EXPANDING THE BAVENO VI CRITERIA FOR THE SCREENING OF VARICES IN PATIENTS WITH COMPENSATED ADVANCED CHRONIC LIVER DISEASE

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Abbreviations:
cACLD: Compensated advanced chronic liver disease
CI: Confidence interval
LSM: Liver stiffness measurement
VNT: Varices needing treatment

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- Study concept and design: JG, SA, JGA, AB, CB, HS, BP, JB.
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ABSTRACT

Patients with compensated advanced chronic liver disease (cACLD) can safely avoid screening endoscopy with a platelet count >150x10^9 cells/L and liver stiffness measurement (LSM) <20 kPa (Baveno VI criteria). However, the total number of avoided endoscopies using this rule is relatively low. We aimed at expanding the Baveno VI criteria and validating them in additional cohorts. Patients from the Anticipate cohort (499 patients with cACLD of different etiologies) were used to study the performance of different thresholds of platelets and LSM for the identification of patients at very low risk (<5%) of having varices needing treatment (VNT). The new criteria (Expanded-Baveno VI) were validated in two additional cohorts from London (309 patients) and Barcelona (117 patients). The performance of the new criteria by etiology of cACLD was also assessed. The best new expanded classification rule was platelet count >110 x10^9 cells/L and LSM <25 kPa. This was validated in the two additional cohorts. Overall, the Expanded-Baveno VI criteria would potentially spare 367 (40%) of endoscopies (21% with Baveno-VI criteria) with a risk of missing VNT of 1.6% (95% CI: 0.7-3.5%) in patients within the criteria and 0.6% (95% CI: 0.3-1.4%) in the overall population of 925 patients evaluated. The Expanded-Baveno VI criteria performed well in cACLD patients with hepatitis C virus, alcoholic and nonalcoholic steatohepatitis. ***Conclusion***: The new Expanded-Baveno VI criteria spare more endoscopies than the original criteria with a minimal risk of missing VNT in most of the main etiologies of cACLD.

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The progressive introduction of noninvasive diagnostic tools, mainly liver elastography, in the management of chronic liver disease, has allowed to identify a population of asymptomatic patients with severe fibrosis/compensated cirrhosis, defined by Baveno VI consensus with the term "compensated advanced chronic liver disease" (cACLD) (1). These patients are at risk of developing any of the two determinants of prognosis in cACLD/compensated cirrhosis: the presence of clinically significant portal hypertension and the presence of gastroesophageal varices (2,3). However, in these cACLD patients identified in their early phases, the prevalence of varices and especially varices needing treatment (VNT, defined as per current Baveno VI guidelines as medium-large varices or small with red signs) is very low.

Based on preliminary information from studies suggesting that liver stiffness measurement (LSM) by transient elastography, in combination with other noninvasive parameters, was useful for "ruling out" cACLD patients needing screening endoscopy (4–7), the Baveno VI recommendations indicated that patients with cACLD a LSM <20 kPa and a platelet count >150x10^9 cells/L have a very low risk of VNT and consequently, can safely avoid screening endoscopy (1). Following that recommendation several studies have now confirmed the validity of this risk classification rule (8–11), which allows sparing between 10 to 30% of screening endoscopies with a very low risk of missing VNT. However, due to the low prevalence of VNT in these cACLD patients (<10%), up to 40% of unneeded endoscopies would still be performed (10).

Possible improvements to the current classification rule have been suggested. One regards the use of noninvasive tests (including platelets and LSM) for a continuous risk prediction model to individualize the decision to perform endoscopy (Anticipate study) (12). Other studies attempt to increase the number of spared endoscopies without rising the risk of VNT missed. Jangouk et al. (13) recently reported a 12% increase in spared endoscopies (with no additional VNT missed) by expanding the Baveno VI criteria to patients with MELD=6. In addition, a stepwise strategy using platelet count >150x10^9 cells/L and MELD=6 without LSM, substantially increased the number of endoscopies avoided, maintaining a very low rate of missing VNT. Finally, changes in the platelet count and LSM cut-offs have been also suggested (5–7,14).

The main aim of the present study was to find and validate a new classification rule for avoiding screening endoscopies in cACLD patients maximizing the number of spared endoscopies, while keeping very low the risk of missing VNT (<5%). Secondary aims of our study were: 1) to analyze the performance of the new classification rule in different etiologies

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of cACLD, and 2) to externally validate the Baveno VI/MELD=6 and platelet/MELD=6 criteria and the performance of the ANTICIPATE continuous model.

METHODS

Study cohorts

Data from three different cohorts were retrospectively reviewed and analyzed (Table 1). In the Anticipate cohort (12), 542 patients from four centers in Europe (one in France, one in Romania, and two in Spain) and one in Canada were evaluated. Patients from the European centers were reported, in part, in previous publications; however, there is no data regarding the total number of patients evaluated before the inclusion (5,15–17). The patients included in that study had cACLD of any etiology defined by LSM ≥10 kPa, Child-Pugh class A and no prior liver decompensation. Patients who had paired data on noninvasive tests (blood tests and transient elastography) and endoscopy within 3 months were included. In total, 499 patients with LSM, endoscopy and platelet count were available for the study.

The cohort from London (8) was selected from two institutions (Royal Free Hospital and St. Mary's Hospital) and a flow chart of patient inclusion has been already reported. In summary, a total of 12331 LSM performed within 2006 and 2015 were evaluated. Of them, 9018 were excluded because of LSM <10 kPa, 548 due to inadequate LSM, 403 were repetitions, 81 had prior decompensation or splanchnic thrombosis, and 1471 no endoscopy within 12 months of elastography. Finally, 310 patients with cACLD were included in this cohort (Table 1). One of the patients from this cohort had had a prior splenectomy and therefore, had an unusually high platelet count; this patient was not considered for the validation, since Baveno VI criteria cannot be applied.

The third cohort, from Hospital Vall d'Hebron in Barcelona, was composed of 117 cACLD patients with hepatitis C chronic infection evaluated before the initiation of direct-acting antivirals therapy in 2015. These patients were assessed with blood tests, transient elastography and endoscopy during 2014-2015 and they do not overlap with the patients from Vall d'Hebron in the Anticipate study. Inclusion criteria were also LSM ≥10 kPa, Child-Pugh class A, no prior decompensation of liver disease and endoscopy within 12 months of elastography. During this period a total of 608 HCV patients were evaluated for treatment. Unrealiable LSM was observed in 47 patients (7.7%) and 300 patients were cACLD patients, from which 117 had an endoscopy performed within 12 months of elastography.

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None of the patients with chronic hepatitis C were on antiviral treatment (interferon-based therapy or direct antivirals agents) at the time of inclusion or had previously received it.

Transient elastography

The three cohorts used transient elastography by Fibroscan® (Echosens, Paris, France) to obtain LSM. The quality criteria used in each cohort for LSM were the criteria recommended at the time of the inclusion of the cohorts: 10 valid measurements obtained with a success rate ≥60% and the interquartile range to median ratio ≤30%. M probe was used in all measurements. Data of the number of unreliable/no valid LSM excluded is not available from the Anticipate cohort.

Design of the study

A sequential analysis plan was designed in order to provide responses for the different aims of the study. The different steps were the following: 1) the Anticipate cohort was first used to validate the performance of the Baveno VI criteria (1); 2) the same cohort was used to explore the expansion of criteria by adding the MELD=6 rule and the platelet/MELD=6 rule (13); 3) the Anticipate cohort was also used to study the expansion of Baveno criteria by using previously proposed modified LSM and platelet cut-offs (4–7,14) and selecting the best classification rule, in terms of endoscopies spared while keeping the risk of missing VNT below 5%; 4) the new selected set of criteria (Expanded-Baveno VI) was then validated in the London and Vall d'Hebron cohorts; 5) the performance of the Anticipate continuous model for predicting risk of VNT was evaluated in the three cohorts by analyzing the rate of endoscopies saved with a decision risk threshold for VNT of 5%; 6) next, the MELD=6 criteria was again added to the new Expanded-Baveno VI criteria; 7) an analysis of the performance of the new criteria by etiology was subsequently carried out, and 8) the effect of the variability of platelet count and LSM in the performance of the new criteria was finally evaluated.

Statistical analysis

Continuous variables were reported as mean ± standard deviation. Qualitative variables were compared using Chi-square test. The main outcome of interest for the validation of criteria was the prevalence of VNT. VNT were defined according to Baveno VI recommendations as small varices (grade 1) with red signs in which beta-blocker therapy is indicated or large varices (grade 2 or 3) in which treatment with beta-blockers or band ligation is needed to prevent first variceal bleeding (1). The main variable used for the optimization of criteria was the percentage of endoscopies spared, while keeping the risk of missed VNT below the pre-defined

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arbitrary <5% threshold. This threshold was decided by experts in the Baveno VI consensus conference who agreed that 5% was a reasonable threshold for missing VNT and later endorsed by the American Gastroenterological Association technical review on hepatic elastography accepting a 5% false negative rate of missing high risk varices (4,12,18). The choice of new cut-off values for the different parameters explored was based on previously published reports (4–7,14). The development of the continuous risk prediction model for VNT using LSM and platelets and its corresponding nomogram was extensively reported in the Anticipate study (12). In brief, a continuous prediction model for VNT was developed by logistic regression using platelet count (capped at $150x10^9$ cells/L) and LSM as covariates. The model was internally validated and corrected for optimism with bootstrapping. A nomogram for individual risk estimation was built based on the corrected logistic regression model. Data was processed using SPSS. For analyses, both SPSS and R statistical platforms were used.

RESULTS

1) Baveno VI criteria in the Anticipate cohort

In the Anticipate cohort, 68 of 499 (14%) patients evaluated were within the Baveno VI criteria for not performing endoscopy (LSM <20 kPa and platelet count $>150x10^9$ cells/L) (Table 2). Among these 68 patients, 62 had no varices, 4 (6%) had low risk varices and 2 (3%; 95% CI: 0.8-10%) presented VNT. This represents that only 2 of 499 patients (0.4%; 95% CI: 0.1-1.4%) had VNT missed and were therefore misclassified. This result shows that Baveno VI criteria perform well in the Anticipate cohort, but the number of spared endoscopies was low.

2) Baveno VI/MELD=6 and platelet/MELD=6 rules

In the Anticipate cohort, 463 patients had data to calculate the MELD score. Among these patients, 63/463 (13.6%) met the Baveno VI criteria for avoiding endoscopy with only 2/63 (3.1%; 95% CI: 0.9-11%) VNT missed. Adding the MELD=6 criteria in those patients who did not meet the Baveno VI criteria, the number of spared endoscopies increased by 34/400 (8.5%) with no additional VNT missed. Thus, by adding the MELD criteria to the Baveno VI criteria, a total of 97/463 (21%) endoscopies could be safely avoided with a low risk of missing VNT (2/97- 2%; 95% CI: 0.5-7%), confirming that the number of spared endoscopies could be safely increased, with a gain of 7% of endoscopies.

The other classification rule proposed by Jangouk, et al. (13) was platelet count $>150x10^9$ cells/L or MELD=6 (without the use LSM). In the Anticipate cohort, 161/463 (35%) patients had

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platelet count >150x10^9 cells/L, of whom 13 patients (8%) had VNT. Twenty-three patients (5%) had platelet count ≤150x10^9 cells/L and MELD=6 with no patients having VNT. Overall, the number of spared endoscopies with these criteria was 184 (39.7%) with 13/184 (7%; 95% CI: 4-11.7%) VNT missed, indicating that more endoscopies might be saved, but an excessive number of VNT (above the pre-defined objective of 5%) would be undetected.

3) Expanding the Baveno VI criteria: the Expanded-Baveno VI criteria

Table 2 shows the exploratory data and the performance of a new criteria based on the expansion of Baveno VI criteria by increasing the LSM cut-off and/or decreasing platelet count in the Anticipate cohort patients. As shown, the combined use of platelet count >110x10^9 cells/L and LSM <25 kPa maximized the number of potentially spared endoscopies, while keeping the rate of VNT missed below the predefined 5% threshold. We propose the name Expanded-Baveno VI criteria for this new classification rule.

4) Validating the Expanded-Baveno VI criteria (platelet count >110x10^9 cells/L + LSM <25 kPa)

Table 3 shows the performance of the new criteria in all three cohorts. Overall, the risk of missing VNT is very low (<2% with a maximum of 3.5% at the upper limit of the 95% confidence interval) and, on average, 40% of endoscopies are saved. The clinical characteristics of the 6 missed patients with VNT are described in supplementary table 1.

Table 4 depicts the risk distribution of VNT missed in the patients within the Baveno VI criteria and the additional patients detected by the new Expanded-Baveno VI criteria (in patients beyond the original Baveno VI criteria). Remarkably the risk of missing VNT is the same in both sub-groups, suggesting that the new patients selected by the expanded criteria are not increasing the risk of missing VNT.

5) Performance of the Anticipate continuous model

By using the continuous predictive model of the Anticipate study with a decision threshold of 5% of risk for VNT in the three cohorts (Table 5), an almost identical observed risk of missing VNT was detected with the three classification methods. While the number of saved endoscopies was higher using the Anticipate continuous model than with the original Baveno VI criteria, the Expanded Baveno-VI criteria maximized the number of saved endoscopies.

6) Adding the MELD=6 to the Expanded-Baveno VI criteria

Overall, 883 patients from the three cohorts had information to calculate the MELD score and 357 (40.4%) were within the new Expanded-Baveno VI criteria. We tested the possibility of

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applying the MELD=6 criterion trying to identify patients at low risk among those not fulfilling the Expanded-Baveno VI criteria (n=526). As shown in table 6, the addition of MELD 6 patients (48/526; 9%) to the 357 patients within the Expanded-Baveno VI criteria spared a total of 405 (45.8%) endoscopies, while the risk of missing VNT remained very low (1.7%; 95% CI: 0.8-3.5%); the gain in endoscopies saved compared to the new criteria (40.4%) was 5.4%.

7) Performance of the Expanded-Baveno VI criteria by etiologies

A subgroup analysis by etiologies of cACLD in all patients from the three cohorts (Table 7) was performed. The main etiology was hepatitis C virus (HCV), followed by alcoholic liver disease and non-alcoholic fatty liver disease. The new rule seems to perform very well in these three main etiologies. The risk of VNT ranged between 0-2.2% and the number of spared endoscopies ranged between 38.5% and 49%. For other etiologies (hepatitis B, cholestatic diseases, mixed viral and alcohol) sub-group numbers are low to reach robust conclusions.

8) Effect of the variability of the parameters in the Expanded-Baveno VI criteria

The variability in LSM and platelet count determinations might have an impact in the proposed new criteria, mainly when dealing with values closer to the proposed cut-offs. Thus, a sensitivity analysis was conducted to account for the effects of the variability of measurements near those thresholds. Evidence from the literature indicates that with experienced personnel, LSM variability can reach 20% (19). As for platelet counts, we performed a small evaluation in 15 HCV patients analyzing and comparing basal counts with 6 and 12 months prior determinations. Considering the extreme values, the oscillation was between -11% to 12%.

Therefore, taking into account the worst case scenario, that is 20% increase in LSM and 10% decrease in platelet count to the Expanded-Baveno VI criteria (platelet count $>100x10^9$ cells/L + LSM <30 kPa), 11 VNT would be missed in 127 additional patients (11/127; 8.6%-95% CI: 5%-15%) not receiving endoscopy.

DISCUSSION

In the present cooperative study, we provide evidence that the original Baveno VI criteria for the screening of varices in cACLD patients can be safely expanded (Expanded-Baveno VI criteria), increasing the number of endoscopies that can be avoided to almost 50%, while keeping the risk of missing VNT very low. In addition, we confirm the validity of the MELD=6 criteria added to the Baveno VI or Expanded-Baveno VI criteria, although the number of

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additionally saved endoscopies is low. Finally, the new classification rule seems to be applicable to all main etiologies of cACLD.

The Baveno VI consensus conference introduced some important novelties regarding the management of cACLD/compensated cirrhosis patients, partly as a consequence of the increasing acceptance of noninvasive testing in chronic liver disease, especially transient elastography. The concept of cACLD, the criteria for avoiding screening endoscopy and the criteria for selecting patients with clinically significant portal hypertension are all based on simple analytical and LSM values (1). The original Baveno VI criteria for the triage of patients for screening endoscopy for varices (platelet count >150x10^9 cells/L + LSM <20 kPa), although well validated in subsequent studies (8–11), were also perceived as conservative; the number of spared endoscopies was relatively low and about 40% of unneeded endoscopies would be performed using those criteria (10). With the new Expanded-Baveno VI criteria (platelet count >110 x10^9 cells/L + LSM <25 kPa), the number of spared endoscopies could be doubled (from 21 to 40%) with a minimal risk of missing VNT (<2%). It has to be acknowledged that similar classification rules (platelet count >100–120 x10^9 cells/L and LSM <25 kPa) had been already reported by different authors before the Baveno VI consensus conference (5–7) and in a recent abstract (14).

The new classification rule has been developed in the Anticipate cohort and validated in two additional cohorts from UK and Spain, including overall over 900 cACLD patients. The two validation cohorts presented a lower prevalence (4.5% and 7.7%, respectively) of VNT than the Anticipate cohort (13.8%). It could be argued that this would have favored the validation of the Expanded-Baveno VI criteria. However, the cACLD population that would mostly benefit from avoiding screening endoscopies is probably the cACLD patients with LSM values between 10 kPa and 25 kPa. It is in the early cACLD population that the risk of having VNT is very low and consequently, avoiding endoscopies is critical. Above LSM 25 kPa the risk of having clinically significant portal hypertension is more than 90-95% (12) and the presence of VNT rises rapidly.

With the new Expanded-Baveno VI criteria, three additional patients with VNT were missed (Table 4 and supplementary table 1). Two of these patients, both from the London cohort, presented one of the classification rule parameters very near the proposed thresholds (platelet count 115x10^9 cells/L and LSM 24.2 kPa). It seems evident that applying the new criteria to patients with values approaching the cut-offs may increase the risk of missing VNT. This is also evidenced, as discussed in the results, by the effect that the variability, both in LSM (19) and platelet counts (20), might have in increasing this risk. Besides measuring liver stiffness with

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the best possible quality criteria (21), it is advisable, in our opinion, to repeat the LSM and platelet count after a short period in patients with values close to the cut-offs to confirm that that remain into the low risk group.

One of the drawbacks of using a single cut-off to separate patients in two groups, is that there is always an unwanted loss of information. We might tend to think that the risk of having VNT in all the patients within the Expanded-Baveno VI criteria is 1.6%, while it is quite obvious that the real risk, better described in the 95% confidence interval, ranges from 0 to at least 3%, being higher in patients approaching the cut-offs. For this reason, although we tend to work with binary decisions and categorical decision rules are best suited for general recommendations, the information of the predicted risk by the continuous model of our prior Anticipate study (12) provides useful and complementary information for an individual patient. Both approaches point to the same conclusions and could be used in combination in real practice, especially in patients with values of platelets and LSM closer to the thresholds of the Expanded-Baveno VI criteria.

Another important information provided by the present study is that the new classification rule performs well when analyzed in the main etiologies of cACLD (Table 7). HCV patients were clearly overrepresented in the cohort and the Expanded-Baveno VI criteria performed very well in this population. However, it is reassuring that in our sample with around 100 patients each with cACLD due to alcoholic and nonalcoholic steatohepatitis, the performance of new criteria was also very good. In hepatitis B patients, although the number of patients is lower, only one VNT was missed. Finally, patients with cholestatic liver diseases constitute a special subgroup of patients who might have portal hypertension in early phases of the disease and clearly our numbers are too low to draw conclusions.

Finally, the MELD=6 criteria seemed a promising tool when added to the Baveno VI criteria in the initial study (13). Even more attractive it was the proposal of using platelet count plus MELD=6, without the need of LSM. From the data of our three cohorts, it is clear that applying the MELD=6 criteria to patients beyond the Expanded-Baveno VI criteria can be safely done, with an additional gain of spared endoscopies of around 5%. By contrast, we were unable to validate the classification rule of MELD=6 without LSM, which would lead to an unacceptable high rate of missed VNT.

Our study has limitations, many of them were already discussed in our previous reports (8,12). In short, the main limitations are the retrospective nature of the data, the time frames between endoscopy and LSM acquisition (up to 12 months), and the quality control of LSM and

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endoscopy reporting. Another important limitation is that including LSM in the classification criteria is in itself a limitation, because transient elastography is not available in all centers. Moreover, we have to keep in mind that LSM cannot be performed in some patients (e.g. obese patients, although this can partially be solved with the use of XL probe) and some factors such alcohol use, aminotransferases flares or heart congestion can increase liver stiffness and therefore provide falsely high LSM values. In these cases an unneeded endoscopy might be performed. Finally, since the XL probe has not been used in our study, information regarding its utility for the Expanded-Baveno VI criteria cannot be provided. Hence, in real world practice, due to all the issues regarding LSM mentioned here, the Baveno VI criteria might not be applicable to all patients.

By contrast, the main strengths of our study are the large number of patients evaluated in many centers from different countries, the sequential validation process in external cohorts and the similar performance of the new classification rule across different etiologies of cACLD.

In summary, the present study demonstrates that the Baveno VI criteria for avoiding screening endoscopy in cACLD patients can be safely expanded. With the new Expanded-Baveno VI criteria (platelet count >110 $x10^9$ cells/L + LSM <25 kPa) more endoscopies are spared (100% increase from 21 to 40%) with a minimal risk of missing VNT in most of the main etiologies of cACLD. The MELD=6 criteria can be safely added to the Expanded-Baveno VI criteria.

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Table 1. Main characteristics of the three cohorts of the study.

	Anticipate cohort N=499	London cohort N=309	Vall d'Hebron cohort N=117	Total N=925
Age, years	58.4±10.8	58.1±11.2	66.3±10.3	59.4±11.2
Male, n (%)	251 (50.3)	208 (67.3)	54 (46)	513 (55.4)
BMI, kg/m^2	27.1±4.8	-*	27.4±3.9	27±5
HCV patients, n (%)	296 (59.3)	168 (54.4)	117 (100)	581 (62.8)
Child-Pugh class A, n (%)	499 (100)	274 (88.7)	112 (95.7)	885 (95.7)
Platelet, x10^9 cells/L	132±64	157±74	134±61	140±68
ALT, UI/L	83±60	82±68	97±62	84.7±63
LSM, kPa	28.1±15.8	23.7±14.5	22.2±10.7	25.9±15.0
No varices, n (%)	281 (56)	238 (77)	84 (71.8)	603 (65.2)
Low risk varices, n (%)	149 (30)	57 (18.5)	24 (20.5)	230 (24.9)
VNT, n (%)	69 (14)	14 (4.5)	9 (7.7)	92 (9.9)

Continuous data expressed as mean ± standard deviation. HCV: Hepatitis C chronic infection; ALT: Alanine-aminotransferase; BMI: Body mass index; LSM: Liver stiffness measurement; VNT: Varices needing treatment. *BMI from the London cohort was not available.

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Table 2. Expanded Baveno VI classification rules to increase the number of spared endoscopies without increasing the risk of VNT missed in the Anticipate cohort.

	Spared endoscopies N=499	**VNT missed**
Platelets >150 + LSM <20 kPa (Baveno VI) (1)*	68 (14%)	2/68 (3%) (0.8-10%)[§]
Platelets >150 + LSM <25 kPa (4-5)	88 (17.5%)	3/88 (3.4%) (1.1-9.5%)
Platelets >150 + LSM <30 kPa (13)	116 (23%)	6/116 (5%) (2.3-10.8%)
Platelets >125 + LSM <25 kPa (13)	126 (25%)	3/126 (2.4%) (0.8-6.7%)
Platelets >120 + LSM <25 kPa (7)	139 (28%)	3/139 (2.2%) (0.7-6%)
Platelets >110 + LSM <25 kPa (Expanded-Baveno VI)	**158 (32%)**	**3/158 (1.9%) (0.6-5.4%)**
Platelets >100 + LSM <25 kPa (4,6)	182 (36.5%)	9/182 (5%) (2.6-9%)

VNT: Varices needing treatment; LSM: Liver stiffness measurement.
*Number of reference. [§] 95% confidence interval

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Table 3. Performance of the Expanded-Baveno VI criteria (platelet count >110 + LSM <25 kPa) in all three cohorts.

Study cohort	Spared endoscopies	VNT missed/ Expanded-Baveno VI*	VNT missed/ All patients§
Anticipate	158/499 (32%)	3/158 (1.9%) (0.6-5.4%)¥	3/499 (0.6%) (0.1-1.9%)
London	161/309 (52%)	3/161 (1.9%) (0.6-5.3%)	3/309 (1%) (0.3-2.8%)
Vall d'Hebron	48/117 (41%)	0/48 (0%) (0.7-9.2%)	0/117 (0%) (0-3.1%)
All cohorts	367/925 (40%)	6/367 (1.6%) (0.7-3.5%)	6/925 (0.6%) (0.3-1.4%)

* Risk of missing VNT in patients within the new Expanded-Baveno VI criteria.
§ Risk of missing VNT in all patients of the cohort.
¥ 95% confidence interval
VNT: Varices needing treatment

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Table 4. Comparison of risk of missing the presence of varices needed treatment (VNT) with Baveno VI and the additional patients detected by the Expanded-Baveno VI criteria.

Study cohort	VNT missed/ Baveno VI[§]	Additional VNT missed/ Expanded-Baveno VI[¥]
Anticipate, n=158[*]	2/68 (3%)	1/90 (1.1%)
London, n=161	1/101 (1%)	2/60 (3.3%)
Vall dHebron, n=48	0/29	0/19
All cohorts, n=367	3/198 (1.5%) (0.5-4.3%)#	3/169 (1.7%) (0.4-5.5%)

[*] Number of patients within the Expanded-Baveno VI criteria.
[§] Risk of missing VNT in patients within the original Baveno VI criteria.
[¥] Additional risk of VNT in patients beyond original Baveno VI criteria, but within the new Expanded-Baveno VI criteria.
95% confidence interval

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Table 5. Performance of the Anticipate study continuous model compared to the Baveno VI and Expanded-BavenoVI criteria.

Study cohort	N	VNT	Anticipate model (≤5% VNT) [§]		Baveno VI criteria LSM<20+pla>150		Expanded-Baveno VI criteria LSM<25+pla>110	
			EGD saved	VNT missed	EGD saved	VNT missed	EGD saved	VNT missed
Anticipate	499	69 (13.8%)	111 (22%)	3/111 (2.7%)	68 (14%)	2/68 (3%)	158 (32%)	3/158 (1.9%)
London	309	14 (4.5%)	137 (44%)	1/121 (0.8%)	101 (32.5%)	1/101 (1%)	161 (52%)	3/161 (1.8%)
Vall d'Hebron	117	9 (7.7%)	44 (38%)	0/40	29 (25%)	0/29	48 (41%)	0/48
All cohorts	925	92 (10%)	292 (32%)	4/292 (1.4%) (0.5-3.4%)[¥]	198[*] (21.5%)	3/198 (1.5%) (0.5-4.3%)	367[*] (40%)	6/367 (1.6%) (0.7-3.5%)

[*] p<0.001, compared with respect to Anticipate model.
[§] Anticipate study model with a decision threshold of 5% of risk for VNT
[¥] 95% confidence interval
VNT: Varices needing treatment; LSM: Liver stiffness measurement; EGD: Esofagogastroduodenoscopy; pla: platelet count.

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Table 6. Number of spared endoscopies and varices needing treatment (VNT) missed by applying the MELD=6 criterion to those patients who do not fulfill the Expanded-Baveno VI criteria**.**

Study cohort	Spared endoscopies	VNT missed
Anticipate	170/463 (36.7%)	3/170 (1.8%) (0.6-5%)*
London	179/308 (58.1%)	4/179 (2.2%) (0.9-5.6%)
Vall d'Hebron	56/112 (50%)	0/56 (0-6.4%)
All cohorts	405/883 (45.8%)	7/405 (1.7%) (0.8-3.5%)

* 95% confidence interval

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Table 7. Performance of the Expanded-Baveno VI criteria by etiologies of cACLD.

Etiology	Spared endoscopies	VNT missed/ Expanded-Baveno VI*	VNT missed/ All patients§
HCV, n=584	236/584 (40%)	3/236 (1.2%) (0.4-3.6%)¥	3/584 (0.5%) (0.2-1.5%)
Alcohol, n=127	49/127 (38.5%)	0/49 (0-7.2%)	0/127 (0-3%)
NASH, n=90	44/90 (49%)	1/44 (2.2%) (0.4-12%)	1/90 (1.1%) (0.2-6%)
HBV, n=61	21/61 (34.4%)	1/21 (4.7%) (0.8-22%)	1/61 (1.6%) (0.3-8.7%)
PBC/PSC, n=20	12/20 (60%)	1/12 (8.3%) (1.5-35%)	1/20 (5%) (0.9-23%)
HCV/Alcohol, n=19	5/19 (26%)	0/5	0/19

* Risk of missing VNT in patients within the new Expanded-Baveno VI criteria.
§ Risk of missing VNT in all patients of the cohort.
¥ 95% confidence interval
VNT: Varices needing treatment; cACLD: Compensated advanced chronic liver disease; HCV: Hepatitis C chronic infection; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B chronic infection; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis.