TITLE PAGE

Title

Non-invasive prediction of high-risk varices in patients with primary biliary cholangitis and primary sclerosing cholangitis

Short Title

Prediction of varices in cholestatic liver diseases

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ABSTRACT

Background: Baveno-VI guidelines recommend that patients with compensated cirrhosis with liver stiffness by transient elastography (LSM-TE) <20kPa and platelets >150,000/mm3 do not need a esophagogastroduodenoscopy (EGD) to screen for varices, since the risk of having varices needing treatment (VNT) is <5%. It remains uncertain if this tool can be used in patients with cholestatic liver diseases (ChLDs): primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). These patients may have a pre-sinusoidal component of portal hypertension that could affect the performance of this rule. In this study we evaluated the performance of Baveno-VI, expanded Baveno-VI (LSM-TE <25 kPa and platelets >110,000/mm3), and other criteria in predicting the absence of VNT.

Methods: This was a multicenter cross-sectional study in four referral hospitals. We retrospectively analyzed data from 227 patients with compensated advanced chronic liver disease (cACLD) due to PBC (n=147) and PSC (n=80) that had paired EGD and LSM-TE. We calculated false negative rate (FNR) and number of saved endoscopies for each prediction rule.

Results: Prevalence of VNT was 13%. Baveno-VI criteria had a 0% FNR in PBC and PSC, saving 39% and 30% of EGDs, respectively. In PBC the other LSM-TE-based criteria resulted in FNRs >5%. In PSC the expanded Baveno criteria had an adequate performance. In both conditions LSM-TE-independent criteria resulted in an acceptable FNR but saved less EGDs.

Conclusions: Baveno-VI criteria can be applied in patients with cACLD due to ChLDs, which would result in saving 30-40% of EGDs. Expanded criteria in PBC would lead to FNRs>5%.

Key Words: Liver cirrhosis, biliary; hypertension, portal; elasticity imaging techniques; esophageal and gastric varices; endoscopy, gastrointestinal.

STUDY HIGHLIGHTS

1 WHAT IS CURRENT KNOWLEDGE

-Baveno-VI criteria recommend using liver stiffness and platelet count to determine the need for screening esophagogastroduodenoscopy (EGD) in patients with compensated cirrhosis

-It remains uncertain if this tool can be safely used in patients with primary biliary cholangitis or primary sclerosing cholangitis

2 WHAT IS NEW HERE

-Baveno-VI criteria to triage patients for EGDs can be applied in PBS/PSC

-Expanded criteria in patients with PBC results in an unacceptable number of missed varices

-Expanded Baveno-VI criteria have an adequate performance in PSC

-In PSC a rule based solely on a platelet count could be potentially used if validated

INTRODUCTION

Variceal bleeding is one of the most feared complications of cirrhosis. Since there are effective treatments for the primary prevention of variceal bleeding, until recently a screening esophagogastroduodenoscopy (EGD) was recommended in all patients with cirrhosis to detect those patients at risk of developing variceal rupture [1]. However, with the progressive introduction of non-invasive methods for the diagnosis of cirrhosis, an increasing number of patients are diagnosed at an earlier, fully compensated stage of the disease, where the prevalence of varices needing treatment (VNT, *i.e.* small varices with high risk stigmata and/or large varices) is lower, resulting in a large number of unnecessary screening endoscopies. Indeed, in recent series of patients with compensated cirrhosis, the prevalence of VNT was as low as 5-15% [2, 3]. This established a need for non-invasive tests (NITs) to triage patients for EGD. Thus, the experts at the Baveno VI consensus conference agreed that it would be acceptable to restrict endoscopic screening to those patients with a predicted risk (on the basis of NITs) of >5% of having VNT [4, 5]. Of note, this 5% threshold was recently endorsed by the American Gastroenterological Association in their guidelines for the use of liver stiffness measurement by transient elastography (LSM-TE) [6]. On this basis the Baveno VI consensus guidelines (and more recently AASLD 2016 guidelines) recommend that in patients with compensated cirrhosis, and with a LSM-TE <20 kPa and platelet count >150 $X10^9$/L, screening EGD can be avoided [4, 5]. This rule has proven robust in the real-world setting in patients with compensated advanced chronic liver disease (cACLD) of viral and alcohol related etiologies, and would save around 20% of screening endoscopies [7]. However, whether this recommendation can be extrapolated to other etiologies of liver disease remains to be defined.

Cholestatic autoimmune liver diseases (ChLDs) are a rare etiology of chronic liver disease that comprise primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). The low prevalence of these conditions has made it difficult to evaluate the performance of Baveno VI criteria in these patients [8]. Hence, most of the studies that were used as a background to support Baveno VI criteria and most of the studies that have validated them afterwards included only a limited number of patients with ChLDs [9]. In the ANTICIPATE study, a large (n=518) multicenter retrospective study assessing different non-invasive prediction tools for the prediction of varices and significant portal hypertension, only 9 patients had ChLDs [9]. In a subsequent study

assessing whether Baveno VI crtieria could be extended, only 20 out of 901 patients had ChLDs [10]. Patients with ChLDs can have other factors that may modify the association between LSM-TE and portal hypertension. On the one hand, a pre-sinusoidal component of portal hypertension has been described in patients with PBC, which might not be properly sensed by LSM-TE [11]. On the other hand, higher cutoff points of LSM-TE are usually present in patients with ChLDs when compared to other etiologies for similar stage of fibrosis or degree of portal hypertension, suggesting that the cholestasis inherent to these patients may lead to overestimation of fibrosis by LSM-TE [12]. These could be considered impediments to extrapolate Baveno VI recommendations [13, 14]. As a result, it is still controversial if Baveno VI criteria can be applied in these patients. The recently published European Association for the Study of the Liver guidelines on PBC advocate for their use [6, 15], while some experts call for caution until validation in this specific population is available [13].

The aim of this study was to evaluate the performance of Baveno VI criteria for triaging patients for EGD in patients with PBC and PSC. In addition, we aimed at assessing if the association between LSM-TE, platelet count, and the presence of VNT in patients with ChLDs is different from that seen in patients with predominantly viral disease. Finally, we tested the performance of recently published additional prediction rules to assess if Baveno VI criteria (which are considered conservative) could be expanded [10, 16-18].

PATIENTS AND METHODS

Study population

This was a multinational retrospective cross-sectional study including patients from four different hospitals: Royal Free Hospital (London, United Kingdom); Vall d'Hebrón Hospital (Barcelona, Spain); University of Alberta Hospital (Edmonton, Canada), and Bern University Hospital (Bern, Switzerland). The institutional review board of each participating center approved the study. A search was performed at each institution's electronic system to identify patients with the diagnosis of ChLDs with visits between March 2009 and December 2017. We included patients with cACLD due to PBC or PSC between 18 and 80 years old and that had paired LSM-TE, EGD, and laboratory results (cell blood count, liver tests), all of them within a 1 year time frame. PBC was defined by a cholestatic liver panel in presence of anti-mitochondrial antibodies and/or a positive liver biopsy. PSC was defined as a cholestatic liver panel in the presence of a compatible image

(magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography) and/or a liver biopsy where secondary causes of sclerosing cholangitis were excluded. The diagnosis of cACLD was based on a LSM-TE >10 kPa. Patients were excluded if they had had a previous event of decompensation (variceal bleeding, ascites, hepatic encephalopathy, or jaundice), if they had been started on a primary prophylaxis strategy for variceal bleeding (either banding or non-selective beta blocker) at the time of the assessment, or if the LSM-TE was poorly reliable according to criteria proposed by Boursier and colleagues (*i.e.* IQR/MED>30% in patients with LSM-TE $\geq$ 7.2 kPa) [19]. The operational definition of VNT comprised small esophageal varices with high risk stigmata, large esophageal varices, with or without high risk stigmata, and/or gastric varices.

Prediction rules and models.

We evaluated the performance of the prediction rules shown in Table 1 [4, 10, 16-18, 20, 21]. To further assess if in patients with ChLDs the association between LSM-TE and VNT is comparable to other etiologies of liver disease, we tested the performance in the present series of the risk prediction model developed in the ANTICIPATE study, using platelet count and LSM-TE [9]. In this model, the probability of VNT is calculated based on the formula: Probability of VNT= $1/(1+e^{-logit})$ where logit= -4.458421 + 1.3193115 * ln(LSM-TE in kPa)-0.016306902 * platelet count (in n $X10^9$/L, with a cap of 150).

Statistical analysis

Numeric variables were described as mean and standard deviation, and categorical variables as absolute and relative frequencies. Based on contingency tables, we calculated the false negative rate (FNR) and the number of endoscopies that could have been saved with each of the proposed prediction rules. The performance of the ANTICIPATE study continuous predictive model was assessed with the c-statistic (discrimination) and by plotting the predicted vs observed rates of VNT (calibration). Since the ANTICIPATE study model was significantly miscalibrated in the PBC sample (the model underpredicted the risk of VNT), it was recalibrated with logistic regression [22]. The recalibrated model was internally validated, and the coefficients shrunk with bootstrapping (200 resamplings). The association between platelet count and VNT in patients with PBC was modeled with logistic regression and also validated with bootstrapping. To assess the rationale of adding the Model for End-stage Liver Disease score (MELD), the Original Mayo Risk Score, or bilirubin to platelet count, as in the Jangouk [18], Levy [20] and Lindor [21] models,

respectively, we evaluated the added predictive value of these variables in a logistic regression analysis. Analysis was conducted with SPSS 20.0 (IBM Corp., Armonk, NY, US) and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria), using the rms package [23].

RESULTS

General characteristics of the study sample

Out of 1123 patients identified by the search strategy, 367 fulfilled inclusion criteria. 140 were excluded from the analysis for the reasons shown in Figures 1a (PBC) and 1b (PSC). Finally, 147 patients with PBC and 80 patients with PSC were included. Table 2 shows the baseline characteristics of the patients. The prevalence of VNT was 14% in patients with PBC and 12% in patients with PSC. This is comparable to recent series including patients with chronic liver disease predominantly due to hepatitis C [10].

Performance of prediction rules in PBC patients

Table 3 shows the performance of the different criteria for triaging PBC patients for EGD. Baveno VI criteria had a 0% FNR. Triaging patients for EGD according to these criteria would have saved 39% of the procedures. Expanded Baveno criteria increased the number of endoscopies that could have been saved to 58%, but at the expense of an increase in the FNR (6%).

The criteria proposed by Tosetti et al. would have saved the same number of endoscopies that the Baveno expanded criteria preserving an acceptable FNR of 1%. Ding et al. criteria application was associated with a FNR of 7%. The Jangouk et al. and Levy et al. criteria, which do not include LSM-TE, had still an adequate FNR, but would have saved only 30% endoscopies. To evaluate the rationale of these constructs, we assessed if MELD added predictive capacity to platelet count. Including either the Original Mayo Risk Score or MELD in a model with platelet count did not improve the prediction of platelet count alone (See Supplementary Results), suggesting that the Jangouk and Levy models have a good performance purely based on the platelet criteria.

The use of the ANTICIPATE continuous predictive model (with a risk threshold of 5%) was also associated with a 0% FNR, and would have saved 45% of the endoscopies. The c-statistic was 0.83 (excellent discrimination). However, the model calibrated accurately the risk of VNT only up to the 5% risk threshold (Figure 2a). Above this threshold, the risk of VNT was markedly underpredicted by the ANTICIPATE model (i.e., patients with a predicted risk of VNT of 10% and 20% had an observed risk of varices of 20% and 40%, respectively). This suggests that the association between LSM-TE values, platelet count, and the risk of VNT is different in patients with PBC as compared with what was found in patients in which hepatitis C was the predominant etiology [9].

Therefore, we attempted to remodel this association by recalibrating the original ANTICIPATE model as described in methods. The corrected model was: 0.45012806+1.0361671*(linear predictor of the anticipate model). A nomogram to calculate the risk of VNT according to the corrected model is shown online as supplementary material (See supplementary Figure 1). Calibration of the corrected model was very good (Figure 2b). With this new model, the pointwise predicted risk of VNT for a LSM-TE value of 25 kPa and a platelet count of 110 $X10^9$/L was 16% (95% CI 10-25), similar to that of values of LSM-TE of 30 kPa and platelets of 125 $X10^9$/L. This suggests that the systematic use of the expanded Baveno VI criteria or the Tosetti criteria would be associated with a substantially higher than 5% risk of missing VNT, and would be inadequate to triage patients with PBC for EGD. Pointwise prediction for LSM-TE value of 20 kPa and a platelet count of 150 $X10^9$/L was 7% (95% CI 4-13). Using a 5% risk threshold with the corrected model would have saved 34% of the endoscopies, with a FNR of 0%.

Performance of prediction rules in PSC patients

Table 3 shows the performance of the different criteria for triaging PSC patients for EGD. Baveno VI criteria had a FNR of 0%, and would save 30% of the endoscopies. Expanded Baveno VI criteria would increase the number of saved endoscopies at the expense of a small increase in the FNR. The prediction rules proposed by Tosetti et al. and Jangouk et al would be associated with a 5% FNR. Lindor criteria saved the same proportion of endoscopies with a FNR of 0%. Of note, neither MELD nor bilirubin improved the predictive value of platelet count alone (See Supplementary Results).

The performance of the ANTICIPATE continuous model was good in terms of discrimination (c-statistic 0.80) and calibration (Figure 3), suggesting that the association between platelet count, LSM-TE, and VNT is not relevantly different in patients with PSC as compared with patients with predominantly viral etiology. Using the proposed 5% risk threshold 33% of endoscopies would have been saved in this sample, with a FNR of 0%.

Platelet count alone had a high discriminative value (c-statistic 0.85), higher than that of the ANTICIPATE model. We then modeled the association between platelet count and VNT. A pointwise value of 200 $X10^9$/L platelet count was associated with a 5% risk of VNT (95% CI 1-14%) (See Supplementary Figure 2). Triaging patients for EGD with a Platelet count <200 $X10^9$/L would have resulted in saving 50% of the endoscopies in this sample, with a 2.5% FNR.

DISCUSSION

In this study we evaluated the performance of the Baveno VI and other criteria for the non-invasive prediction of VNT in patients with cACLD due to autoimmune ChLDs, specifically PBC and PSC. The studies in which these criteria were based included a low number of patients with PBC and PSC. Despite the lack of data, their use has been recommended in the most recent guidelines for the management of PBC [15]. In addition, recent studies proposed to expand Baveno VI criteria with less conservative parameters [10]. Therefore, there is a need for validation studies of the original and the expanded criteria specifically in patients with ChLDs. We decided to assess PBC and PSC separately as their background histology and natural history are different.

In the present series of patients, Baveno VI criteria had a 0% FNR in both PBC and PSC patients, suggesting that they can be applied in these settings to triage patients for EGD, saving 39% and 30% of EGDs, respectively. If the ANTICIPATE-Plt-LS model had been used to restrict EGD to patients with a predicted risk of VNT> 5%, 45% and 33% of the EGDs would have been saved in PBC and PSC patients, respectively, with a 0% FNR in both conditions. The advantage of this model is that it provides continuous predictions according to platelet count and LSM-TE.

It is important to emphasize that the performance of these prediction rules depend on the pre-test probability of VNT in the population. Therefore, they should not be applied in patients with

decompensated cirrhosis, which have significantly higher risk of varices. In this study we included patients with LSM-TE ≥10 kPa, based on the proposed definition of cACLD in the Baveno guidelines. Previous results suggest that no patients with F4 would be missed using this strategy, and only a minority of patients with advanced cirrhosis had values below this threshold [12]. Furthermore, in the study of Huet and colleagues only 1 patient out of 32 with F3 fibrosis had a portohepatic gradient > 10 mmHg [24]. Therefore, the chances of missing patients with PBC and clinically significant portal hypertension with our inclusion criteria is negligible. The estimated prevalence of VNT in patients with cACLD is 5-15% [7] which was roughly the pre-test probability that was found in our population (13% and 11% in patients with PBC and PSC, respectively), reinforcing the fact that our inclusion criteria selected the target population in which this decision rules would be applied.

In patients with PBC, the use of the other criteria tested in this study either result in a too high number of missed VNT or in a lower number of saved endoscopies. The use of the Jangouk and Levy criteria, despite saving less endoscopies than the Baveno VI criteria, would provide a safe triage of patients for EGD in centers without access to LSM-TE. The expanded Baveno criteria were associated with a risk of VNT above what is considered acceptable. Indeed, the association between LSM-TE, platelet count and the risk of VNT was clearly different in patients with PBC than our previous observations in patients with predominantly viral disease (Figure 2a). PBC patients had a higher prevalence of varices than that predicted by the ANTICIPATE-Plt-LS model. We provide in the present study a new PBC-specific nomogram to predict the risk of VNT in patients with PBC using platelet count and LSM-TE. The reasons for these differences cannot be fully elucidated with the present data. It is well established that the major site of resistance to portal blood flow in patients with PBC is mainly located at the presinusoidal level [25]. This has been suggested to be related to changes of nodular regenerative hyperplasia, inflammation predominantly in the portal tracts, and obliterative portal venopathy [24]. Since these are different from what is observed in other etiologies of cirrhosis, it could be speculated that these phenomena have a lower impact in LSM-TE values than the histological changes of viral hepatitis and alcohol-related cirrhosis. Thus, with similar levels of LSM-TE, patients with PBC would have higher levels of portal hypertension than patients with other etiologies. This will be difficult to demonstrate, since a portal vein puncture, which is a rather invasive procedure, is required to adequately estimate the portal pressure gradient in patients with PBC [24]. Whether spleen

stiffness measurement can add to the information provided by LSM-TE and platelets alone in patients with ChLDs, needs to be investigated [13]. Of note, we did not include in our analysis the Newcastle Varices in PBC Score because it has been designed and validated to predict varices in general and not specifically VNT [26].

In patients with PSC, the expanded Baveno criteria had an adequate performance selecting patients for EGD. This was in keeping with the observation that, contrary to patients with PBC, in patients with PSC the association between platelet count, LSM-TE, and VNT was comparable to the one observed in patients with mainly viral disease, as shown by the good calibration of the ANTICIPATE-Plt-LS model. The criteria suggested by Lindor et al, not using LSM-TE, would have had an acceptable FNR but would have only saved 30% of endoscopies, which is the same number of studies saved by the original Baveno VI criteria. Importantly, we found that platelet count itself had an excellent discriminative capacity to detect VNT. In our sample, using a 200 $X10^9$/L threshold, which is the one used in the Lindor criteria, would lead to a FNR of 0% while saving 48% of endoscopies. As discussed below, this finding is based in a small number of observations and should be taken with caution. If further validated in new studies, this would simplify the triage of patients with PSC in need for EGD.

This study has limitations. First, it was retrospective and this might have introduced selection and verification bias, since the results of the NITs, even in the absence of clear guidelines, could have informed the choice of performing or not and EGD, and the endoscopists presumably were non-blinded to the results of the NITs. Second, there was an accepted window of one year between the NITs and the EGD, with the potential of variation in the values of the tests within this time frame. Indeed, Baveno VI suggests repeating LSM-TE and platelet count yearly to reassess the need to perform diagnostic EGD, and this recommendations should be followed accordingly also in patients with ChLDs [4]. Third, the number of patients with the target condition (VNT) was small, especially in patients with PSC. This results in some uncertainty in the precision of our estimates of performance of the proposed prediction rules. Finally, we did not factor in our calculations the number of technical failures when performing LSM-TE. Factoring in the technical failures would not change our estimations of the FNRs, but would slightly decrease the number of endoscopies that could be saved using LSM by TE-based rules.

The potential cost advantages of a strategy that would save ~30-40% of EGDs in these patients was not specifically assessed in this study. However, previous data showed that applying a model that would save 30% of EGDs (based on platelet count and the presence/absence of splenomegaly) was cost-effective [27]. The use of the Baveno VI prediction rule would need to factor in the cost of point-of-care LSM-TE. This might be variable, but generally low in high-volume specialized units, in which it is commonly embedded in the standard of care.

Finally, a final validation of the application of non-invasive criteria to select patients for screening EGD would come from a non-inferiority randomized control trial, comparing the risk of variceal bleeding in patients undergoing universal screening EGD *vs* patients selected for EGD based on non-invasive tests. Considering that the expected rate of VNT in compensated cirrhosis is ~15%, and that the risk of variceal bleeding in patients on primary prophylaxis (either with non-selective beta-blockers or endoscopic variceal ligation) is low, around 10%/year [28], such a trial would require a very large sample size or a long follow-up to accrue enough events.

In conclusion, the current study validates the use of Baveno-VI criteria (LSM by TE <20 and platelet count >150 $x10^9$) for triaging patients with cACLD due to PBC and PSC for EGD. This strategy could save 30-40% of screening endoscopies. Expanding these criteria in patients with PBC would lead to FNR higher than 5%. In patients with PSC, a rule based solely on platelet count ($\geq$200 $X10^9$/L) could be potentially used if validated in additional studies.

REFERENCES

1. de FR. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J.Hepatol.* 2010;53:762-768.
2. 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;39:1180-1193.
3. D'Amico G, Garcia-Tsao G and Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J.Hepatol.* 2006;44:217-231.
4. de Franchis R and 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;63:743-752.

5. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. 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;65:310-335.
6. Singh S, Muir AJ, Dieterich DT, et al. American Gastroenterological Association Institute Technical Review on the Role of Elastography in Chronic Liver Diseases. *Gastroenterology*. 2017;152:1544-1577.
7. Augustin S, Pons M and Genesca J. Validating the Baveno VI recommendations for screening varices. *J Hepatol*. 2016.
8. Moctezuma Velazquez C and Abraldes JG. Non-invasive diagnosis of esophageal varices after Baveno VI. *Turk J Gastroenterol*. 2017;28:159-165.
9. 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.
10. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology*. 2017.
11. Ali AH, Sinakos E, Silveira MG, et al. Varices in early histological stage primary biliary cirrhosis. *J Clin Gastroenterol*. 2011;45:e66-71.
12. Corpechot C, El NA, Poujol-Robert A, et al. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. *Hepatology*. 2006;43:1118-1124.
13. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. *J Hepatol*. 2017.
14. Abraham SC, Kamath PS, Eghtesad B, et al. Liver transplantation in precirrhotic biliary tract disease: Portal hypertension is frequently associated with nodular regenerative hyperplasia and obliterative portal venopathy. *Am J Surg Pathol*. 2006;30:1454-1461.
15. European Association for the Study of the Liver. Electronic address eee and European Association for the Study of the L. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *J Hepatol*. 2017.
16. Tosetti G L-MV, Aghemo A, Lampertico P, D´Ambrosio R, Viganes M, Grossi G, Fraquelli M, Colombo M, Primignani M. Abstract. Screening of oesophagogastric varices in virus-related compensated advanced chronic liver disease: Baveno VI criteria and beyond. *Hepatology*. 2016;64:843A.
17. 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;36:240-245.
18. Jangouk P, Turco L, De Oliveira A, et al. Validating, deconstructing and refining Baveno criteria for ruling out high-risk varices in patients with compensated cirrhosis. *Liver Int*. 2017.
19. Boursier J, Zarski JP, de Ledinghen V, et al. Determination of reliability criteria for liver stiffness evaluation by transient elastography. *Hepatology*. 2013;57:1182-1191.
20. Levy C, Zein CO, Gomez J, et al. Prevalence and predictors of esophageal varices in patients with primary biliary cirrhosis. *Clin Gastroenterol Hepatol*. 2007;5:803-808.
21. Treeprasertsuk S, Kowdley KV, Luketic VA, et al. The predictors of the presence of varices in patients with primary sclerosing cholangitis. *Hepatology*. 2010;51:1302-1310.
22. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., et al. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. *Med.Decis.Making*. 2001;21:45-56.
23. Harrell FE. rms: Regression Modeling Strategies. . *R package version 5.1-0.* 2017;https://CRAN.R-project.org/package=rms.
24. Huet PM, Vincent C, Deslaurier J, et al. Portal hypertension and primary biliary cirrhosis: effect of long-term ursodeoxycholic acid treatment. *Gastroenterology*. 2008;135:1552-1560.

25. Lebrec D, Sicot C, Degott C, et al. Portal hypertension and primary biliary cirrhosis. *Digestion*. 1976;14:220-226.
26. Patanwala I, McMeekin P, Walters R, et al. A validated clinical tool for the prediction of varices in PBC: the Newcastle Varices in PBC Score. *J Hepatol*. 2013;59:327-335.
27. Chalasani N, Imperiale TF, Ismail A, et al. Predictors of large esophageal varices in patients with cirrhosis [see comments]. *Am.J.Gastroenterol.* 1999;94:3285-3291.
28. Funakoshi N, Duny Y, Valats JC, et al. Meta-analysis: beta-blockers versus banding ligation for primary prophylaxis of esophageal variceal bleeding. *Ann Hepatol*. 2012;11:369-383.

Table 1. Prediction rules.	
Baveno VI (4)	Platelet count >150 $X10^9$/L and LSM-TE <20 Kpa
Expanded Baveno VI [10]	Platelets >110 $X10^9$/L and LSM-TE <25 kPa
Tosetti (16)	Platelets >125 $X10^9$/L and LSM-TE <30 kPa
Jangouk (18)	Platelets>150 $X10^9$/L or MELD=6
Ding (17)	Platelets$\geq$100 $X10^9$/L and LSM-TE $\leq$25 kPa
Levy (20)	Platelets$\geq$140 $X10^9$/L and Original Mayo Risk Score<4.5
Lindor (21)	Platelets $\geq$205 $X10^9$/L and TB<1.7mg/dl (29 umol/L).
Levy criteria are only for patients with PBC and Lindor criteria for patients with PSC. LSM-TE: Liver stiffness measure by transient elastography; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; TB: Total bilirubin	

Table 2. Baseline characteristics.		
	PBC (n=147)	**PSC (n=80)**
Age, years ± SD	59.1 ± 11.5	44.8 ± 16.9
Male sex, n(%)	20 (14)	54 (68)
BMI, kg/m^2 ± SD	26.5 ± 5.2	19.7 ± 11.2
No esophageal varices, n (%) Small, n (%) -Small with high risk stigmata, n (%) Large, n (%)	98 (67) 30 (20) 0 19 (13)	51 (64) 20 (25) 0 9 (11)
Gastric varices, n (%)	4 (3)	4 (5)
VNT, n (%)	20 (14)	10 (12)
Portal hypertensive gastropathy, n(%)	43 (29)	22 (28)
Stiffness, kPa ± SD	25 ± 16.9	30.4 ± 20.7
IQR/med	14.4 ± 7.5	12.4 ± 7
INR ± SD	1.1 ± 0.2	1.2 ± 0.3
Creatinine, umol/L ± SD	67.5 ± 17.9	74.7 ± 54.5
Bilirubin, umol/L ± SD	23.7 ± 28.4	37.6 ± 63.4
Albumin, g/dl, ± SD	3.7 ± 0.5	4.2 ± 3.2
Platelets, x 10^9 cells/L ± SD	199.2 ± 104	207.2 ± 101.9
AST, UI/L ± SD	70.7 ± 56.2	90 ± 69
ALT, UI/L ± SD	70.5 ± 65.5	93.8 ± 70.8
Alkaline phosphatase, UI/L ± SD	297.2 ± 217	365.7 ± 243.9
MELD ± SD	8.2 ± 3	9.6 ± 5.3
Mayo PBC score ± SD	4.9 ± 1.1	-
PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; BMI: body mass index; VNT: varices needing treatment; kPa: kilopascals; IQR: interquartile range; INR: international normalized ratio; AST: aspartate		

aminotransferase; ALT: alanine aminotransferase; MELD: model for end stage liver disease; SD: standard deviation.

Table 3: Performance of the different criteria to rule out VNT.				
	PBC (n=147)		**PSC (n=80)**	
VNT, n (%)	**20 (14)**		**10 (12)**	
	Saved EGDs n (%)	**FNR n (%)**	**Saved EGDs n (%)**	**FNR n (%)**
Baveno VI (4) LSM<20 AND Pla>150	58 (39)	0	24 (30)	0
Expanded Baveno (10) LSM<25 AND Pla>110	86 (58)	5 (6)	36 (45)	1 (3)
Abraldes et al. (9) LSM + Pla model, (risk threshold of 5%)	66 (45)	0	26 (33)	0
Ding et al. (17) LSM≤25 AND Pla≥ 100	89 (60)	6 (7)	37 (46)	1 (3)
Tosetti et al. (16) LSM<30 AND Pla>125	87 (59)	1 (1)	41 (51)	2 (5)
Jangouk et al. (18) Pla>150 OR MELD=6	45 (31)	0	21 (26)	1 (5)
Levy et al. (20) Pla≥140 AND Mayo<4.5	43 (29)	1 (2)	-	-
Lindor et al. (21) Pla≥205 AND TB<1.7	-	-	27 (34)	0

VNT: Varices needing treatment (large varices or small varices with high-risk stigmata); LSM: Liver stiffness by transient elastography; Pla: Platelets/mm^3; EGD: esophagogastroduodenoscopy; FNR: False negative rate (% of missed VNT); PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; TB = Total bilirubin.

Figure 1. Flow diagram showing the disposition of patients. (A) Disposition of PBC patients. (B) Disposition of PSC patients. EGD: Esophagogastroduodenoscopy; LSM: Liver stiffness measure; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.

Figure 2. Performance (in terms of calibration) of the original and recalibrated ANTICIPATE model in patients with Primary biliary cholangitis. (A) shows the calibration plot of the original ANTICIPATE model. This model under-predicted the risk of varices needing treatment (VNT). (B) shows the calibration plot of the re-calibrated ANTICIPATE model, which showed an excellent agreement between predicted and observed probabilities of VNT. The bars over the X axis shows the distribution of the patients according to predicted risks.

Figure 3. Calibration plot of the original ANTICIPATE model in patients with Primary sclerosing cholangitis. The agreement between predicted and observed probabilities of varices needing treatment was excellent. The bars over the X axis shows the distribution of the patients according to predicted risks.