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## **Including Ratio of Platelets to Liver Stiffness Improves Accuracy of Screening for Esophageal Varices That Require Treatment**

**Short Title:** Personalized esophageal varice screening

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**Abbreviations:**

B6C: Baveno VI criteria

cACLD: compensated advanced chronic liver disease

CLD: chronic liver disease

EB6C: expanded Baveno VI criteria

EGD: esophagogastroduodenoscopy

EV: esophageal varices

INR: international normalized ratio

LSM: liver stiffness measurement

MELD: model for end-stage liver disease

NAFLD: non-alcoholic fatty liver disease

NIT: non-invasive test

NPV: negative predictive value

PLER: platelet/liver elastometry ratio

PLEASE: platelet/liver elastometry ratio adjusted on etiology, sex, INR

PPV: positive predictive value

VCTE: vibration-controlled transient elastometry

VNT: varices needing treatment

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Oana Farcau: critical revision of the manuscript, data collection

Davide Festi: study supervision, critical revision of the manuscript, data collection

Horia Stefanescu: critical revision of the manuscript, data collection

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Salvatore Petta: critical revision of the manuscript, data collection

Paul Calès: study concept and design, analysis and interpretation of data, drafting of the manuscript, data collection, statistics, guarantor of the article (including final responsibility for the decision to submit for publication)

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**Background & Aims:** Based on platelets and liver stiffness measurements, the Baveno VI criteria (B6C), the expanded B6C (EB6C), and the ANTICIPATE score can be used to rule out varices needing treatment (VNT) in patients with compensated chronic liver disease. We aimed to improve these tests by including data on ratio of platelets to liver stiffness.

**Methods:** In a retrospective analysis of data from 10 study populations, collected from 2004 through 2018, we randomly assigned data from 2368 patients with chronic liver disease of different etiologies to a derivation population (n=1579; 15.1% with VNT, 50.2% with viral hepatitis, 28.9% with nonalcoholic fatty liver disease, 28.9% with alcohol-associated liver disease, 20.8% with model for end-stage liver disease scores of  $9.5\pm 3.0$ , and 93.0% with liver stiffness measurements  $\geq 10$ kPa) or a validation population (n=789). Test results were compared with results from a sequential algorithm (VariScreen). VariScreen incorporated data on platelets or liver stiffness measurements and then ratio of platelets to liver stiffness measurement, adjusted for etiology, patient sex, and international normalized ratio.

**Results:** In the derivation population, endoscopies were spared for 23.9% of patients using the B6C (VNTs missed in 2.9%), 24.3% of patients using the ANTICIPATE score (VNTs missed in 4.6%), 34.5% of patients using VariScreen (VNTs missed in 2.9%), and 41.9% of patients using the EB6C (VNTs missed in 10.9%). Differences in spared endoscopy rates were significant ( $P\leq 0.001$ ) except for B6C vs ANTICIPATE and in missed VNT only for EB6C vs the others ( $P\leq 0.009$ ). VariScreen was the only safe test regardless of sex or etiology (missed VNT  $\leq 5\%$ ). Moreover, VariScreen secured screening without missed VNT in patients with model for end-stage liver disease scores  $> 10$ . This overall strategy performed better than a

safety did not differ significantly among populations.

**Conclusions:** In a retrospective study of data from 2368 patients with chronic liver disease, we found that the B6C are safe whereas the EB6C are unsafe, based on missed VNT. The VariScreen algorithm performed well in patients with chronic liver disease of any etiology or severity—it is the only test that safely rules out VNTs and can be used in clinical practice.

**Words:** 363 (n ≤260)

**Keywords:**

Portal hypertension; non-invasive diagnosis; Baveno VI criteria; cirrhosis; MELD



Non-invasive tests (NITs) have been widely validated as accurate predictors of liver fibrosis or portal hypertension complications such as esophageal varices (EVs). In 2015, the original Baveno VI criteria (B6C), based on platelets and LSM, made it possible to rule out varices needing treatment (VNT) <sup>1</sup>. The B6C's aim is to avoid unnecessary esophagogastroduodenoscopy (endoscopy hereafter), the rate of which may be exaggerated by liver fibrosis NITs <sup>2</sup>. Although largely validated, the clinical impact of the B6C was judged modest, providing a spared endoscopy rate of only about 20% <sup>3</sup>. Therefore, several authors proposed improvements. For example, the expanded B6C (EB6C), with more permissive cutoffs, doubled the spared endoscopy rate <sup>4</sup>. These NITs are applied in chronic liver disease (CLD) according to severity, with a lower limit defined by LSM  $\geq 10$ kPa and an upper limit by the lack of complications defining compensated advanced CLD (cACLD) according to Baveno VI consensus <sup>1</sup>.

The current situation raises a two-tiered question: which current proposal offers the best combination of platelets and LSM, and can that currently-best proposal be improved? Another issue is to define the population where these NITs can be applied. Thus, in the work reported here, our two main objectives were i) to compare the performance of different NITs employing platelets and LSM to rule out VNT in a large CLD population; and ii) to build and validate a new algorithm to improve VNT screening safety and performance. Our secondary objectives were to evaluate the impact of the clinical background (mainly CLD severity and etiology) on these tests. Thus, we compared an overall strategy (NITs performed in all patients) and a selective strategy (NITs performed in cACLD and endoscopy in all other patients) to screen VNT. Therefore, for this study, we included patients with CLD regardless of main disease etiology and liver function severity.

## **Participants**

In this retro-prospective study, data from patients with CLD were collected from centers participating in studies wherein VNT was usually the main outcome and VCTE the measurement outcome. The protocol conformed to the Declaration of Helsinki and received approval from the ethics review boards of all participating centers. All patients gave informed consent. The included patients were retrospectively randomized in derivation (2/3) and validation (1/3) populations with stratification on VNT and etiology.

Patients included in previously-recorded CLD subpopulations of any main etiology (alcoholic, non-alcoholic fatty liver disease (NAFLD), hepatitis B or C virus) were eligible for inclusion if they had undergone an endoscopy to determine EV size. Platelets count, LSM by VCTE (using the M probe), known EV stage and a maximum delay of six months between endoscopy and LSM or platelets were the four minimum inclusion data. Interventional treatment for portal hypertension complications (TIPS, band ligation or sclerotherapy of EV) was an exclusion criterion. Total patient recruitment counted 4132 patients across 10 subpopulations and 47 centers (details in Supplemental Material). Finally, 2368 patients were included: 1579 in the derivation and 789 in the validation populations (Figure 1). All authors had access to the study data and had reviewed and approved the final manuscript.

## **Methods**

### ***Data collection***

The main laboratory data were liver function tests, blood cell count and serum creatinine. The model for end-stage liver disease (MELD) score included bilirubin, international normalized ratio (INR) and creatinine.

*Endoscopy* - A standard endoscopy was performed by an experienced operator, and grades of EV were recorded.

*LSM* - All LSMs were performed by experienced operators using VCTE, specifically M probe-equipped Fibroscan devices (Echosens, Paris, France). Patients with LSM using the XL probe only were not included because this group was too small to be separately evaluated (Figure 1). LSM reliability was defined according to the criteria of Boursier et al <sup>5</sup>.

### ***Definitions***

*Objectives* - The main objective was to evaluate outcome measurements in current and new NITs. The secondary objectives were to evaluate outcome measurements of all NITs as a function of clinical background (age, sex, CLD etiology and severity), and to propose a sequential algorithm based on simple initial clinical rules and with limited test calculations.

*Outcome* - The main outcome was VNT, defined as large EV (grade 2 or 3, i.e., a diameter  $\geq 5$  mm).

*Outcome measurements* - The main outcome measurements for the NITs were the spared endoscopy rate as the performance descriptor and the missed VNT rate as the safety descriptor. The spared endoscopy rate was calculated as the ratio between the number of patients with a low VNT prevalence according to the NIT and the total number of patients. This corresponded to the negative test rate and was dependent on VNT prevalence. The missed VNT rate was calculated with the number of patients with missed VNT as the numerator and the number of patients with VNT as the denominator (other definitions are

0% in CLD with poor liver function (severe CLD hereafter, MELD score  $\geq 10$ : see Supplemental Material). The negative likelihood ratio (LR-) was a secondary outcome measurement. LR- is the ratio of 1 - sensitivity for VNT (i.e., missed VNT rate) divided by specificity for missed VNT, and therefore theoretically independent of VNT prevalence.

### ***Previous tests evaluated***

Three published tests were compared: the B6C, the EB6C and the ANTICIPATE score <sup>7</sup>. Details are provided in the Supplemental Material.

### ***Construction of new algorithm***

*Principles* - In terms of their construction and application, NITs are either “selective”, i.e., intended for CLDs of a specific severity, or “overall”, i.e., unrestricted. These limits affect cutoff values. Here, we developed the two types but, considering their results, chose to report new selective NITs only in the Supplemental Material. Obviously, the ideal overall NIT must have a high spared endoscopy rate, but it must also provide a missed VNT rate that both falls under the  $\leq 5\%$  threshold globally and decreases with liver severity. Indeed, the risk and the severity of EV bleeding markedly increase as a function of liver severity <sup>8</sup>.

*New tests* - Currently, in the B6C, platelets and LSM are used with their own cutoffs, producing a cutoff pair. However, this latter varies in the literature. The *platelets/liver elastometry ratio* (PLER) has the strong advantage of circumventing the cutoff pair choice dilemma, since it confers a single cutoff for a fixed rate of missed VNT. We observed that sex, age, etiology and INR or MELD score were independent significant predictors of VNT in addition to PLER. Moreover, PLER significantly interacted with etiology, sex and INR.

Therefore, we constructed a score for VNT diagnosis based on these five variables, called

in the Supplemental Material. Cutoffs of the PLER or PLEASE scores were determined to provide binary tests indicating a VNT rate  $\leq 5\%$  or  $> 5\%$ .

Finally, we developed a sequential algorithm, named VariScreen<sup>PLI</sup> for *varice screening by platelets, LSM and INR*, which includes three optional steps to reduce calculations whenever possible (Figure 2). VariScreen<sup>PLI</sup>, called VariScreen hereafter, is different from our previous algorithm, VariScreen<sup>CE</sup>, based on CirrhoMeter (blood test) and esophageal capsule endoscopy<sup>9</sup>. First, PLER needed to be calculated only in patients at risk of VNT, i.e., those having platelets  $\leq 402$  G/l and even LSM  $\geq 9$  kPa. Second, when PLER was  $\geq 17$ , the VNT risk was 0% and endoscopy unnecessary. Third, when PLER was  $< 6.2$ , the VNT prevalence was  $> 5\%$  in all clinical settings and endoscopy was mandatory. The grey zone between PLER scores  $\geq 6.2$  and  $< 17$  required PLEASE calculation. The three new NITs are available as a free calculator (<http://forge.info.univ-angers.fr/~gh/wstat/pler-please-variscreen.php>).

### ***Statistics***

Quantitative variables were expressed as mean $\pm$ standard deviation and compared using the Student t test or analysis of variance (ANOVA). Qualitative variables were expressed as proportions and compared using the Chi<sup>2</sup> test or Fisher test when unpaired and the Cochran or McNemar test when paired. Data were reported according to STARD and Liver FibroSTARD<sup>10</sup> statements and analyzed on a partial intention-to-diagnose basis. Thus, all data were analyzed irrespective of VCTE reliability criteria<sup>5</sup> (except in one NAFLD subpopulation<sup>11</sup>) but missing data were not replaced and patients with unsuccessful examinations (LSM and endoscopy) were not included. Scores including independent predictors were determined by binary logistic regression. Sample size calculation is quoted in the Supplemental Material.

USA).

## **RESULTS**

### **Patient characteristics**

*Derivation population* - Nearly two-thirds of the 1579 patients were men (Table 1). Viral CLD was the most frequent etiology (50%), followed by NAFLD (29%) and alcoholic CLD (21%). LSMs  $\geq 10$  kPa were observed in 93.0% of patients. VNT prevalence was 15.1%. Severe fibrosis (F3 or F4 Metavir) estimated by LSM<sup>12</sup> was observed in 90% of patients. Patients with VNT were more frequently male or of alcoholic etiology and had more severe CLD.

*Validation population* - None of the characteristics of the 789 patients were significantly different from those of the derivation population (Table 1).

### **Test characteristics**

#### ***Performance and safety***

*Derivation population* - All NITs had a missed VNT rate  $< 5\%$  except for the EB6C where it was 10.9% (95% CI: 7.0-15.3) and furthermore significantly higher than the rates of all other NITs (Table 2). The spared endoscopy rate was significantly different between tests ( $p < 0.001$ , except B6C vs ANTICIPATE:  $p = 0.751$ ): B6C: 23.9% (21.8-26.2), ANTICIPATE: 24.3% (21.9-26.4), VariScreen: 34.5% (31.9-36.8) and EB6C: 41.9% (39.1-44.3).

*Validation population* - Again, all the NITs had a safe missed VNT rate except for the EB6C where it was 11.7% (6.4-17.9) and furthermore significantly higher than the rates of all other

( $p < 0.001$ , except B6C vs ANTICIPATE:  $p = 0.320$ ) in the same increasing order: B6C: 23.7% (20.7-26.6), ANTICIPATE: 25.0% (21.9-27.9), VariScreen: 36.2% (32.7-39.4) and EB6C: 44.4% (40.8-47.8). Test performance and safety were not significantly different between populations.

### ***Other characteristics***

Diagnostic indices are provided in Table 3. Briefly, the only test with LR-  $\leq 0.1$  in both populations was VariScreen while EB6C was distinguished by a far higher LR- (0.23) compared to the other tests. The patient rates at each step of the VariScreen algorithm in the derivation population are detailed in Figure S1 in the Supplemental Material.

### **Sensitivity analysis**

#### ***NIT performance and safety***

The impact of confounding factors (details in the Supplemental Material) on NIT performance and safety is reported in Table S1.

#### ***NIT secureness***

Securing NITs mainly requires a detailed analysis of their safety in high MELD scores but also consideration as to whether the drop in performance in high MELD scores is worthwhile. Therefore, the impact of the MELD score is detailed here as a function of MELD deciles. The spared endoscopy rate decreased linearly as a function of MELD score in all NITs (Figure 3A). The number of missed VNT remained relatively stable and low (one to two) across MELD deciles in all NITs except EB6C. This latter again showed an unsecured profile, with

performance was low in the high MELD scores. However, their interest does merit analysis through the post-test probability gain. The LR- are presented as a function of MELD deciles in Figure 3C. LR- curves as a function of cumulatively decreasing MELD deciles showed that only two NITs, B6C and VariScreen, gave excellent results (LR- always  $<0.1$ ) with a perfect LR- ( $=0$ ) in the last three MELD deciles, i.e., the most severe CLD. Finally, VariScreen and B6C were the only secured test with no missed VNT in MELD score  $\geq 10$ , (Table S2).

### **Clinical application**

PLER lent itself to a simple clinical rule: when platelets (expressed in the usual G/l units) are  $\geq 10$  times (in viral or alcoholic CLD) or  $\geq 15$  times (in NAFLD) the LSM value (expressed in kPa with VCTE), VNT prevalence is below  $\approx 5\%$  and endoscopy can be avoided (details in Supplemental Material). Although VariScreen performed roughly the same as the PLEASE test alone (Table S3), it showed greater clinical relevance: first, it avoided calculations, e.g., PLER was avoided in 5.6% (5.5-6.7%) and PLEASE in 64.5% (62.1-67.0%) of patients in the derivation population. Second, VariScreen was safer than the PLEASE test as the missed VNT rate was 0% in MELD score  $\geq 10$  in both populations. Finally, VariScreen offered simplicity via an easy-to-use calculator based on successive, optional, simple queries on patient characteristics (<http://forge.info.univ-angers.fr/~gh/wstat/pler-please-variscreen.php>). The calculator includes a reliability analysis between tests that optimized performance: 35.7% vs 34.5% in the derivation population,  $p < 0.001$ .



**Main results** - We found the B6C to be robust and safely applicable regardless of etiology and liver severity. However, the missed VNT rate was borderline in NAFLD (7.4%) and the spared endoscopy rate modest in alcoholic CLD (16.0%). In contrast, despite their high spared endoscopy rate, the EB6C were disqualified because of a high missed VNT rate (11-12%) and a lack of robustness with disparate performance across etiologies and sexes. Our findings on the EB6C's missed VNT rate reflect those of previous studies <sup>6</sup>. In this work, for the first time, we also validated the ANTICIPATE score as a test to spare endoscopy. It offered good performance and robustness, apart the same limits mentioned above for the B6C: a borderline missed VNT rate in NAFLD (7.4%) and a low spared endoscopy rate in alcoholic CLD (17.2%). Finally, among the safe NITs presented here to spare endoscopy, VariScreen offered the best performance. Our derivation and validation populations had similar characteristics and displayed similar NIT results, aspects that reinforce the external validity of our results.

**Originalities** - First, our population was the largest to date with a large spectrum in liver function and etiologies. Therefore, the robustness of NITs could be reported according to the three main influencing factors: sex, CLD etiology and severity. We found that the influences of etiology and sex were only moderate but that of severity was marked. Indeed, VNT prevalence, platelets and LSM are strongly related to liver severity <sup>13</sup>. This results in the reduction of the performance of NITs in severe CLD. Accordingly, the Baveno VI statements suggest applying B6C in cACLD. In comparison to previous studies, we were more able to examine the applicability of NITs according to liver severity. For the B6C, we found an unsatisfactory spared endoscopy rate in severe CLD (8% in the third MELD tertile), confirming the Baveno VI statement that these criteria underperform in severe CLD.

problem. Indeed, VariScreen provided secureness (0% missed VNT in MELD  $\geq 10$ ), robustness and better performance in severe CLD (13% spared endoscopy in the third MELD tertile). This figure may seem low, but it reflects the most improved post-test probability, with a perfect LR- of 0 in the highest MELD deciles (Figure 3C). Here, the LR- reflects the effectiveness of the endoscopy-sparing effect of the NIT<sup>14</sup>.

Finally, we had enough patients to evaluate the new NITs in NAFLD (29%) and alcoholic CLD (21%) and moreover our present study is the first to validate the B6C in the latter. Our results suggest that several NITs can be used in alcoholic CLD, albeit with a significantly lower spared endoscopy rate (<20% except for VariScreen at 25%). Concerning NAFLD, the spared endoscopy rates of all NITs were highly satisfactory but the missed VNT rate was safe only for VariScreen. In the present study, we lowered the LSM cutoff for VNT presence from 10 to 9 kPa. This increased endoscopy rate by 0.5% but reduced missed VNT by 1.4%, which significantly impacted the safety limit (details in Supplemental Material).

**Limits** - Our study comprised numerous centers, which necessarily induced variability.

However, the performances of the published tests observed here were very similar to those of previous studies<sup>2,3,15</sup>, which validates our data record. Moreover, there were no significant differences between the 10 subpopulations for the main outcomes. Our study was retrospective in design, but data were prospectively recorded and VNT was the main outcome regarding data collection (except in the prospective CIRVIR and NAFLD-B6C studies). The Baveno VI statements define VNT as large EV and grade one EV with red signs<sup>1</sup>. Here, we did not include grade one EV with red signs for two reasons. First, many data had been collected before the Baveno VI statements were published. Second, significant differences in the prevalence of grade one EV with red signs was observed between centers<sup>16</sup>. The issue of grade one EV with red signs merits a fully prospective study. We decided to analyze the

upper limit for B6C application). Indeed, the quantitative MELD score has several advantages over qualitative variables reflecting complications. It results in less recording variability and treatment influence, and furthermore eases interaction testing and cutoff determination.

Within this line, treatments were not evaluated due to their multiplicity and variable recordings. However, the B6C have been validated in viral cirrhosis with sustained virological response or under non-selective beta-blockers<sup>17</sup>. Moreover, normal transaminases, considered as a surrogate marker of inactive CLD, did not impact the NIT hierarchy in the present study. Concerning NAFLD, we note that XL probe LSMs must not be used in NITs for VNT constructed with M probe LSMs (details in Supplemental Material): the performance of the VCTE XL probe needs further study. The VariScreen formula seems somewhat complex since there are cutoffs for platelets and/or LSMs specific to each etiology and sex, but they only reflect interactions by confounding factors that must be considered according to recent recommendations on diagnostic scores<sup>10</sup>.

The most important putative limit to consider is the clinical application of NITs for VNT as a function of liver severity. VariScreen provided the best safety profile (no missed VNT) in severe CLD (MELD score  $\geq 10$ ) regardless of etiology. Finally, we consider that a secured strategy, i.e., one without missed VNT in severe CLD, can be applied despite a low spared endoscopy rate for two reasons. Firstly, it is very safe as concerns risky VNT. Secondly, it also increases safety in clinical use since there is no MELD limit to inadvertently neglect (a possibility with unsafe tests in real life). The 5.0% missed VNT rate of VariScreen was borderline in the validation population. Therefore, independent validation is needed (see requirements in Supplemental Material).

***Clinical application*** - PLER can be used at bedside: when the platelet count (G/l) is  $\geq 10$ -fold the LSM value (kPa with VCTE) in viral and alcoholic CLD, or  $\geq 15$ -fold the LSM value in

250 G/l and LSM at 25 kPa would not need endoscopy. For a better-performing diagnosis, we recommend the VariScreen algorithm, which did not require a calculator in 65% of the patients in the present population. Moreover, as its initial diagnostic tools are commonly employed in the clinic, this algorithm can be applied to the general CLD population in whom the sparing effect will be amplified. Our calculator is freely available for use both in clinical practice (tailored to the patient) and in research (for database analyses). According to the influence of delays between endoscopy and LSM or blood biology on main outcome measurements, a negative NIT should be repeated every six months, corresponding to the usual cirrhosis surveillance interval. Finally, an overall strategy, where NITs are applied to all patients offers better performance than a selective strategy where NITs are applied only in compensated patients (details in Supplemental Material).

**Conclusion** - In the present study, we comprehensively show that the Baveno VI criteria are robust whatever the etiology or severity of CLD (with a small safety limit in NAFLD), but that the expanded Baveno VI criteria are unsafe due to a high missed VNT rate. We present an easy-to-use and universally-deployable score (PLER) with very simple rules (platelets  $\geq$  ten-fold LSM = no endoscopy in viral and alcoholic CLD). We prefer however the sequential VariScreen algorithm for its applicability in all main-etiology CLDs and especially its security in severe CLD. VariScreen was the only test for ruling out VNT that was safe for wide use in clinical practice. This overall strategy performed better than a selective strategy restricted to compensated CLD.

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	Derivation			All	Validation	$p^{ab}$
	No VNT	VNT	$p^{ac}$		All	
Patients (n)	1340	239	-	1579	789	-
Age (years)	59.4±10.9	59.1±11.1	0.712	59.3±10.9	59.0±11.2	0.436
Sex (% male)	60.4	74.9	<0.001	62.6	65.1	0.239
Etiology (%):	-	-	0.006	-	-	0.999
Viral	50.3	49.8	0.889	50.2	50.2	1
NAFLD	30.1	22.6	0.020	28.9	28.9	1
Alcoholic	19.6	27.6	0.007	20.8	20.9	1
VNT (%)	0	100	-	15.1	15.2	1
BMI (kg/m <sup>2</sup> )	28.6±6.1	27.8±4.0	0.024	28.5±5.8	28.1±5.6	0.204
AST (IU/l)	71±52	74±47	0.433	71±51	74±62	0.427
ALT (IU/l)	67±60	57±45	0.003	66±58	68±59	0.277
Normal transaminases (%)	15.9	10.5	0.040	15.0	14.9	0.949
Albumin (g/l)	40.4±5.4	37.0±5.7	<0.001	39.9±5.6	39.6±5.6	0.262
Bilirubin (µmol/l)	17±14	32±48	<0.001	20±23	19±17	0.488
INR	1.1±0.2	1.3±0.2	<0.001	1.2±0.2	1.2±0.2	0.953
Platelets (G/l)	155±73	116±68	<0.001	149±74	149±76	0.940
Creatinine (µmol/l)	73±33	67±18	0.025	72±31	71±35	0.531
MELD score	9.1±2.6	11.5±3.7	<0.001	9.5±3.0	9.4±3.0	0.485
LSM (kPa)	25±17	39±20	<0.001	27±18	28±19	0.459
LSM ≥10 kPa (%)	92.1	98.3	<0.001	93.0	92.4	0.612
LSM reliability (%):	-	-	0.004	-	-	0.717
Very reliable	24.4	34.1	-	26.1	27.9	-
Reliable	66.4	51.2	-	63.8	63.0	-
Poorly reliable	9.2	14.7	-	10.1	9.0	-
LSM cutoff for VNT (kPa)	-	9.0	-	-	10.6 <sup>d</sup>	-
Metavir F stage by LSM (%):	-	-	<0.001	-	-	0.743
<F3 (≤10.8 kPa)	11.4	2.5	<0.001	10.1	10.8	0.596
F3 (10.9-17.6 kPa)	32.5	11.7	<0.001	29.3	28.1	0.549
F3/4 (17.7-25.7 kPa)	21.4	15.9	0.052	20.8	19.4	0.496
F4 (≥25.8 kPa)	34.7	69.9	<0.001	40.0	41.7	0.434

LSM: liver stiffness measurement, VNT: varices needing treatment, CO: cut-off. The comparison of the validation and whole populations as a function of VNT is detailed in Table S4 in Table S5.

VNT. <sup>d</sup> One outlier value at 6.3 excluded.



	B6C	EB6C	ANTICIPATE	VARISCREEN	<i>p</i> <sup>a</sup>
<b>Derivation population (1579 patients):</b>					
Missed VNT (%)	2.9 (0.9-5.2)	10.9 (7.0-15.3)	4.6 (2.0-7.4)	2.9 (0.9-5.1)	<0.001 <sup>b</sup>
Spared EGD (%)	23.9 (21.8-26.2)	41.9 (39.1-44.3)	24.3 (21.9-26.4)	34.5 (31.9-36.8)	<0.001 <sup>c</sup>
<b>Validation population (789 patients):</b>					
Missed VNT (%)	1.7 (0.0-4.3)	11.7 (6.4-17.9)	0.8 (0.0-3.1)	5.0 (1.0-9.3)	<0.001 <sup>d</sup>
Spared EGD (%)	23.7 (20.7-26.6)	44.4 (40.8-47.8)	25.0 (21.9-27.9)	36.2 (32.7-39.4)	<0.001 <sup>e</sup>
<b>Derivation vs validation population (2368 patients) (<i>p</i><sup>f</sup>):</b>					
<i>Missed VNT</i>	0.723	0.860	0.068	0.373	-
<i>Spared EGD</i>	0.919	0.252	0.723	0.411	-

EGD: esophagogastroduodenoscopy, VNT: varices needing treatment

Color legend: missed VNT (% in VNT): ≤5: safe, >10: unsafe, intermediate; spared EGD (%): ≥20: satisfactory, <10: unsatisfactory, intermediate

<sup>a</sup> Paired Cochran test

<sup>b</sup> Differences in missed VNT rate were significant only between EB6C vs others (p<0.001 by paired McNemar test)

<sup>c</sup> Differences in spared EGD rates were significant between all tests (p≤0.001 except for B6C vs ANTICIPATE: p=0.751)

<sup>d</sup> Differences in missed VNT rate were significant only between EB6C vs others (p≤0.039)

<sup>e</sup> Differences in spared EGD rates were significant between all tests (p≤0.001 except for B6C vs ANTICIPATE: p=0.320)

<sup>f</sup> Unpaired Fisher test

descriptors are sensitivity (since 1- sensitivity = missed VNT rate) and LR- (= missed VNT rate/specificity).

	<b>B6C</b>	<b>EB6C</b>	<b>ANTICIPATE</b>	<b>VARISCREEN<sup>a</sup></b>
<b>Derivation population (1579 patients):</b>				
Accuracy (%) <sup>b</sup>	38.2	<b>53.7</b>	38.0	49.8
Sensitivity (%)	<b>97.1</b>	<b>89.1</b>	<b>95.4</b>	<b>96.7</b>
Specificity (%)	27.7	<b>47.4</b>	27.8	41.4
PPV (%)	19.3	<b>23.2</b>	19.1	22.7
NPV (%)	98.1	96.1	97.1	<b>98.6</b>
LR+	1.34	<b>1.69</b>	1.32	1.65
LR-	<b>0.11</b>	<b>0.23</b>	<b>0.17</b>	<b>0.08</b>
<b>Validation population (789 patients):</b>				
Accuracy (%) <sup>b</sup>	38.4	56.0	39.9	<b>63.1</b>
Sensitivity (%)	<b>98.3</b>	<b>88.3</b>	<b>99.2</b>	<b>95.0</b>
Specificity (%)	27.7	50.2	29.3	<b>57.4</b>
PPV (%)	19.6	24.1	20.1	<b>28.6</b>
NPV (%)	98.9	96.0	<b>99.5</b>	98.5
LR+	1.36	1.77	1.40	<b>2.23</b>
LR-	<b>0.06</b>	<b>0.23</b>	<b>0.03</b>	<b>0.09</b>

PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio. The best indices among tests are shown in bold. Color legend: 1- sensitivity or missed VNT (% in VNT): ≤5: safe, >10: unsafe, intermediate; LR-: ≤0.1: excellent (large decrease of post-test VNT probability), >0.1 & ≤0.3: good (significant decrease), >0.3 & ≤0.5: fair (moderate decrease), >0.5 & ≤1: poor (small decrease)

<sup>a</sup> Results including reliability analysis

<sup>b</sup> Correctly classified

**Figure 1. Patient inclusion flowchart.**

**Figure 2. VariScreen algorithm:** VNT screening strategy in CLD, first as a function of biomarkers (platelets, LSM) then ensuing PLER score and PLEASE test as necessary.

**Figure 3. VNT diagnosis by NITs as a function of MELD deciles in the whole population.**

(A) Spared endoscopy rate (%). (B) Missed VNT number. Whole population. (C) Cumulative LR- of NITs as a function of decreasing MELD deciles. The 9<sup>th</sup> LR- on the right corresponds to cumulated MELD deciles 10 and 9 and so on in decreasing order. Thus, the LR- of the first MELD decile (#1) corresponds to the global test LR-.

### **Supplemental Material**

The Supplemental Material includes 11 tables and 4 figures.

We thank the co-investigators of the VEB6 (validation of expanded Baveno VI criteria) group as a function of subpopulations:

Monocenter subpopulations:

- Angers (SNIFF 95 study, France): François Buisson, Arthur Berger, Carlotta Carboni (and Bologna), Frédéric Oberti, Isabelle Fouchard, Jérôme Boursier, Adrien Lannes, Gilles Hunault, Paul Calès.
- Bologna (Italy): Elton Dajti, Vanessa Luigina Alemanni, Giovanni Marasco, Federico Ravaioli, Antonio Colecchia, Davide Festi.
- Cluj (Romania): Horia Stefanescu, Oana Farcau, Anca Maniu, Andreea Ardelean, Petra Fischer, Crina Grigoras, Bogdan Procopet.
- Bern (Swiss): Annalisa Berzigotti.
- Toulouse (France): Christophe Bureau, Marie Angèle Robic, Maeva Guillaume.
- Bondy (France): Nathalie Ganne-Carriè, Nathalie Barget.

Multicenter subpopulations:

- VO-VCO (PHRC, France): Sylvie Sacher Huvelin, Paul Calès, Dominique Valla, Christophe Bureau, Anne Olivier, Frédéric Oberti, Jérôme Boursier, Jean Paul Galmiche, Jean Pierre Vinel, Clotilde Duburque, Alain Attar, Isabelle Archambeaud, Robert Benamouzig, Marianne Gaudric, Dominique Luet, Patrice Couzigou, Lucie Planche, Emmanuel Coron, Jean-Baptiste Hiriart, Faiza Chermak, Maude Charbonnier.
- M116 study (Echosens, Italy, Romania, France, United Kingdom): Horia Stefanescu, Giovanni Marasco, Paul Calès, Mirella Fraquelli, Matteo Rosselli, Nathalie Ganne-Carriè,

Andreone, Giuseppe Mazzella, Davide Festi.

- B6C NAFLD group: Salvatore Petta<sup>1</sup>, Giada Sebastiani<sup>2</sup>, Elisabetta Bugianesi<sup>3</sup>, Mauro Vigano<sup>4</sup>, Vincent Wai-Sun Wong<sup>5</sup>, Annalisa Berzigotti<sup>6</sup>, Anna Ludovica Fracanzani<sup>7</sup>, Quentin M. Anstee<sup>8,9</sup>, Fabio Marra<sup>10,11</sup>, Marco Barbara<sup>1</sup>, Vincenza Calvaruso<sup>1</sup>, Calogero Camma<sup>1</sup>,

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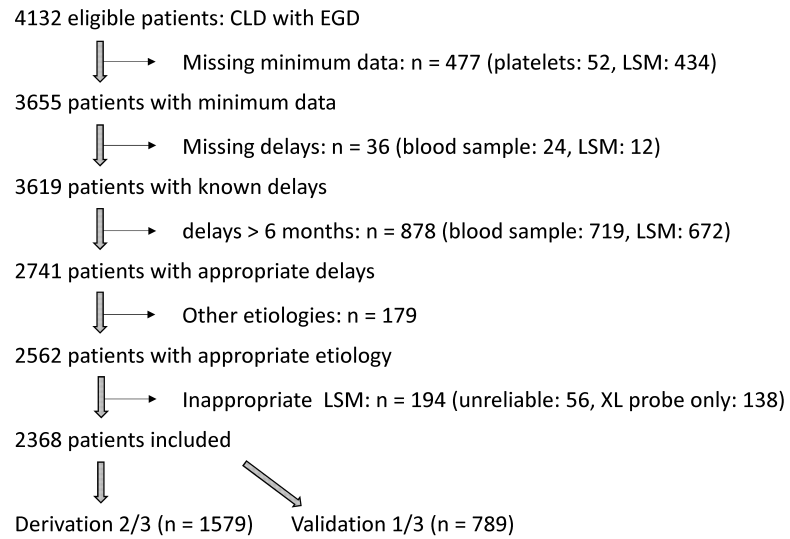
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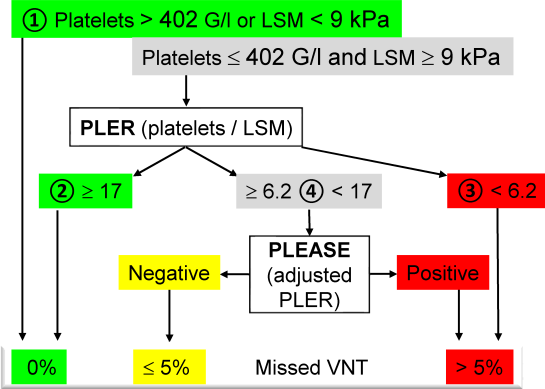
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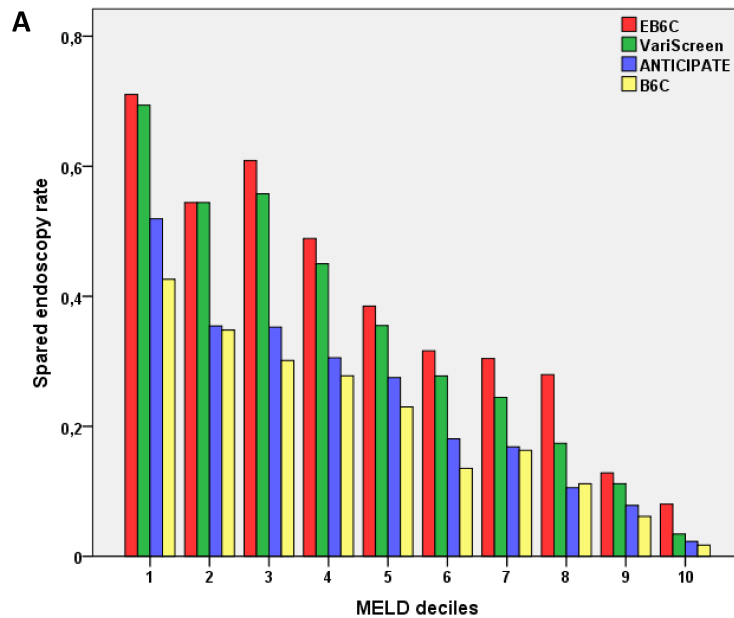
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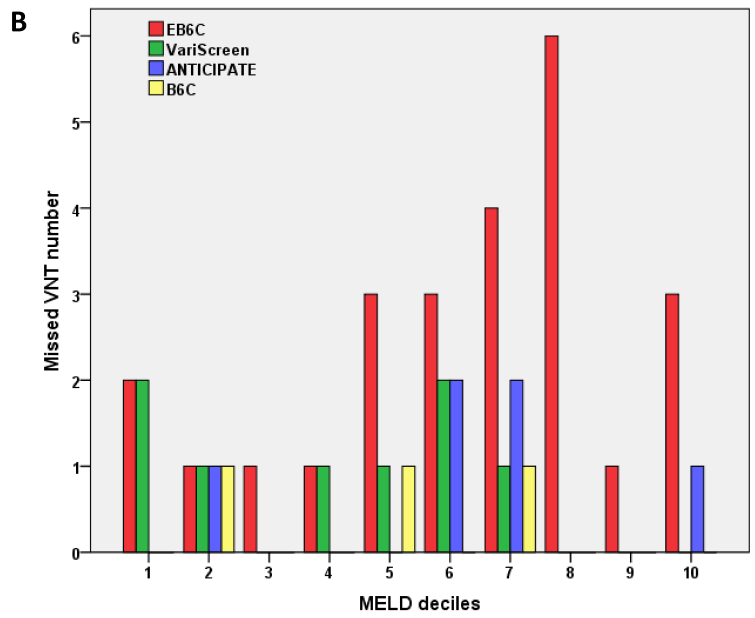




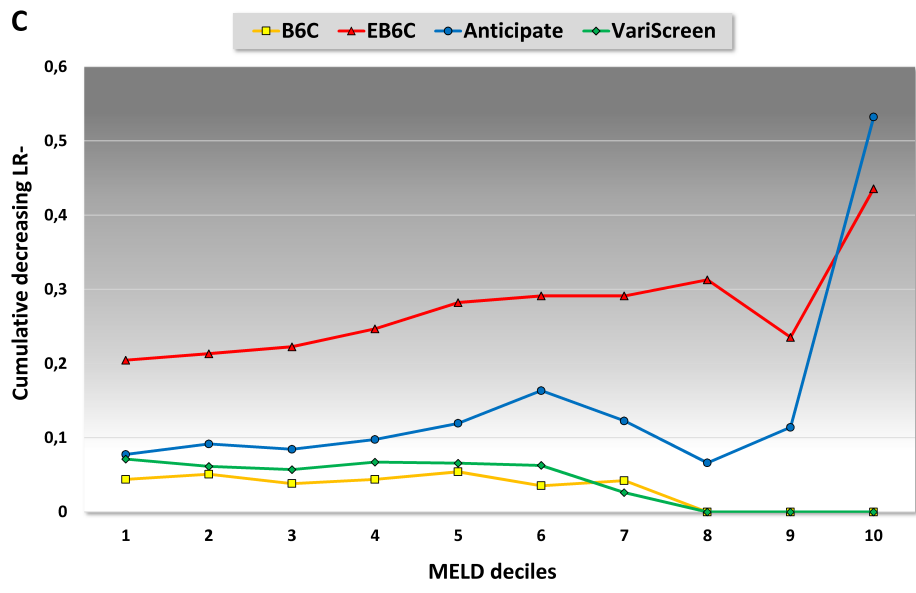




Lower MELD score: 6.4 6.8 7.4 7.7 8.2 8.7 9.2 10.0 11.0 13.3



Lower MELD score: 6.4 6.8 7.4 7.7 8.2 8.7 9.2 10.0 11.0 13.3

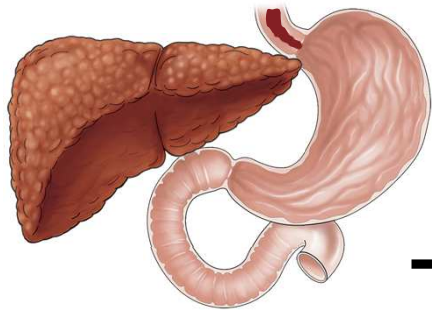


Background: on platelets and liver stiffness measurements, the Baveno VI criteria (B6C), the expanded B6C (EB6C), and the ANTICIPATE score can be used to rule out varices needing treatment (VNT) in patients with compensated chronic liver disease.

Findings: A retrospective study of data from 2368 patients with chronic liver disease found that the B6C are safe whereas the EB6C are unsafe, based on missed VNT. The VariScreen algorithm performs well in patients with chronic liver disease of any etiology or severity.

Implications for patient care: The VariScreen is the only test that safely rules out VNTs and can be used in clinical practice regardless of severity.

# The non-invasive VariScreen algorithm rules out varices needing treatment irrespective of the severity of chronic liver diseases in around 35% of patients



VariScreen uses blood platelets, liver stiffness measurement (LSM) and optionally INR:

