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Non-invasive diagnosis of esophageal varices after Baveno VI

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Review

ABSTRACT

A major complication of portal hypertension in patients with cirrhosis is the development of esophageal varices with the associated risk of variceal bleeding. Hence, the Baveno consensus on portal hypertension in its first five editions had recommended surveillance with periodic upper endoscopies in these patients to identify in a timely fashion the development of esophageal varices and initiate a primary prophylaxis strategy in those at a high risk of bleeding. For the first time, the Sixth Baveno Consensus on Portal Hypertension (Baveno VI) recommended using non-invasive tools to rule out the presence of varices with a high risk of bleeding. According to Baveno VI, surveillance endoscopy is not necessary for patients with "compensated advanced chronic liver disease" (cACLD) who have normal platelets (>150×10^9/L) and a liver stiffness measure (LSM) <20 kPa. In this review, we will briefly describe the currently available non-invasive methods to predict the presence of varices, such as serum tests, imaging, and elastography. We will also discuss the rationale that led to Baveno VI recommendation and describe the studies that have validated Baveno VI criteria after its publication. Finally, we will mention some potential caveats and suggest some areas for future research.

Keywords: Hypertension, portal, esophageal and gastric varices, liver cirrhosis, elasticity imaging techniques

INTRODUCTION

A major complication of portal hypertension in patients with cirrhosis is the development of esophageal varices, with an ensuing risk of variceal bleeding. Hence, the Baveno consensus on portal hypertension in its first five editions had recommended surveillance with periodic upper endoscopies in these patients to identify in a timely fashion the development of esophageal varices and initiate a primary prophylactic strategy in those at a high risk of bleeding. For the first time, the Sixth Baveno Consensus on Portal Hypertension (Baveno VI) recommended using non-invasive tools to rule out the presence of varices with a high risk of bleeding. According to Baveno VI, surveillance endoscopy is not necessary for patients with "compensated advanced chronic liver disease" (cACLD) who have normal platelets (>150´10^9/L) and a liver stiffness measure (LSM) <20 kPa (1). This recommendation has recently been endorsed by the American Association for the Study of Liver Diseases clinical guidance for the management of portal hypertensive bleeding in cirrhosis (2). Putting this recommendation into practice could spare 20%-40% of surveillance endoscopies (1), reducing the costs and burden of this invasive procedure. In this review, we will briefly describe the currently available non-invasive methods to predict the presence of varices, discuss the rationale that led to Baveno VI recommendation, describe the studies that have validated Baveno VI criteria after its publication, mention potential pitfalls, and finally suggest some areas for future research.

Stages of Chronic Liver Disease

The progression of chronic liver disease has been divided into stages, each of them with a different prognosis (3,4). The spectrum of chronic liver disease includes the onset of cACLD, the development of clinically significant portal hypertension (CSPH), the formation of varices, decompensation, and a "further decompensation" stage (Figure 1) (5). The term cACLD is new and it encompasses patients with early compensated cirrhosis as well as patients with severe fibrosis, as it is difficult

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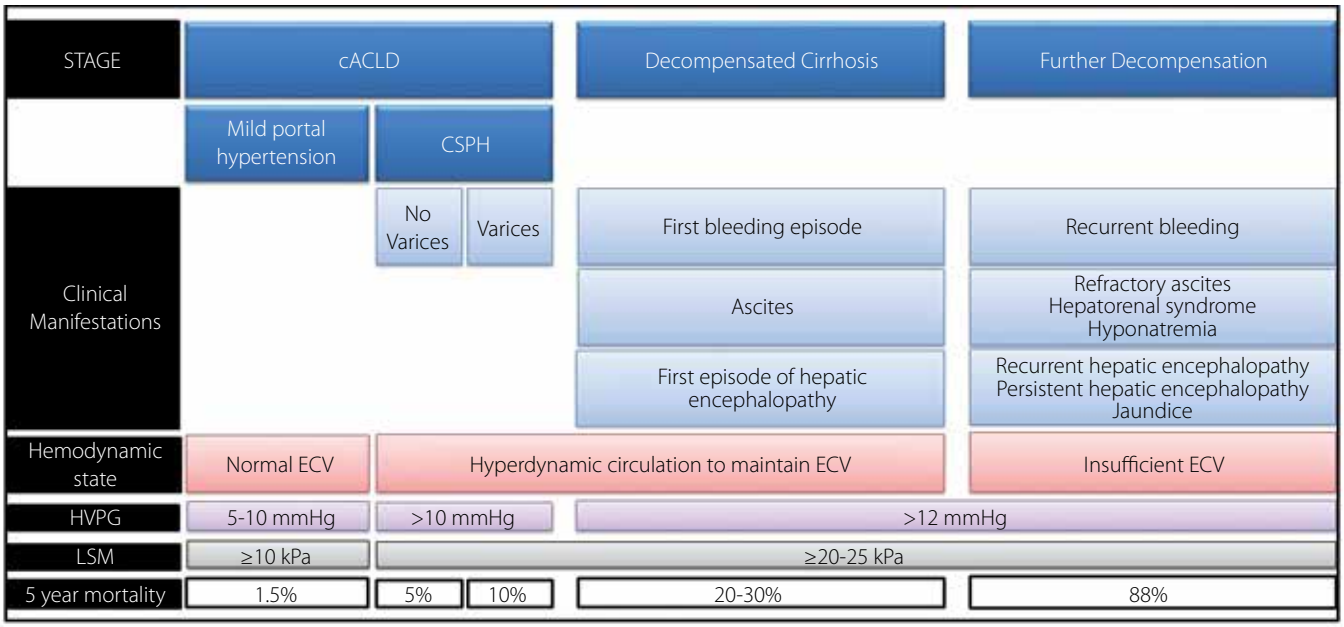

Figure 1. Stages of chronic liver disease
ECV: effective circulating volume

to distinguish between them (2). Baveno VI recommended a cutoff point of liver stiffness of <10 and >15 kPa to rule-out and rule-in cACLD, respectively (1).

Patients with compensated and decompensated cirrhosis have a mean survival of 12 and 2 years, respectively (3). The development of CSPH, defined as a hepatic venous pressure gradient (HVPG) ≥10 mmHg in patients with compensated cirrhosis, is an event that markedly worsens prognosis, as patients without CSPH do not develop esophageal varices or complications related to portal hypertension (6). Furthermore, it is above this threshold that patients with cirrhosis develop a hyperdynamic circulation. Therefore, CSPH is considered as the most important predictor of decompensation. The 5-year risk of decompensation in patients with and without CSPH is 40% and 10%, respectively (2,7). In addition to this, mortality in patients with CSPH who have developed varices is higher than in patients without varices (Figure 1) (8).

Patients with compensated cirrhosis develop varices at a rate of 7%-8% per year (9). In the case of patients with small varices (<5 mm), they progress to large varices at a rate of 10%-12% per year (10). Primary prophylaxis refers to strategies applied to prevent the first episode of variceal bleeding. Randomized controlled trials have shown that either non-selective beta-blockers or endoscopic variceal ligation is effective to reduce the risk of bleeding in patients with high-risk varices, either large varices or small varices with red signs (1). These varices are globally called varices needing treatment (VNT). There is no evidence to support a beneficial effect of beta- blockers in patients with no varices (11). When it comes to small varices without red signs, even though it may seem reasonable to start a pharmacological treatment to prevent variceal growth, yet there is no sufficient evidence to recommend this strategy. A meta-analysis of six studies failed to show any benefit of prescribing beta-blockers to patients with no or small varices. A subanalysis of the three studies which evaluated the progression from small to large varices was also negative. However, there was significant heterogeneity among the studies. Importantly, patients treated with beta-blockers had more adverse events than patients taking placebo (12,13). A more recent randomized clinically controlled trial, not included in the above-mentioned meta-analysis, showed that carvedilol was effective in delaying the progression of small to large esophageal varices (14). However, further confirmatory evidence would be needed before this can be recommended. At present, therefore, initiation of primary prophylaxis for variceal bleeding requires identifying the presence of VNT. To this end, the Baveno consensus has traditionally recommended surveillance with periodic upper endoscopies in patients with liver cirrhosis. However, Baveno VI, for the first time, recommended the use of non-invasive methods to triage patients who would benefit from surveillance endoscopy. Specifically, patients with an LSM <20 kPa and normal platelets (>150x10^9) are considered to have a probability of having VNT of <5% and do not need to undergo endoscopy. Of note, the patient has to be reassessed on a yearly basis (1).

Non-Invasive Methods for the Detection of VNT

There has been extensive research regarding the use of non-invasive methods to diagnose CSPH, the development of varices, and VNT. In this review, we will only address studies focused on identifying VNT because this is what triggers a therapeutic intervention, either initiating a beta-blocker or endoscopic variceal ligation (1). Non-invasive methods can roughly be categorized into four groups: serum tests, imaging, elastography, and the combination of these methods.

Table 1. Performance of non-invasive serological methods for prediction of high-risk varices*

Index	Identification of high-risk varices				
	Sensitivity	Specificity	PPV	NPV	AUC
APRI	57	56	35	76	0.57
FIB-4	71	56	40	82	0.63
Forns	70	62	58	82	0.66
Lok Score	71	68	50	84	0.70
Forns Index+Lok Score	84	73	58	91	0.80
Platelets					
<150,000	54	75	49	80	0.65
Fibro Test®**	92	21	33	86	0.77

Modified from reference 15.
*Includes small varices with high-risk stigmata and large varices.
**Only assessed prediction of large esophageal varices.
AUC: area under the curve; APRI: AST to platelet ratio index; PPV: positive predictive value; NPV: negative predictive value

Serological methods offer the advantage of accessibility and a reasonable cost, as they usually use simple parameters such as platelets, aspartate aminotransferase, alkaline aminotransferase, and demographic variables. Some of the most common parameters were studied extensively in a retrospective set of 510 and a prospective set of 110 patients with cirrhosis. The results of this study, as well as the accuracy of FibroTest® (BioPredictive, Paris, France) for detection of VNT, are shown in Table 1 (15,16).

In the case of imaging methods, some parameters measured by Doppler ultrasound have shown reasonable predictive value (17). However, the limitations of this method include that it is highly observer-dependent. Cross-sectional studies such as computed tomography (CT) and magnetic resonance imaging (MRI) are considered to be specific, but not sensitive enough. Moreover, MRI is not easily accessible, and CT exposes the patient to radiation (18).

Liver stiffness measure with elastographic methods has received massive attention in the last decade. The most commonly used method has been vibration-controlled transient elastography (TE) (FibroScan®; Echosens, Paris, France). LSM-TE has been extensively studied in the prediction of large varices with some variability in the results but in most studies showing a negative predictive value (NPV) above 90% (19-21). Nevertheless, studies were highly heterogeneous and this made it difficult to establish a defined threshold value that could be used to triage patients not needing endoscopy. In the case of spleen stiffness measurement (SSM), a meta-analysis showed a suboptimal performance for the detection of VNT, with sensibility and specificity of 81% and 66%, respectively, but, again, there was a significant heterogeneity among studies (22). A meta-analysis (presented so far in abstract form) compared SSM and LSM for the detection of varices and evidenced a better performance of SSM with an AUR of 0.88 and 0.80, respectively (23). Interestingly, one group requested the manufacturers of FibroScan® to modify the software to be able to detect SSM above 75 kPa. As a result, the NPV to exclude large varices increased to 100%. This encouraging result would require further confirmation (24). LSM assessed by other methods, such as Acoustic Radiation Force Impulse, shear-wave elastography, and magnetic resonance elastography, has shown promising results but available data is still scarce (25,26).

When trying to combine LSM-TE with serological tests, the best accuracy was obtained when adding the Lok Score, with an NPV of 94% for large varices (27). The combination of LSM-TE and SSM shows the same NPV of 94% for large varices (22). As expected, an algorithm that takes into account these three results (LSM-TE, SSM, and the Lok Score) increased its performance, with an NPV of 100% for large varices (28), but this algorithm lacks external validation.

The LSM-spleen diameter to platelet ratio score (LSPS) has shown an NPV of 93.3% for VNT in patients with HBV cirrhosis (29). The value of LSPS was recently confirmed in a study including mostly patients with hepatitis C cirrhosis (the ANTICIPATE study), where LSPS was able to identify patients with a very low probability of VNT (<5%) and had an area under the curve (AUC) of 0.79 (30).

The platelet-to-spleen ratio (PSR) is an easy-to-calculate index, described by Giannini and colleagues that initially showed an excellent performance for predicting varices (31). However, in validation studies, it did not perform as well when compared with other methods (30,32). A meta-analysis of 20 studies calculated a sensibility and specificity of 92% and 87%, respectively, but there was a significant heterogeneity among the included studies, with some of them showing NPV as low as 43% (33,34).

Despite this large corpus of data on the value of non-invasive tools to predict the presence of varices, rather surprisingly, these did not permeate clinical practice until very recently. A significant barrier for this lack of knowledge translation has been, in our view, the use of diagnostic performance measurements without direct clinical interpretation, such as sensitivity, specificity (which are reverse probabilities, indicating the chances of a positive or negative test based on the presence or absence of disease) (35), and receiver operating characteristics curves (which inform the discriminative capacity of the test across the spectrum of values, but not the chances of having the target condition) (36). Another barrier has been the reliance in single cut-offs derived from the dichotomization of the predictors. From a statistical point of view, it is not unexpected that every study would yield a different "optimal" cut-off to predict varices, which has limited both the application of these tests in practice and the combination of different studies in meta-analysis.

More recently, a multicenter Canadian-European study (the ANTICIPATE study) (30) addressed these issues by providing a different approach to report the performance of non-invasive tests. The bottom line of that study was to use risk prediction

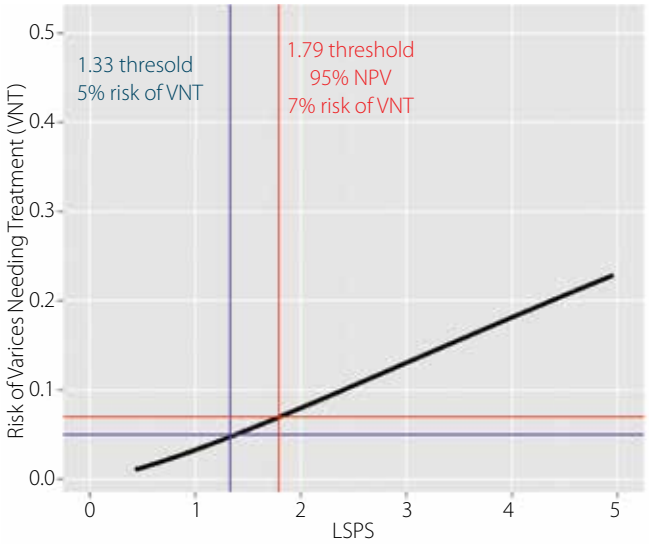

Figure 2. Illustration of the difference between a 5% risk threshold of VNT and a cut-off with 95% NPV to rule-out VNT. The plot shows the association between LSPS score and the risk of VNT. A cut-off of 95% NPV (an LSPS of 1.79) identifies a group of patients with a pooled risk of VNT of 5%. This means that, necessarily, a significant number of patients in this group would have a risk of VNT more than 5%. A decision threshold of 5% (an LSPS of 1.33) sets the maximum allowed risk to avoid endoscopy in 5% [based on data from the ANTICIPATE study (30)].

modeling techniques to address the relevant clinical question, i.e., what would be the risk of VNT given a certain value of different non-invasive tests. The assumption was that this could increase the applicability of these tests to define decision thresholds to triage patients in which endoscopy could be avoided. The study assessed in 518 patients with cACLD the accuracy of LSM-TE, a model combining LSM-TE and platelet count, LSPS, and PSR to predict the presence of VNT (that were present in 13% of the patients). The study provided nomograms for these 4 predictors, assigning a probability of VNT for each value of the predictors. This study was instrumental, both from a conceptual point of view and by providing a large international cohort of patients, in developing the Baveno VI criteria.

Rationale for the Baveno VI Criteria

An endoscopy is an invasive procedure that has the potential for complications and in some cases may be an unnecessary burden for some patients. Besides, with the increasing use of non-invasive methods, the population of patients with cACLD is growing, subsequently increasing the overload of endoscopy units (37,38). Although the ideal non-invasive tool would be able to select patients with a 0% risk of VNT, and therefore no patient with VNT would be missed, this is an unrealistic scenario. Taking this into account, during the Baveno Consensus Conference, it was agreed that a prediction rule that would be able to select patients with a risk of VNT lower than 5% and at the same time would save a relevant number of endoscopies could be a reasonable trade-off (1). It is important to emphasize that this criterion is different from a test with an NPV of 95% (Figure 2). In the case of a 95% NPV, the test would identify a group of patients with an overall risk of having varices of 5%. This 5% figure would be the mean of the pooled risks of the patients included in this group, that is, in this group, a relevant number of patients could have risk of varices over 5%, and this would not be in keeping with the "less than 5% risk" concept. This is different from a decision threshold of ≥5% risk to perform an endoscopy.

A second agreement was that the combined use of more than one non-invasive method would be better than any method alone (39,40). Finally, looking for simplicity and clinical practice applicability, Baveno VI considered that a simple rule using platelets and LSM-TE would be more useful than other combinations, as methods incorporating spleen diameter/volume had the inconvenience that these ultrasound measurements are highly observer-dependent and therefore subject to variability. In addition, it was taken into account that, although very promising, methods measuring SSM were still undeveloped and had a high failure rate. The Baveno VI consensus, thus, proposed that patients with compensated cirrhosis do not need surveillance endoscopy if platelets are in the normal range (>150x10^9/L) and LSM-TE is <20 kPa, as this combination identifies the 5% risk threshold of having VNT (1).

Prospective Validation of Baveno VI Recommendation

After the Baveno VI Conference, there have been a number of studies validating the recommendation of circumventing upper endoscopy in those patients with cACLD with normal platelets and LSM-TE <20 kPa. These studies have targeted different cACLD populations as can be seen by the variable prevalence of varices among them, which could be as low as 23% and as high as 65%. Of note, studies with a prevalence of varices more than 40% probably included patients with advanced cirrhosis, in whom using non-invasive tests to triage patients for endoscopy is not recommended. The main etiologies of cACLD were viral and alcohol-related. Overall, the percentage of missed VNT has been 2% or less in all of them, in keeping with the proposed <5% threshold defined by Baveno VI. In these studies, around 20% of endoscopies could have been saved by applying the criteria (41).

Maurice et al. (42) showed in 310 patients with cirrhosis an NPV of the Baveno criteria of 98%. Of note, 11% of the patients had decompensated cirrhosis. In a subsequent study, Perezzo et al. (43) included 99 patients with HCV cACLD. NPV was 100% and adding SSM to the model did not provide additional benefit. Tosetti et al. (44) showed a 100% sensitivity and NPV of Baveno criteria in 165 patients with virus-related cACLD. When the authors modified the cut-off points of LSM to <25 kPa and platelets to >125x10^9/L, NPV was still 100%, which would suggest that maybe less conservative cut-off points could be used. However, data-driven modification of a set of criteria generally leads to over-optimistic performance estimates. Turco et al. (45) also validated Baveno VI criteria in two different cohorts, one in the United States consisting of 205 patients and another in Italy consisting of 111 patients, achieving an NPV of 100%.

Again, a data-driven modification of the thresholds to <21 kPa and >110x10^9/L platelets did not decrease the performance of the criteria. They additionally proposed that in those patients with results above these cut-off points, an MELD (model for end-stage liver disease) score lower than 7 could be used to rule out the presence of VNT. The use of these expanded criteria would have resulted in an increase from 22% to 50% in the number of saved endoscopies. In the study by Ding et al. (38), an NPV of 100% was achieved in both the training (n=71) and validation (n=200) cohorts using cut-off points of ≤25 kPa and ≥100x10^9/L for platelets.

A recent random-effects model meta-analysis that included 15 studies that used platelet count and LSM to identify patients with esophageal varices found that the percentage of missed VNT was no more than 4%. A 4.5-fold risk reduction of VNT in patients with normal platelets and low stiffness was calculated, with a sensitivity of 93%, specificity of 30%, NPV of 97%, and positive predictive value (PPV) of 14%. When including only studies using the thresholds proposed by Baveno VI, the percentage of missed VNT was 3.1%. Of note, there was no significant heterogeneity among the studies. However, the definition of VNT was different among the studies and although most were conducted in compensated patients, four of them also included decompensated patients in the analysis (46).

Limitations of the Baveno Criteria

When compared with the gold standard for diagnosing VNT (i.e., endoscopy), the recommendation made by Baveno VI is not 100% accurate and has some limitations, discussed below.

First, LSM-TE may show day-to-day variations (47) and might additionally vary with the position of the probe (48), body mass index, and the operator (39). In addition to this, LSM-TE may not be technically feasible in up to 20% of patients because of obesity, which is a problem due to the fact that NAFLD (non-alcoholic fatty liver disease) is becoming the most common liver disease. This problem has been partially addressed by using the XL probe, which can increase success rate to almost 85% (49). Nevertheless, this probe may give lower stiffness measures and studies that have validated LSM-TE for the prediction of high-risk varices have used the M probe, questioning whether the same thresholds can be applied with both probes.

Second, in order for LSM-TE to be reliable, it should be done by an experienced operator, defined as someone who has performed more than 100 examinations (50). Moreover, access to TE is limited in under-developed countries, where applicability of less accurate but more accessible models will need to be intentionally validated.

Third, as stated by European Association for the Study of Liver guidelines, TE should always be interpreted according to the clinical context and considering the results of other tests. It is important to identify *a priori* any comorbidity or condition that may affect the results of liver stiffness and/or platelet count, as that would make its results unreliable. Congestive heart failure, transaminases flares, post-prandial status, extrahepatic cholestasis, and excessive alcohol intake can falsely elevate the measurement of LSM (50). On the other hand, several factors might have a significant impact in platelet count. HCV/HBV and HIV infections may lead to thrombocytopenia by immune-mediated mechanisms, independent of portal hypertension, whereas a past splenectomy might falsely normalize the platelet count in the presence of severe portal hypertension (51,52). Indeed, in the study done by Maurice and colleagues, one of the two cases, where VNT was missed by the Baveno VI criteria, had a previous splenectomy (42).

Finally, it is important to emphasize that the recommendations have been designed to be applied in patients with cACLD and not in patients with decompensated cirrhosis. The post-test probability of VNT <5% with the Baveno VI criteria may not apply to patients with decompensated cirrhosis, where the pre-test probability of VNT is much higher.

Future Areas of Research

In patients at low risk of VNT, the Baveno VI consensus suggests yearly re-assessment of the non-invasive tests to assess for potential disease progression. Only long-term follow-up studies will be able to determine whether this strategy is able to identify the development of VNT in a patient who was previously considered at low risk. Along these lines, a recent study (53) evaluating 156 patients without VNT who had LSM and platelets within Baveno VI criteria showed that the decrease in platelets and/or the increase in LSM during follow-up was associated with progression of portal hypertension, defined as the appearance and/or growth of varices. On the other hand, with emerging therapies able to improve fibrosis and subsequently LSM, such as direct antiviral agents in the case of HBV/HCV or obeticholic acid in NAFLD, it will be necessary to assess whether screening endoscopies can be avoided when the patient reaches an LSM of <20 kPa, as the post-treatment relationship between elastography and fibrosis, portal hypertension, and/or varices might not be the same as in untreated patients (54-56).

The role of etiology is another major source of controversy. The predominant etiology in most of the studies that have validated the Baveno VI recommendation has been viral hepatitis, alcohol being the second in frequency. Initial results show that the same thresholds can be used independently of the etiology of the liver disease (30,42), but studies specifically designed to validate Baveno prediction rule in other etiologies are needed. Finally, maybe less stringent criteria can be applied using a lower cut-off of platelets and/or a higher cut-off point for LSM, to spare more endoscopies, but that would again require further modeling and validation studies. The ultimate validation of this strategy would require a randomized controlled trial, comparing the incidence of the relevant outcome (variceal bleeding)

between a group using this strategy to triage patients for endoscopy and a group subject to universal endoscopy policy, including a cost and quality-of-life analysis (30).

In conclusion, Baveno VI recommendations to triage patients with compensated cirrhosis in need of screening endoscopy have proven robust in the real-world setting. Further studies are needed to address specific concerns such as its validity in non-viral etiologies of cACLD, in studies done with the XL probe, and whether different thresholds may be used to increase the number of surveillance endoscopies that can be spared. In addition to this, validation of models that do not incorporate LSM-TE is still needed for expanding their use in places where elastography is not accessible.

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REFERENCES

1. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63: 743-52. [CrossRef]
2. Garcia-Tsao G, Abraldes J, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017; 65: 310-35. [CrossRef]
3. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44: 217-31. [CrossRef]
4. D'Amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014; 39: 1180-93. [CrossRef]
5. Abraldes J. The value of non-invasive tests for risk stratification in patients with compensated cirrhosis. Mamara Medical Journal 2016; 29: 55-8. [CrossRef]
6. Hernandez-Gea V, Berzigotti A. Clinical evaluation and prognosis. Dig Dis 2015; 33: 515-23. [CrossRef]
7. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007; 133: 481-8. [CrossRef]
8. Bruno S, Zuin M, Crosignani A, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long-term prospective study. Am J Gastroenterol 2009; 104: 1147-58. [CrossRef]
9. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005; 353: 2254-61. [CrossRef]
10. Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol 2003; 38: 266-72. [CrossRef]
11. Garcia-Tsao G. Preventing the development of varices in cirrhosis. J Clin Gastroenterol 2007; 41(Suppl 3): S300-S4.
12. Qi XS, Bao YX, Bai M, Xu WD, Dai JN, Guo XZ. Nonselective beta-blockers in cirrhotic patients with no or small varices: A meta-analysis. World J Gastroenterol 2015; 21: 3100-8. [CrossRef]
13. Di Pascoli L, Buja A, Bolognesi M, et al. Cost-effectiveness analysis of beta-blockers vs endoscopic surveillance in patients with cirrhosis and small varices. World J Gastroenterol 2014; 20: 10464-9. [CrossRef]
14. Bhardwaj A, Kedarisetty CK, Vashishtha C, et al. Carvedilol delays the progression of small oesophageal varices in patients with cirrhosis: a randomised placebo-controlled trial. Gut 2016: pii: gutjnl-2016-311735.
15. Sebastiani G, Tempesta D, Fattovich G, et al. Prediction of oesophageal varices in hepatic cirrhosis by simple serum non-invasive markers: Results of a multicenter, large-scale study. J Hepatol 2010; 53: 630-8. [CrossRef]
16. Thabut D, Trabut JB, Massard J, et al. Non-invasive diagnosis of large oesophageal varices with FibroTest in patients with cirrhosis: a preliminary retrospective study. Liver Int 2006; 26: 271-8. [CrossRef]
17. Piscaglia F, Donati G, Serra C, et al. Value of splanchnic Doppler ultrasound in the diagnosis of portal hypertension. Ultrasound Med Biol 2001; 27: 893-9. [CrossRef]
18. de Franchis R. Non-invasive (and minimally invasive) diagnosis of oesophageal varices. J Hepatol 2008; 49: 520-7. [CrossRef]
19. Castera L, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. J Hepatol 2012; 56: 696-703. [CrossRef]
20. Shi KQ, Fan YC, Pan ZZ, et al. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. Liver Int 2013; 33: 62-71. [CrossRef]
21. Kazemi F, Kettaneh A, N'Kontchou G, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006; 45: 230-5. [CrossRef]
22. Singh S, Eaton JE, Murad MH, Tanaka H, Iijima H, Talwalkar JA. Accuracy of spleen stiffness measurement in detection of esophageal varices in patients with chronic liver disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014; 12: 935-45 e4.
23. Ma X, Wang L, Wu H, et al. Spleen stiffness is superior to liver stiffness for predicting esophageal varices in chronic liver disease: a meta-analysis. PloS One 2016; 11: e0165786.
24. Calvaruso V, Bronte F, Conte E, Simone F, Craxi A, Di Marco V. Modified spleen stiffness measurement by transient elastography is associated with presence of large oesophageal varices in patients with compensated hepatitis C virus cirrhosis. J Viral Hepat 2013; 20: 867-74. [CrossRef]
25. Ronot M, Lambert S, Elkrief L, et al. Assessment of portal hypertension and high-risk oesophageal varices with liver and spleen three-dimensional multifrequency MR elastography in liver cirrhosis. Eur Radiol 2014; 24: 1394-402. [CrossRef]
26. Elkrief L, Rautou PE, Ronot M, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology 2015; 275: 589-98. [CrossRef]

27. Stefanescu H, Grigorescu M, Lupsor M, et al. A new and simple algorithm for the noninvasive assessment of esophageal varices in cirrhotic patients using serum fibrosis markers and transient elastography. J Gastrointestin Liver Dis 2011; 20: 57-64.
28. Stefanescu H, Radu C, Procopet B, et al. Non-invasive menage a trois for the prediction of high-risk varices: stepwise algorithm using lok score, liver and spleen stiffness. Liver Int 2015; 35: 317-25. [CrossRef]
29. Kim BK, Han KH, Park JY, et al. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. Am J Gastroenterol 2010; 105: 1382-90. [CrossRef]
30. Abraldes JG, Bureau C, Stefanescu H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The "Anticipate" study. Hepatology 2016; 64: 2173-84. [CrossRef]
31. Giannini E, Botta F, Borro P, et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. Gut 2003; 52: 1200-5. [CrossRef]
32. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 2013; 144: 102-11. [CrossRef]
33. Ying L, Lin X, Xie ZL, Hu YP, Shi KQ. Performance of platelet count/spleen diameter ratio for diagnosis of esophageal varices in cirrhosis: a meta-analysis. Dig Dis Sci 2012; 57: 1672-81. [CrossRef]
34. de Mattos AZ, de Mattos AA. Platelet count/spleen diameter ratio: is there sufficient evidence for its use? Dig Dis Sci 2012; 57: 2474.
35. Moons KG, Harrell FE. Sensitivity and specificity should be de-emphasized in diagnostic accuracy studies. Acad Radiol 2003; 10: 670-2. [CrossRef]
36. Mallett S, Halligan S, Thompson M, Collins GS, Altman DG. Interpreting diagnostic accuracy studies for patient care. BMJ 2012; 345: e3999.
37. Rudler M, Benosman H, Lebray P, et al. Screening for esophageal varices in patients newly diagnosed with cirrhosis in 2011:84% of upper gastrointestinal endoscopies are futile. Hepatology 2011; 54(Suppl): 935A.
38. Ding NS, Nguyen T, Iser DM, et al. Liver stiffness plus platelet count can be used to exclude high-risk oesophageal varices. Liver Int 2016; 36: 240-5. [CrossRef]
39. Perazzo H, Fernandes FF, Gomes A, Terra C, Perez RM, Figueiredo FA. Interobserver variability in transient elastography analysis of patients with chronic hepatitis C. Liver Int 2015; 35: 1533-9. [CrossRef]
40. de Franchis R, Dell'Era A. Invasive and noninvasive methods to diagnose portal hypertension and esophageal varices. Clin Liv Dis 2014; 18: 293-302. [CrossRef]
41. Augustin S, Pons M, Genesca J. Validating the Baveno VI recommendations for screening varices. J Hepatol 2017; 66: 459-60. [CrossRef]
42. Maurice JB, Brodkin E, Arnold F, et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. J Hepatol 2016; 65: 899-905. [CrossRef]
43. Perazzo H, Fernandes FF, Castro Filho EC, Perez RM. Points to be considered when using transient elastography for diagnosis of portal hypertension according to the Baveno's VI consensus. J Hepatol 2015; 63: 1048-9. [CrossRef]
44. Tosetti G, Aghemo A, Lampertico P, et al. Abstract. Screening of oesophagogastric varices in virus-related compensated advanced chronic liver disease: Baveno VI criteria and beyond. Hepatology 2016; 64: 843A.
45. Turco L JP, de Oliveira AL, Garcia-Tsao G. Abstract. Validating and refining non-invasive Baveno criteria for ruling out high-risk varices. Hepatology 2016; 64.
46. Marot A, Trepo E, Doerig C, Schoepfer A, Moreno C, Deltenre P. Liver stiffness and platelet count for identifying patients with compensated liver disease at low risk of variceal bleeding. Liver Int 2016; DOI: 10.1111/liv.13318. [Epub ahead of print] [CrossRef]
47. Nascimbeni F, Lebray P, Fedchuk L, et al. Significant variations in elastometry measurements made within short-term in patients with chronic liver diseases. Clin Gastroenterol Hepatol 2015; 13: 763-71 e1-6.
48. Ingiliz P, Chhay KP, Munteanu M, et al. Applicability and variability of liver stiffness measurements according to probe position. World J Gastroenterol 2009; 15: 3398-404. [CrossRef]
49. Lombardi R, Buzzetti E, Roccarina D, Tsochatzis EA. Non-invasive assessment of liver fibrosis in patients with alcoholic liver disease. World J Gastroenterol 2015; 21: 11044-52. [CrossRef]
50. European Association for Study of L, Asociacion Latinoamericana para el Estudio del H. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015; 63: 237-64. [CrossRef]
51. Baydoun A, Maakaron JE, Halawi H, Abou Rahal J, Taher AT. Hematological manifestations of celiac disease. Scand J Gastroenterol 2012; 47: 1401-11. [CrossRef]
52. Joo EJ, Chang Y, Yeom JS, Lee YG, Ryu S. Hepatitis B infection is associated with an increased incidence of thrombocytopenia in healthy adults without cirrhosis. J Viral Hepat 2017; 24: 253-8. [CrossRef]
53. Thabut D, Layese R, Bourcier V, et al. Abstract. New recommendations of Baveno VI conference for the screening of portal hypertension: An independent sequential vaidation in pateints with compensated viral cirrhosis taking into account virological status (ANRS CO12 CIRVIR COHORT). J Hepatol 2016; 64: 159-82. [CrossRef]
54. D'Ambrosio R, Aghemo A, Fraquelli M, et al. The diagnostic accuracy of Fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. J Hepatol 2013; 59: 251-6. [CrossRef]
55. Bachofner JA, Valli PV, Kroger A, et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2016; DOI: 10.1111/liv.13256. [Epub ahead of print] [CrossRef]
56. Knop V, Hoppe D, Welzel T, et al. Regression of fibrosis and portal hypertension in HCV-associated cirrhosis and sustained virologic response after interferon-free antiviral therapy. J Viral Hepat 2016; 23: 994-1002. [CrossRef]