAFLD. A cross-sectional study of 104 consecutive adults who underwent MRE, VCTE, and liver biopsy was performed. The authors found MRE to be more accurate than VCTE in identifying liver fibrosis (stage 1 or more)⁽⁴¹⁾.

For the diagnosis of cirrhosis in adults with NAFLD, the American Association of Gastroenterology (AGA) reported that the use of the MRE is more advantageous than the VCTE in a scenario of high prevalence of cirrhosis, as it presents fewer false-positive results, reducing the number of patients undergoing liver biopsy⁽⁴²⁾. The possibility of evaluating a large sample volume, with the potential to assess the entire liver volume, is recognized as one of the main advantages of MRE compared to other methods for staging liver fibrosis. This characteristic is a great advantage in staging since fibrosis often has a heterogeneous distribution. Comparatively, biopsy covers about 1/50.000 of the liver volume, and VCTE covers about 1/100⁽³⁶⁾.

The main limitations of MRE include low availability, high cost, failures due to hepatic iron overload and some general contraindications for performing magnetic resonance. In addition, rigidity cut-offs for different etiologies have yet to be established⁽³⁶⁾. MRE is the most accurate non-invasive method for detecting and staging liver fibrosis, especially in obese patients with ascites.

Hepatic elastography in the diagnosis of CSPH

The non-invasive diagnosis of CSPH in patients with cACLD of different etiologies was recently evaluated in a cohort study with 836 patients with VCTE paired with PVHG, where patients with LSM ≥ 10 kPa and without prior decompensation of liver disease⁽⁴³⁾. Portal hypertension was observed in more than 90% of cACLD patients, regardless of etiology, except for patients with non-alcoholic steatohepatitis - NASH (60.9%). In the latter population, this fact was more evident in obese patients with NASH (53.3%). When evaluating the presence of CSPH, the behavior was similar, being also lower in patients with NASH (50.5%), especially if obese (30.8%).

An LSM ≤ 15 kPa with platelet levels $\geq 150.000/\text{mm}^3$ ruled out CSPH in most etiologies, while the best cut-off point for determining CSPH in alcoholic liver disease, chronic hepatitis B, chronic hepatitis C, and patients with NASH was ≥ 25 kPa. In obese patients with NASH, the positive predictive value was only 62.8%, so a nomogram was proposed to predict CSPH in patients with NASH (ANTICIPATE-NASH), where BMI was also considered⁽⁴³⁾.

Interestingly, the study demonstrates that decompensation in advanced NAFLD can occur at lower levels of PVHG⁽⁴⁴⁾. This study has the rationale that the accuracy of PVHG in NAFLD may not reflect the actual pressure of the portal vein. It is a multicenter cross-sectional study of 548 patients with advanced NAFLD versus 444 patients with cACLD caused by hepatitis C virus. Median PVHG was lower in the advanced NAFLD cohort (13 vs 15 mmHg), despite similar liver function and higher rates of decompensation in the advanced NAFLD cohort (32% vs 25%; $P=0.019$). The authors conclude that patients with advanced NAFLD have a higher prevalence of decompensation at any assessed portal hypertension level (compared to those with advanced chronic liver disease caused by the hepatitis C virus).

In the last Baveno meeting⁽⁵⁾, the “rule of 5” was presented. An LSM < 10 kPa in the absence of clinical or imaging events excludes compensated ACLD, where there is a slight chance ($< 1\%$) of decompensation or mortality. LSM between 10 and 15 kPa suggests cACLD; LSM ≤ 15 kPa and platelets $> 150.000/\text{mm}^3$ exclude CSPH (sensitivity and NPV $> 90\%$); LSM ≥ 15 kPa is highly suggestive of cACLD and LSM ≥ 25

kPa is highly suggestive of CSPH (specificity and PPV >90%). In this scenario, there is a high risk of endoscopic signs of portal hypertension and decompensation (less in obese patients with NAFLD). Although in need of validation, the ANTICIPATE-NASH model (LSM, platelets, BMI) can be used to predict the risk of CSPH in patients with compensated NASH-cACLD. More recently, a validation study confirmed that ANTICIPATE model performed well in predicting the presence of CSPH in NASH cirrhosis and suggested a new model using FIB-4 score plus albumin (FIB4+) to predict CSPH where VCTE is not available⁽⁴⁵⁾.

Considering the cost of VCTE with Fibroscan[®], it is interesting to evaluate other non-invasive methods for diagnosing CSPH. Although most studies have been conducted with the Fibroscan[®], there could also be space for ARFI techniques. In this regard, an update of the consensus of the Society of Radiologists in Ultrasound Liver Elastography⁽³¹⁾ proposed the “rule of 4” in evaluating patients with cACLD, including patients with viral etiology and NAFLD. In this scenario, patients with ≥ 17 kPa (2.4 m/s) could be considered as having CSPH. It does not mention any difference in the use of p-SWE compared to 2D-SWE, although it points out that more studies are needed for a more definitive answer regarding the cut-off levels used in predicting the different stages of the disease.

In the non-invasive detection of CSPH in cACLD, Vuille-Lessard et al.⁽⁴⁶⁾ believe that p-SWE is not recommended to identify CSPH. However, considering that the performance of 2D-SWE is probably consistent with the VCTE, the heterogeneity of the cut-offs (16 to 38 kPa) indicates a lack of standardization. Although the method looks promising, more data is awaited.

When monitoring patients with cACLD, an LSM <20 kPa and platelets >150,000/mm³ would indicate a low probability of HRBV, ruling out the need for endoscopy. However, these patients must be followed annually with elastography. In patients with contraindication/intolerance to NSBB, endoscopy should be performed if LSM ≥ 20 kPa and platelets <150,000/mm³⁽⁵⁾.

Baveno VII suggests monitoring those patients with LSM between 7–10 kPa and ongoing liver injury. Decreased LSM correlates with a lower risk of

decompensation and death (decrease $\geq 20\%$ with LSM <20 kPa or reduction to less than 10 kPa)⁽⁵⁾.

Regarding the decrease of LSM, a study evaluated non-invasive tests in diagnosing CSPH after curing hepatitis C⁽⁴⁷⁾. They evaluated 418 patients with PVHG ≥ 6 mmHg and sustained virological response (SVR) who underwent post-treatment PVHG. Three hundred twenty-four patients also had LSM/platelet paired data. These patients were validated for decompensation in 755 patients with SVR-cACLD. In the PVHG/non-invasive testing cohort, for those with cACLD, the pre/post-treatment prevalence of CSPH was 80% and 54%, respectively. For certain values of LSM/platelets, PVHG tended to be lower post-treatment, indicating the need for specific algorithms. The post-treatment LSM/platelet combination produced high diagnostic accuracy in CSPH patients with cACLD (AUC 0.884; 95%CI 0.843–0.926). A post-treatment LSM <12 kPa and platelets >150,000/mm³ excluded CSPH (sensitivity: 99.2%), while an LSM ≥ 25 kPa was highly specific for CSPH (93.6%). In the validation cohort, the 3-year risk of decompensation was 0% in patients who met the criteria LSM <12 kPa and platelets >150,000/mm³, whereas in patients with post-treatment LSM ≥ 25 kPa, the risk of decompensation was 9.6%. The authors conclude that non-invasive tests can estimate the likelihood of CSPH after HCV cure and predict clinical outcomes. Thus, patients with LSM <12 kPa and Platelets >150,000/mm³ could be discharged from portal hypertension surveillance if no cofactors are present, whereas those with LSM ≥ 25 kPa require surveillance/treatment.

In the consensus of Baveno VII⁽⁵⁾, it is suggested that after the removal/suppression of the etiological factors in patients with cACLD, surveillance should be carried out with the criteria of de Baveno VI, especially when the etiology of the liver disease is related to hepatitis B and C viruses. After SVR, surveillance is no longer necessary if LSM <12 kPa and platelets >150,000/mm³. In cACLD using NSBB without CSPH after removal/suppression of etiological factors, endoscopy is recommended in 1-2 years and if there are no GEV, suspension of NSBB is recommended⁽⁴⁸⁾.

Splenic elastography in the diagnosis of CSPH

Liver stiffness correlates with the severity of liver fibrosis up to the threshold of CSPH⁽⁴⁹⁾. In patients

with CSPH, the strength of the correlation between liver stiffness and fibrosis decreases, probably due to an increasing role of extrahepatic factors, especially the increase in portal venous inflow as portal hypertension progresses⁽⁵⁰⁾. In this way, spleen stiffness has been proposed as a more specific technique for evaluating liver fibrosis in patients with CSPH. However, studies have yet to be performed to provide reliable cut-off values⁽³¹⁾.

It has been shown that splenic stiffness measurement (SSM) is related to the progression of hepatic fibrosis, and in patients with hepatitis B or C infection, SSM is increased even though the LMS is unchanged^(51,52). Subsequent studies have demonstrated that SSM was positively correlated with HVP and had good performance in predicting CSPH and GEV in cACLD patients^(53,54). Also, it has been indicated that although SSM is associated with portal hypertension, it is insufficient to accurately assess its severity⁽⁵⁵⁾. Further studies have suggested that SSM could reliably rule out the presence of HRBV in cirrhotic patients independently of the etiology of cirrhosis^(56,57).

In the same way, a recent systematic review and meta-analysis evaluated the studies on the diagnostic accuracy of SSM in detecting CSPH, severe portal hypertension, GEV, and HRBV in patients with cACLD. In this study, 32 studies (3,952 patients) were identified, reporting the accuracy of SSM in diagnosing portal hypertension and/or GEV in adults with cACLD. The results of this meta-analysis indicated that SSM, by current techniques, had good accuracy in detecting portal hypertension and GEV in cACLD patients. AUCs for the diagnosis of CSPH exceeded 90%, and AUCs for any GEV and HRBV diagnosis reached 87% and 83%, respectively. SSM was able to predict the presence of CSPH with good sensitivity and specificity (85% and 86%, respectively). SSM was considered a promising method to detect portal hypertension and GEV with good diagnostic accuracy, and it would be a helpful non-invasive surveillance tool for clinicians in managing cACLD patients⁽⁵⁸⁾.

The acquisition technique is the same as that for the liver, aside from the measurements being taken between the left ribs with the patient in a supine or slight right lateral position. Considering that significant portal pressures are not expected at lower levels

of fibrosis, SSM should only be taken in patients with cACLD⁽³¹⁾. It appears that SSM shows a better correlation with portal pressure than LSM does⁽⁵³⁾. Portal hypertension leads to splenic congestion, increasing splenic stiffness, and it may even cause splenic fibrosis⁽⁵⁹⁾. In healthy individuals, the spleen is stiffer than the liver. Several studies, most of which were performed with vibration-controlled transient elastography, have shown that SSM is more reliable in patients with portal hypertension than LSM for assessing the risk of CSPH and esophageal varices^(53,60,61). However, there are differences in cut-off values between studies, and the level of evidence is still too low to recommend SSM in the diagnostic work-up of patients with cirrhosis⁽³¹⁾. For ARFI-based techniques, limited studies suggest that abdominal wall thickness and splenic longitudinal diameter are independent predictors of successful SSM⁽⁵⁹⁾. When using 2D SWE, it was demonstrated that CSPH is unlikely in patients with SSM less than 26.6 kPa (3.0 m/sec)⁽⁶²⁾. Algorithms that combine LSM and SSM, or platelets count, have been proposed⁽⁶³⁾. In a multicenter study in which LSM and SSM were available in 109 patients, this algorithm had a sensitivity of 89.2% and a specificity of 91.4% to rule in CSPH⁽⁵⁵⁾. However, in a series of 191 patients⁽⁶⁴⁾, this algorithm has not been validated. The Baveno VII Consensus recommends that SSM using VCTE can be used in cACLD due to viral hepatitis to rule out and rule in CSPH (SSM <21 kPa and SSM >50 kPa, respectively). Validation of the best cut-off using a 100 Hz specific VCTE probe, as well as using pSWE and 2D-SWE is needed. Also, SSM ≤40 kPa by VCTE can be used to identify subjects with a low probability of HRBV, in whom endoscopy could be avoided⁽⁵⁾.

The high failure rate (15–30%) observed with SSM, mostly with VCTE and 2D-SWE, and the upper measurement of 75 kPa (specific to VCTE) have made SSM challenging to implement to this date. Using the same probes and software for LSM may not be appropriate, but SSM by VCTE has improved significantly with the use of a spleen-dedicated VCTE examination, where the SW frequency is set at 100 Hz instead of 50 Hz⁽⁴⁶⁾.

Given the data compiled in the literature^(4,5,18,43), we believe an algorithm can be recommended, as shown in FIGURE 1.

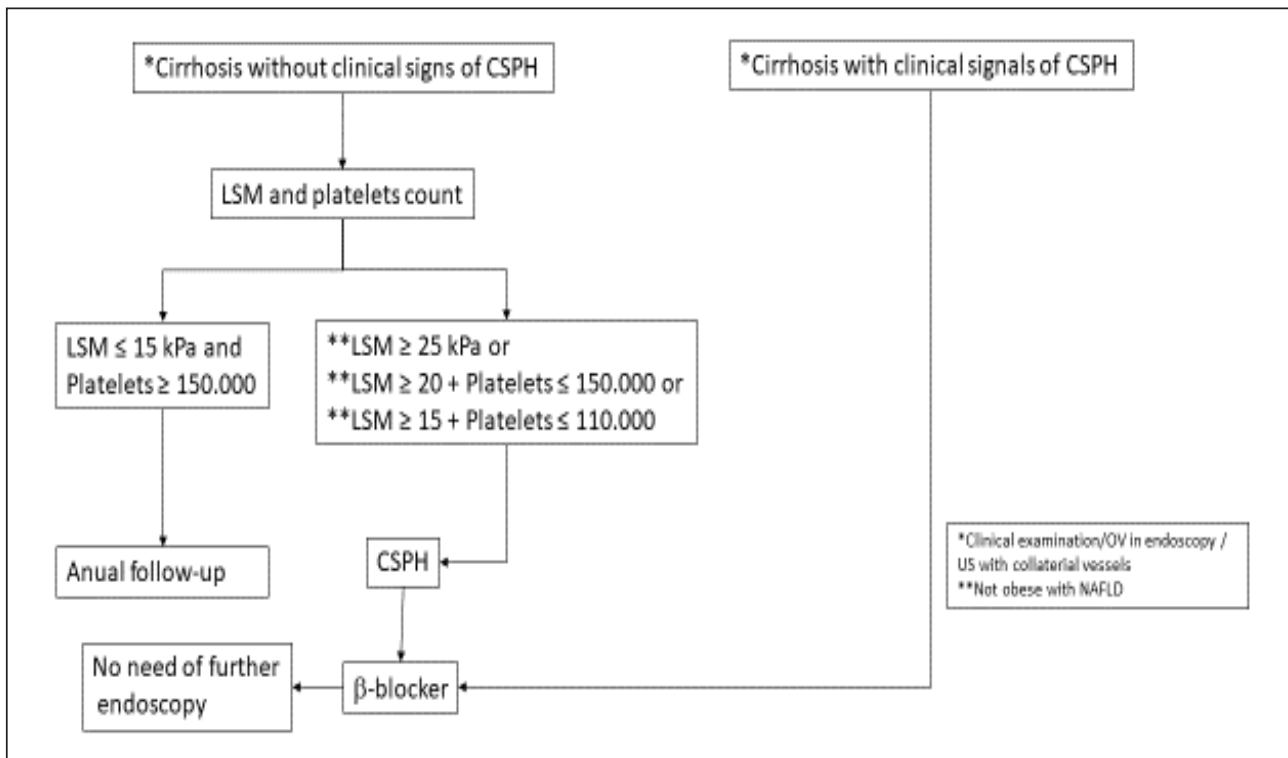


FIGURE 1. Conduct in the prevention of CSPH in a patient with cACLD.

CSPH: clinically significant portal hypertension; cACLD: compensated advanced chronic liver disease; LSM: liver stiffness measurement.

CONCLUSION

It would be of interest to design studies evaluating the evolutionary outcome of a liver disease contemplating the role of carvedilol vs placebo in patients with CSPH diagnosed by non-invasive tests. We have often used carvedilol in cirrhotic patients with signs of CSPH in the absence of contraindications. In those in which CSPH is only identified through non-invasive methods (platelets and elastography), we suggest individualizing the use of the medication.

Authors' contribution

Mattos AA and: Tovo CV conceptualized the stu-

dy; Mattos AZ, Sartori GP, Both GT, Mattos AA and: Tovo CV contributed equally to drafting the article and making critical revisions related to important intellectual content of the manuscript. All authors have read and approved the final version of the article to be published.

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RESUMO – Trata-se de uma revisão narrativa que visa discutir a importância dos métodos elastográficos na avaliação da hipertensão portal clinicamente significativa (HPCS) em pacientes cirróticos, onde os autores propõem um algoritmo para avaliação desses pacientes. Na doença hepática crônica avançada compensada, o objetivo é prevenir o desenvolvimento de HPCS, e naqueles já com HPCS prevenir o aparecimento de varizes gastroesofágicas (VGE) e outras complicações da hipertensão portal. Na cirrose compensada, a prevalência de VGE é de 30–40% e 10–20% são varizes com risco de sangramento, portanto o uso de métodos não invasivos dispensaria o paciente de endoscopia. A elastografia hepática é um método não invasivo, seguro e reprodutível, disponível através de várias técnicas: elastografia transitória (VCTE), onda de cisalhamento (SWE) e elastografia por ressonância magnética. O Baveno VII apresentou a “regra dos 5” para VCTE: medida da rigidez hepática (LSM) ≤ 15 kPa e plaquetas $>150.000/\text{mm}^3$ excluem HPCS enquanto um LSM ≥ 25 kPa é altamente sugestivo de HPCS. Além disso, foi proposta a “regra dos 4” para SWE: pacientes com ≥ 17 kPa podem ser considerados como portadores de HPCS. Por fim, a medição da rigidez do baço (SSM) foi proposta como uma técnica mais específica para prever a presença de HPCS. Em conclusão, a elastografia ganhou prestígio na avaliação não invasiva de pacientes com doença hepática crônica avançada, ao permitir a adoção de medidas profiláticas ao sugerir a presença de HPCS.

Palavras-chave – Hipertensão portal; elastografia; cirrose.

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