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Extending and validating the Baveno VI criteria for the exclusion of high-risk varices

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Abstract

Aim*:* The updated Baveno VI guidelines recommend that screening for high-risk varices (HRV) by esophago-gastroduodenoscopy (EGD) can be avoided in patients with compensated advanced chronic liver disease (cACLD) who have liver stiffness LSM<20 kPa and platelet count PLT>150,000/L. The aims of this study were to validate extended Baveno VI criteria in patients with chronic liver disease and to establish cut-off values for our cohort. **Materials and Methods***:* This retrospective study included 839 patients with liver cirrhosis evaluated by Transient Elastography (TE), biological tests, and upper endoscopy, all within one year. The Baveno VI criteria were validated on a sub-group of 728 patients (Cohort 1, randomly selected from the study sample) and tailored cut-off points were determined. The remaining 111 patients comprised the validating set (Cohort 2) for these specific cut-off values. **Results***:* In Cohort 1, Baveno VI criteria had 86.2% accuracy. The calculated cut-offs to rule-in HRV were PLT<150,000/mm^3 and LSM >35.3 kPa; while to rule-out HRV they were PLT >150.000/mm^3 and LSM <19.6 kPa. In patients in the "grey-zone", by multivariate analysis, albumin was independently associated with HRV at a cut-off of <3.4 g/dl. In the validation cohort, the calculated rule out cut-offs had 100% accuracy. **Conclusions***:* The Baveno VI criteria had a good accuracy for exclusion of HRV in this large cohort of cirrhotic patients. Adding an albumin-related threshold increased performance and broadened applicability. Using the calculated rule-out criteria for HRV, all unnecessary EGD could be excluded.

Keywords: high-risk oesophageal varices; liver stiffness; liver cirrhosis; transient elastography; Baveno VI

Introduction

Variceal bleeding is a common and severe complication in liver cirrhosis. Twenty years ago, published data showed a 25-30% mortality at the first variceal bleeding episode and a 40-50% mortality during 1-2 years follow up in untreated patients, which increased by another 30% in subsequent bleeding episodes [1]. Current data indicate a 3-fold decrease in hospital mortality in variceal haemorrhages, due to variceal banding ligation, early administration of vasoactive drugs (before endoscopy), antibiotic prophylaxis and restrictive transfusion strategy (haemoglobin target of 7 g/dL) [2].

Primary and secondary prophylaxis is the key for decreasing mortality through variceal haemorrhage. This is why many studies are being conducted to identify the risk factors involved and the non-invasive methods of diagnosis of portal hypertension. Prophylactic therapy with beta-blockers or elastic band ligation is recommended in patients with high-risk varices (HRV – small varices with red wale marks or large varices). Esophago-gastroduodenoscopy (EGD) is the gold-standard to assess the presence and size of varices. However, it is an invasive and expensive procedure with associated risks, especially when intravenous sedation is performed [3-6].

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Different studies have tested Transient Elastography (TE; FibroScan) in the prediction of liver cirrhosis complications, in an attempt to find a non-invasive screening method for these patients. Published studies demonstrated the usefulness of TE in prediction of clinically significant portal hypertension (HVPG >10 mmHg), in the setting of compensated chronic liver disease [7-14].

The updated Baveno VI guidelines recommend that screening for EGD can be avoided in patients with compensated advanced chronic liver disease (cACLD) who have liver stiffness <20 kPa and a platelet count >150,000/μL [15].

Some studies have been made to validate the Baveno VI criteria, with good results, but all of them reported rather small numbers of cases [15-17].

The aim of this study was to validate the Baveno VI criteria in patients with chronic liver disease in order to assess their ability to rule out the presence of HRV and avoid unnecessary endoscopies. The secondary aim was to establish the best cut-off values tailored for our centre, to successfully rule out patients with HRV.

Materials and Methods

Subjects

This retrospective study included patients with liver cirrhosis admitted in our department between January 2009 and September 2018. All patients with the final diagnosis of liver cirrhosis were included in the study if TE, laboratory tests and EGD were performed within one year, no matter if they were previously treated for their aetiology or not. The diagnosis of liver cirrhosis was based on laboratory tests, physical examination, ultrasound findings, elastography and radiological evidence. The severity of liver cirrhosis was assessed by the Child Pugh's score. Exclusion criteria were: subjects with ascites, previous oesophageal varices bleeding, encephalopathy, hepatocarcinoma, AST and ALT values over 100 IU/L and jaundice.

Subject characteristics, epidemiological data and laboratory tests were collected from the medical records. The study sample of 839 patients was split into two subgroups: (i) Cohort 1 for extending and validating the Baveno VI criteria to predict HRV and for establishing the applicable tailored cut-off values for TE and platelet count in cases of HRV; (ii) Cohort 2 for subsequent validation of the tailored cut-off values, determined for our centre. The needed number of subjects for Cohort 2 was determined as 111 to reach a statistical power 1-beta=0.9, at significance level alpha=0.05, with area under the Receiver Operating Characteristic (ROC) AUC=0.7 and the expected balance between control and case observations kappa less than 3. The 111 subjects for Cohort 2 were randomly selected from the study sample and the remaining 728 records comprised Cohort 1.

Being a non-interventional retrospective study no Ethical approval was needed to conduct this study. Participants gave their informed written consent to undergo TE, endoscopy and blood tests as a routine work-up during their assessment.

Transient Elastography

TE was carried out by using FibroScan™ (Echosens, Paris, France). TE was performed after at least four hours of fasting. Only patients with 10 validated measurements and an interquartile range (IQR) of less than 30% of the median liver stiffness value were included. M and XL probes were used according to the body mass index. TE was performed by physicians with at least 6 months experience in using this method.

Oesophageal Varices

Oesophageal varices identified via endoscopy were classified according to the Baveno VI consensus. Patients with large oesophageal varices (grade II and III in Japanese classification) or small oesophageal varices with red wales or gastric varices were considered as HRV. All endoscopies were performed by experienced endoscopists.

Statistical Analysis

Descriptive statistics were produced for demographic, clinical and laboratory characteristics for this study sample of patients. The Shapiro-Wilk test was used to test the normal distribution of quantitative variables. When quantitative variables were normally distributed, the results were expressed as mean values and SD, otherwise median and interquartile range (IQR; 25^{th}-75^{th} percentile) were reported; qualitative variables were summarized as counts and percentages. Comparisons between groups were performed using the Chi-squared test for categorical variables or the Student's t test for continuous variables. Statistical significance was set at $p < 0.05$. The diagnostic performance of Baveno VI and the cut-off values were assessed by using ROC curves and the area under the ROC (AUROC) curve analysis by using the Bayesian analysis. The optimal criterion was calculated taking into account the disease prevalence and the costs of false positive and false negative and sensibility/specificity greater than 90%, depending on what we wanted (rule-in or rule out the disease). Positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (-LR) were calculated. Data analysis was performed with MedCalc Statistical Software version 18.10 (MedCalc Software bvba, Ostend, Belgium) and R 3.6.3 packages (including "pROC").

Results

Patients' Characteristics

Eight hundred thirty-nine patients met the inclusion criteria and were included in the study, out of which 728 were assigned to Cohort 1. The mean age was 59.7 years, and the majority of patients (60.4%) were male. Regarding the observed aetiology, the most frequent causes of liver cirrhosis were: chronic hepatitis C (48.8%), followed by alcohol abuse (24.1%) and chronic hepatitis B (7.1%). One hundred eleven patients were assigned to Cohort 2, with a mean age of 60.2 years, the majority being men (51.3%). Patients' characteristics are summarized in Table I.

Validation of the Baveno VI Criteria in Cohort 1

In cohort 1, 461/728 (63.3%) patients met the Baveno VI criteria to exclude the presence of HRV. The performance of Baveno VI criteria applied in the study group for excluding the presence of oesophageal varices resulted as it follows: AUROC=0.71, 95%CI (0.65-0.87), p<0.0001; Se=28.5%; Sp=91.2%, NPV=86.2%; PPV=61.2%; +LR=0.78. Using these criteria, we could have saved 144 endoscopies (19.7%).

Specific cut-off values in Cohort 1

The best thresholds to rule in HRV in Cohort 1 (728 patients) were identified at PLT<150.000/ L and LSM>35.3 kPa and the best thresholds to rule out significant oesophageal varices were identified at PTL>150.000/L and LSM <19.6 kPa. Table II shows the diagnosis performance for these threshold values.

Validation of the new extended Baveno VI criteria in Cohort 2

We validated the diagnostic accuracy for our new criteria in the Cohort 2 of 111 patients. If we used the cut-off

Table I. Main clinical and demographic characteristics

Characteristics	Cohort 1 (N=728)	Cohort 2 (N=111)	p-values
Gender (Men)	440 (60.4)	57 (51.3)	0.06
Age (years)	59.7 ± 11.1	60.2 ± 9.8	0.65
Platelets count (x10^3/L, mean)	210.5 ± 47.2	200.2 ± 43.5	0.03
Albumin (g/dl)	3.6 ± 0.65	3.5 ± 0.67	0.07
Total bilirubin	1.4 ± 0.5	1.3 ± 0.6	0.05
AST	69.0 ± 12.3	57.8 ± 10.8	<0.0001
ALT	51.0 ± 9.2	54.1 ± 10.1	0.001
AF	75.2 ± 11.2	68.2 ± 9.4	<0.0001
GGT	195.5 ± 22.1	180.2 ± 15.9	<0.0001
Varices			
No Varices	223 (30.6)	51 (45.9)	0.001
Grade I	103 (14.1)	8 (7.2)	0.04
HRV	402 (55.3)	52 (46.8)	0.09
Aetiology			
HCV	355 (48.7)	42 (37.8)	0.03
HBV	52 (7.1)	11 (9.9)	0.29
Alcoholic	176 (24.1)	34 (30.6)	0.14
HBV+HCV	6 (0.8)	1 (0.8)	0.99
HBV+HDV	29 (3.9)	4 (3.2)	0.71
NASH	24 (3.2)	1 (0.8)	0.15
HBV + alcoholic	21 (2.8)	3 (2.5)	0.85
HCV + alcoholic	17 (2.3)	2 (1.7)	0.68
PBC	11 (1.5)	0	0.19
Autoimmune	6 (0.8)	1 (0.8)	0.99
Cardiac	6 (0.8)	1 (0.8)	0.99
Idiopathic	25 (4.0)	11 (8.9)	0.02
Child – Pugh Class			
A	447 (64.4)	66 (59.)	0.28
B	281 (38.6)	45 (40.6%)	0.68

Data are presented as mean ± standard deviation, or as number (%). HCV = chronic hepatitis C, HBV = chronic hepatitis B, HDV = chronic hepatitis D, NASH = non-alcoholic steatohepatitis, PBC = primary biliary cirrhosis, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma glutamyl transferase, AF = alkaline phosphatase

Table II. Diagnostic accuracy for rule in and rule out significant oesophageal varices of new Baveno VI.

	AUROC	Se	Sp	NPV	PPV	+LR	-LR
Rule in	0.78	64.9%	80.0%	64.9%	80.1%	3.26	0.44
Rule out	0.95	100%	87.8%	100%	49.0%	1.15	0.19

AUROC = aria under the receiver operating characteristic curve; Se = sensibility, Sp = specificity; NPV = negative predictive value; PPV = positive predictive value; +LR = positive likelihood ratio; -LR = negative likelihood ratio

for ruling out, 18/111 met the criteria and none of them had HRV, Se=100%. If we used the rule in cut-off, 30/111 met the criteria and none of them had HRV, leading to Sp=100%. Diagnosis accuracy was 100% in all cases.

"Grey zone"

Regarding the „grey zone" (i.e. LS between 19.6 kPa and 35.3 kPa), 247/728 (33.93%) patients from Cohort 1 were in this zone. We analysed the factors that could predict the presence of HRV in this area, taking into account the following: age, AST, ALT, GGT, FA, platelets, and albumin values. In univariate analysis, the AST, ALT, platelets and albumin values were significantly associated with the presence of HRV (p=0.01, p=0.002, p=0.01 and p=0.002, respectively). In multivariate analysis, only albumin was an independent factor associated with the presence of HRV (p=0.01). The best cut-off value for albumin for predicting HRV was ≤3.4 g/dl, with Se=49.3% and Sp=80.0%.

Splitting the grey zone into two groups, according to the platelets count, we further evaluated the albumin cut-off value of 3.4 g/dl as a HRV predictor: 121/247 (48.9%) patients had the PLT >150.000/L and 126/247 (51.1%) had PLT <50.000/L. Although we found a significant influence of albumin level as a HRV predictor in both groups (p<0.0001), the Odds Ratios (OR) were different: a value of albumin ≤3.4 g/dl in the group with PLT count >150,000/L would increase the risk of HRV 15 times (OR=15.1, 95%CI: 12.3-89.5); the same cut-off albumin value in the group with PLT count >150.000/L would increase the HRV risk 65 times (OR=64.8, 95%CI: 22.5-112.1).

We verified the predictive value of albumin ≤3.4 g/dl in Cohort 2: 86/111 patients had a TE value between 19.6 kPa and 35.3 kPa, out of which 56/86 patients had the albumin value ≤3.4 g/dl. From these 56 patients, 52 had HRV, leading to a 92.8% accuracy of the cut-off value ≤3.4 g/dl for the albumin level.

We found the serum albumin level as a reliable discriminating marker, so it was added to the Baveno VI criteria, leading to the following performance in ruling out the HRV: AUROC=0.90, 95%CI (0.87-0.99); Se=57.8%, Sp=87.6%; PPV=50.0%, NPV=90.7%; +LR=14.3. The increase in NPV was highly significant (p<0.0001). Combining the Baveno VI criteria with the cut-off value of 3.4 g/dl for the albumin, 209 (28.7%) endoscopies would have been saved, a highly significant difference from the 19.7% endoscopies saved by applying the Baveno VI criteria alone (p<0.0001).

Discussion

The best predictor for significant portal hypertension and the risk of variceal bleeding is the measurement of the Hepatic Venous Pressure Gradient (HVPG). However, the technique is not only difficult to perform in all cases, but generally with reduced accessibility, thus we consider endoscopy as a gold standard method to diagnose portal hypertension, by assessing the presence of oesophageal or gastric varices.

After the Baveno VI Conference, there were a number of studies validating the recommendation of circumventing upper endoscopy in patients with liver cirrhosis with normal platelets and LSM by TE <20 kPa. The percentage of misclassified patients was estimated to be <5%, but approximately 20% of endoscopies could have been saved by applying these criteria [16,18]. The prospective study conducted by Protopapas et al [19] reported a similar avoidance rate of 20.6%. Our study confirmed this percentage, with the actual value of 19.7% potentially saved endoscopies when applying the Baveno VI criteria alone.

All previous studies assessing TE as predictor of large varices found good sensitivity, but rather poor specificity. Meta-analyses reported the following pooled values: Se=0.81, 95%CI (0.79-0.84); Sp=0.71, 95%CI (0.69-0.73); +LR=2.63, 95%CI (2.15-3.23) and –LR=0.27, 95%CI (0.22-0.34) [18,20]. Moreover, the NPV values reported for the Baveno criteria in smaller studies by Maurice et al [21], Turco et al [22] and Perezzo et al [23] were high: 98% and up to 100%. Tosetti et al modified the cut-off points of LSM to <25 kPa and platelets to >125x10^9/L, also leading to NPV of 100%, which suggested that less conservative cut-off points might be applied [24]. The NPV values we ascertained in this large cohort, then subsequently validated in a separate cohort, confirmed the previously reported high values and reliably support this ruling out approach.

Employing the liver stiffness and platelet count for excluding the patients at a high-risk of varices has been investigated. Marot et al published a meta-analysis of

15 trials evaluating the usefulness of a given cut-off for liver stiffness <20 kPa and platelet count over 150.000/mm³ to rule out the presence of HRV, with no more than 4% missed varices, although most of these studies included only patients with compensated liver cirrhosis [25]. Several other noninvasive methods, such as portal vein Doppler assessment and spleen diameter, or routine biological parameters, such as platelet count, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been tested as predictors of significant portal hypertension [26]. In the univariate analysis in our retrospective evaluation, AST, ALT and platelet count also proved to be significant predictors of HRV. On the other hand, the statistical significance did not hold for multivariate analysis.

Summing up, in cohort 1 (which included 728 patients with liver cirrhosis), the best thresholds to rule out HRV were identified at PLT>150,000/L and LSM <19.6 kPa, while for ruling in HRV the cut-offs were PLT<150,000/L and LSM >35.3 kPa. All values were confirmed in the validation cohort. The apparent differences between the two cohorts (i.e. suggested by the small p-values in Table I) are not clinically relevant: they were simply generated by the large cohorts in this study, leading to small standard errors for the continuous proportional variables. The patients in the study sample were randomized into cohort 1 or cohort 2. Therefore, the two cohorts were equivalent from the clinical point of view.

According to our findings, an unnecessary endoscopy can be safely avoided in patients with PLT>150,000/L and LSM <19.6 kPa. In contrast, we definitely have to screen subjects with PLT<150,000/L and LSM >35.3 kPa. A large group of patients (247) were in the so-called „grey zone", not fulfilling either the rule-in or rule-out criteria. We found that a serum albumin level ≤3.4 g/dl would be a reliable predictor for HRV in both cohorts. By adding it to the Baveno VI criteria, we increased the NPV from 86.2% to 90.7%. The albumin is known to be related to both the nutritional status [27] and to the early oesophageal varices re-bleeding after ligation [28]. Therefore, it was not surprising it was confirmed as a good predictor for HRV in our study.

The main limitations of the present research are generated by its retrospective design: the timing between TE and upper endoscopy was up to one year, some patients underwent beta-blocker therapy and the sample included both treated and untreated patients with reference to the disease aetiology. Supplementary markers could have been employed to complement the Baveno VI criteria in ruling out the HRV, such as serum markers of liver fibrosis (APRI score, or FIB-4 score), alanine amino-transferase and total bilirubin, as Zhou H et al [29] proposed. These hypotheses should be further investigated in future research. However, the limitations were compensated by the large study cohort of cirrhotic patients over a wide etiological spectrum, and the subsequent validation on the independent cohort.

Conclusions

The use of Baveno VI criteria in our large cohort of cirrhotic patients had 86.2% accuracy for exclusion of HRV. By adding a serum albumin cut-off of <3.4 g/dl we increased the performance of Baveno VI criteria. In our centre, a cut-off value of TE <19.6 kPa in patients with platelets >150.000/L, led to 100% accuracy in ruling out the high-risk varices.

Conflicts of interest: none

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