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Qualification en Hépato-gastro-entérologie.

Risk factors for esophageal varices needing treatment: application to their non-invasive diagnosis

Facteurs de risque pour les varices œsophagiennes nécessitant un traitement : application au diagnostic non invasif

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Sous la direction de Monsieur le Professeur Paul Calès

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ABBREVIATIONS

ALD :	alcoholic liver disease
B6C :	Baveno VI criteria
CLD :	chronic liver disease
EV :	esophageal varices
INR :	international normalized ratio
LIP :	LSM / (prothrombin index * platelets)
LSM :	liver stiffness measurement
MELD :	model for end-stage liver disease
NAFLD :	non-alcoholic fatty liver disease
NIT :	non-invasive test
PI :	prothrombin index
PHT :	portal hypertension
VCTE :	vibration-controlled transient elastometry
VNT :	varices needing treatment

TABLE OF CONTENTS

RISK FACTORS FOR ESOPHAGEAL VARICES NEEDING TREATMENT : APPLICATION TO THEIR NON-INVASIVE DIAGNOSIS

Short Title: VNT RISK FACTORS

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Keywords:

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ABSTRACT

Background and Aims:

The epidemiology of varices needing treatment (VNT) has been evaluated under limited conditions in chronic liver disease (CLD). The main objective was to evaluate VNT risk factors, in a large multiple-etiology population unrestricted for liver severity, to improve the VNT non-invasive diagnosis.

Methods:

2,290 patients with CLD were included in a retro-prospective multicenter study. Their characteristics were age: 59±11 years; male sex: 63.5%; etiologies: virus: 50.0%, NAFLD: 29.5%, alcohol: 20.5%; BMI: 28.4±5.8 kg/m²; MELD score: 9.5±3.0; liver stiffness ≥10kPa: 92.9%; VNT prevalence: 14.9%.

Results:

The independent VNT predictors were etiology, sex, platelets, prothrombin index (PI), liver stiffness, albumin and ALT, with no role for age, BMI, AST, creatinine and MELD score. However, there were significant interactions, i.e., age with PI, LSM with platelets and BMI with etiology. Covariate-adjusted BMI in patients with VNT was lower in NAFLD (p=0.002) but higher in alcoholic CLD (p=0.009) compared to patients without VNT. These risk factors and their ratio, due to several interactions, were included in new non-invasive scores. The $SCOUT_{13}$ score was far more discriminant (VNT AUROC: 0.826, p<0.001) than published scores, e.g. Anticipate (0.771) or a new score (LSM/(prothrombin index*platelets)) called LIP (0.778). The new $VariScreen_3$ provided three VNT risk categories: ≤5%, >5% and <100%, 100% (i.e. a new category). $VariScreen_3$ spared more endoscopies (40.2%, p<0.001) than other safe tests: Baveno VI criteria (24.1%), Anticipate (24.7%), LIP (35.2%) or $VariScreen_2$ (35.3%).

Conclusions:

VNT prevalence varies significantly according to etiology, liver function and fibrosis, sex in all etiologies, and BMI differently according to etiology. The risk factor interplay significantly improves the performance of diagnostic tests for VNT which can be applied irrespective of liver severity.

275 words (≤275)

INTRODUCTION

The original Baveno VI criteria (B6C) enabled the wide clinical acceptance of non-invasive tests (NITs) for varices needing treatment (VNT). The B6C are based on platelets and liver stiffness measurement (LSM) [1], this latter assessed by vibration-controlled transient elastography (VCTE), and aimed at ruling out VNT. Although largely validated [2-6], their clinical impact has been judged modest, providing a spared esophagogastroduodenoscopy (endoscopy hereafter) rate of only about 20% [3, 7]. Therefore, several authors have proposed improvements [8-11].

Evaluations of NITs as a function of etiologies of chronic liver disease (CLD) have indeed been performed, and their results have led to adaptations of B6C cut-offs in non-alcoholic fatty liver disease (NAFLD), for example [12]. However, NIT performance should also vary as a function of VNT epidemiological factors, but these latter have been poorly evaluated [13, 14] or not demonstrated probably due to the low sample sizes of previous studies. We have collected an extensive database of patients with esophageal varices (EVs) as the main outcome [15]. Thus, for the work presented here, we focused on VNT epidemiology, recognizing however that several clinical characteristics, especially CLD etiology and centers, might influence the conditions of patient recruitment and therefore observed epidemiology. Thus, our primary aim was to determine the epidemiological risk factors linked to VNT in clinical practice through raw or observed data. Our secondary aims were to evaluate, first, adjusted risk factors to minimize the biases linked to patient recruitment and, second, the interplay between risk factors to improve non-invasive VNT diagnosis which was the ultimate goal.

PATIENTS AND METHODS

Participants

In this post-hoc analysis of prospectively collected data, data from patients with CLD were collected from a number of centers participating in several 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 study participants gave informed consent. Patients included in previously-recorded CLD subpopulations of any main etiology (alcoholic CLD (ALD), NAFLD, hepatitis B or C virus) were eligible for inclusion if they had undergone an endoscopy to determine EV size. A platelet count, successful 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 criteria. Interventional treatment for portal hypertension (PHT) complications (TIPS, band ligation or sclerotherapy of EV) and incomplete data for liver function tests (especially albumin) were exclusion criteria. Also, patients were included irrespective of LSM values and liver severity (i.e. non limited to compensated advanced CLD (cACLD)) to enable a less biased analysis of risk factors. Of the 4132 patients across 47 centers (details in [15]) eligible for the study, 2290 were finally included in it (**Figure 1**).

Methods

Data collection

Clinical data - The main clinical data were age, sex, height, body weight and CLD etiology. The main laboratory data were liver function tests, blood cell count and serum creatinine

(measured in each center). The model for end-stage liver disease (MELD) score included bilirubin, the international normalized ratio (INR) and creatinine [16].

Endoscopy - A standard endoscopy was performed by experienced operators, 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 they were not sufficiently numerous to be separately evaluated (**Figure 1**). Technical characteristics are detailed elsewhere [17].

Definitions

Objectives - The primary objective was to evaluate epidemiological factors linked to VNT as observed in clinical practice. The secondary objectives were to a) adjust epidemiological factors to limit biases attributable to patient recruitment conditions, b) unmask risk factors hidden by interactions between them, and finally c) improve non-invasive VNT diagnosis by considering these risk factors and their interactions.

Outcome - The main outcome was VNT, defined as large EV (grade 2 or 3, i.e., a diameter ≥5 mm [18]).

Outcome measurements - The primary outcome measurement was raw VNT prevalence. The main secondary outcome measurements were VNT prevalence adjusted on covariates and the evaluation of interactions between the main risk factors through descriptive analysis and statistical tests. Another secondary outcome measurement was VNT progression as a function of liver severity expressed by INR. Metavir fibrosis stages were estimated by LSM [19].

Comparators - The new tests were compared to published tests: Baveno VI criteria (B6C) [1], expanded B6C (EB6C) [9], Anticipate [20], PLER, PLEASE and VariScreen2 [15].

Statistics

Quantitative variables were expressed as mean ± 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^2 test or Fisher test when unpaired and the Cochran or McNemar test when paired. Correlations were measured by the non-parametric Spearman correlation coefficient (rs). The relationships between the main quantitative descriptors and their covariates were described by the analysis of covariance (ANCOVA). First, ANCOVA enables a description of the independent predictors of a raw dependent variable. Second, it provides the mean of dependent variables adjusted on covariates. Independent VNT predictors were determined by backward binary logistic regression. INR or PI was the privileged variable for liver function since MELD was supplanted by PI as the independent VNT predictor. PI was chosen over INR because it was the liver function descriptor the most predictive of VNT. However, in descriptive results, INR was preferred for its positive correlation with VNT course and its more universal use. For further logistic modeling, we systematically tested interactions between the four main epidemiological factors: age, sex, etiology and PI. Additional interactions were determined according to non-linear correlation curves. Models with variable collinearity ($r>0.8$) were always excluded. Data were reported according to STARD [21] and Liver FibroSTARD [22] statements, and analyzed on a partial intention-to-diagnose basis. Thus, all patients were included irrespective of reliability criteria of VCTE [23] (except in one NAFLD subpopulation [12]) but missing data were not replaced and patients with unsuccessful examinations (LSM and endoscopy) were not included. Details on test construction are provided in the Supplemental Material. The main statistical analyses were performed using SPSS version 18.0 (IBM, Armonk, NY, USA).

RESULTS

1. Patient characteristics

1.1. Whole population

This population included 2290 CLD patients (**Table I**), nearly two-thirds of whom were men. Viral CLD was the most frequent etiology (50%); other etiologies included NAFLD (29.5%) or ALD (20.5%). LSMs ≥10 kPa were observed in 93% of patients. Severe fibrosis (F3 or F4 Metavir) was observed in 90% of patients, 20% of whom had early cirrhosis and 41% definitive cirrhosis. Thus, 72% of VNT were observed in cirrhosis estimated by the LSM classification.

1.2. Patient characteristics as a function of etiology

These results are detailed in **Table II**. Almost all characteristics were significantly different between etiologies. Briefly, patients with ALD were more frequently male, had more severe CLD, higher LSMs and the highest VNT prevalence. Patients with NAFLD had higher BMIs, advanced age, the lowest prevalence of VNT, normal transaminases, and the lowest AST levels. Patients with viral CLD had the lowest platelet count despite the lowest MELD score.

2. VNT characteristics

2.1. Raw data

The raw VNT prevalence was 14.9% (95% CI: 13.4-16.5) in the whole population, 14.6% (12.6-16.6) in viral CLD, 12.0% (9.6-14.4) in NAFLD and 20.0% (16.4-23.7) in ALD. Also, 98.5% of VNT were observed in LSM ≥10 kPa. Patients with VNT were more frequently male or affected by ALD and had more severe CLD (**Table I**). The raw VNT prevalence as a function of sex, etiology and INR tertiles is shown in **Figure 2A**. The particularities for females with ALD are detailed in the Supplemental Material. The raw odds ratio of VNT for men was 1.76 (1.36-2.28) in the whole population, 1.49 (1.05-2.12) in viral CLD, 1.64 (1.00-2.69) in NAFLD and 2.45 (1.28-4.68) in ALD.

The patient characteristics as a function of VNT presence in each etiology are detailed in Supplemental **Table S1**. Briefly, most previously-observed significant characteristics of VNT were also observed in each etiology with the exception of increased BMI and decreased age in ALD with VNT, contrary to other etiologies.

2.2. Adjusted data

The odds ratio of VNT for men was 1.68 (1.29-2.18) when adjusted on etiology and 1.55 (1.19-2.03) when adjusted on etiology and INR tertiles. We evaluated VNT prevalence adjusted on all other factors according to ANCOVA. Adjustment enables a comparison of VNT prevalence between etiologies by making their clinical backgrounds similar. As sex and etiology interacted (p=0.045) for the prediction of raw VNT prevalence, additional ANCOVA was performed in each etiology. Thus, sex was an independent VNT predictor in viral CLD (p=0.023) and ALD (p=0.001) but not in NAFLD (p=0.197). The comparison of raw and

adjusted VNT prevalences is described as a function of etiology and sex in **Table S2** and **Figure 2B**. Briefly, adjustment moderately but significantly increased VNT prevalence in NAFLD, with a more marked increase in females, compared to raw prevalence; this negated the significant decrease observed in females vs males in the raw data. By contrast, adjustment markedly decreased VNT prevalence in ALD, even in females.

3. VNT predictors

3.1. Robust predictors

The independent VNT predictors in the whole population were sex, etiology, platelets, LSM, markers of liver function (INR, PI, bilirubin, albumin) and ALT. Age, BMI, AST, creatinine and MELD score were not independent predictors (details in **Table S3**). The robust VNT predictors across etiologies (details in **Table S4**) were INR or PI and the platelets/LSM ratio called PLER [15] (see Supplemental Material). The following predictors were unmasked through interaction analysis.

3.2. Age impact

We further evaluated the role of age as it interacted with PI. The correlation of age with other variables was inversed between patients with or without VNT (**Figure S1A**). That observation reflected an interaction between age and the variables. Thus, in patients without VNT, the youngest patients had significantly higher platelets (and ALT) as expected (**Table S5**). By contrast, in patients with VNT, the youngest patients unexpectedly had significantly altered liver function and LSMs compared to the oldest patients.

3.3. BMI impact

3.3.1. Univariate analysis

In the whole population, BMI was significantly increased in NAFLD (**Table II**), as expected, and in females (**Table S6**). It was however significantly decreased in VNT (**Table I**).

3.3.2. Multivariate analysis

In the whole population, BMI was not an independent predictor of VNT as previously related (details in **Table S7**). There was a significant interaction between BMI and etiology ($p<0.001$) and thus the risk factors were tested in each etiology. BMI was not predictive of VNT in viral CLD ($p=0.971$), negatively predictive in NAFLD ($p=0.001$) and positively predictive in ALD ($p=0.031$).

3.3.3. Ajusted BMI

Mean adjusted BMI in patients with VNT was significantly lower in NAFLD ($p=0.002$) and significantly higher in ALD ($p=0.036$) compared to patients without VNT (**Figure 2C**). Thus, the same discrepant differences were observed in both the raw and adjusted BMI as a function of VNT between NAFLD and ALD (**Figure 2C** and **Table S8**). Furthermore, the non-significant increase of raw BMI observed in ALD patients with VNT compared to ALD patients without VNT became significant after BMI adjustment. Thus, the relationship between VNT and BMI was robust (as a function of covariables), which reinforces the discrepant BMI relationship with VNT across etiologies.

3.4. Summary of risk factors

In all etiologies, the independent VNT risk factors were male sex, liver dysfunction, increased LSM and thrombocytopenia (**Table S9**). Some factors were etiology-specific: decreased activity in viral CLD, and BMI either decreased in NAFLD or increased in ALD. The relationships between the main risk factors are described in **Figure 2D**.

4. Clinical application

Different scores were derived by using the previous risk factors. We selected either a simple ratio LSM / (PI*platelets) called LIP and three algorithms including numerous risk factors and ratio called scores of usual tests (SCOUT). Details are provided in the Supplemental Material.

Scores to diagnose VNT - The AUROC of SCOUT13 (0.826) was higher ($p<0.001$) than that of other scores: PLER (0.766), Anticipate (0.771), LIP (0.778) and PLEASE (0.789) (**Table III** and **Figure 3A**). SCOUT13 was well calibrated for VNT risk (**Figure 3B**). SCOUT13 was able to reach a 100% sensitivity in a patient subset as other scores but also a 100% specificity in a patient subset by contrast to other tests (**Figure 3A** and **4A**).

Tests to spare endoscopy - A new test, called Variscreen3, was constructed by using the cut-offs of three SCOUTs (**Figure 4B**). B6C, Anticipate, Variscreen2 and Variscreen3 were safe (missed VNT <5.0%) but not EB6C (missed VNT: 11.4%, $p<0.001$ vs each other test). The spared endoscopy rate was by increasing order: B6C: 24.1%, Anticipate: 24.7%, LIP: 35.2%, Variscreen2: 35.3%, Variscreen3: 40.2% and EB6C: 42.9% ($p<0.001$ for each pair comparison except for B6C vs Anticipate: $p=0.393$ and LIP vs Variscreen2, $p=1$) (**Table IV**). Secureness, defined by no missed VNT in MELD score ≥10 [15], was quite excellent with LIP as for VariScreen2 and excellent with VariScreen3 (only one missed VNT) (**Figure 3C**).

DISCUSSION AND CONCLUSION

Originalities - First, our population was the largest to date to be used for the evaluation of VNT in CLD. It also comprised the three main CLD etiologies and a broad spectrum of liver function. Those qualities allowed us to evaluate the epidemiology of VNT according to the main risk factors: CLD etiology, liver severity and especially sex. Second, with the size of the test population, we were able to evaluate multiple interactions and resultantly unmask the role of BMI. Thus, we demonstrated several new VNT risk factors in the present study.

Main results - The risk factors for VNT in the present study were etiology, male sex, parameters classically reflecting liver function (albumin, bilirubin, INR or PI), PHT (platelets) and liver fibrosis (LSM). Furthermore, BMI, inflammation (ALT) and age interactions were demonstrated in some etiologies and are discussed separately. We thus identified five categories of robust, independent VNT predictors: etiology, sex, liver function, PHT and liver fibrosis, the last three of which are closely linked.

Platelets and LSM - The roles of platelets (PHT) and LSM (liver fibrosis) have already been extensively described especially as independent VNT predictors [8]. However, we found here a strong interaction between platelets and LSM, and indeed the platelets/LSM ratio significantly increased the prediction of VNT compared to its composite variables [15]. This was especially useful in ALD where platelets and LSM alone were not independent VNT predictors, whereas their ratio was (**Table S4**). Interestingly, 2.9% of patients with LSM <10 kPa had VNT (details in Supplemental Material). The exclusion of these patients would distort the accepted rate of missed VNT used in the B6C conditions, i.e., ≤5%. It should be noted that there is no particular documentation for the Baveno cut-off of 10 kPa [1] and it was

probably settled upon so as to furnish an easily-memorized, round number. Furthermore, in an earlier work, we found that 8.3% of patients with cirrhosis on liver biopsy had LSMs <10 kPa [24]. Therefore, if viral CLDs are included in studies, endoscopy should be considered with LSMs as low as 9 kPa.

Liver function - The role of liver function was already suspected because PHT had been previously linked to it [25]. The role of liver function as an independent predictor of VNT is however poorly documented by contrast to EV [26]. A transversal study showed that Child Pugh class B was an independent risk factor of VNT [11], and two longitudinal studies showed that a high initial Child-Pugh score [27, 28] and a smaller improvement in the Child-Pugh score during follow-up [27] were independent predictors of VNT occurrence. Our present study demonstrated a close relationship with liver function, as VNT prevalence linearly increased as a function of INR (**Figure S1B**). Finally, bringing PI into the equation to form the LSM / (PI*platelets) ratio significantly increased the accuracy for VNT detection compared to the aforementioned platelets/LSM ratio [15]. This also demonstrates the interest of exploiting multiple interactions (**Figure S1A**).

Etiology - The role of etiology was poorly documented for VNT epidemiology. Lee et al did however report an increased VNT prevalence in ALD with borderline significance (p=0.058) in multivariate analysis [29]. Merli et al reported an increased progression to VNT in ALD in multivariate analysis [28]. We provide here prevalences by etiology that merit discussion. Raw VNT prevalence was higher in ALD than it was in viral CLD or NAFLD. Adjustment on covariates however significantly reduced VNT prevalence in ALD (**Figure 2B**, **Table S2**), suggesting that the higher raw prevalence was attributable to the more severely affected liver function in that disease. Thus, the natural history of VNT occurrence reconstructed as a function of liver function is quite different from that provided by observed (raw) VNT prevalences in clinical practice.

Sex - To our knowledge, the role of sex in VNT has never been demonstrated. Heretofore, it has been shown as a predictive factor only in univariate (but not multivariate) analysis in HBV cirrhosis [30]. In the present study however, we found the role of sex to be robust, as it persisted in viral CLD and ALD after adjustment on covariates. This role might be related to a negative effect of estrogen on angiogenesis [31] or liver fibrogenesis [32]. We found that VNT prevalence was low in women with ALD despite their poor liver function. We attributed that aspect to a lower prevalence of obesity in those patients (details in Supplemental Material).

Age - Age has not been shown to be an independent VNT predictor in previous studies. In our work, the role of age was challenging to interpret for two reasons: first, the date of (initial) endoscopy was variable with respect to the start of CLD, which in turn was variable with respect to age, and age interacted with liver function. Thus, younger patients with VNT had unexpectedly more altered liver function and LSMs than older patients with VNT did (in contrast to patients without VNT). This apparent paradox might be attributed to the natural history of VNT, with its high death rate in younger patients. Indeed, in patients with VNT, bleeding risk is maximum in young patients and the death rate grows with CLD severity [33].

BMI - The role of BMI in VNT has never been demonstrated. In a small population of 63 Japanese patients with compensated HCV cirrhosis, increased BMI was the only independent predictor of EV [34]. In our present study, BMI was an independent VNT predictor when increased in ALD or decreased in NAFLD. The influence of metabolic syndrome on PHT has already been observed, and obesity has been shown to be associated with PHT [35] or decompensation [36]. Furthermore, BMI has been independently associated with PHT or with EV in univariate (but not in multivariate) analysis [37] and steatosis degree was the only independent PHT predictor in another study [38]. Our apparently paradoxical observation of decreased BMI in NAFLD patients with VNT might result from the natural history of BMI in

NAFLD. This latter is characterized by high initial BMI but progressive decrease of it as a function of time or liver function. This was reflected by sarcopenia, as our patients with NAFLD and VNT had initially the lowest creatinine levels (**Figure S2A**) or creatinine/ BMI ratios (**Figure S3A**). Considering ALD, on one hand, our patients had higher LSMs or fibrosis levels (**Figure S2B**), and on the other, BMI and alcohol are independent risk factors for cirrhosis and thus increased BMI precedes cirrhosis in different etiologies [39, 40]. Therefore, in ALD, a high BMI is associated with increased fibrosis, which favors PHT, liver dysfunction [41] and thus VNT. The amount of fibrosis is higher in ALD than in other etiologies at similar Metavir fibrosis stages [42]. In our work, BMI was well correlated with creatinine in the lowest INR tertile contrary to the others (**Figure S3B**). Taken together, these results argue against a predominant role for fluid retention in the relationship between BMI and VNT, at least in the first INR tertile. However, the role of BMI deserves further study, especially in compensated CLD.

Limits - Our study involved several centers, which necessarily induced variability especially for the conditions of patient recruitment. However, we performed several adjustments on patient characteristics with good measurement reproducibility [15] to attenuate this intercenter variability. Our study was retrospective in design, but data were prospectively recorded and VNT was the main outcome as concerned data collection in most subpopulations. According to the Baveno VI statements, VNT are defined as large EV and grade 1 EV with red signs [1]. However, we did not include grade 1 EV with red signs for two reasons. First, many data had been collected before the Baveno VI statements were published, and thus information on red signs was missing in a substantial proportion of them. More importantly, in a recent fully prospective subpopulation, we observed significant differences in the prevalence of grade 1 EV with red signs between centers [43], which

statistically affected outcome measurements. This issue merits a fully prospective study. We decided to analyze the impact of liver severity using the MELD score (or preferably INR) and not clinical complications. 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 statistical analysis. Additionally, Child-Pugh, including complications, and MELD scores have shown similar prognostic values in most cases [44]. Treatments were not evaluated due to their multiplicity and variable recordings. However, several checks were made, e.g. normal transaminases to consider inactive CLD and similarity of INR correlations with other variables to consider oral anticoagulants that might be more prevalent in NAFLD.

Summary of VNT epidemiology - The observed or raw data in the clinical practice of study conditions were as follows. In ALD, endoscopy and VNT diagnosis occurred earlier, and VNT prevalence and CLD severity were higher compared to other etiologies. In NAFLD, the VNT diagnosis occurred later (10 years after ALD), but the VNT prevalence and CLD severity were lower compared to other etiologies. In all etiologies, raw VNT prevalence was lower in women.

As several risk factors impacting VNT prevalence, especially liver function and etiology, might influence patient recruitment, a less biased comparison of VNT prevalence was made after adjustment. This markedly changed the epidemiological landscape since the highest VNT prevalence shifted to NAFLD (not significantly compared to viral CLD) while the lowest prevalence was observed in ALD. Risk factors other than etiology remained unchanged from the raw data. Thus, the adjusted VNT prevalence remained lower in women (not significantly in NAFLD). Also, the significance of the relationship between BMI and VNT increased after adjustment: BMI predicted VNT when decreased in NAFLD and when increased in ALD.

Finally, all main factors had similar independent roles for VNT, regardless of adjustment, except for etiology and BMI, which was discordant among the three etiologies (**Table S9**).

Clinical application - In the previous study on VNT screening, we have shown that an overall strategy, i.e. irrespective of liver severity, was more performant than a selective strategy, i.e. restricted by liver severity cut-offs like in cACLD [15]. However, this strategy had to be secured, i.e. without missed VNT in severe CLD with MELD ≥10 since death rate of variceal bleeding is correlated with liver severity. Therefore, we developed an algorithm called VariScreen2 which was more performant and secured than previous tests [15].

In the present study, we developed two new tests. The first test, LIP, was simple, performant and secured however it was not able to reach a 100% specificity for VNT in a patient subset. This score was mainly developed for the VNT diagnosis, estimating the precise VNT risk. The second test was a composite algorithm, VariScreen3 requiring a calculator, developed for endoscopy sparing. This was the most performant safe test providing three VNT risk categories: ≤5%, >5% and <100%, 100%. Finally, for VNT diagnosis, we prefer SCOUT13 since it was more discriminant than LIP, especially reaching a 100% specificity in a patient subset; however, it requires a calculator.

In the present exploratory study, there was no validation set population. However, the optimism bias was reflected by the narrow 95%CI of VariScreen3: 2.8-7.3% of missed VNT. It should be also underlined that the definition of missed VNT used was the less optimistic [45]. The new tests should be validated in independent populations. A robust validation requires a large population as previously discussed [45].

Until now, the unnecessary endoscopies were look for in patients with a very low VNT prevalence. In the present study, we show that it was also possible to expend this concept to patients with a very high VNT prevalence. The tests developed here made easy the

determination of 100% specificity cut-off for VNT (**Figure 4A**). In addition, the corresponding cut-offs (around scores at 0.8) were robust since most patients with cut-offs >0.6 had still VNT. For example, in SCOUT13 ≥ 0.6, the VNT prevalence was 78.9% (**Figure 3B**). On the other side, the VNT prevalence was 0% in SCOUT13 ≤ 0.00834 (11.4% of patients) meaning that this score also reached a 100% sensitivity in a patient subset.

Finally, the knowledge of risk factors might help reduce the great deficit in VNT surveillance, which impacts mortality in cirrhosis [46].

Conclusion - The present large series identified several independent risk factors for VNT: male sex, alcohol etiology, liver dysfunction, increased liver fibrosis (LSM) or PHT (platelets), and a discordant role of BMI as a function of etiology. These risk factors improved the performance of non-invasive tests without additional cost compared to clinical practice.

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LIST OF FIGURES

LIST OF TABLES

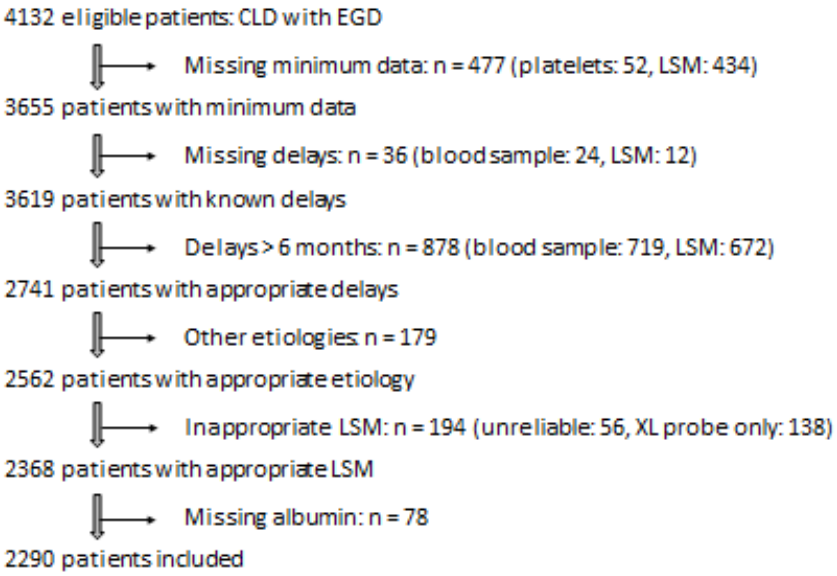
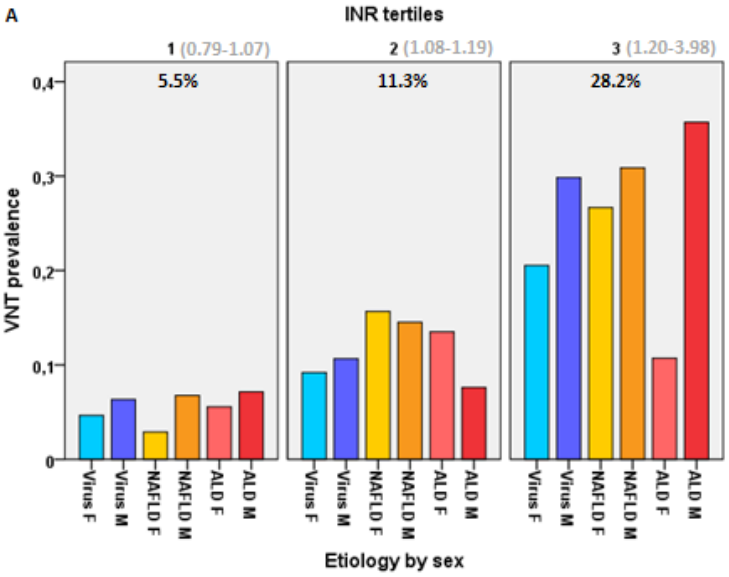
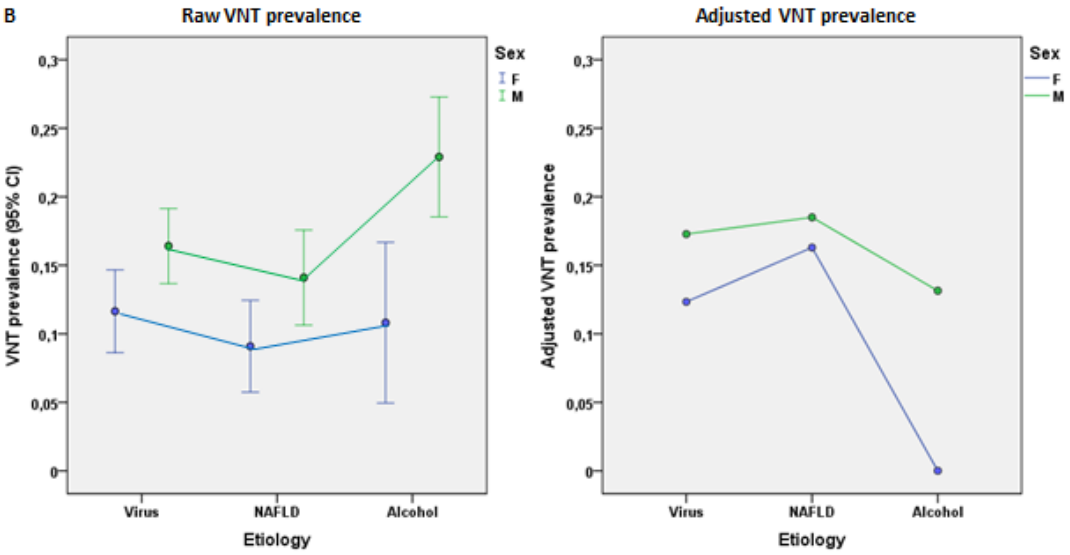
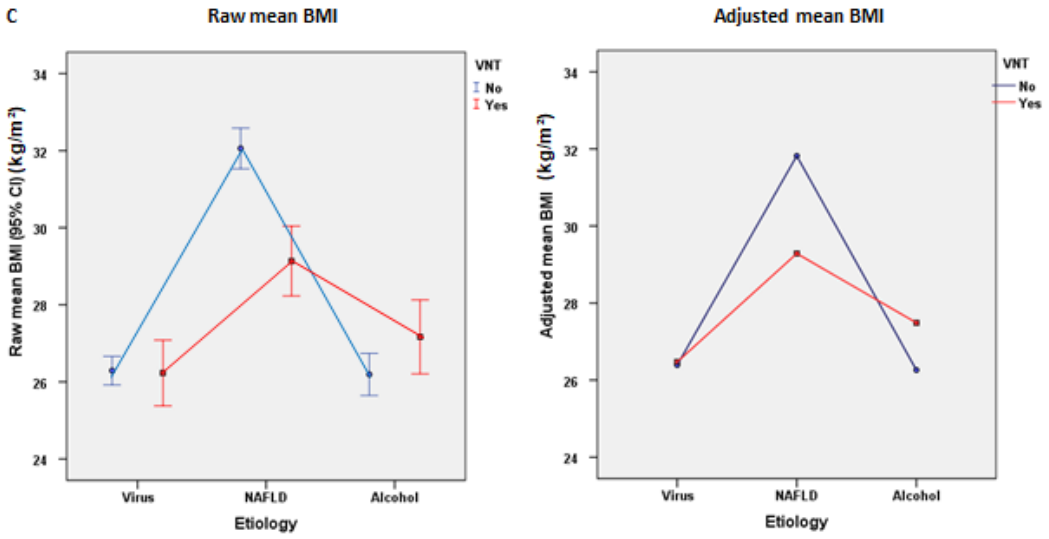


Fig.1. Patient inclusion flowchart.


A
INR tertiles
1 (0.79-1.07)
2 (1.08-1.19)
3 (1.20-3.98)
5.5%
11.3%
28.2%
VNT prevalence
0,4
0,3
0,2
0,1
0
Virus F
Virus M
NAFLD F
NAFLD M
ALD F
ALD M
Etiology by sex


B
Raw VNT prevalence
Adjusted VNT prevalence
Sex
F
M
VNT prevalence (95% CI)
Adjusted VNT prevalence
0,3
0,25
0,2
0,15
0,1
0,05
0
Virus
NAFLD
Alcohol
Etiology


C
Raw mean BMI
Adjusted mean BMI
VNT
No
Yes
Raw mean BMI (95% CI) (kg/m²)
Adjusted mean BMI (kg/m²)
34
32
30
28
26
24
Virus
NAFLD
Alcohol
Etiology

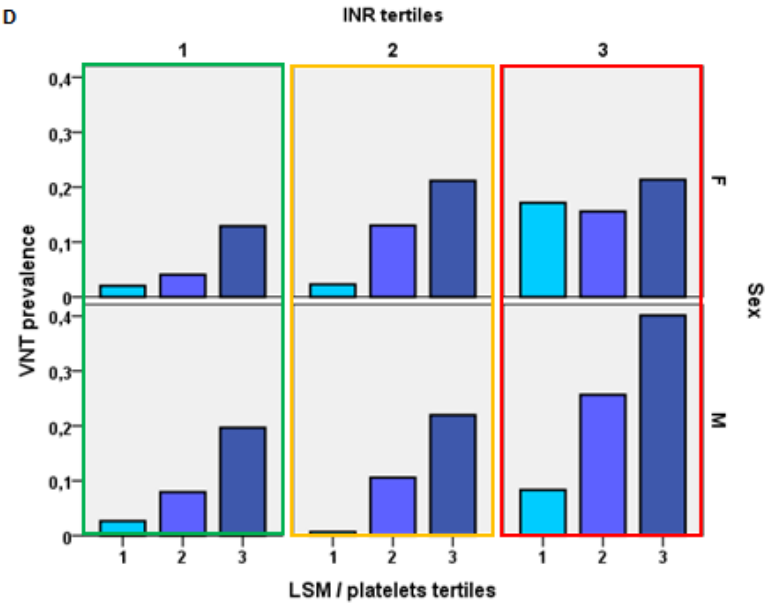


Fig. 2. Main risk factors of VNT. Panel (A): raw VNT prevalence as a function of the three main factors: etiology, sex and liver function (INR); top percentages indicate mean VNT prevalence per tertile. Panel (B): comparison of raw and adjusted VNT prevalences as a function of etiology and sex. Panel (C): mean BMI as a function of VNT and etiology. Panel (D): raw VNT prevalence as a function of the four independent predictors in the whole population: sex, liver function (INR), and platelets and LSM merged in their ratio owing to their interaction.

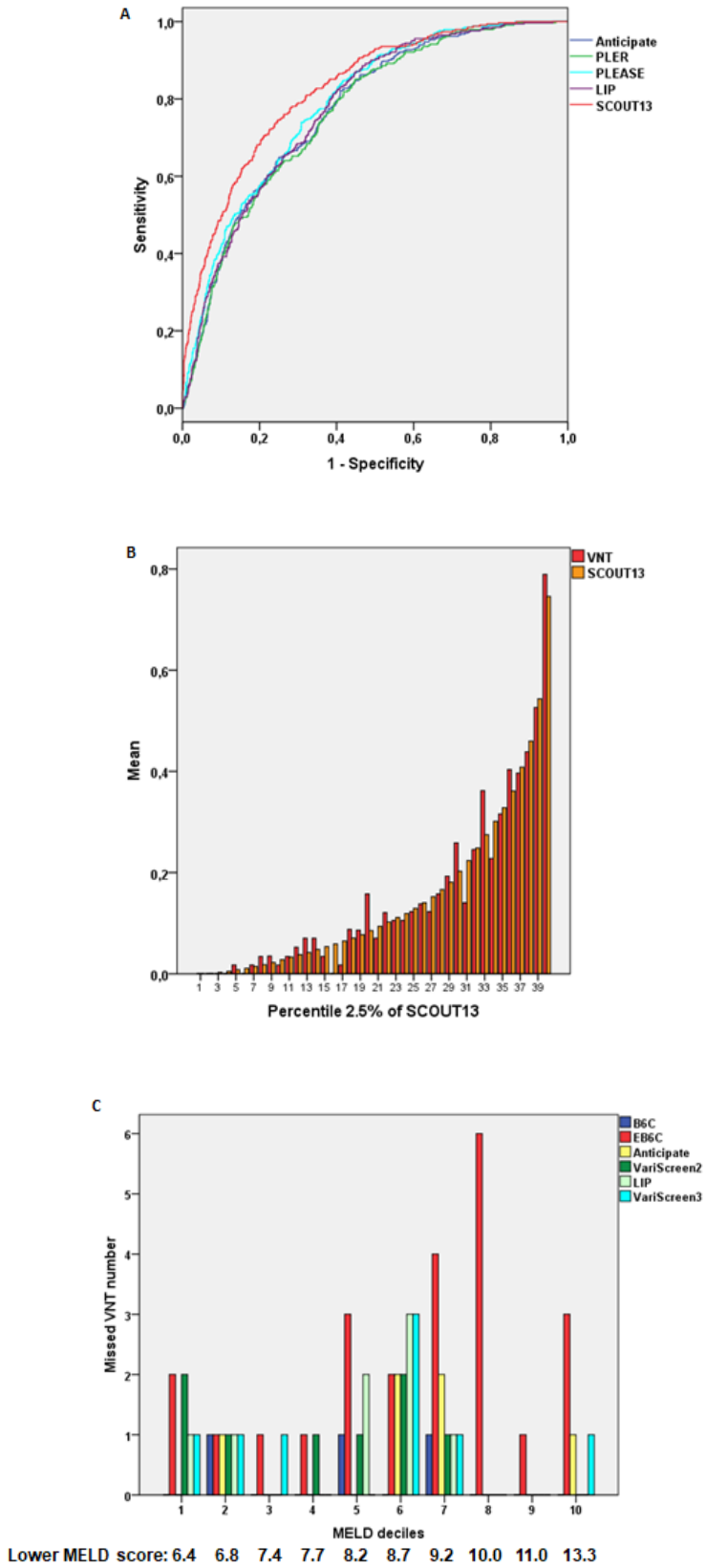


Fig. 3. Characteristics of VNT tests. Panel (A): AUROC for VNT. Panel (B): calibration of SCOUT13. Panel (C): missed VNT as a function of MELD deciles.

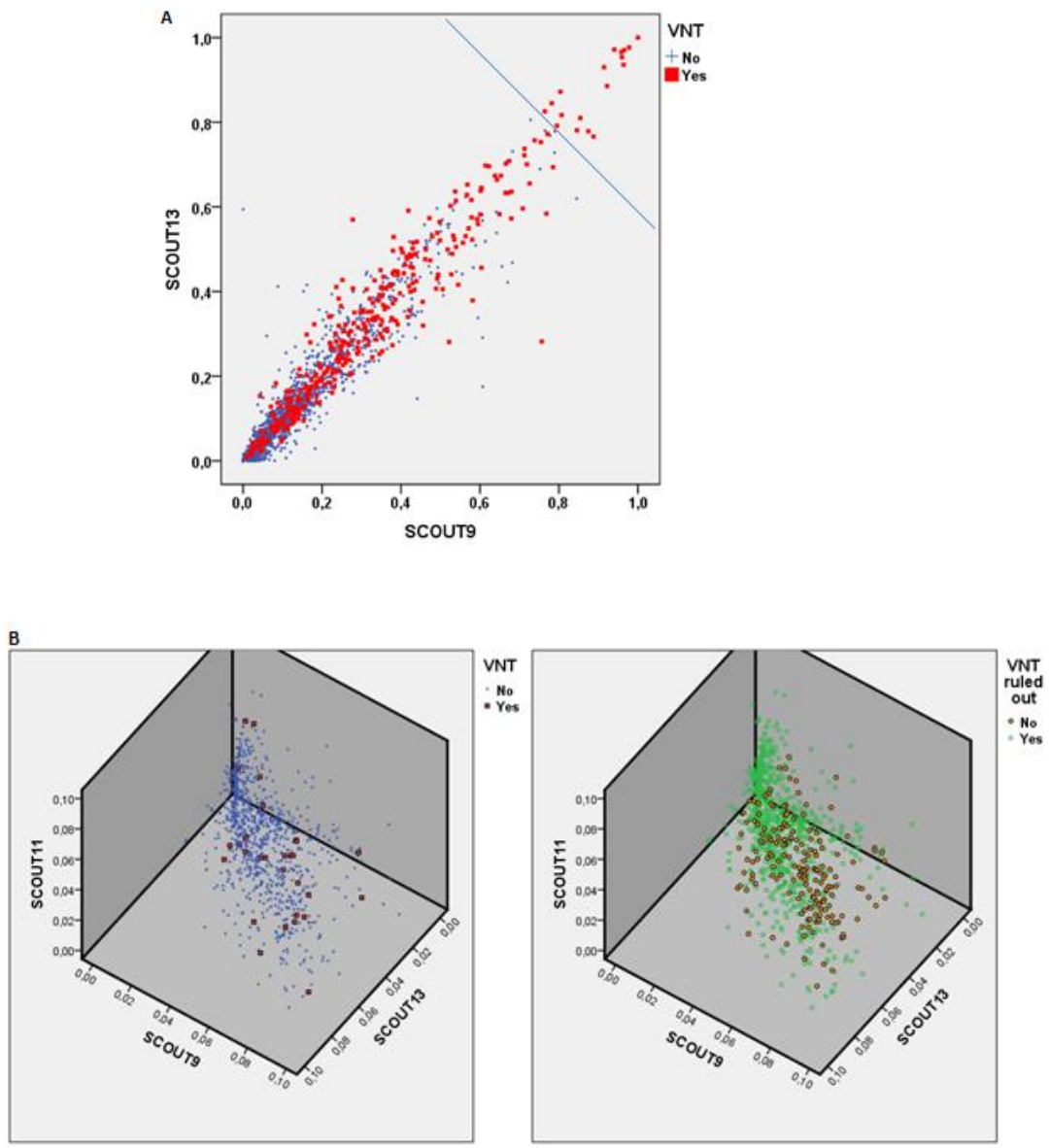


Fig. 4. Construction of new tests. Panel (A): scatter plot of SCOUT scores to diagnose VNT with a single cut-off (oblique line) determining a 100% specificity for VNT (upper right corner). Panel (B): scatter plot of SCOUT scores to spare endoscopy with three cut-offs (one parallel to each axis not shown) determining a zone with 95% sensitivity for VNT (orange circles) and a zone with spared endoscopies (green circles); axes are truncated.

Table I. Patient characteristics in the whole population and as a function of VNT.

	All	**No VNT**	**VNT**	***p*** [a]
Patients (n)	2290	1948	342	-
Age (years)	59.2±11.0	59.1±11.0	59.4±11.0	*0.629*
Sex (% male)	63.5	61.7	74.0	*<0.001*
Etiology (%):	-	-	-	*0.001*
Viral	50.0	50.2	48.8	*0.341*
NAFLD	29.5	30.5	23.7	*0.006*
Alcoholic	20.5	19.3	27.5	*<0.001*
VNT (%)	14.9	0	100	-
Delay LSM EGD (months)	1.7±1.2	1.7±1.2	1.6±1.2	*0.009*
Delay blood testing EGD (months)	1.6±1.3	1.6±1.3	1.4±1.3	*0.009*
BMI (kg/m²)	28.4±5.8	28.6±6.0	27.5±4.2	*0.001*
AST (IU/l)	72±55	71±52	79±70	*0.032*
ALT (IU/l)	67±59	68±60	58±45	*<0.001*
Normal transaminases (%)	15.0	15.6	11.7	*0.046*
Albumin (g/l)	39.8±5.6	40.4±5.4	36.8±5.7	*<0.001*
Bilirubin (µmol/l)	19±22	17±14	31±44	*<0.001*
INR	1.17±0.23	1.15±0.22	1.30±0.25	*<0.001*
Prothrombin index (%)	83±16	85±15	73±15	*<0.001*
Platelets (G/l)	149±75	155±75	115±66	*<0.001*
Creatinine (µmol/l)	72±33	73±35	67±19	*0.014*
MELD score	9.5±3.0	9.1±2.7	11.5±3.8	*<0.001*
LSM (kPa)	27.1±18.0	25.0±16.8	39.0±19.9	*<0.001*
LSM ≥10 kPa (%)	92.9	91.9	98.5	*<0.001*
LSM reliability (%):	-	-	-	*0.011*
Very reliable	26.8	25.3	33.9	-
Reliable	63.4	65.4	53.8	-
Poorly reliable	9.8	9.3	12.4	-
Metavir F stage by LSM (%):	-	-	-	*<0.001*
<F3 (≤10.8 kPa)	10.2	11.6	2.3	-
F3 (10.9-17.6 kPa)	29.1	32.3	10.8	-
F3/4 (17.7-25.7 kPa)	20.0	15.2	20.0	-
F4 (≥25.8 kPa)	40.7	35.3	71.6	-

LSM: liver stiffness measurement, VNT: varices needing treatment, EGD: endoscopy.

[a] No VNT vs VNT: Student's t test or Chi² test / Fisher test.

Table II. Patient characteristics as a function of etiology in the whole population.

	Virus	**NAFLD**	**ALD**	***p*** [a]			
				All	**V vs N**	**V vs A**	**N vs A**
Patients (n)	1145	676	469	-	-	-	-
Age (years)	58.5±11.3	**62.5±10.3**	56.0±9.9	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Sex (% male)	61.7	57.7	**76.3**	*<0.001*	*0.092*	*<0.001*	*<0.001*
VNT (%)	14.6	**12.0**	**20.0**	*0.001*	*0.120*	*0.009*	*<0.001*
Delay endoscopy (months):							
LSM	1.3±1.1	2.8±0.6	1.1±1.1	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Blood testing	1.2±1.2	2.8±0.7	0.9±1.0	*<0.001*	*<0.001*	*<0.001*	*<0.001*
BMI (kg/m²)	26.3±4.2	**31.7±6.1**	26.4±4.9	*<0.001*	*<0.001*	*0.739*	*<0.001*
AST (IU/l)	75±55	**56±66**	68±53	*0.005*	*0.005*	*0.040*	*0.077*
ALT (IU/l)	80±68	56±42	49±47	*<0.001*	*<0.001*	*<0.001*	*0.040*
Normal transaminases (%)	17.3	**3.0**	21.3	*<0.001*	*<0.001*	*0.066*	*<0.001*
Albumin (g/l)	39.8±5.1	41.6±4.4	37.3±7.1	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Bilirubin (µmol/l)	18±19	15±13	29±32	*<0.001*	*0.009*	*<0.001*	*<0.001*
INR	1.17±0.19	1.09±0.14	1.30±0.34	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Prothrombin index (%)	83±14	91±14	75±18	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Platelets (G/l)	**132±63**	176±83	153±77	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Creatinine (µmol/l)	73±28	79±21 [b]	67±42	*<0.001*	*0.117*	*0.001*	*0.002*
MELD score	8.9±2.4	9.2±2.4 [b]	**10.9±3.9**	*<0.001*	*0.315*	*<0.001*	*<0.001*
LSM (kPa)	23±13	25±16	**40±24**	*<0.001*	*0.048*	*<0.001*	*<0.001*
LSM ≥10 kPa (%)	92.1	94.8	92.1	*0.065*	*0.028*	*1*	*0.082*
LSM cut-off for VNT (kPa)	9.0	10.3 [c]	10.0	-	-	-	-
LSM reliability (%):	**-**	-	-	*<0.001*	*0.361*	*<0.001*	*0.312*
Very reliable	20.9	26.8	37.3	-	-	-	-
Reliable	69.9	60.7	52.3	-	-	-	-
Poorly reliable	9.3	12.5	10.5	-	-	-	-

LSM: liver stiffness measurement, VNT: varices needing treatment. V: virus, N: NAFLD, A: ALD. Specific characteristics of each etiology in bold.
[a] Student's t test / ANOVA or Chi² test / Fisher test.
[b] MELD score was available in 9.1% of NAFLD due to missing creatinine.
[c] One patient at 6.3 kPa considered as outlier.

Table III. Discrimination of diagnostic scores for VNT.

	Anticipate	**PLEASE**	**SCOUT$_{13}$**	**PLER**	**LIP**
AUROC	0.771	0.789	0.826	0.766	0.778
p [a]:					
Anticipate	-	*0.044*	*<0.001*	*0.062*	*0.130*
PLEASE		-	*<0.001*	*0.008*	*0.151*
SCOUT$_{13}$			-	*<0.001*	*<0.001*
PLER				-	*<0.001*
LIP					-

[a] Paired Delong test

Table IV. Performance of tests to spare endoscopy.

	B6C	**EB6C**	**Anticipate**	**VariScreen$_2$**	**LIP**	**VariScreen$_3$**	**p[a]**
Missed VNT (%)	2.6 (0.9-4.5)	11.4 (7.9-15.0)	3.5 (1.5-5.7)	4.1 (2.1-6.2)	5.0 (2.8-7.3)[b]	5.0 (2.8-7.6)[b]	*<0.001*[c]
Spared endoscopy (%)	24.1 (22.3-25.8)	42.9 (40.7-45.1)	24.7 (22.8-26.4)	35.3 (34.1-38.2)	35.2 (33.2-37.2)	40.2 (38.1-42.2)	*<0.001*[d]

VNT: varices needing treatment.

[a] Paired Cochran test

[b] 4.97%

[c] EB6C vs each other test: p<0.001, other pair comparisons: p>0.05 by McNemar test

[d] each pair comparison: p<0.001 except for B6C vs Anticipate: p=0.393 and VariScreen$_2$ vs LIP: p=1 by McNemar test

SUPPLEMENTAL MATERIAL

Content :

Introduction

Illustrations referenced in red characters refer to the main text, those in blue to the present Supplemental Material. Tables S1-9 and Figures S1-S3 are referred to in the main text whereas Tables S10-13 and Figures S4-S5 depict additional data.

BMI predictors

Univariate analysis

Relationship with epidemiological factors - As expected, BMI was significantly increased in NAFLD vs viral CLD or ALD (Table II) whatever the VNT status (Table S6A). In the whole population, BMI was significantly decreased in males, especially in patients without VNT (Table S6B). However, in this group of patients without VNT, there was an opposite effect of sex between etiologies with, in males vs females, a significantly decreased BMI in viral CLD and a significantly increased BMI in ALD (Table S6C).

Relationship with VNT - In the whole population, BMI was significantly decreased in patients with VNT (Table I); moreover, this significant decrease was observed in NAFLD (Table S6A) or in males (Table S6B). Finally, a detailed analysis showed that the significant BMI decrease in VNT was only observed in NAFLD, whatever the sex (Table S6C).

Discussion - Three significant decreases in BMI were observed, first according to VNT presence in NAFLD; according to sex (especially in patients without VNT) either, second decrease, in males with viral CLD or, third decrease, in females with ALD. The relationship between BMI and sex depends on the population under consideration [1]. For example, BMI in CLD might be decreased in females [1, 2]. Finally, the impact of sex on BMI in the present population differed according to etiology.

Multivariate analysis

In the whole population, VNT was not a significant predictor of raw BMI but it did significantly interact with etiology ($p<0.001$) (Table S10). VNT, age and sex were significant but discordant predictors of BMI as a function of etiology. Thus, in ALD, VNT, increased age and male sex independently predicted

a higher BMI, whereas in other etiologies, these three variables independently predicted a lower BMI (except for no significant VNT role in viral CLD and no significant sex role in NAFLD).

Adjusted BMI

Of note, the comparison as a function of sex showed that adjusted mean BMI was, in males, significantly decreased in viral CLD and increased in ALD (Table S8). This confirmed the different impact of sex on BMI according to etiology.

Special groups

Females with ALD

Females with ALD were discordant for the relationship between VNT prevalence and liver function (Figure 2A). They were characterized by the most severe liver function (lowest PI) and lesions (highest LSM after males with ALD) and the lowest BMI and age (Table S11). ALD was the only etiology where BMI or obesity was significantly decreased in females vs males. In females with ALD, BMI was the lowest in those without VNT and the highest in those with it (Figure S4). In contrast, in females with ALD, BMI was an independent positive predictor of VNT while interacting with liver function (Table S7). Finally, there was an apparent paradox in females with ALD: low VNT prevalence due to low obesity prevalence while BMI favored VNT. This description is factual but the generalization of the epidemiological characteristics of females with ALD should be cautious since this group was relatively small (111 patients of whom 12 had VNT).

Patients with LSM <10 kPa

The 163 patients with LSM <10 kPa were compared as a function of VNT in Table S12. Although there were only five of them, the patients with VNT were significantly more likely to be females (100%), and to have lower platelet counts and higher MELD scores or LSMs. Thus, these female patients, all of whom had reliable LSMs, were clearly characterized by more severe CLD and especially marked thrombocytopenia which argues against an observer error for VNT diagnosis. Patients with cirrhosis and LSM <10 kPa are not uncommon: in another population, we observed a median LSM of 7.6 kPa (IQR: 7.0-8.6 kPa, extremes: 3.3-9.5 kPa) in 8.3% of 193 patients with LSM <10 kPa and cirrhosis on liver biopsy [3].

Non-invasive tests

Statistics

Predictive scores for VNT (dependent variable) were calculated according to backward binary logistic regression in the whole population. All independent variables were evaluated; interactions were evaluated and variables responsible for colinearity were excluded. Significant interactions led to the

construction of several ratio of variables. Among these ratios, we selected ratio LSM / (PI*platelets) called LIP as a simple test. As sex and etiology interacted with several other variables, models were also calculated in each sex/etiology pair. Thus, we obtained several models and we then calculated the prevalence of score range to rule out VNT with 95% sensitivity. We chose three models which were complementary to provide the largest prevalence of ruling out zone (Figure 4B). To diagnose VNT, we chose the model with the highest AUROC for VNT. BMI was not included in models for clinical reasons (risk factor variable and not validated) and statistical reasons (multiple interactions precluding a performant model since subgroups increased the percentage value of one missed VNT among lower numbers of VNT). This was a TRIPOD type 1a study [4].

Formula

Scores to diagnose VNT

LIP: LSM / (PI*platelets)

The following SPSS syntax (IBM, Armonk, NY, USA) is easily translatable in other programming languages. In any case, what are important to note are the cutoff values for variables.

$SCOUT_9$:

```
compute SCOUT9 = -1.
do if (Etiology = virus) and (Sex = F).
compute SCOUT9 = Pre21.
else if (Etiology = virus) and (Sex = M).
compute SCOUT9 = Pre22.
else if (Etiology = NAFLD) and (Sex = F).
compute SCOUT9 = Pre23.
else if (Etiology = NAFLD) and (Sex = M).
compute SCOUT9 = Pre24.
else if (Etiology = ALD) and (Sex = F).
compute SCOUT9 = Pre2.
else if (Etiology = ALD) and (Sex = F).
compute SCOUT9 = Pre25.
end if.
execute.
```

With:

Pre21 = 1/(1+EXP(2.277724 - (0.398624*((LSM*ALT)/(PI*platelets))) - (-0.0000187*((platelets*ALT*PI)/LSM)) - (1.433736*(bilirubin/albumin))))

Pre22 = 1/(1+EXP(-1.034581 - (-0.006197*platelets) - (-0.0000277*((platelets*ALT*PI)/LSM)) - (-1859.698512*(LSM/(platelets*ALT*PI))) - (-0.4353547*(PI/LSM)) - (0.920517*(bilirubin/albumin))))

Pre23 = 1/(1+EXP(8.754240- (-3785.707798*(LSM/(platelets*ALT*PI))) - (5.509261*(albumin/platelets)) - (178.100405*(INR/ albumin))))

Pre24 = 1/(1+EXP(-4.574013 - (-0.205625*albumin) - (-8159.006768*(LSM/(platelets*ALT*PI))) - (4.879234*(LSM/platelets)) - (4.123608*(albumin/platelets))))

Pre2 = 1/(1+EXP(-(13.911697+ (-0.270035*age) + (-0.228950*PI) + (-0.116042*(platelets/LSM) + (0.003970* (age*PI)))))

Pre25 = 1/(1+EXP(-0.7420378 - (0.010834*bilirubin) - (-0.216538*(PI/LSM)) - (-0.061107*(albumin/INR))))

$SCOUT_{11}$:

```
Compute SCOUT11 = -1.
do if (Etiology = virus) or (Etiology = ALD).
Compute SCOUT11 = 1/(1+EXP(-4.531803 - (0.591014*sex) - (0.004168*platelets) - (-0.077716*albumin) - (0.010209*bilirubin) - (-0.014855*LSM) - (-0.038486*PI) - (-0.099643*(platelets/LSM)) - (-82.460257*(LSM /(PI*platelets))) - (0.436581* Etiology_2cl) - (-0.0000119*((platelets*ALT*PI)/LSM)) - (-31.199098*(INR/albumin)) -(6.088110*Anticipate))).
else if (Etiology = NAFLD) or (Etiology = ALD).
Compute SCOUT11 = 1/(1+EXP(-4.531803 - (0.591014*sex) - (0.00416*platelets) - (-0.077716*albumin) - (0.0102109*bilirubin) - (-0.014855*LSM) - (-0.038486*PI) - (-0.099643*(platelets/LSM)) - (-82.460257*(LSM /(PI*platelets))) - (0.626993* Etiology_2cl) - (-0.0000119*((platelets*ALT*PI)/LSM)) - (-31.199098*(INR/albumin)) - (6.088110*Anticipate))).
end if.
execute.
```

With Etiology_2cl: 0 for ALD and 1 for virus or NAFLD

$SCOUT_{13}$:

```
compute SCOUT13= -1.
do if (Etiology = virus) and (Sex = F).
compute SCOUT13= Pre35.
else if (Etiology = virus) and (Sex = M).
```

compute SCOUT13= Pre36.
else if (Etiology = NAFLD) and (Sex = F).
compute SCOUT13= Pre37.
else if (Etiology = NAFLD) and (Sex = M).
compute SCOUT13= Pre38.
else if (Etiology = ALD) and (Sex = F).
compute SCOUT13= Pre2.
else if (Etiology = ALD) and (Sex = F).
compute SCOUT13= Pre39.
end if.
execute.

With:
Pre35 = 1/(1+EXP(2.725016 - (0.035907*bilirubin) - (-0.0000136*((platelets*ALT*PI)/LSM) - (3.078987*Anticipate)))
Pre36 = 1/(1+EXP(0.005774 - (0.029436*bilirubin) - (-0.0000277*((platelets*ALT*PI)/LSM) - (-0.407338*(PI/LSM))))
Pre37 = 1/(1+EXP(6.754867 - (0.052116*bilirubin) - (-0.0000254*((platelets*ALT*PI)/LSM) - (-5336.226731*(LSM/ (platelets*ALT*PI)) - (4.446406*(albumin/platelets)) - (121.647761*(INR/albumin)))
Pre38 = 1/(1+EXP(15.960020 - (0.539138*PI) - (348.200999*(LSM/ (platelets *PI)) - (-8831.749640*(LSM/ (platelets*ALT*PI)) - (3.980294*(albumin/platelets)) - (-0.228078* (albumin/INR)) - (-0.326081* PI/INR)))
Pre2 = 1/(1+EXP(-(13.911697+ (-0.270035*age) + (-0.228950*PI) + (-0.116042*(platelets/LSM) + (0.003970 * (age*PI)))))
Pre39 = 1/(1+EXP(-8.146832 - (-0.106042*albumin) - (0.010890*bilirubin) - (-0.055023*PI) - (-0.051462* (platelets/LSM) - (-42.984747*(INR/albumin))))

Units: LSM (kPa with M probe of VCTE (Fibroscan)), prothrombin index (PI: %), platelets (G/l), ALT (IU/l), albumin (g/l) bilirubin (µmol/l).

Test to spare endoscopy

Cut-offs used in VariSreen$_3$ were:
1/ Zones to rule out VNT:

First step from scatter plot $SCOUT_9$ vs $SCOUT_{11}$(Figure 4B): zone with missed VNT <5%: $SCOUT_9$ < 0.038448 or $SCOUT_{11}$ < 0.046655

Then, additional zones with missed VNT = 0% from scatter plot $SCOUT_9$ vs $SCOUT_{13}$ in patients remaining outside the previous zone defined for $SCOUT_9$ vs $SCOUT_{11}$:

$SCOUT_{13}$ < 0.039456 or $SCOUT_9$ < 0.088824 - (1.081099*$SCOUT_{13}$)

2/ Zone to rule in VNT (plot $SCOUT_9$ vs $SCOUT_{13}$, Figure 4A):

$SCOUT_9$ > 1.505231 - (0.897250*$SCOUT_{13}$)

Results

The main characteristics of the four new scores are detailed in Table S13. LIP includes 3 biomarkers and each SCOUT 8 biomarkers. The discrimination of diagnostic scores for VNT is presented in Table III. The performance of tests to spare endoscopy is presented in Table IV.

LIP - It should be noted that LIP was chosen as simple score since the AUROC (0.778) of LSM / (PI * platelets) ratio was superior to that (0.775) of the corresponding ratio using INR instead of PI: (LSM * INR) / platelets ratio. The interest of LIP is to be far simpler to calculate than Anticipate and PLEASE scores while being as performant as Anticipate (0.771) or PLEASE (0.789) but more performant than the platelets / LSM ratio called PLER (0.766, p<0.001) recently published [5]. The interest of a ratio is that there is only one cut-off to determine the accepted missed VNT rate (Figure S5A). By contrast, if we consider a scatter plot of the three composite variables, there would be an arbitrary choice among a multitude of cut-offs, like in B6C or EB6C. Figure S5B shows that the 95% sensitivity zone for VNT of LIP was much larger than that of its composite variables. The limits of LIP are twice compared to $SCOUT_{13}$. The score does not directly estimate the VNT prevalence (unless using the logit of LIP). There is no zone of 100% specificity for VNT (Figure S5A).

$SCOUT_{13}$ - $SCOUT_{13}$ was far more discriminant for VNT than other scores (AUROC: 0.826) and well calibrated (Figure 3B) offering an estimated VNT prevalence varying from 0% to 100% (Figure 3A and 4A).

$VariSreen_3$ - Among safe tests, $VariSreen_3$ spared significantly more endoscopy (40.2%). This was obtained thanks to a ruling out zone for VNT at 39.4% of patients and an additional ruling in zone at 0.8% of patients with 100% specificity for VNT.

References

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[3] Ducancelle A, Leroy V, Vergniol J, Sturm N, Le Bail B, Zarski J, et al. A single test combining blood markers and elastography is more accurate than other fibrosis tests in the main causes of chronic liver diseases J Clin Gastro 2017;51:639-649.

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[5] Berger A, Ravaioli F, Farcau O, Festi D, Stefanescu H, Buisson F, et al. Including Ratio of Platelets to Liver Stiffness Improves Accuracy of Screening for Esophageal Varices That Require Treatment. Clin Gastroenterol Hepatol 2020.

Table S1A. Patient characteristics in the whole population as a function of VNT in each etiology.

	Virus			NAFLD			ALD		
VNT	**No**	**Yes**	***p*** [a]	**No**	**Yes**	***p*** [a]	**No**	**Yes**	***p*** [a]
Patients (n)	978	167	-	595	81	-	375	94	-
Age (years)	58.4±11.5	59.0±10.5	*0.552*	62.2±10.4	65.3±9.4	***0.011***	56.2±9.7	55.2±10.9	*0.417*
Sex (% male)	60.4	69.5	***0.031***	56.3	67.9	***0.047***	73.6	87.2	***0.004***
BMI (kg/m²)	26.3±4.3	26.2±3.8	*0.902*	32.1±6.3	29.2±3.9	***<0.001***	26.2±5.0	27.2±4.4	*0.104*
BMI / age (kg/(m².yr))	0.48±0.13	0.47±0.12	*0.573*	0.54±0.20	0.45±0.10	***<0.001***	0.48±0.11	0.52±0.12	*0.004*
AST (IU/l)	74±52	78±71	*0.455*	47±24	134±183	*0.221*	67±54	76±48	*0.122*
ALT (IU/l)	82±69	68±55	***0.004***	57±43	52±31	*0.370*	51±50	43±30	*0.191*
Normal transaminases (%)	17.6	15.2	*0.504*	3.2	1.8	*1*	23.7	11.7	***0.011***
Albumin (g/l)	40.2±5.0	37.7±4.6	***<0.001***	42.1±4.0	38.1±5.5	***<0.001***	38.1±6.9	34.0±6.7	***<0.001***
Bilirubin (µmol/l)	16±9	29±44	***<0.001***	14±8	21±31	*0.074*	26±24	43±49	***0.001***
INR	1.15±0.19	1.26±0.18	***<0.001***	1.07±0.13	1.18±0.13	***<0.001***	1.26±0.32	1.47±0.33	***<0.001***
Prothrombin index (%)	84±13	74±13	***<0.001***	92±14	81±12	***<0.001***	78±18	63±16	***<0.001***
Platelets (G/l)	138±63	99±55	***<0.001***	183±82	124±71	***<0.001***	157±78	137±73	***0.025***
Creatinine (µmol/l)	74±29	70±19	*0.082*	80±20	69±28	*0.161*	68±46	63±17	*0.290*
MELD score	8.6±2.1	10.5±3.0	***<0.001***	9.0±1.6	11.3±5.6	*0.279*	10.4±3.7	13.1±4.1	***<0.001***
LSM (kPa)	21.3±11.8	33.7±15.7	***<0.001***	23.1±14.5	36.1±21.3	***<0.001***	37.7±24.0	51.0±20.6	***<0.001***

LSM: liver stiffness measurement, VNT: varices needing treatment. [a] no VNT vs VNT: Student's t test or Chi² test / Fisher test: difference VNT vs no VNT: positive, negative. Discrepancy of significant VNT impact between etiologies. Significant predictors in bold.

Table S1B. Patient characteristics in the whole population as a function of etiology in each VNT status.

	No VNT				VNT			
Etiology	**Virus**	**NAFLD**	**ALD**	***p*** [a]	**Virus**	**NAFLD**	**ALD**	***p*** [a]
Patients (n)	978	595	375	-	167	81	94	-
Age (years)	58.4±11.5	62.2±10.4	56.2±9.7	*<0.001*	59.0±10.5	65.3±9.4	55.2±10.9	*<0.001*
Sex (% male)	60.4	56.3	73.6	*<0.001*	69.5	67.9	87.2	*0.003*
BMI (kg/m²)	26.3±4.3	32.1±6.3	26.2±5.0	*<0.001*	26.2±3.8	29.2±3.9	27.2±4.4	*<0.001*
AST (IU/l)	74±52	47±24	67±54	*<0.001*	78±71	134±183	76±48	*0.077*
ALT (IU/l)	82±69	57±43	51±50	*<0.001*	68±55	52±31	43±30	*<0.001*
Normal transaminases (%)	17.6	3.2	23.7	*<0.001*	15.2	1.8	11.7	*0.027*
Albumin (g/l)	40.2±5.0	42.1±4.0	38.1±6.9	*<0.001*	37.7±4.6	38.1±5.5	34.0±6.7	*<0.001*
Bilirubin (µmol/l)	16±9	14±8	26±24	*<0.001*	29±44	21±31	43±49	*0.003*
INR	1.15±0.19	1.07±0.13	1.26±0.32	*<0.001*	1.26±0.18	1.18±0.13	1.47±0.33	*<0.001*
Prothrombin index (%)	84±13	92±14	78±18	*<0.001*	74±13	81±12	63±16	*<0.001*
Platelets (G/l)	138±63	183±82	157±78	*<0.001*	99±55	124±71	137±73	*<0.001*
Creatinine (µmol/l)	74±29	80±20	68±46	*0.004*	70±19	69±28	63±17	*0.015*
MELD score	8.6±2.1	9.0±1.6	10.4±3.7	*<0.001*	10.5±3.0	11.3±5.6	13.1±4.1	*<0.001*
LSM (kPa)	21.3±11.8	23.1±14.5	37.7±24.0	*<0.001*	33.7±15.7	36.1±21.3	51.0±20.6	*<0.001*

LSM: liver stiffness measurement, VNT: varices needing treatment.
[a] ANOVA or Chi² test; difference between etiologies: highest or lowest value. Large discrepancy of etiology impact between VNT status

Table S2. VNT prevalence (95% CI) as a function of main risk factors (etiology and sex) with values either raw or adjusted on other covariables[a] by ANCOVA.

	Virus			NAFLD			ALD		
Sex	**F**	**M**	***p***	**F**	**M**	***p***	**F**	**M**	***p***
Raw prevalence:									
Each sex	11.6 (8.5-14.8)	16.4 (13.8-19.0)	*0.026*	9.1 (5.7-12.3)	14.1 (10.8-17.7)	*0.047*	10.8 (5.0-17.1)	22.9 (18.7-27.3)	*0.005*
Both sexes	14.6 (12.6-16.7)			12.0 (9.8-14.5)			20.0 (16.3-24.0)		
Adjusted [b] prevalence in:									
Each etiology	11.8 (8.7-14.8)	16.3 (13.9-18.7)	*0.023*	10.2 (6.6-13.7)	13.3 (10.3-16.3)	*0.197*	9.1 (2.1-16.2)	23.4 (19.5-27.3)	*0.001*
Whole population :									
Each sex	12.3 (9.2-15.5)	17.3 (14.7-19.8)	*NA*	16.3 (12.3-20.3)	18.5 (15.1-21.9)	*NA*	0.0 (-6.4-6.3)	13.1 (9.4-16.8)	*NA*
Both sexes [c]	15.5 (13.5-17.5)			17.8 (15.1-20.5)			9.4 (6.0-12.7)		
p vs raw prevalence	*0.559*			*0.003*			*0.001*		

F: females, M: males, NA: not available.

[a] Covariables: age, platelets, albumin, bilirubin, INR, PI, ALT, LSM, sex, platelets/LSM ratio.

[b] Adjustment performed in each etiology or in the whole population.

[c] $p<0.001$ between all, $p=0.190$ virus vs NAFLD, $p=0.003$ virus vs ALD, $p<0.001$ NAFLD vs ALD.

Table S3. Multivariate analysis for VNT by logistic regression in the whole population (2290 patients). p values [a] and influence [b] of variables are simultaneously reported.

Model # **Variable(s) tested**	**1** **Single variables** [c]	**2** **+ platelets/LSM**	**3** **+other interactions**
R^2	*0.240*	*0.258*	*0.265*
Etiology:			
All	0.001	0.004	0.013
Virus	0.003	0.008	0.012
NAFLD	<0.001	0.001	0.006
Platelets	<0.001	0.318	0.289
ALT	0.011	0.007	0.011
Bilirubin	0.006	0.003	0.003
INR	0.001	0.003	0.507
LSM	<0.001	0.452	0.453
PI	<0.001	<0.001	<0.001
Albumin	<0.001	0.001	0.002
Sex (male)	<0.001	<0.001	0.010
Age	0.238	0.453	<0.001
Platelets / LSM ratio	-	<0.001	<0.001
Sex * PI	-	-	0.062
Age * PI	-	-	0.464
Age * Etiology	-	-	0.863
Age * Sex	-	-	0.530
Etiology * Sex	-	-	0.425
Etiology * PI	-	-	0.997
Age / PI	-	-	<0.001
PI / age	-	-	0.531

LSM: liver stiffness measurement, PI: prothrombin index (%).

[a] -: not tested.

[b] Influence on VNT: positive, negative β coefficient.

[b] MELD score was not an independent predictor in a subpopulation (details not shown); BMI is specifically addressed in Table S7.

Table S4. Multivariate analysis for VNT by logistic regression in each etiology. p values [a] and influence [b] of variables are simultaneously reported.

	Virus		NAFLD		ALD	
Interactions tested	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Patients (n)	*1145*		*676*		*469*	
R^2	*0.277*	*0.297*	*0.267*	*0.288*	*0.217*	*0.261*
Platelets	**0.001**	0.536	**<0.001**	0.182	0.685	0.206
ALT	**0.004**	**0.004**	0.197	0.221	0.301	0.193
Bilirubin	**<0.001**	**0.001**	0.462	0.734	0.279	0.295
INR	**0.041**	0.078	0.085	**0.014**	**0.024**	0.065
LSM	**<0.001**	**0.009**	**0.038**	0.794	0.362	0.679
PI	**0.007**	0.319	**0.017**	0.452	**<0.001**	**0.001**
Albumin	0.166	0.276	**0.002**	**0.005**	**0.033**	0.110
Sex (male)	**0.035**	**0.033**	0.113	0.740	**0.001**	**0.025**
Age	0.293	**0.033**	0.372	**0.002**	0.850	**0.016**
Platelets / LSM	-	**<0.001**	-	**0.001**	-	**0.025**
Sex * PI	-	0.265	-	0.955	-	0.100
Age * PI	-	0.533	-	**0.004**	-	**0.001**
Age * sex	-	0.305	-	0.092	-	0.920
Age / PI	-	0.786	-	**0.004**	-	0.455
PI / age	-	**0.011**	-	0.767	-	**0.020**

LSM: liver stiffness measurement, PI: prothrombin index (%).

Bold variables: most robust predictor across groups (for the same vertical variable list).

[a] Significant predictors in bold.

[b] Influence on VNT: positive, negative β coefficient.

Table S5. Age impact. Variables (mean±SD or %) as a function of groups distinguished by median age (in VNT) and VNT status.

	No VNT				**VNT**			
Age (yrs)	**<59.5**	**≥59.5**	***p***	**Trend [a]**	**<59.5**	**≥59.5**	***p***	**Trend [a]**
Patients (n)	995	953			169	173		
Platelets (G/l)	161±77	150±72	***0.001***	↘	116±67	114±65	*0.682*	≈
ALT (IU/l)	75±66	61±54	***<0.001***	↘	60±44	56±46	*0.411*	≈
Bilirubin (µmol/l)	18±16	17±11	*0.082*	≈	38±59	23±16	***0.002***	↘
INR	1.15±0.22	1.14±0.22	*0.267*	≈	1.36±0.28	1.23±0.20	***<0.001***	↘
LSM (kPa)	25.6±17.7	24.4±15.9	*0.110*	≈	44.3±20.6	33.9±17.9	***<0.001***	↘
Prothrombin index (%)	85±16	86±15	*0.293*	≈	69±16	77±14	***<0.001***	↗
Albumin (g/l)	40.4±5.7	40.3±5.0	*0.615*	≈	36.4±6.1	37.1±5.4	*0.250*	≈
Sex (% male)	67.3	55.8	***<0.001***	↘	79.3	68.8	***0.036***	↘
Platelets / LSM	10.3±9.8	9.1±8.8	***0.005***	↘	3.3±2.7	4.4±3.8	***0.003***	↗
LSM / PI	0.34±0.32	0.31±0.26	***0.019***	↘	0.71±0.43	0.47±0.30	***<0.001***	↘
LSM [b] / (platelets.PI)	0.32±0.56	0.28±0.30	***0.036***	↘	0.76±0.57	0.53±0.46	***<0.001***	↘

LSM: liver stiffness measurement, PI: prothrombin index (%).

[a] Age impact: ↘: variable decreased, ↗: variable increased, ≈ : variable stability, red: discordance as a function of VNT status. Bold: significant difference.

[b] x 100.

Table S6. BMI (mean ± SD) as a function of VNT according to etiology and/or sex.

A. BMI according to etiology							
	Virus (V)	**NAFLD (N)**	**ALD (A)**	*p all* [a]	*p V vs N* [b]	*p V vs A* [b]	*p N vs A* [b]
No VNT	26.3±4.3	32.1±6.3	26.2±5.0	***<0.001***	***<0.001***	*0.793*	***<0.001***
VNT	26.2±3.8	29.1±3.9	27.2±4.4	***<0.001***	***<0.001***	*0.142*	***0.003***
p [a]	*0.902*	***<0.001***	*0.104*	-	-	-	-

B. BMI according to sex				
	All	**F**	**M**	*p* [c]
All	28.4±5.8	29.0±6.4	28.1±5.4	***0.005***
No VNT	28.6±6.0	29.1±6.6	28.2±5.6	***0.019***
VNT	27.5±4.2	28.1±4.6	27.3±4.1	*0.192*
p [a]	***0.001***	*0.153*	***0.006***	-

C. BMI according to etiology and sex									
Etiology		**Virus**			**NAFLD**			**ALD**	
Sex	**F**	**M**	***p*** [c]	**F**	**M**	***p*** [c]	**F**	**M**	***p*** [c]
No VNT	27.0±5.1	25.9±3.7	***0.006***	32.3±6.5	31.9±6.0	*0.422*	24.4±5.2	26.8±4.8	***<0.001***
VNT	26.9±4.2	25.9±3.7	*0.301*	29.5±3.7	29.0±4.0	*0.618*	27.8±7.1	27.1±4.0	*0.785*
p [a]	*0.911*	*0.880*	-	***0.002***	***<0.001***	**-**	*0.077*	*0.608*	-

VNT: varices needing treatment, F: females, M: males. Significant differences in bold.

Overall results of BMI as a function of VNT are reported in Table 1 or as a function of etiology in Table 2.

[a] ANOVA.

[b] Unweighted post hoc comparison.

[c] Unpaired Student's t test: difference males vs females: positive, negative, discordance with other etiologies.

Table S7. Multivariate analysis for VNT by logistic regression, including BMI, as a function of sex and etiology. p values and influence [a] of variables are simultaneously reported.

	All etiologies		Virus		NAFLD		ALD					
Interaction	**Without**	**With [b]**	**Without**	**With**	**Without**	**With**	**Without**	**With**	**W/o F**	**With F**	**W/o M**	**With M**
Patients (n)	*1612*	*1612*	*588*	*588*	*618*	*618*	*406*	*406*	*87*	*87*	*319*	*319*
R^2	*0.257*	*0.293*	*0.294*	*0.310*	*0.322*	*0.322*	*0.262*	*0.304*	*0.210*	*0.309*	*0.274*	*0.317*
BMI	0.273	0.803	0.318	0.971	0.001	0.001	0.031	0.127	0.037	0.077	0.134	0.056
Etiology	0.001	<0.001	-	-	-	-	-	-		-	-	-
Age	0.107	0.128	0.898	0.059	0.488	0.488	0.123	0.334	0.297	0.803	0.491	0.948
Sex (male)	0.001	0.001	0.143	0.144	0.121	0.121	0.003	0.007	-	-	-	-
Platelets	<0.001	0.331	0.015	0.620	0.004	0.004	0.685	0.125	0.889	0.742	0.888	0.158
ALT	0.160	0.109	0.104	0.058	0.533	0.533	0.552	0.381	0.247	0.114	0.418	0.389
Albumin	<0.001	0.001	0.085	0.071	0.002	0.002	0.200	0.504	0.526	0.149	0.182	0.313
Bilirubin	0.028	0.015	0.007	0.002	0.698	0.698	0.142	0.381	0.110	0.162	0.065	0.136
INR	0.001	0.003	0.050	0.060	0.061	0.061	0.008	0.016	0.976	0.631	0.018	0.025
PI	<0.001	<0.001	0.026	0.009	0.016	0.016	<0.001	<0.001	0.018	0.013	0.001	<0.001
LSM	<0.001	0.226	<0.001	0.122	0.001	0.001	0.352	0.983	0.994	0.712	0.290	0.942
Platelets/LSM	-	<0.001	-	<0.001	-	0.421	-	0.153	-	0.755	-	0.146
BMI*etiology	-	<0.001	-	-	-	-	-	-	-	-	-	-
BMI * PI	-	0.834	-	0.073	-	0.657	-	0.770	-	0.023	-	0.888
BMI * sex	-	0.310	-	0.136	-	0.148	-	0.031	-	-	-	-
BMI * age	-	0.003	-	0.051	-	0.406	-	0.230	-	0.799	-	0.538
BMI / age [c]	-	0.003	-	0.684	-	0.500	-	0.001	-	0.696	-	0.012

F: females, M: males. [a] Influence: positive, negative β coefficient. The influence must be interpreted with caution when interaction is tested. Thus, the influence of a single BMI changes in ALD since BMI has significant influence in interaction terms.

[b] Other interaction terms are not described.

[c] The interaction term between BMI and age was also tested as a ratio because of their respective inverse influence on VNT.

Table S8. Mean BMI (95% CI) as a function of VNT or sex in each etiology; BMI values either raw or adjusted on other covariables [a] by ANCOVA.

	Virus			**NAFLD**			**ALD**		
VNT	**No**	**Yes**	***p***	**No**	**Yes**	***p***	**No**	**Yes**	***p***
Raw mean BMI [b]:									
	26.3 (25.9-26.7)	26.2 (25.4-27.1)	*0.902*	32.1 (31.5-32.6)	29.1 (28.3-30.0)	*<0.001*	26.2 (25.7-26.7)	27.2 (26.3-28.1)	*0.104*
Adjusted mean BMI in:									
Whole population	26.4 (25.9-26.9)	26.5 (25.3-27.6)	*NA*	31.8 (31.3-32.3)	29.3 (28.1-30.5)	*NA*	26.3 (25.7-26.9)	27.5 (26.3-28.7)	*NA*
Each etiology	26.3 (26.0-26.7)	25.9 (24.9-26.9)	*0.421*	32.0 (31.5-32.5)	29.7 (28.3-31.1)	*0.002*	26.1 (25.6-26.6)	27.4 (26.4-28.4)	*0.036*
Sex	**F**	**M**	***p***	**F**	**M**	***p***	**F**	**M**	***p***
Raw mean BMI [b]:									
	27.0 (26.3-27.6)	25.9 (25.5-26.2)	*0.003*	32.0 (31.3-32.9)	31.5 (30.9-32.1)	*0.244*	24.7 (23.6-25.9)	26.9 (26.3-27.4)	*<0.001*
Adjusted mean BMI in:									
Whole population	27.4 (26.6-28.0)	25.9 (25.3-26.4)	*NA*	31.9 (31.2-32.5)	31.4 (30.8-31.9)	*NA*	24.7 (23.6-25.9)	26.8 (26.2-27.4)	*NA*
Each etiology	27.2 (26.6-27.8)	25.7 (25.3-26.2)	*<0.001*	31.9 (31.2-32.6)	31.5 (31.0-32.1)	*0.390*	25.1 (24.1-26.1)	26.8 (26.3-27.3)	*0.003*

F: females, M: males, NA: not available.

[a] Covariables: age, platelets, albumin, bilirubin, INR, PI, ALT, LSM, platelets/LSM ratio, sex.

[b] Detailed comparison in Table S6.

Table S9. Summary of independent VNT risk factors as a function of etiology.

	Sex (male)	Liver dysfunction	Liver stiffness	PHT (thrombocytopenia)	BMI	Inflammation (ALT)	Age [a]
Virus	↗	↗	↗	↗	-	↘	↺
NAFLD	(↗) [b]	↗	↗	↗	↘	-	↺
ALD	↗	↗	↗ [c]	↗ [c]	↗	-	↺

Impact on VNT prevalence: ↘: decreased, ↗: increased, ↺: indirect impact through interaction. Details in Table S7 and Table C3 in Complementary Material for BMI.

[a] Impact through interaction with liver dysfunction, therefore age influence on VNT prevalence should be thoroughly interpreted (see Tables S4 and S7).

[b] p=0.113.

[c] Through platelets/LSM ratio having direct impact on VNT prevalence.

Table S10. Covariable influence on raw BMI by ANCOVA as a function of etiology. p values and influence [a] of variables are reported.

	All etiologies			Virus	NAFLD	ALD
Interactions tested	**No**	**Yes** [b]	**Yes** [b]	**Yes**	**Yes**	**Yes**
Patients (n)	*1612*	*1612*	*1612*	*588*	*618*	*406*
VNT	0.302	0.740	0.190	0.421	**0.002**	**0.036**
Etiology	**<0.001**	0.144	**0.054**	-	-	-
Age	**<0.001**	**0.001**	**<0.001**	**0.024**	**<0.001**	**<0.001**
Sex (male)	0.135	0.169	0.977	**<0.001**	0.390	**0.003**
Platelets	0.346	0.086	**0.032**	0.383	**<0.001**	0.113
ALT	0.451	0.235	0.174	0.760	0.058	0.553
Albumin	0.720	0.792	0.938	0.457	**0.004**	0.271
Bilirubin	0.725	0.275	0.509	0.102	0.147	0.249
INR	0.318	0.364	0.195	0.636	0.930	0.369
LSM	**<0.001**	0.570	0.709	**0.005**	0.876	0.207
PI	**0.002**	**0.002**	**0.001**	0.639	0.163	**0.018**
Platelets / LSM	**-**	**<0.001**	**<0.001**	0.400	**<0.001**	**0.001**
VNT * etiology	**-**	**<0.001**	-	-	-	-
Sex * etiology	**-**	**-**	**<0.001**	-	-	-

-: not tested. Significant differences in bold.

[a] Influence: positive, negative β coefficient.

[b] One different interaction with etiology tested.

Table S11A. Main patient characteristics as a function of sex in each etiology.

	Virus			NAFLD			ALD		
	M	**F**	***p*** [a]	**M**	**F**	***p*** [a]	**M**	**F**	***p*** [a]
Patients (n)	707	438	-	390	286	-	358	111	-
VNT (%)	16 .4	11 .6	**0 .026**	14 .1	9 .1	**0 .047**	22 .9	10 .8	**0 .005**
Age (yrs)	56.9±11.0	61.1±11.4	**<0.001**	61.8±10.4	63.5±10.2	**0.043**	55.8±9.9	56.6±9.9	0.430
BMI (kg/m²)	25.9±3.6	27.0±5.0	**0.003**	31.5±5.9	32.0±6.4	0.244	26.9±4.6	24.7±5.5	**<0.001**
Obesity (%)	11.7	25.6	**<0.001**	55.2	58.2	0.461	24.5	13.8	**0.041**
LSM (kPa)	23±14	22±13	0.234	25±17	24±15	0.209	41±24	39±24	0.459
Platelets (G/l)	131±59	134±69	0.344	171±82	184±83	**0.042**	149±71	163±95	0.166
PI (%)	83±14	83±14	0.780	89±15	94±13	**<0 .001**	75±18	74±18	0 .480
INR	1.17±0.20	1.16±0.19	0.723	1.10±0.15	1.06±0.11	**<0 .001**	1.30±0.34	1.31±0.33	0.665
Albumin (g/l)	40.0±5.1	39.5±5.0	0.082	41.7±4.3	41.4±4.6	0.317	37.7±6.9	35.9±7.5	**0 .020**
Bilirubin (µmol/l)	18±12	18±27	0 .861	16±16	14±8	**0 .007**	29±31	31±34	0.392
ALT (IU/l)	83±73	75±59	0.058	56±37	56±48	0.862	50±50	46±36	0.423
MELD score	9.0±2.3	8.8±2.4	0.165	9.4±2.8	9.0±1.7	0.384	10.9±3.9	11.0±4.1	0.725

F: females, M: males. Bold: significant difference.

[a] Fischer or Student t test: difference males vs females: positive, negative. Discrepancy of significant sex impact with other etiologies.

Table S11B. Main patient characteristics as a function of sex in each etiology in patients with VNT.

	Virus			**NAFLD**			**ALD**			**All (*p* [a])**	
	M	**F**	***p*** [b]	**M**	**F**	***p*** [b]	**M**	**F**	***p*** [b]	**M**	**F**
Patients (n)	116	51	-	55	26	-	82	12	-	253	89
Age (yrs)	57.3±10.5	62.8±9.7	***0.002***	65.2±9.9	65.5±8.2	*0.889*	55.0±11.0	57.1±10.6	*0.531*	***<0.001***	***0.044***
BMI (kg/m²)	25.9±3.7	26.9±4.2	*0.301*	29.0±4.0	29.5±3.7	*0.618*	27.1±4.0	27.8±7.1	*0.785*	***<0.001***	*0.147*
Obesity (%)	12.7	32.0	*0.062*	34.0	50.0	*0.212*	21.3	33.3	*0.416*	***0.031***	*0.399*
LSM (kPa)	35±15	31±16	*0.131*	37±22	33±20	*0.436*	52±20	44±22	*0.229*	***<0.001***	*0.076*
Platelets (G/l)	94±41	109±78	*0.123*	126±73	118±69	*0.603*	138±75	126±52	*0.598*	***<0.001***	*0.710*
PI (%)	74±13	75±15	*0.589*	80±12	82±11	*0.464*	63±16	67±20	*0.353*	***<0.001***	***0.016***
INR	1.26±0.17	1.25±0.19	*0.817*	1.18±0.13	1.16±0.13	*0.441*	1.48±0.33	1.43±0.38	*0.616*	***<0.001***	***0.002***
Albumin (g/l)	37.7±4.7	37.6±4.5	*0.819*	38.0±5.4	38.2±5.8	*0.850*	33.8±7.0	35.0±5.0	*0.570*	***<0.001***	*0.168*
Bilirubin (µmol/l)	26±20	34±75	*0.272*	22±37	18±9	*0.660*	45±52	28±17	*0.264*	***<0.001***	*0.519*
ALT (IU/l)	69±46	67±72	*0.895*	56±33	43±24	*0.079*	44±31	38±23	*0.479*	***<0.001***	*0.114*
MELD score	10.5±2.9	10.4±3.2	*0.820*	- [c]	- [c]	-	13.4±4.1	12.1±4.2	*0.329*	***<0.001***	*0.239*

F: females, M: males. Bold: significant difference.

[b] ANOVA.

[a] Student t test: difference males vs females: positive, negative. Discrepancy of significant sex impact with other etiologies.

[c] Only 4 patients in each sex.

Table S12. Patient characteristics as a function of VNT in the population with LSM <10 kPa.

	All	**No VNT**	***p*** [ab]	**VNT**	***p*** [bc]
Patients (n)	163	158	-	5	-
Age (years)	56.5±10.8	56.3±10.7	*0.126*	63.8±12.9	*0.227*
Sex (% male)	69.3	71.5	***0.002***	0.0	-
Etiology (%):	-	-	*0.424*	-	-
Viral	55.8	55.1	*0.385*	80.0	-
NAFLD	21.5	21.5	*1*	20.0	-
Alcoholic	22.7	23.4	*0.589*	0.0	-
BMI (kg/m²)	26.2±4.8	26.1±4.9	*0.474*	27.7±3.7	*0.322*
AST (IU/l)	49±34	48±34	*0.669*	56±38	*0.439*
ALT (IU/l)	54±42	54±42	*0.789*	49±39	*0.675*
Normal transaminases (%)	32.0	33.1	*0.177*	0.0	-
Albumin (g/l)	43.0±5.2	43.1±5.1	*0.063*	38.8±5.8	*0.085*
Bilirubin (µmol/l)	16±12	16±12	*0.103*	25±5	***0.014***
INR	1.08±0.14	1.08±0.14	***0.048***	1.21±0.21	*0.085*
Platelets (G/l)	185±72	188±71	***<0.001***	84±17	***<0.001***
Creatinine (µmol/l)	72±17	72±16	*0.270*	63±27	*0.183*
MELD score	8.2±1.8	8.1±1.8	*0.264*	9.2±0.3	***0.021***
LSM (kPa)	7.3±1.8	7.2±1.8	*0.105*	8.5±1.2	***0.045***
LSM reliability (%):	-	-	*0.574*	-	-
Very reliable	23.8	24.7	-	0.0	-
Reliable	73.8	72.7	-	100	-
Poorly reliable	2.5	2.6	-	0.0	-

LSM: liver stiffness measurement.

[a] Student's t test or Chi² test / Fisher test. [b] no VNT vs VNT. [c] Non parametric Mann-Whitney test.

Table S13. Main characteristics of new scores: construction population, AUROC for VNT, biomarkers and cut-offs for VNT.

	LIP	**$SCOUT_9$**	**$SCOUT_{11}$**	**$SCOUT_{13}$**
Population	Overall	Etiology by sex	Overall	Etiology by sex[a]
AUROC	0.778	0.825	0.810	0.826
Biomarkers:				
LSM	x	x	x	x
Platelets	x	x	x	x
PI	x	x	x	x
ALT	-	x	x	x
Albumin	-	x	x	x
Bilirubin	-	x	x	x
INR	-	x	x	x
Age	-	x	-	x
Sex	-	-	x	-
VNT cut-off:				
95% sensitivity ≥	0.001258	0.038448 [b]	0.046655 [b]	0.039456 [c]
100% specificity	None	Combined cut-off [d]	-	Combined cut-off [d]

[a] Compared to $SCOUT_9$, more interactions were evaluated in $SCOUT_{13}$. The complementarity of both scores is shown in Figure 4A, especially the 100% specificity subset for VNT.

[b] $SCOUT_9$ and $SCOUT_{11}$ cut-offs are used together to provide 95% sensitivity.

[c] The $SCOUT_{11}$ cut-off provides an additional zone for spared endoscopy with 0% missed VNT thanks to a cut-off for 100% VNT sensitivity.

[d] For SCOUT scores, there is a single cut-off for $SCOUT_9$ and $SCOUT_{13}$ used together: $SCOUT_9 > 1.505231 - (0.897250 * SCOUT_{13})$ (Figure 4A).

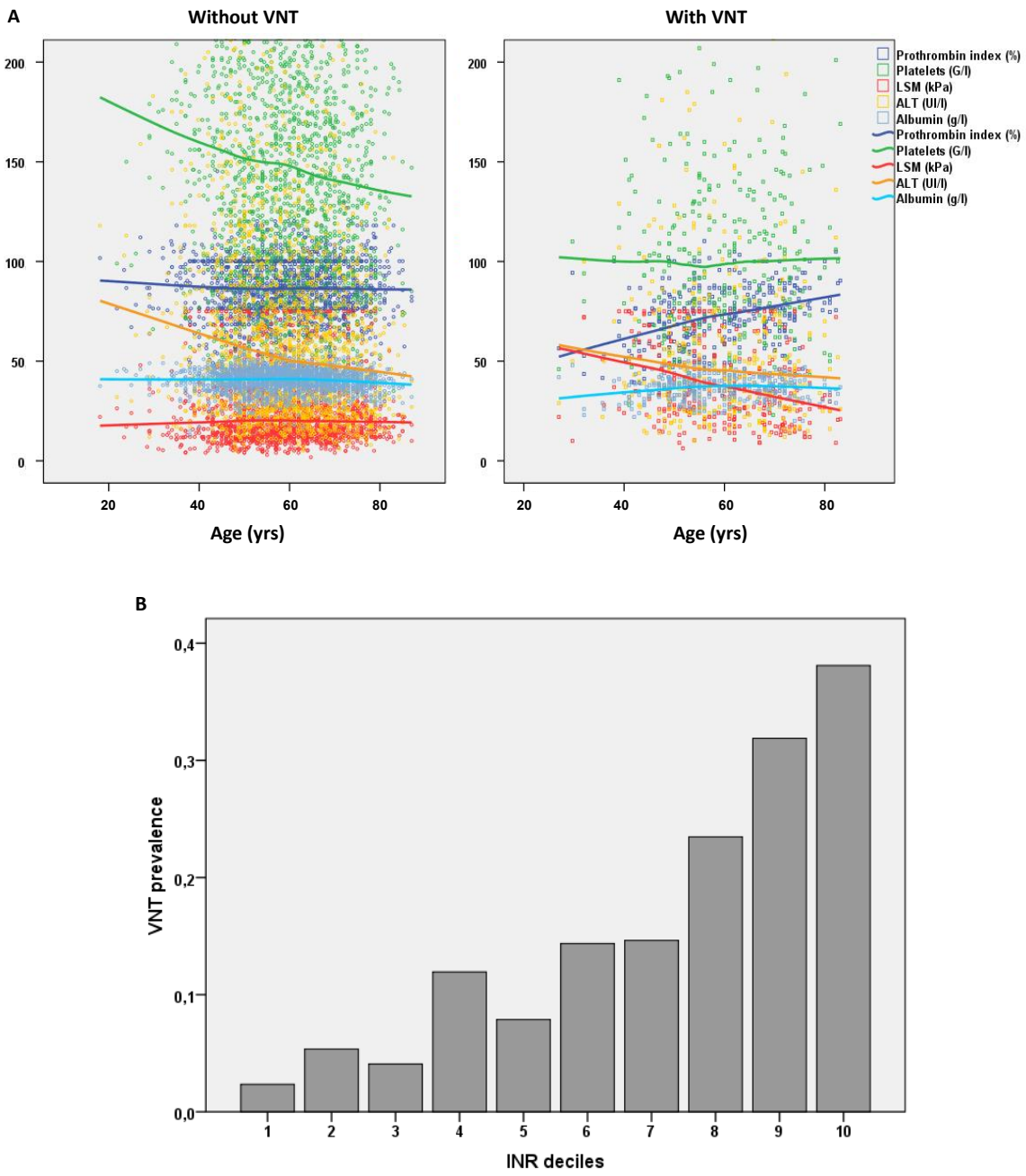

Fig. S1. VNT progression. Panel (A): risk factor progression as a function of age according to VNT status. Panel (B): VNT prevalence as a function of INR deciles.

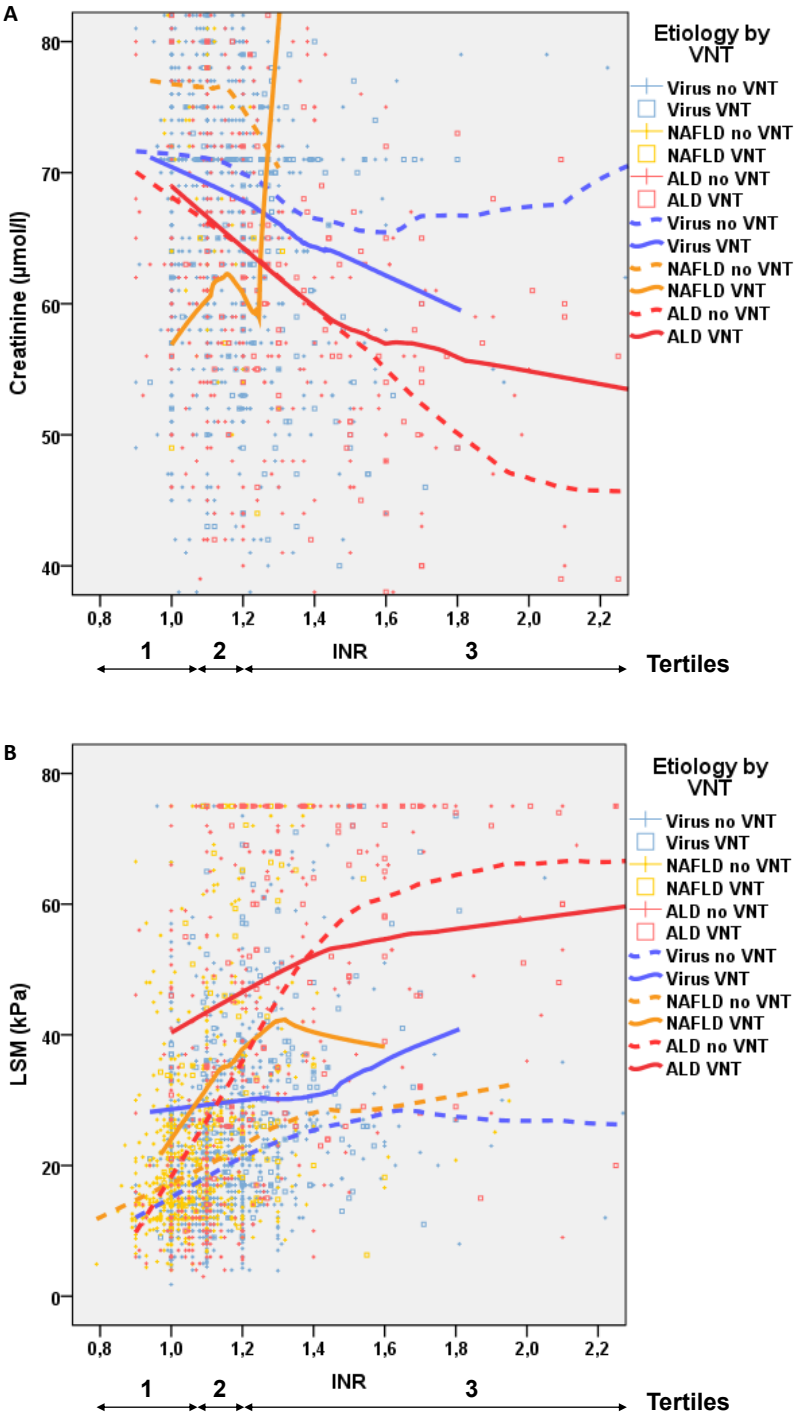

Figure S2. Progression of risk factors (Y axis) as a function of INR course (X axis) according to etiology and VNT (plain curves). Curves indicate non-linear regression. Axes were truncated. Panel A: creatinine, the subgroup NAFLD/VNT with INR >1.2 should be cautiously interpreted since the marked increase in creatinine is due to a few patients with kidney failure. Panel B: LSM.

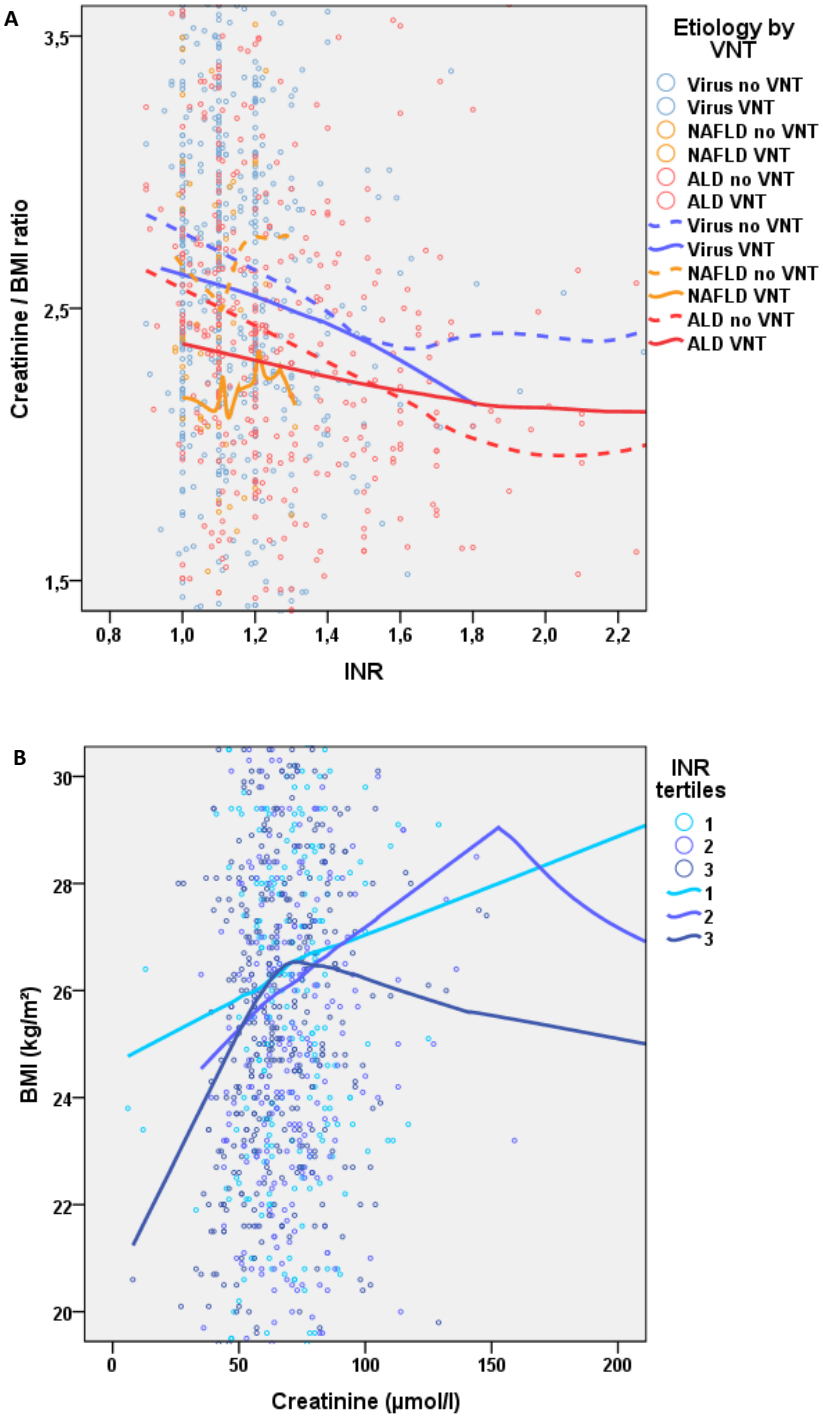

Figure S3. Relationship between BMI and creatinine (surrogate marker of sarcopenia); curves indicate non-linear regression. Panel A: progression of creatinine/BMI ratio as a function of INR according to etiology/VNT groups. Panel B: scatter plot of BMI vs creatinine as a function of INR tertiles. In the first tertile, there is a perfect positive linear correlation: creatinine reflects muscular mass. In other tertiles, there are thresholds between different slopes reflecting interaction; the second slope with negative linear correlation is attributable to liver dysfunction (sarcopenia) and/or kidney dysfunction that occurs in liver dysfunction.

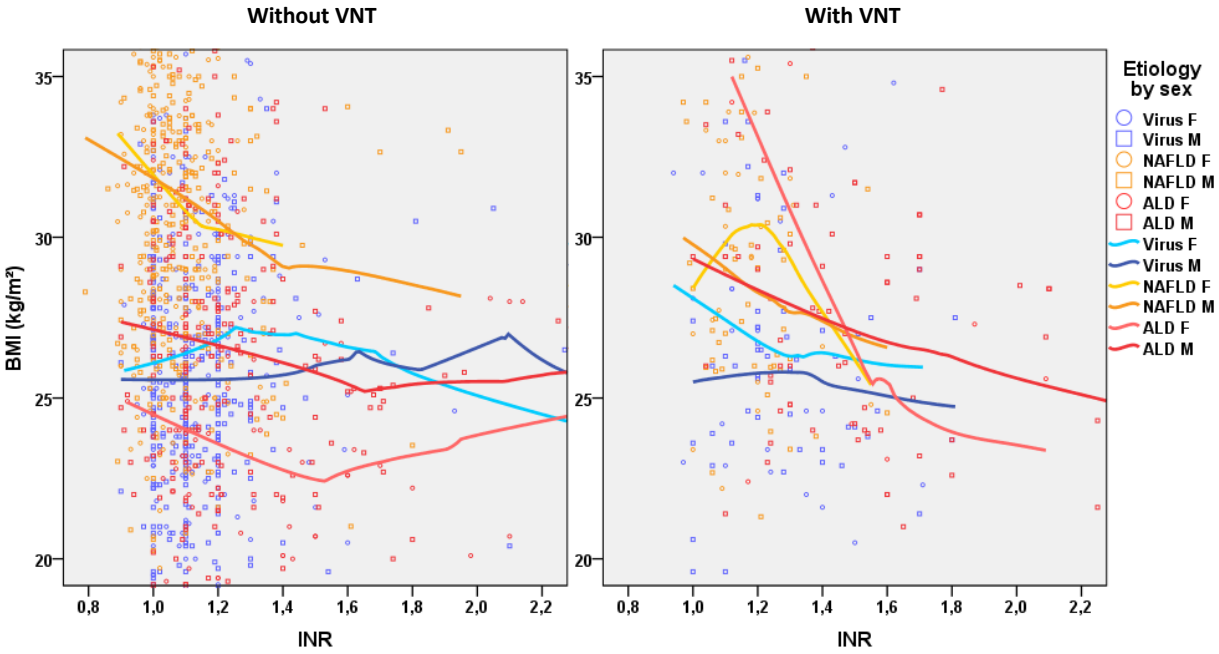

Figure S4. Progression of BMI (Y axis) as a function of INR course (X axis) according to etiology and VNT. Curves indicate non-linear regression. Axes were truncated.

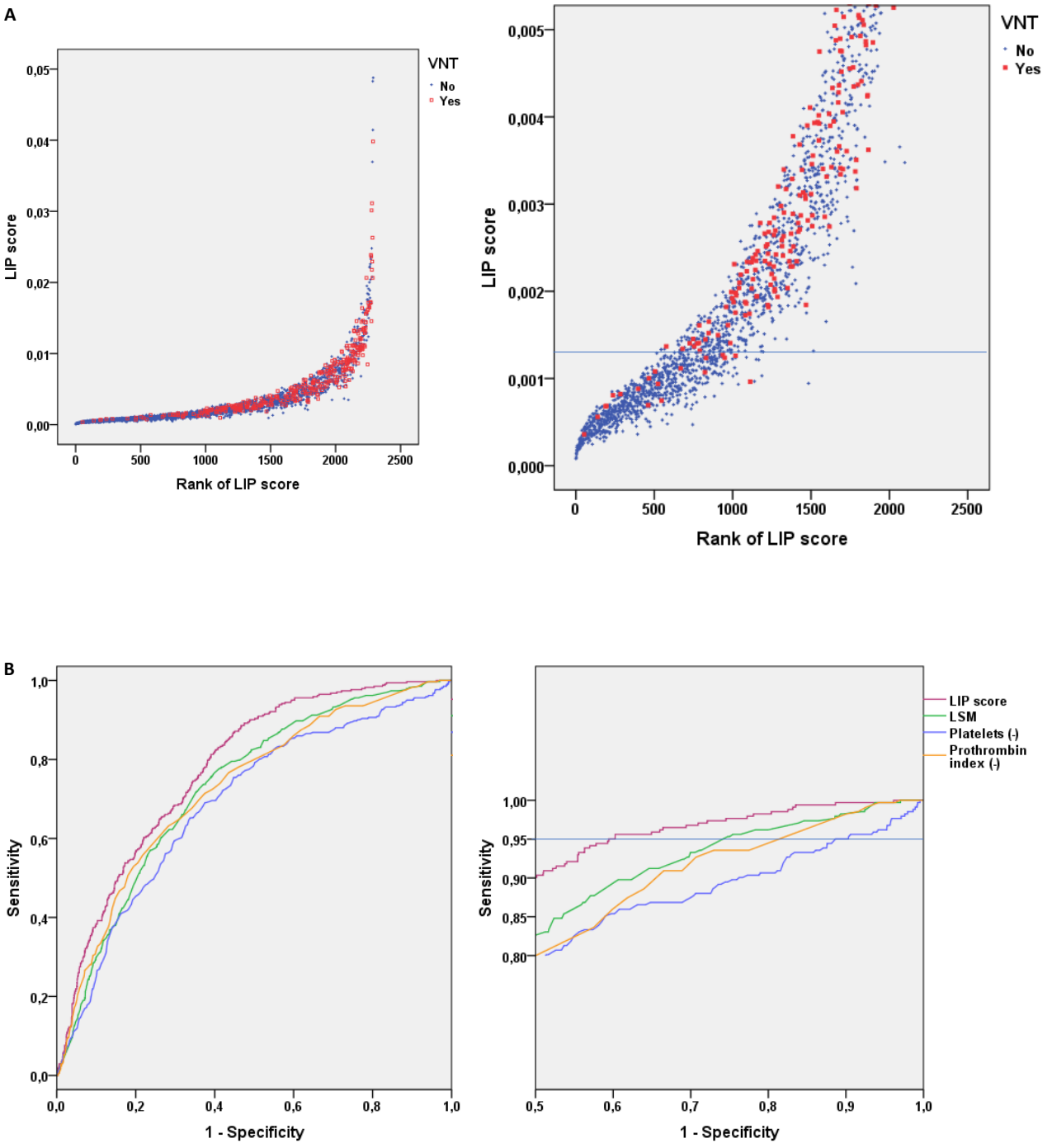

Figure S5. LIP score characteristics. Panel A: scatter plot of LIP score against its value rank; the detail of right panel shows the single cut-off of 95% sensitivity for VNT (horizontal line). Panel B: AUROC of LIP score and its composite variables for VNT; the detail of right panel shows that the 95% sensitivity zone for VNT (horizontal line) was much larger for LIP score than its composite variables. Platelets and PI are expressed with negative values since they vary inversely with VNT prevalence contrary to LIP and LSM.

CORNU Isabelle

Facteurs de risque pour les varices œsophagiennes nécessitant un traitement

RÉSUMÉ

Introduction : L'épidémiologie des varices œsophagiennes nécessitant un traitement (VNT) a été évaluée dans des conditions restreintes dans les hépatopathies chroniques. Pour la présente étude, l'objectif principal était d'évaluer les facteurs de risque des VNT dans une grande population d'étiologies multiples, sans restriction quant à la sévérité hépatique.

Méthodes : 2290 patients atteints d'hépatopathies chroniques ont été inclus dans une étude multicentrique rétro-prospective. Leurs principales caractéristiques étaient : âge : 59±11 ans ; sexe masculin : 63,5% ; étiologies : virus : 50,0%, NAFLD : 29,5%, alcool : 20,5% ; IMC : 28,4±5,8 kg/m² ; score MELD : 9,5±3,0 ; dureté hépatique (LSM) ≥10kPa : 92,9% ; prévalence des VNT : 14.9%.

Résultats : La prévalence brute des VNT était significativement augmentée chez les hommes et les hépatopathies alcooliques et diminuée chez les NAFLD par rapport aux hépatites virales. Les prévalences brutes et ajustées des VNT étaient, respectivement, virus : 14,6 % et 15,5 % (p=0,559), NAFLD : 12,0 % et 17,8 % (p=0,003), alcool : 20,0 % et 9,4 % (p<0,001) avec p<0,001 entre étiologies. Les principales différences significatives chez les patients avec VNT étaient un score MELD et une proportion d'hommes plus élevés, ainsi qu'un IMC et une créatininémie plus faibles vs les patients sans VNT. Les prédicteurs indépendants des VNT étaient l'étiologie, le sexe, les plaquettes, le taux de prothrombine (TP), la LSM, l'albumine et l'ALT, sans rôle pour l'âge, l'IMC, l'AST, la créatinine et le score MELD. Cependant, il y avait des interactions significatives : l'âge avec le TP, LSM avec les plaquettes et l'IMC avec l'étiologie. Ainsi l'IMC moyen ajusté chez les patients avec VNT était diminué dans les NAFLD (p=0,002) mais augmenté dans les hépatopathies alcooliques (p=0,009) par rapport aux patients sans VNT. Les autres interactions ont conduit à développer le score simple LSM / (plaquettes . TP) dont l'AUROC pour les VNT (0,779) était supérieure (p<0,001) aux AUROCs des plaquettes (0,692), du TP (0,728) et de la LSM (0,729). Le taux d'endoscopies épargnées par le rapport LSM / (plaquettes . TP) était de 35,2 % (95% IC : 33,2-37,1) contre 24,1 % (22,3-25,8) pour les critères de Baveno VI (p<0,001) avec un taux de VNT manquées de 5,0 % (2,8-7,0) contre 2,6 % pour les critères de Baveno VI (0,9-4,5) (p=0,057).

Conclusions : La prévalence des VNT varie significativement selon l'étiologie, la fonction et la fibrose hépatiques, et le sexe dans toutes les étiologies, et l'IMC différemment selon l'étiologie. L'application de l'interaction des facteurs de risque aux scores diagnostiques des VNT améliore leurs performances pour prédire soit le risque de VNT, soit exclure les VNT.

Mots-clés : Hypertension portale ; varices oesophagiennes ; epidemiologie ; prévalence ; indice de masse corporelle

Risk factors for esophageal varices needing treatment: application to their non-invasive diagnosis

ABSTRACT

Background and Aims : The epidemiology of varices needing treatment (VNT) has been evaluated under limited conditions in chronic liver disease (CLD). The main objective was to evaluate VNT risk factors, in a large multiple-etiology population unrestricted for liver severity, to improve the VNT non-invasive diagnosis.

Methods : 2,290 patients with CLD were included in a retro-prospective multicenter study. Their characteristics were age: 59±11 years; male sex: 63.5%; etiologies: virus: 50.0%, NAFLD: 29.5%, alcohol: 20.5%; BMI: 28.4±5.8 kg/m²; MELD score: 9.5±3.0; liver stiffness ≥10kPa: 92.9%; VNT prevalence: 14.9%.

Results : The independent VNT predictors were etiology, sex, platelets, prothrombin index (PI), liver stiffness, albumin and ALT, with no role for age, BMI, AST, creatinine and MELD score. However, there were significant interactions, i.e., age with PI, LSM with platelets and BMI with etiology. Covariate-adjusted BMI in patients with VNT was lower in NAFLD (p=0.002) but higher in alcoholic CLD (p=0.009) compared to patients without VNT. These risk factors and their ratio, due to several interactions, were included in new non-invasive scores. The $SCOUT_{13}$ score was far more discriminant (VNT AUROC: 0.826, p<0.001) than published scores, e.g. Anticipate (0.771) or a new score (LSM/(prothrombin index*platelets)) called LIP (0.778). The new $VariScreen_3$ provided three VNT risk categories: ≤5%, >5% and <100%, 100% (i.e. a new category). $VariScreen_3$ spared more endoscopies (40.2%, p<0.001) than other safe tests: Baveno VI criteria (24.1%), Anticipate (24.7%), LIP (35.2%) or $VariScreen_2$ (35.3%).

Conclusions : VNT prevalence varies significantly according to etiology, liver function and fibrosis, sex in all etiologies, and BMI differently according to etiology. The risk factor interplay significantly improves the performance of diagnostic tests for VNT which can be applied irrespective of liver severity.

Keywords : Portal hypertension; esophageal varices; epidemiology; prevalence; body mass index

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