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Noninvasive assessment of portal hypertension in cirrhosis: Liver stiffness and beyond

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Abstract

Liver stiffness measurement (LSM) is a good, but still limited tool to noninvasively assess complications and prognosis in patients with advanced liver disease. This review aims to consider the role of LSM for the diagnosis of portal hypertension-related complications and for assessment of prognosis in cirrhotic patients, and to highlight the drawbacks as well as some alternatives for improving the performance. Hence, this field is far from being closed, and deserves more attention. There is still a place for more carefully designed studies to find new, innovative and reliable approaches.

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Key words: Liver stiffness; Portal hypertension; Complication; Spleen stiffness; Prediction

Core tip: This review aims to consider the role of liver stiffness measurement for the diagnosis of portal

hypertension-related complications and for assessment of prognosis in cirrhotic patients, and to highlight the drawbacks as well as some alternatives for improving the performance.

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INTRODUCTION

Invasive state of the art for the assessment of portal hypertension: The clinical importance of hepatic vein portal gradient

Development of clinically significant portal hypertension (CSPH) is a major step in the natural history of patients with chronic liver disease (CLD) and is associated with clinical decompensation and development of portal hypertension (PH)-related complications.

PH is diagnosed when the hepatic vein portal gradient (HVPG) has a value > 5 mmHg. HVPG is measured by calculating the difference between wedged and free pressures in the hepatic vein using a pressure catheter inserted *via* the transjugular route under fluoroscopic guidance. CSPH is established when HVPG is > 10 mmHg; at this value the risk of developing ascites or esophageal varices (EV) being much higher, while if HVPG is > 12 mmHg, the risk of variceal bleeding increases^[1].

It is considered that HVPG is a better indicator of liver function than transaminase level, viral kinetics or even liver biopsy^[2], mainly because the majority of patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) chronic hepatitis with significant fibrosis (\geq F2 METAVIR) have a HVPG value > 5 mmHg^[3], and

achieving sustained virological response in HCV cirrhotics is correlated with a significant reduction of HVPG^[3].

HVPG > 10 mmHg became a true milestone in the clinical history of cirrhotic patients. It was validated as an important independent predictor not only for EV development^[4,5], but also for the first episode of clinical decompensation^[6] or the risk of developing hepatocellular carcinoma (HCC)^[7]. In patients who have already experienced an episode of decompensation, HVPG > 16 mmHg predicts mortality, independently from the MELD score^[8], and an HVPG increase of 1 mmHg also increases by 3% the risk of death while on the waiting list for liver transplant^[9].

HVPG > 12 mmHg is another important milestone, being the threshold for decompensation (development of ascites and variceal bleeding)^[5]. If HVPG decreases below 12 mmHg (because of therapy or spontaneously) the risk of bleeding is significantly diminished and EV regress in size^[10]. If HVPG is measured during an episode of variceal bleeding, a value > 20 mmHg predicts failure to control bleeding, the odds ratio being 5 times higher than for HVPG < 20 mmHg^[11].

Measurement

Based on these findings, HVPG is recommended to all patients with cirrhosis at the time of diagnosis for risk and prognosis assessment^[12,13]. Furthermore, HVPG appears to be the ideal instrument to assess the response to therapy in cirrhotic patients with CSPH, the target being an HVPG value < 12 mmHg, or a decrease of at least 20% as compared with baseline^[11,13]. Not achieving these targets is the best independent predictor of re(bleeding)^[14] with a 2 to 4-fold higher relative risk for nonselective beta-blocker non-responders^[15]. But, despite its excellent diagnostic and prognostic value, HVPG is an invasive procedure available only in specialized centres, and therefore it has a low availability and high management costs^[16].

On the other hand, screening for EV requires esogastroduodenoscopy (EGD) at the diagnosis of cirrhosis, and every one to three years depending on whether EV were or were not found at the beginning^[13]. From the economic point of view, this is not a very good approach, since only 7% of the patients will develop varices each year^[17] and only 21% at the 5-years interval^[18]. This is why the Baveno V panel, in order to better stratify patients submitted to endoscopy, recommended identification and validation of alternative noninvasive surrogate markers for PH^[13].

Liver stiffness (LS) measurement (LSM) is an elastometric technique that uses the principle of vibration-controlled transient elastography to assess tissue elasticity^[19]. In CLD patients it was proved to be a very useful tool to assess significant fibrosis and to rule out cirrhosis^[20,21]. Moreover, in patients with liver cirrhosis (LC), LS was able to distinguish between compensated and decompensated patients^[22], and to predict prognosis in patients with CLD^[23].

This review aims to examine the role of LSM for the

diagnosis of PH-related complications and for assessment of prognosis in cirrhotic patients, and to highlight the drawbacks as well as to discuss the alternatives available to enhance LS performance in this field.

ROLE OF LSM IN CIRRHOTIC PATIENTS

Overview of LSM as a diagnostic tool

LS has an excellent accuracy for diagnosis of cirrhosis: AUROC of 0.9-0.99 for cut-off values ranging from 9 to 26.6 kPa, the best appearing to be 13.01 kPa, as a recent meta-analysis reports^[21]. In cirrhotic patients, in order to understand what is happening in more advanced stages of the disease, once PH has occurred, it became of great interest to exploit the entire range of stiffness values - up to 75 kPa - that the device (FibroScan®) is able to measure. In this respect, the cut-off values for different complications were previously shown with negative predictive values above 90% as follows: 27.5 kPa for large EV (LEV); 37.5 kPa for Child B or C cirrhosis; 49.1 kPa for development of ascites; 53.7 kPa for development of hepatocellular carcinoma; or 62.7 kPa for variceal bleeding^[23].

A strong positive correlation was found between LS and HVPG in patients with HCV-related liver disease and advanced (F3-F4) fibrosis ($r^2 = 0.61$, $P < 0.0001$)^[24]. The same correlation was independently demonstrated in patients with HCV recurrence after liver transplantation ($r^2 = 0.83$, $P < 0.001$)^[25]. As expected, LS values increase gradually alongside the increment in HVPG as the LC progresses^[26]. Overall, LS has a 90% sensitivity and 80% specificity for the diagnosis of CSPH^[27].

As far as the presence of EV is concerned, LS showed lower AUROC values, between 0.76 and 0.84^[25,28,29]. For cut-off values of 13.9, 17.6 and 21.1 kPa respectively, LS showed a good sensitivity (0.95, 0.9 and 0.79), but a lower specificity (0.43, 0.43 and 0.7)^[25,29,30]. Other studies showed a correlation between LS values and size of the varices^[29,30], while some researchers failed to demonstrate any^[25]. For cut-off values of 19 and 30.5 kPa, respectively, LS showed a high sensitivity, but a low specificity and positive predictive value for prediction of LEV^[29,30]. In fact, for detection of varices or especially of LEV, LS did not perform better than platelet count^[31] or FibroTest^[32]. However, a possible role of LS for the prediction of variceal bleeding cannot be excluded^[31,33]. As a recent meta-analysis^[28] and a critical review^[34] show, the studies investigating the issue of LS in advanced liver disease are contradictory, mainly because of population heterogeneity, different prevalence of CSPH and/or (L)EV and cross-sectional design, which lead to lower diagnostic accuracy and a wider range of cut-off values. It can be stated that LSM is not good enough to replace EGD for (large) EV detection in cirrhotic patients, because reported specificity and positive predictive values are too low for routine clinical practice.

Role of LSM as prognostic tool

LS is, undoubtedly, more than a tool for measuring liver

fibrosis. It has become an important instrument to assess the clinical course of CLD patients. Not only can LS assess the actual complications, but it permits long term risk classification and stratification^[35]. The first data in this respect came from a retrospective study which demonstrated a 5 times higher risk to develop hepatocellular carcinoma in HCV patients with a baseline LSM > 25 kPa as compared with those with values below 10.5 kPa^[36]. Seven out of eight other studies investigating this association found an increased hazard ratio (varying from 1.03 to 1.36) to develop HCC in patients with increased LS at diagnosis, irrespective of liver disease etiology^[37].

LS was also associated with clinical decompensation in several prospective studies. LS value < 21.1 kPa was found to be as accurate as HVPG < 10 mmHg for selecting patients who would not develop liver- or PH-related events in a follow-up period of 24 mo (negative predictive value of 86.3% and 100% for LSM, as compared with 85.7% and 100% for HVPG)^[38]. In another retrospective study, LS predicted overall 5-year survival (96% *vs* 47% in patients with baseline LS < 9.5 kPa or > 40 kPa)^[24]. In prospective settings these findings are maintained, showing that a 3 year increment in LS value with more than 1 kPa is associated with poorer clinical outcome and increased mortality in the additional 2-year follow up period^[39]. Subgroup analysis of the above mentioned study shows that any increase in LS value in those patients with baseline LSM > 14 kPa has a worse prognosis in terms of both development of complications or survival. These findings are fully supported by a recent meta-analysis^[38] that confirms the prognostic value of LS measurement for development of clinical decompensation, HCC and mortality, with a risk ratio of 1.07, 1.11 and 1.22, respectively. Overall, baseline LSM has a 1.32 risk ratio to predict liver-related events.

Unmet expectations

In-depth analysis of the correlation between LS and HVPG shows the loss of linearity for HVPG values > 12 mmHg. In the study of Vizzutti *et al*^[24], although the overall correlation coefficient is good ($r = 0.61$) when it is analysed for HVPG values > 12, it drops up to 0.17 ($P = 0.02$), while for HVPG < 12 it is 0.67 ($P < 0.0001$). These findings are even more evident in the study of Reiberger *et al*^[26] that finds for patients with HVPG < 12 mmHg a correlation coefficient of 0.951, while in patients with values > 12 mmHg it decreases up to 0.538 ($P = 0.0004$) and the almost perfect linear correlation is completely lost. Both groups explain this situation by the fact that in advanced stages of cirrhosis, the degree of PH becomes largely independent from the increased hepatic resistance (which is assessed by LS), while extrahepatic components (*e.g.*, hyperdynamic circulation, peripheral vasodilatation, *etc.*) become more important. In favour of this hypothesis is the evidence brought by Reiberger *et al*^[26], which shows that in patients with CSPH undergoing non-selective beta-blocker (NSBB) therapy for primary prophylaxis of variceal bleeding, the LS and HVPG are better correlated

($r = 0.746$, $P = 0.0001$). However, the latter study failed to demonstrate the possibility to assess the response to NSBB therapy, so that LS cannot entirely replace the pivotal role of HVPG in management of cirrhotic patients. There is, however, new evidence that demonstrates the ability of LS to respond to changes in portal pressure, such as elevation after meal ingestion^[40].

Also, there are confusing data coming from special populations regarding monitoring disease progression using LSM. In primary biliary cirrhosis, it was proved that baseline and serial LS measurements are better prognosis predictors than other evaluation methods^[41], while in the Asian population baseline LSM appears to be more reliable than serial measurements in assessing progression of PH^[42].

IT TAKES TWO TO TANGO (COMBINATION OF LSM AND SERUM TESTS FOR INCREASED DIAGNOSTIC ACCURACY)

Serum fibrosis markers or composite scores have also been used to predict complications of liver cirrhosis or PH. From very simple tests such as platelet count or prothrombin index^[43] to more specific ones such as hyaluronic acid^[44] or type IV collagen^[45], all have correlated with the presence of EV to various degrees, but their accuracy (AUROC) did not exceed 0.7. In order to increase the diagnostic accuracy of EVs, combinations of markers were envisaged, tested and some of them validated, such as aspartate transaminase (AST)-alanine transaminase ratio^[46], AST to platelet ratio index (APRI)^[47], or platelet count to spleen diameter ratio^[46,48]. Complex scores (of which some were patented) were also tried as noninvasive predictors of EV in LC patients. Of them, the combination of Lok score and Forns index was more cost-effective than endoscopy for detecting patients with varices and had a diagnostic accuracy that varied between 73.3% and 79.8%, depending on the etiology of liver disease^[49]. For the diagnosis of cirrhosis, the Sequential Algorithms for Fibrosis Evaluation (“SAFE”) biopsy was proposed by Sebastiani *et al*^[50], an algorithm that combined the APRI and FibroTest, which correctly classified almost 75% of the patients as cirrhotics/noncirrhotics. After its extensive validation in predicting fibrosis stages, FibroTest® was tried as a surrogate marker for both HVPG and EV in patients with LC. Although the team that developed the score found a very high NPV (100%) for a cut-off of 0.75^[52], FibroTest could not be internally validated, showing a diagnostic value for EV similar to that of platelet count or of the Child-Pugh score^[51].

However, it should not be forgotten that all these instruments (both FibroScan and serum fibrosis markers) were designed for detection of significant (or severe) fibrosis in patients with CLD and that their diagnostic value was mainly proved in HCV patients. In the settings of liver fibrosis, it was proved that the combined ap-

proach (elastometry and serum tests) performs better^[52]. But, as previously shown, both FibroScan and serum tests showed a certain ability to predict the presence of CSPH or EV. This observation simply leads to the idea of combining the two methods, in order to meet the principle announced by Pinzani *et al*^[53]: for an accurate diagnosis it is required for two distinct noninvasive tests to tie. This approach was previously used to combine ultrasound and common biological findings and demonstrated that patients with a serum prothrombin activity > 70%, a portal vein diameter > 13 mm, and a platelet count < 100000 are at risk to have EV^[54].

As for the combinations between LS and serum biomarkers, two different approaches were used; these will be briefly discussed below.

Stepwise approaches

The Bordeaux group proposed a stepwise algorithm to detect cirrhosis, and this relies on the concordance between FibroTest and FibroScan. Using this approach, LC could be diagnosed with an accuracy of 93% and liver biopsy could be avoided in almost 80% of cases^[55]. This approach has not yet been used to assess PH-related complications, maybe because FibroTest is a costly test. Based on our own data and those of others^[29], we proposed a stepwise approach that relies on the concordance between LS and Lok score (< 19 kPa and < 0.6, or > 38 kPa and > 0.8). This algorithm correctly classified 53% of patients with LEV and 64% of patients without EV^[56].

Super scores

Other authors combined clinical data, serum markers and LS in an empirical way, or using regression equations.

LSM-spleen diameter to platelet ratio score (LSPS) is calculated as the product of liver stiffness and the ratio between spleen diameter and platelet count (LSPS = LSM × spleen diameter/platelet count)^[57]. As LSPS values are increasing, the risk of having/developing high-risk varices in HBV-related cirrhosis also increases. Using two threshold values (< 3.5 and > 5.5, respectively), 90.3% of patients could have been correctly classified with regard to having high-risk varices. In these patients, during a median follow up of 29 mo, LSPS was found to be an independent predictor of EV bleeding, for a cut-off value > 6.5^[58].

Esophageal varices risk score (EVRS) combines the same variables (LSM, spleen size and platelet count) into a regression equation according to the following formula: $-4.364 - 0.538 \times \text{spleen diameter} - 0.049 \times \text{platelet count} - 0.044 \times \text{LS} + (0.001 \times \text{LS} \times \text{platelet count})$ ^[59]. In a population of 172 cirrhotics (in whom the prevalence of EV was 31.6% and of LEV 11.9%), EVRS at a value ≥ 0.20 predicted the presence of EV with good accuracy, both in the training set (AUROC: 0.9, Se: 70.3%, Sp: 76.5%) and the validation one (75% correctly classified).

Similarly, the same group calculated a PH risk score, by combining the same variables, according to the follow-

ing formula: $-5.953 + 0.188 \times \text{LS} + 1.583 \times \text{sex}$ (1: male; 0: female) + $26.705 \times \text{spleen diameter/platelet count ratio}$. For a cut-off of 0.63, this approach correctly classified more than 85% of patients, with an AUROC of 0.93 in both training and validation cohorts^[59].

THINKING OUTSIDE THE BOX (CHANGING SIDES TO ASSESS SPLEEN STIFFNESS)

Proof of concept and factors for success

Spleen involvement in PH and LC is still a matter of debate, although splenomegaly is one of most important clinical signs used for diagnosis. Splanchnic congestion and/or hyperplasia and fibrosis are discussed as generating factors for splenomegaly^[60]. Whichever the case, it is logical to presume that besides enlargement, the spleen also reacts by changing its density, a physical characteristic that became assessable using elastography. First data about spleen stiffness (SS) measurement came from MRI studies, which showed in 35 patients with varying degrees of chronic liver disease and 12 healthy volunteers, using an elastography protocol, a highly significant correlation between liver and spleen stiffness in patients with portal hypertension^[61].

Our group was the first to use SS measurement (SSM) by transient elastography, showing that values become higher as the liver disease is more advanced^[62]. In our cohort of 191 patients (of which, 137 cirrhotics, 59% with EV and 44% with LEV) SS correlated well with LS, the association being higher ($r = 0.587$) in patients with varices. We also managed to assess the factors related to SSM failure, which were elements associated with spleen size. Another report found that spleen transversal diameter > 4 cm is associated with successful measurement of SS^[63].

SSM for diagnosis

Our initial report found a higher SS value in patients with EV, as compared with those without. The best cut-off to discriminate between them was 46.4 kPa, which showed a good accuracy (AUROC = 0.781) and a high PPV (93.4%). However, we found significant interpolation and could not distinguish between EV grades (similarly with LS). Nevertheless, if LS and SS are used together (LSM > 19 kPa for high sensitivity and SSM > 55 kPa for high specificity) the diagnostic accuracy of EV increased up to 88.5%^[62]. Confirmation of these findings came from another study that found that LS and SS are independently associated with presence of varices (LS: OR = 1.149, $P = 0.035$; SS: OR = 1.068, $P = 0.03$)^[64].

Evidence about SSM in cirrhotic patients was taken further by Colecchia *et al*^[63], who found in a cohort of 100 patients a significant correlation between SS and HVP ($r^2 = 0.78$). In fact, the correlation was stronger than LS and HVP ($r^2 = 0.7$). SS has a better sensitivity (for the same specificity) than LS to rule-in the presence of EV and PH stages (both HVP > 10 and HVP > 12).

A meta-analysis of published data about SS (measured either by transient elastography or by other techniques - such as acoustic radiation force imaging or real time shear-wave - found a pooled sensitivity of 0.78 for detection of any EV and of 0.81 for detection of LEV, while the pooled specificity was 0.76 and 0.65, respectively^[65]. Based on these data, SS is not yet accurate enough to replace EGD for EV assessment.

Better data with technique optimization

Since the beginning of its use, an intrinsic characteristic of the machine (FibroScan) seemed to interfere with the results. Apparently spleen is stiffer than liver, and in every patient group, regardless of their variceal status or the grade of their varices, we reached the highest value measurable by the device (75 kPa) causing serious interpolation. These findings lead to the hypothesis that if FibroScan could measure values beyond 75 kPa, we would possibly obtain better data^[62]. Indeed, the manufacturer kindly developed a modified calculation algorithm for SS (not commercially available) that permits estimation of stiffness values up to 150 kPa after analysing the raw data of each elastogram.

Using this method, we found in a cohort of 80 patients with HCV-related cirrhosis that modified SS (mSS) discriminates better between classes and has a good accuracy to predict the presence of very high risk (grade 3) varices: (AUROC: 0.903, cut-off: 75 kPa, Se: 100%, Sp: 69.01%, PPV: 29%, NPV: 100%)^[66]. These findings were further confirmed by another group which found in a cohort of 112 Child-Pugh A cirrhotics due to HCV an improved accuracy to predict LEV (AUROC: 0.82, cut-off: 54.0 kPa, Se: 80%, Sp: 70%)^[67]. In this report, mSS - unlike LS or SS - was independently associated with LEV in multivariate analysis and correctly classified 70% of patients.

SSM for prognosis

Very recently, Colecchia *et al.*^[68] found in a cohort of 92 VHC compensated cirrhotic patients that MELD score and SS value at baseline are independently correlated with clinical decompensation and may predict liver-related events during two years of follow up. Indeed, the 54 kPa cut-off value could discriminate between patients with low/high risk of events (NPV = 0.975). This finding may add a new valuable use for the method, besides the ones already demonstrated; SS may play a role as a triage test allowing the selection of patients with low risk of decompensation.

WHAT NEWS FROM THE LAND OF SHADOWS?

Ultrasonography (US) is the “almost perfect” noninvasive imaging tool, since it is easily available (even at bedside), non-irradiating, cheap and reproducible. It is, however, highly dependent on the technology and operator and using contrast agents increases the costs. It is widely known

that US has high specificity for the diagnosis of cirrhosis, but the sensitivity is rather low. Splenomegaly and left lobe nodularity^[69] are the most reliable signs for a positive diagnosis.

There was a great amount of expectation and hope from Doppler US, because of its dynamic character and ability to assess vascular flow. Initial reports found mean velocity of the portal vein, hepatic artery resistance index or splenic artery resistance index as suitable targets, and further combined them into composite scores that showed better diagnostic performance. Between them, congestion index of the portal vein: portal vein cross sectional area/mean portal vein flow velocity^[70] and portal hypertension index: [(hepatic artery RI × 0.69) × (splenic artery RI × 0.87)]/portal vein mean velocity^[71] appear to be the most reliable, the latter having for a value < 1 m/s⁻¹, 100% sensitivity and 88.6% specificity to detect PH patients from healthy controls.

In later years, contrast enhanced ultrasound (CEUS) was widely used, mainly for characterization of focal liver lesions. CEUS was also used, however, for assessing diffuse liver diseases, showing a reduction of hepatic vein arrival time and hepatic transit time in patients with cirrhosis, and demonstrating the hyperdynamic circulation and intrahepatic arterial-venous shunts^[72]. Only recently, CEUS was used to specifically assess PH in compensated cirrhotic patients by estimating regional hepatic perfusion (RHP) as the product between microbubbles velocity and microbubble concentration in a post-processing analysis of contrast replenishment in the selected area after microbubble destruction^[73]. RHP correlated with MELD score and ICG clearance, and most importantly, showed a tendency to correlate with portal pressure decrease after *iv* propranolol administration (the correlation was, however, not significant at $P = 0.08$, most probably because of the small sample size, 10 patients).

IS IT TIME FOR “MENAGE À TROIS”?

In the quest for the best noninvasive approach to patients with advanced liver disease, a combination of tests seems to be the way to go.

Using ARFI as the elastographic technique and regression analysis, Bota *et al.*^[74] composed a LEV prediction score: $-0.572 + 0.041 \times \text{LS (m/s)} + 0.122 \times \text{SS (m/s)} + 0.325 \times \text{ascites (1, absent, 2, present)}$. For a cut-off value > 0.395, the performance to detect LEV was good (AUROC 0.721, for correctly classifying 69.6% of patients).

Our group also combined LS, SS and serum markers to enhance the accuracy of the previously proposed algorithm. Our approach proposes as a first step the use of LS and calculation of Lok score. If LS is < 19 kPa and Lok score < 0.6, the risk of LEV is very low, while if LS is > 38 kPa and the Lok score > 0.8 the likelihood of LEV is high. For the non-concordant cases, we added SS as a discriminant second step, using 55 kPa as cut-off value to rule in LEV. The algorithm correlated well with LEV ($r = 0.456$, $P < 0.0001$) and correctly classified 68%

of patients, with a Se of 95% and a NPV of 92%^[75].

OPEN HORIZONS

Undoubtedly, stiffness measurement (of liver and/or the spleen) represents a major step forward in the management of patients with advanced liver disease. From a surrogate of liver fibrosis, LS became an independent variable associated with the presence of PH-related complications, risk of decompensation or survival. Similarly, SS appears to be slightly better in assessment of PH complications and (L) EV in cirrhotic patients, and there is growing evidence that it also plays an important role in prognosis. Dynamic CEUS evaluation may be a valuable additional tool to assess PH changes in these patients. A combination of noninvasive approaches increases the diagnostic performance, but for the moment EGD and HVPG cannot be excluded from the work-up of patients with chronic liver diseases. Unfortunately, there is no noninvasive method that can acceptably monitor the response to therapy in these patients. There is also a lack of data about the monitoring of disease progression using LS or other noninvasive methods.

Hence, this field is far from being closed, and deserves more attention. There is still a place for more carefully designed studies to find new, innovative and reliable approaches.

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