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Prediction of Esophageal Varices by Liver Stiffness and Platelets in Persons with HIV infection and Compensated Advanced Chronic Liver Disease

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Short title: Prediction of esophageal varices in HIV

Summary:

People living with HIV are at high risk for cirrhosis and esophageal varices. Baveno VI and expanded Baveno VI criteria based on transient elastography and platelets can spare esophagogastroduodenoscopies. These criteria can be safely expanded to HEPAVIR and HIV cirrhosis criteria

Abstract

Background

Human immunodeficiency virus (HIV)-infected individuals are at increased risk of cirrhosis and esophageal varices. Baveno VI criteria, based on liver stiffness measurement (LSM) and platelet count, have been proposed to avoid unnecessary esophagogastroduodenoscopy (EGD) screening for esophageal varices needing treatment (EVNT). This approach has not been validated in HIV-infected patients.

Methods

HIV-infected patients from eight prospective cohorts were included if they fulfilled the following criteria: 1) compensated advanced chronic liver disease (LSM >10 kPa); 2) availability of EGD within 6 months of reliable LSM. Baveno VI (LSM <20 and platelets >150,000), expanded Baveno VI (LSM <25 and platelets >110,000) and HEPAVIR criteria (LSM <21) were applied to identify patients not requiring screening EGD. Criteria optimization was based on the percentage of EGD spared, while keeping the risk of missing EVNT below 5%.

Results

507 HIV-infected patients were divided into a training (n=318) and a validation set (n=189). EVNT were found in 7.5%. In the training set, Baveno VI, expanded Baveno VI and HEPAVIR criteria spared 10.1%, 25.5% and 28% EGD, while missing 0%, 1.2% and 2.2% EVNT, respectively. The best thresholds to rule out EVNT were platelets >110,000 and LSM <30 kPa (HIV cirrhosis criteria), with 34.6% EGD spared and 0% EVNT missed. In the validation set, HEPAVIR and HIV cirrhosis criteria spared 54% and 48.7% EGD, while missing 4.9% and 2.2% EVNT, respectively.

Conclusions

Baveno VI criteria can be extended to HEPAVIR and HIV cirrhosis criteria while sparing a significant number of EGD, thus improving resource utilization for HIV-related compensated advanced chronic liver disease.

Keywords: esophagogastroduodenoscopy, transient elastography, Baveno VI criteria, HCV coinfection, variceal bleeding.

Introduction

Liver disease is a leading cause of non-AIDS related deaths in people living with the human immunodeficiency virus (HIV)[1]. HIV-infected individuals present with multiple risk factors for liver injury, including coinfections with hepatitis C (HCV) and B (HBV) viruses, frequent metabolic comorbidities triggering non-alcoholic fatty liver disease (NAFLD), excessive alcohol intake, and antiretroviral therapy (ART)-related hepatotoxicity[2-5]. This hypothetical multi-hit process can lead to faster progression of liver fibrosis to cirrhosis, hepatocellular carcinoma (HCC), and complications associated with portal hypertension, such as variceal bleeding[6-10].

The diagnosis of esophageal varices (EV), and especially large (grade 2/3) EV requiring primary prophylaxis (EV needing treatment, EVNT), is of paramount prognostic importance in all patients with cirrhosis[11, 12]. However, EVNT are not frequent in patients with compensated cirrhosis, and access to esophagogastroduodenoscopy (EGD) can be problematic in the context of primary and secondary care HIV clinics. Strategies to reduce referral to hepato-gastroenterology units for unnecessary EGD screening may be crucial in this setting. The Baveno VI guidelines proposed that patients with compensated advanced chronic liver disease (cACLD) with a liver stiffness measurement (LSM) by transient elastography <20 kPa and a platelet count >150,000/μL can avoid screening endoscopy[13]. Baveno VI criteria have been validated in patients with cACLD of various etiologies and in a meta-analysis[14-18]. Expanded Baveno VI criteria, obtained by optimizing LSM and platelets thresholds, have been proposed to spare a higher proportion of unnecessary EGD when compared to Baveno VI criteria[13, 19]. Ad hoc validation of these criteria is important considering that HIV-infected patients may have higher frequency of thrombocytopenia unrelated to liver disease and that LSM presents with specific cut-offs and diagnostic accuracy in this setting[20-25]. Moreover, the pathogenesis of liver fibrosis portending the

development of cirrhosis is more complex and involves a number of discrete mechanisms unique to HIV infection[26].

We used data from eight clinical cohorts of HIV-infected individuals to fulfill the following aims: (i) validate the Baveno VI and expanded Baveno VI criteria, based on platelets and LSM, and the HEPAVIR criteria, based on LSM and developed in the setting of HIV/HCV coinfection, to identify patients at low risk of EVNT and EV bleeding[12]; (ii) optimize those criteria in the specific setting of HIV infection by maximizing the number of spared EDG while minimizing the EVNT missed[16]; and (iii) determine the safety of these strategies by means of assessing the risk of variceal bleeding.

Patients and methods

Study design and population

We conducted a retrospective analysis of eight real-life longitudinal cohorts that aimed to screen liver diseases in HIV-infected patients. Consecutive HIV-infected adults aged >18 years with cACLD were eligible. Inclusion criteria were presence of a reliable LSM and an EGD within 6 months of LSM. cACLD was defined by LSM >10 kPa[19]. Alcohol intake >20 g/day during the previous year (evaluated by interview of patients on amount, frequency and type) was considered as significant alcohol intake. Patients with previous decompensating events from liver cirrhosis (Child-Pugh B and C), HCC, liver transplantation, prophylactic EV banding, portal or splenic vein thrombosis, non-cirrhotic portal hypertension and splenectomy were excluded. The combined study cohort included: 318 patients from the HEPAVIR-Cirrhosis Cohort, which is a prospective multicenter cohort recruiting consecutive HIV/HCV coinfected patients with compensated cirrhosis from 7 hospitals in Andalusia, southern Spain, since 2006; 54 patients from the LIVEHIV Cohort, which is a prospective screening program for liver fibrosis and NAFLD running since 2013 at McGill University Health Centre, Montreal; 37 patients from Centre d'Investigation de la Fibrose Hépatique, Bordeaux University Hospital; 42 from the Division of Gastroenterology and Hepatology, Imperial College London and Department of Hepatology, Royal Free Hospital London; 20 patients from the Division of Infectious Diseases, Azienda Ospedaliera Universitaria Paolo Giaccone, University of Palermo; 20 patients from National Institute of Infectious Diseases Evandro Chagas-Oswaldo Cruz Foundation, Rio de Janeiro; 8 patients from the Division of Gastroenterology, University of Modena and Reggio Emilia; and 8 patients from Department of Medicine I, University Hospital Bonn.

Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the hospital Internal Review Boards and their Ethics Committees, and written informed consent was obtained from all patients.

Clinical and biological parameters

Data collected at the time of enrollment included demographic information, HIV and medications history, body mass index (BMI), liver biochemistries, hematological and virological parameters. EGD was performed by a small number of experienced operators at each Hospital. At endoscopy, high-risk EV warranting primary prophylaxis against EV bleeding (EVNT) were defined by medium or large size (grade 2/3) or the presence of high-risk stigmata findings (red wale marks, cherry red spots)[13].

Transient elastography

Transient elastography was performed with the FibroScan (Echosens, Paris, France) medical device, using the M probe. When available, the XL probe was used in cases of failure of transient elastography with the M probe or if the BMI was greater than 30 kg/m^2. In each center, LSM was assessed after at least 4 hours fasting, by a trained operator who had previously performed at least 300 examinations. The following criteria were applied to define the result of transient elastography as reliable: at least 10 valid LSM, and an interquartile range (IQR) <30% of the median LSM[27]. LSM were performed at cohort entry and then every 12 months. The examination chosen for this analysis was the closest to EGD.

Outcome measures

As primary outcome, we validated the diagnostic accuracy of Baveno VI (favorable status, LSM <20 kPa and platelets >150,000)[13], expanded Baveno VI (favorable status, LSM <25 kPa and platelets >

110,000)[19] and HEPAVIR criteria (favorable status, LSM <21 kPa)[12, 13, 19, 28]. We then optimized those criteria (new HIV cirrhosis criteria) by maximizing the number of spared EGD while minimizing the EVNT missed. Episodes of incident variceal bleeding were prospectively collected by means of a dedicated outcome measures form at all centers. Patients were followed from their first LSM (baseline, or time zero) until they had an episode of variceal bleeding, died, withdrew consent, were lost to follow-up (no visits for more than 1.5 years), or until administrative censoring (November 31, 2018).

Statistical analysis

The training set was defined as the subcohort of patients from the HEPAVIR-Cirrhosis cohort (n=318), while the remaining patients from the other centres acted as validation set (n=189). Performance evaluations were made in terms of percentage of spared endoscopies, percentage of missed EV, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios. Confidence intervals (CIs) for sensitivity, specificity and accuracy were "exact" Clopper-Pearson CI, those for likelihood ratios were calculated using the Log method[29]. CI for predictive values were the standard logit CI given by Mercaldo et al[30]. The training set was used to find a different combined threshold of LSM and platelets count, the HIV cirrhosis criteria, which maximized the absolute number of spared endoscopies while keeping the risk of missed EVNT below 5% (or, equivalently, while constraining the NPV to be at least 95%). The 5% false negative rate of undetected EVNT was agreed as a reasonable criterion by experts in the Baveno VI consensus conference and later adopted by the American Gastroenterological Association and several other authors[13, 16]. The performance of thresholds was subsequently evaluated in the validation set. We estimated incidence rates of variceal bleeding by dividing the number of participants developing the outcome by the number of person-years (PY) of follow-up. Poisson count models were used to calculate CIs for incidence rates. A two-sided level of significance of 5% was used for all statistical inferences. Statistical analysis was performed using STATA 13.1.

Results

Patient characteristics

The baseline characteristics of the 507 patients with HIV-related cACLD are shown in Table 1. The M probe was used in most of the cases (97.5%). Overall, EVNT and small EV were present in 7.5% and 16.8% of cases, respectively. When compared to patients with no EVNT, those with EVNT had higher LSM (38.1, standard deviation (SD) 16.4 vs. 26.2, SD 13.6 kPa; p<0.001), and lower platelets (95.2, SD 40.2 vs. 137.0, SD 61.8 10^9/L; p<0.001). Supplemental Table S1 reports patients' characteristics in the validation set by HCV coinfection status.

Diagnostic accuracy of LSM and platelets-based criteria for EVNT

In the training set, 32 patients (10.1%) had a favorable Baveno VI status as a rule-out for EVNT of whom none had EVNT (Table 2). When looking at expanded Baveno VI criteria, 81 patients (25.5%) had a favorable status as a rule-out for EVNT, of whom 1 (1.2%) had EVNT. Finally, 89 (28%) patients had favorable status according to HEPAVIR criteria, of whom 2 (2.2%) had EVNT. Consistently, NPV for EVNT was 100%, 98.8% and 97.8% for Baveno VI, expanded Baveno VI and HEPAVIR criteria, respectively. HEPAVIR criteria would have allowed an absolute reduction of 17.9% and 2.5% of EGD more than Baveno VI and expanded Baveno VI while keeping a rate of missed EVNT below the critical 5% threshold. Furthermore, we identified platelets >110,000 and LSM <30 kPa (HIV cirrhosis criteria) as the best thresholds to rule-out EVNT in the training set. None of the patients meeting favorable status by HIV cirrhosis criteria had EVNT (Table 2). The use of these thresholds would have spared 34.6% of EGD. HIV cirrhosis criteria would have allowed an

absolute reduction of 24.5%, 9.1% and 6.6% of EGD more than Baveno VI, expanded Baveno VI and HEPAVIR criteria, respectively. In the validation set, HIV cirrhosis criteria missed 2 patients (2.2%) with EVNT while maintaining a NPV at 97.8%. HEPAVIR criteria would have spared 5.3% EGD more than HIV cirrhosis criteria, while keeping a rate of missed EVNT below the critical 5% threshold (4.9%). Figure 1 reports the distribution of EVNT and small EV according to favorable status of the non-invasive criteria in the pooled cohort. We also conducted a sensitivity analysis by HCV coinfection status in the validation set. The prevalence of EVNT was lower in HIV mono-infected patients as compared to HIV/HCV coinfected patients (2.4% vs. 11.6%). All the criteria performed better in HIV mono-infected patients (Table 3). Supplemental Table S2 presents the main characteristics of patients with favorable status according to non-invasive criteria who had EVNT.

Incidence of bleeding during follow-up

Over a mean follow-up time of 35.4 (SD 21.4) months, 20 (3.9%; 95% CI: 2.3-5.6%) patients bled in the pooled cohort, accounting for an incidence rate of 1.2 per 1000 PY (95% CI, 0.8-1.9). None of the patients classified as favorable status at baseline by Baveno VI or HEPAVIR criteria developed a first variceal bleeding during follow-up. Thus, the NPV of these strategies to predict a variceal bleeding during follow-up was 100%. For expanded Baveno VI and HIV cirrhosis criteria, only one patient classified as favorable status bled during follow-up. This patient, who was classified as favorable by both expanded Baveno VI and HIV cirrhosis criteria, had chronic HCV infection, a non-significant alcohol intake and was not infected by HBV. He had a LSM of 21.8 kPa and $119x10^9$/L platelets at baseline. Initial EGD showed no varices. He was afterwards incarcerated but returned to follow-up after release from prison. Two years and two months after the initial EGD he suffered an acute variceal bleeding. LSM and platelets at bleeding were 27.4 kPa and $51x10^9$/L, respectively. Consequently, he would have been classified as unfavorable status by all criteria at the bleeding episode.

Discussion

In this multicenter clinical cohort of HIV-infected patients with cACLD, we found that criteria specifically developed in HIV-infected patients to rule out EVNT, i.e. the HEPAVIR and the new HIV cirrhosis criteria, performed better than Baveno VI and expanded Baveno VI criteria, allowing to safely spare a significant number of EGD. Furthermore, we validated longitudinally our findings, demonstrating that the incidence of EV bleeding was very low in patients fulfilling the HEPAVIR or the HIV cirrhosis criteria. Finally, we propose using the HIV cirrhosis criteria when evaluating HIV-infected patients with cACLD to minimize the number of EGD, with a high yield to predict the absence of EVNT.

Portal hypertension has a major impact on the natural history of liver cirrhosis[11]. While in the past liver cirrhosis was considered a single diagnosis with poor prognosis, recent years have seen an evolution of its definition to a rather dynamic condition. In this clinicopathological spectrum, portal hypertension underlies most of the clinical complications of cACLD[31]. Moreover, in the setting of variceal bleeding a 6-week mortality rate of 11.1-40% has been reported[32]. Early identification of EVNT is a key clinical need to start variceal bleeding prophylaxis. HIV-infected patients are exposed to multiple risk factors for liver cirrhosis. First, alcohol abuse is frequent[33]. Second, HIV-infected individuals have high rates of HCV or HBV coinfection, estimated to be 11-14% and 10%, respectively[34, 35]. Third, hepatotoxicity is a common side effect of ART, either by direct cell stress, mitochondrial damage, or through its association with metabolic complications[2]. Fourth, there is growing concern about the epidemic of NAFLD in HIV-infected patients, with prevalence ranging between 13 and 65%[4]. Fifth, a direct cytopathic effect of HIV on the hepatocytes has been reported[26]. Consequently, a relative high frequency of liver cirrhosis has been reported in the setting of HIV infection[7, 8, 12].

Baveno VI expert recommendations suggest to avoid EGD screening for EVNT in patients with LSM <20 kPa and platelets >150,000[13]. In the present study, we found that Baveno VI and expanded Baveno VI criteria would have spared 10.1% and 25.5% of unnecessary EGD by missing 0% and 1.2% EVNT, respectively, in the training set. In the validation set, the number of spared EGD was 22.8% and 42.3% for Baveno VI and expanded Baveno VI, respectively, while missed EVNT were 0% and 2.5%. The number of spared EGD is somewhat lower than those reported in other etiologies of liver disease, such as viral hepatitis and NAFLD[15, 16]. This finding confirms the relevance of validating those criteria in the setting of HIV infection[20-25].

In the HEPAVIR cohort, a LSM <21 kPa showed a 100% NPV to exclude the presence of EVNT in HIV/HCV coinfected patients with cirrhosis[28]. Long-term follow-up data confirmed the validity of this strategy as no individual with LSM <21 kPa experienced a EV bleeding in the HEPAVIR cohort[12]. In the present study, HEPAVIR criteria would have spared 28% and 54% EGD by missing 2.2% and 4.9% EVNT in the training and validation set, respectively. Importantly, none of the incident bleeding episodes occurred in patients with a LSM <21 kPa both at the EGD examination or at bleeding. The same cut-off has been proposed for non-invasive identification of clinically significant portal hypertension by recent guidelines[36].

In the training set, we identified 30 kPa for LSM and 110,000 for platelets as the best thresholds to rule-out EVNT. These new HIV cirrhosis criteria would have spared 34.6% of unnecessary EGD while missing 0% EVNT, thus demonstrating the best yield to rule-out EVNT in HIV-related cACLD. This was confirmed in the validation set, with 48.7% EGD spared while missing 2.2% EVNT. The better performance of a lower threshold of platelets could be linked to thrombocytopenia unrelated to liver disease. As for LSM, the better accuracy of a higher threshold may be related to the high frequency of hepatic steatosis reported in HIV-infected patients, including studies from our cohorts, which may affect LSM[3, 37-40]. We could also speculate on other reasons why a higher LSM cut-off

may be more accurate, including chronic HIV or toxicity of ART which may contribute to liver inflammation potentially affecting LSM. Indeed, the concept that higher LSM cut-off performs better in HIV infection applies also to the diagnosis of cirrhosis[24]. HIV cirrhosis criteria also proved to be safe, as only one patient classified as favorable status bled during the follow-up. However, this patient would have been classified as unfavorable at the bleeding episode, pointing out the need of continuous surveillance for progression of portal hypertension, with yearly determination of LSM and platelets, as per Baveno VI recommendations[13]. We found that non-invasive criteria performed better in HIV mono-infected patients, where the prevalence of EVNT was lower. Similarly, Petta et al reported better performance of Baveno VI and expanded Baveno VI criteria when the prevalence of EVNT was low, as lower false negative rates are expected[16]. When using the non-invasive criteria in clinical practice, it is important to contextualize as the prevalence of the disease influences the performance of non-invasive tests.

Our study has several strengths. The large sample size of our pooled cohort, the stringent criteria for the interval between EGD and LSM (<6 months) and the availability of follow-up data render our data robust. Moreover, we used a homogeneous cohort from a single center as training set, and a heterogeneous cohort of patients from different centers as validation, mimicking a real-life setting. Several limitations of our study must be acknowledged. First, the analysis of the data was retrospective and the evaluation of EV size has been performed by several endoscopists. However, the same issue was present in similar studies[16, 19, 41]. Moreover, in our study both prevalence of EVNT and performance of tested criteria were similar among centers (data not shown). Second, due to the limited numbers of tests, we could not validate our findings with the XL probe. Previous studies have reported different thresholds of the M and XL probes[16]. Third, by applying non-invasive criteria, designed to rule-out EVNT, we missed a small proportion of patients with EVNT. This data is clinically relevant because the presence of EV affects the prognosis of cirrhotic patients via a higher risk of liver decompensation and death[11]. However, yearly retesting of the patients should capture those patients transiting in lower platelets or higher LSM values, considered worthy of EGD

screening. Fourth, our study included mainly HIV/HCV confected patients, as such our findings in HIV mono-infected patients should be cautiously interpreted and considered exploratory. Fifth, the incidence of bleeding we reported is somewhat lower than previous data, possibly due to the inclusion of HIV mono-infected patients and to the adoption of lower LSM cut-off for study entry[12].

In conclusion, in a large cohort of HIV-infected patients with cACLD we demonstrated that HEPAVIR and HIV cirrhosis criteria can safely spare 37.7% and 39.8% of unnecessary EGD by missing 3.7% and 1% of EVNT in the pooled cohort, respectively, which is a better performance than Baveno VI and expanded Baveno VI criteria. Our data suggest that there is no increase in the risk of bleeding during the follow-up for patients with favorable status according to those criteria, provided they are reassessed every year. These findings can be used for resource optimization to select HIV-infected patients who need to undergo screening EGD. Further validation studies are needed to confirm our findings, particularly in HIV mono-infected patients.

Authors contributions

NM contributed to study design, data and interpretation of the data, statistical analysis and first draft of the manuscript. GM, FT, ARJ, MRV, RW, RJ, GG, FS, HP, MBK, AC, PG, PW and VL contributed to data and interpretation of data. CSP, JM, JBM and SP contributed to study design, data and interpretation of the data. GS contributed to conception, study design, data and interpretation of the data, statistical analysis and first draft of the manuscript. All authors approved the final version of the article.

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Conflict of interest

GM has acted as speaker for Merck, Gilead, ViiV, Jansenn, and has served as an advisory board member for ViiV, Gilead and Jansenn. JM received honoraria for speaking at the HIV Clinical Updates course. GG has acted as speaker for Merck, Gilead, ViiV, served as an advisory board member for Merck and ViiV and has received research funding from Merck, Gilead and ViiV. FS has acted as a speaker for GORE and COOK and received unrestricted research funding from the same companies. JR has received honoraria for consulting or speaking at educational events from Abivax, Abbvie, Gilead, Janssen, Merck and ViiV. CB has received honoraria for lectures and/or consultancies from AbbVie, Gilead, Janssen, MSD, ViiV. MBK has acted as a consultant for ViiV, Gilead, Janssen and Merck and received research funding from Merck and ViiV. PG has acted as consultant for Merck and Gilead. PW has acted as consultant for BMS, Gilead, Merck, Novartis. GS has acted as speaker for Merck, Gilead, Abbvie, ViiV, served as an advisory board member for Merck, Gilead and Novartis and has received research funding from Merck and Echosens. NM, CSP, JP, FT, ARJ, MJRV, RHW, AC, RJ, HP, JM, SP, VdL have nothing to disclose.

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Table 1. Baseline demographic, metabolic, laboratory and instrumental features of patients with HIV-related cirrhosis (n=507).

	Pooled cohort (n=507)	**Training set** (n=318)	**Validation set** (n=189)	**p °**
Age (years)	53.3 (6.4)	54.3 (5.4)	51.6 (7.6)	<0.001
Female (%)	87 (17.2)	36 (11.3)	51 (27.0)	<0.001
Ethnicity (%) *				
Caucasian	438 (94.8)	318 (100)	120 (83.3)	<0.001
Black	15 (3.3)	0	15 (10.4)	
Other	9 (1.9)	0	9 (6.3)	
BMI (Kg/m^2) *	24.5 (4.1)	24.8 (4.1)	24.1 (4.2)	0.107
Significant alcohol intake (%) *	67 (16.2)	56 (17.5)	34 (14.6)	0.162
Prior IDU (%)	370 (72.3)	289 (90.9)	81 (42.9)	<0.001
HIV duration (years)	24.8 (9.3)	28.5 (7.5)	18.6 (8.7)	<0.001
CD4 cell count (cells/μL)	501.1 (319.3)	480.3 (316.9)	537.6 (321.2)	0.054
Undetectable HIV viral load (≤ 50 copies) (%)	372 (73.3)	223 (70.1)	149 (78.8)	0.032
Current ART regimen (%) *				
NRTI	388 (89.2)	284 (91.0)	104 (84.6)	0.039
NNRTI	112 (25.7)	79 (25.3)	33 (26.8)	0.275

PI	210 (48.3)	142 (45.5)	68 (55.3)	0.060
Integrase inhibitors	145 (33.3)	100 (32.1)	45 (36.6)	0.204
Anti-HCV Ab pos (%)	465 (91.7)	318 (100)	147 (77.8)	<0.001
HBsAg pos (%)	18 (3.6)	7 (2.2)	11 (5.8)	0.033
HCV RNA pos (%) *	388/450 (86.2)	318/318 (100)	70/132 (53.0)	<0.001
INR	1.10 (0.23)	1.09 (0.17)	1.11 (0.33)	0.376
Platelets (10^9/L)	131.5 (61.0)	128.5 (57.0)	136.4 (67.1)	0.161
ALT (IU/L)	84.6 (62.4)	89.2 (57.3)	76.6 (69.7)	0.029
AST (IU/L)	84.2 (54.6)	88.2 (49.0)	77.0 (61.0)	0.028
Total bilirubin (µmol/L)	17.2 (13.0)	16.9 (11.1)	17.3 (15.7)	0.520
Albumin (g/L)	40.6 (5.5)	41.0 (5.1)	39.9 (6.1)	0.037
LSM (kPa)	27.8 (14.6)	31.2 (14.8)	22.1 (12.3)	<0.001
EVNT (%)	38 (7.5)	20 (6.3)	18 (9.5)	0.18
Small EV (%)	85 (16.8)	53 (16.7)	32 (16.9)	0.40

Legend: Continuous variables are expressed as mean (standard deviation) and categorical variables are expressed as frequencies (%). ° comparison between training and validation cohort. For the comparison, *p*-values were computed using a chi-squared test for categorical variables and a Student's T test for continuous variables. * Data on ethnicity was available for 462 patients. BMI was available in 325 patients. Data on significant alcohol intake and ART regimen were available in 413 and 435 patients, respectively. Data on HCV RNA positivity was available for 450/465 HIV/HCV coinfected

patients. Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; EV, esophageal varices; EVNT, esophageal varices needing treatment; HIV, human immunodeficiency virus; IDU, injection drug use; INR, international normalized ratio; IU, international units; LSM, liver stiffness measurement; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, Protease Inhibitors.

Table 2. Diagnostic accuracy for EVNT of Baveno VI, expanded Baveno VI, HEPAVIR and new HIV cirrhosis criteria by favorable status in the training (n=318) and validation set (n=189).

	Baveno VI (platelets >150 + LSM <20)	**Expanded Baveno VI** (platelets >110 + LSM <25)	**HEPAVIR** (LSM <21)	**HIV cirrhosis** (platelets >110 + LSM <30)
Training set (n=318)				
Sensitivity (%)	100 (79.9-100)	95 (73.1-99.7)	90 (66.8-98.2)	100 (79.9-100)
Specificity (%)	10.7 (7.5-14.9)	26.8 (21.9-33.3)	29.2 (24.1-34.7)	36.9 (31.5-42.7)
PPV (%)	6.9 (4.4-10.7)	8.02 (5.02-12.4)	7.8 (4.8-12.3)	9.6 (6.1-14.6)
NPV (%)	100 (86.6-100)	98.8 (92.3-99.9)	97.8 (91.3-99.6)	100
LR+	1.12 (1.08-1.17)	1.30 (1.15-1.47)	1.27 (1.08-1.50)	1.59 (1.45-1.73)
LR-	0	0.19 (0.03-1.27)	0.34 (0.09-1.29)	0
Spared EGD (%)	32 (10.1)	81 (25.5)	89 (28)	110 (34.6)
Missed EVNT (%)	0/32 (0)	1/81 (1.2)	2/89 (2.2)	0/110 (0)
Validation set (n=189)				
Sensitivity (%)	100 (89.8-100)	88.9 (63.9-98.05)	72.2 (46.4-89.3)	88.9 (63.2-98.05)

Specificity (%)	12.3 (7.7-19.04)	45.6 (38.04-53.4)	56.7 (48.9-64.2)	52.6 (44.9-60.3)
PPV (%)	25.1 (18.9-32.4)	14.7 (8.9-23.04)	14.9 (8.5-24.5)	16.5 (10.01-25.7)
NPV (%)	100 (78.1-100)	97.5 (90.4-99.6)	95.1 (88.4-98.2)	97.8 (91.6-99.6)
LR+	1.14 (1.07-1.21)	1.63 (1.32-2.02)	1.67 (1.20-2.33)	1.88 (1.50-2.36)
LR-	0	0.24 (0.07-0.91)	0.49 (0.23-1.04)	0.21 (0.06-0.79)
Spared EGD (%)	43 (22.8)	80 (42.3)	102 (54.0)	92 (48.7)
Missed EVNT (%)	0/43 (0)	2/80 (2.5)	5/102 (4.9)	2/92 (2.2)

Legend: Results are reported as number or percentage and 95% CI. Abbreviations: EGD, esophagogastroduodenoscopy; EVNT, esophageal varices needing treatment; HIV, human immunodeficiency virus; LR, likelihood ratio; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value.

Table 3. Diagnostic accuracy for EVNT of Baveno VI, expanded Baveno VI, HEPAVIR and new HIV cirrhosis criteria (favorable status) in validation set (n=189) split by HCV coinfection status.

	Baveno VI (platelets >150 + LSM <20)	**Expanded Baveno VI** (platelets >110 + LSM <25)	**HEPAVIR** (LSM <21)	**HIV cirrhosis** (platelets >110 + LSM <30)
HIV/HCV coinfection (n=147)				
Sensitivity (%)	100 (80.5-100)	88.2 (63.6-98.5)	70.6 (44.0-89.7)	88.2 (63.6-98.5)
Specificity (%)	22.3 (15.5-30.4)	41.5 (33.0-50.5)	53.9 (44.9-62.6)	48.5 (39.6-57.4)
PPV (%)	14.4 (13.3-15.6)	16.5 (13.6-19.8)	16.7 (12.3-22.3)	18.3 (15.0-22.2)
NPV (%)	100	96.4 (87.9-99.0)	93.3 (86.8-96.8)	96.9 (89.4-99.2)
LR+	1.29 (1.17-1.41)	1.51 (1.20-1.89)	1.53 (1.07-2.19)	1.71 (1.35-2.18)
LR-	0	0.28 (0.08-1.06)	0.55 (0.26-1.16)	0.24 (0.07-0.90)
Spared EGD (%)	29 (19.7)	56 (38.1)	75 (51.0)	65 (44.2)
Missed EVNT (%)	0/29 (0)	2/56 (3.6)	5/75 (6.7)	2/65 (3.1)
HIV mono-infection (n=42)				
Sensitivity (%)	100 (2.5-100)	100 (2.5-100)	100 (2.5-100)	100 (2.5-100)

Specificity (%)	34.2 (20.1-50.6)	58.5 (42.1-73.7)	65.9 (49.4-79.9)	65.9 (49.4-79.9)
PPV (%)	3.6 (2.9-4.4)	5.6 (3.9-7.8)	6.7 (4.5-9.9)	6.7 (4.5-9.9)
NPV (%)	100	100	100	100
LR+	1.52 (1.22-1.89)	2.41 (1.68-3.47)	2.93 (1.91-4.48)	2.93 (1.91-4.48)
LR-	0	0	0	0
Spared EGD (%)	14 (33.3)	24 (57.1)	27 (64.3)	27 (64.3)
Missed EVNT (%)	0/14 (0)	0/24 (0)	0/27 (0)	0/27 (0)

Legend: Results are reported as number or percentage and 95% CI. Abbreviations: EGD, esophagogastroduodenoscopy; EVNT, esophageal varices needing treatment; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LR, likelihood ratio; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value.

Figure legends

Figure 1. Proportion of patients with no varices, small varices and EVNT in the pooled cohort (n=507) according to favorable status of non-invasive criteria.

Figure 1