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REVIEW / DERLEME

The value of non-invasive tests for risk stratification in patients with compensated cirrhosis

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Introduction

Liver cirrhosis is characterized by a long compensated phase, with a median survival from diagnosis of around 12 years. When decompensation occurs (variceal bleeding, jaundice, hepatic encephalopathy or ascites) the expected median survival is around two years [1,2]. Whereas there are a number of well-validated scores for prognosis prediction and risk stratification in patients with decompensated cirrhosis, these are very limited in the case of compensated cirrhosis [1]. The two most widely validated prognostic factors in compensated cirrhosis are the presence of clinically significant portal hypertension (CSPH) [3], defined as a hepatic venous pressure gradient ≥10 mmHg, and the presence of esophageal varices [1]. The gold standard tests to assess CSPH and varices are hepatic vein catheterism and endoscopy, respectively [4]. However, these tests, especially hepatic vein catheterism, are relatively invasive and impractical for the frequent follow-up of these patients. This has fostered the interest in the use of non-invasive tools for the assessment of patients with compensated cirrhosis.

Predicting clinically significant portal hypertension

In patients with compensated cirrhosis and without varices the presence of CSPH is associated with increased risk of variceal development and decompensation [3,5]. The 5-yr risk of decompensation in patients without CSPH is 10%, whereas this figure increases to 40% in patients with CSPH. In addition, patients with CSPH are at higher risk of developing hepatocellular carcinoma, as compared with patients without CSPH [6], and this was independent from the severity of cirrhosis. Identifying patients with CSPH is a useful way for the risk stratification of compensated cirrhotic patients. This information might be useful to inform the patient about the prognosis of his condition and to plan the frequency of the follow-up. In addition CSPH can be used to stratify patients in randomized trials, or to target the population of patients at higher risk of decompensation with specific treatments. However, it is important to note that, at present, the diagnosis of CSPH, in itself, does not have therapeutic consequences, since there are not effective therapeutic interventions to prevent decompensation or the development of varices.

Among patients with compensated cirrhosis the prevalence of CSPH is around 60-70 % in the recent series (Table I). This means that when applying any non-invasive diagnostic test to this population the pre-test probability of the condition is very high, making it unlikely that any of these test might be useful to exclude this condition (i.e. to decrease this pre-test probability to a post-test probability low enough, such as less than 10%, so that CSPH can be excluded). Therefore, non-invasive tests might help to identify patients with a very high probability of CSPH but are not useful to rule-out this condition. As an example, all the anatomical imaging methods (ultrasound, CECT or CE MRI) can identify abdominal porto-systemic collaterals, which are pathognomonic of CSPH. Similarly, the presence of varices at endoscopy unequivocally states the presence of CSPH [7]. However, the absence of porto-systemic collaterals on imaging or of varices at endoscopy does not allow to rule-out CSPH. Other signs of portal hypertension on imaging have been reviewed elsewhere [8]. This high pre-test probability of CSPH applies to patients with an established diagnosis of cirrhosis, but might be much lower if concepts such as “compensated advanced chronic liver

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disease", which would include patients at earlier stages of liver disease, are widely adopted [9]. In that case the role of non-invasive test in ruling-out CSPH should be re-evaluated.

Table I. Prevalence of clinically significant portal hypertension in recently published series.

Study	Patients Characteristics	Prevalence of Clinically Significant Portal Hypertension
Groszmann, et al 2005 [5]	Compensated cirrhosis, no varices	57%
Villanueva, et al [31]	Compensated cirrhosis	66%
Reiberger, et al 2012 [32]	Cirrhosis	63%
Augustin, et al 2014 [19]	Advanced fibrosis/ cirrhosis	65%
Berzigotti, et al 2013 [33]	Compensated Cirrhosis	67%
Colecchia, et al 2012 [23]	Compensated cirrhosis	65%
Kitson, et al 2015 [34]	Cirrhosis (91% Child A)	73%

Among non-invasive techniques, transient elastography has gained unparalleled momentum in the last few years. Transient elastography peformed with Fibroscan® (Echosens, Paris, France) is the elastography technique most thoroughly evaluated so far [10]. The equipment consists in an ultrasound transducer probe mounted on the axis of a vibrator. Mild amplitude and low frequency vibrations are transmitted to the liver tissue, inducing an elastic shear wave that propagates through the underlying liver tissue. Pulse-echo ultrasonic acquisitions are performed to follow the shear wave and measure its speed. The velocity of propagation of the wave is directly related to the tissue stiffness (the harder the tissue the faster the shear propagates), which is measured in kilo Pascals (kPa). A limitation of the technique is its applicability. It cannot be used in patients with ascites. In addition, in 15-20% of patients without ascites low quality values or no readings at all can be obtained, mainly due to obesity [11]. A thorough description of Fibroscan quality criteria can be found in recent guidelines [12]. The XL probe, specifically designed for obese patients, can overcome this problem but values are less validated and seam around 1 kPa lower than those obtained with the regular probe [13,14]. Though this technique is designed to assess liver fibrosis, factors different from liver fibrosis might influence liver stiffness values. Inflammation, cholestasis, liver congestion, and postprandial hyperemia increase liver stiffness independently of fibrosis [12].

Initial studies showed that Fibroscan values correlate with HVPG [15]. This correlation is good in HVPG values up to 10 mmHg, but it is much worse above these values [15]. This might be explained by the fact that liver stiffness would only reflect the contribution of increased hepatic resistance to portal hypertension, but not that of increased blood flow, more prominent in advanced portal hypertension [16].

Fibroscan has proved accurate for discriminating patients with and without CSPH, with a mean AUROC of 0.93 in a recent meta-analysis [17], and can be currently considered the backbone of non-invasive diagnosis of portal hypertension [8]. LS ≥21 kPa has a high specificity to predict CSPH [8]. However, for the reasons detailed above, no Fibroscan threshold can reliably exclude CSPH in patients with established cirrhosis. The combination of Fibroscan with spleen size and platelet count, either integrated in a single parameter [18] or as a pragmatic sequential algorithm [19], further improves LSM accuracy. For the first time in it sixth edition, the Baveno International Consensus in Portal Hypertension [20] included a recommendation to support the use of non-invasive tests to diagnose CSPH in patients with viral cirrhosis (LSM ≥20-25 kPa alone or in combination with spleen size and platelet count). In patients with non-viral cirrhosis, in particular with NAFLD, this has not been sufficiently validated. Since a new wave of new therapies for NAFLD will be soon available, with likely a high cost, validation non-invasive prediction of CSPH would be highly desirable to prioritize the patients in need for more urgent therapy. Other methods to measure liver stiffness, such as ARFI [21] and 2D-Real Time-Shear wave elastography [22] and new parameters (spleen stiffness) [23] have been proposed with initial promising results, but require further validation.

Though prediction of CSPH in itself is a relevant end-point, the ideal tool in this population would be a well-calibrated model (that could include non-invasive markers and clinical information) to predict the risk of clinical decompensation and of liver cancer in patients with cirrhosis of different etiologies [24].

Predicting varices and varices needing treatment

Endoscopy is the gold-standard for the diagnosis of varices, and it was widely accepted until very recently that every patient with cirrhosis should have a screening endoscopy [25]. However, endoscopy is uncomfortable for the patient, and the performance of a screening endoscopy in every patient with cirrhosis is a burden for endoscopy units. This will be a greater problem in the future, since the prevalence of cirrhosis is on the rise, due to the increasing incidence of NAFLD [26] and the earlier diagnosis of cirrhosis with non-invasive techniques. Therefore, there is a need for non-invasive tools to triage patients in need for endoscopy.

The diagnosis of the presence of any-size varices is a useful prognostic marker, since it is a sign of CSPH [7] and marks the transition from Stage 0 to Stage 1 cirrhosis as defined by D'Amico [2, 27]. However, it does not have specific therapeutic consequences, since treatment for preventing bleeding is only recommended in patients with large varices or in patients with small varices but high-risk stigmata (such as red signs over the varices) [20]. In addition, the prevalence (or pre-test probability) of varices is relatively high (30-40%), even in compensated patients. Again, this might be lower if the wider definition "compensated chronic advanced liver disease" is adopted in clinical practice [20]. In a recent study in patients with compensated Child-Pugh A cirrhosis and with a prevalence of varices of 40%, no non-invasive test (or combination of them) could identify a population with a low risk (<10%) of varices [28]. This means that if the goal is to predict any-size varices, then an endoscopy has to be performed. On the other hand, the prevalence of varices needing treatment (large varices or small varices with red signs) [20] in patients with compensated cirrhosis is much lower (around 15%) [28]. In this case, several non-invasive tests, including Fibroscan, platelet-to-spleen ratio, the combination of Fibroscan with platelet count and the combination of spleen diameter, platelet count and Fibroscan (LSPS, first described in [29]) have a high accuracy to exclude the presence of varices needing treatment [28]. Since spleen diameter is the parameter that is less consistently measured across centers, the Sixth Baveno Consensus Conference [20] recommended the use of a decision rule based on platelet count and Fibroscan to triage patients in need for endoscopy. In patients with compensated Child-Pugh A cirrhosis and with a liver stiffness < 20 kPa associated to platelet count> 150,000/mm3, endoscopy could be safely avoided, since the probability of finding high-risk varices is lower than 5% [20]. In a recent study, it was estimated that this strategy would reduce in around 30% the number of diagnostic endoscopies [28]. The consensus recommendations also suggested that yearly liver stiffness and platelet count could be used to decide when patients should undergo screening endoscopy [20]. It is important to note that this recommendation was made for all aetiologies of cirrhosis, though the studies assessing this issue were mainly done in patients with viral etiology. Also, this recommendation only applies to patients with compensated cirrhosis. All patients with decompensated cirrhosis should undergo endoscopy, since prevalence of varices is much higher.

As for CSPH, newer techniques such as liver stiffness assessed by ARFI [21] and spleen stiffness assessed either with ARFI [21] or Fibroscan [23,30] have been tested to assess for varices. Spleen stiffness is technically challenging, and quality criteria for spleen stiffness measurements are still lacking. Lastly, ideally non-invasive test should not only predict the presence of varices, but also the risk of variceal bleeding [24], but this has not been thoroughly assessed so far.

Conclusion

In patients with compensated cirrhosis non-invasive tests can be used to rule-in the presence of CSPH. However, they cannot identify a subpopulation of patients with a risk of having CSPH low enough so that CSPH can be safely excluded. All patients with decompensated cirrhosis should have a screening endoscopy, since the risk of having varices is very high. In patients with compensated cirrhosis, a simple prediction rule based on Fibroscan values and platelet count can be used to triage patients in need for endoscopy.

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