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ORIGINAL ARTICLE

Prognostic value of non-invasive scores based on liver stiffness measurement, spleen diameter and platelets in HIV-infected patients

Amine Benmassaoud[1] | Juan Macias[2] | Adèle Delamarre[3] | Anaïs Corma-Gomez[2] | Giovanni Guaraldi[4] | Jovana Milic[4] | Jürgen K. Rockstroh[5,6] | Kathrin Van Bremen[5,6] | Emmanuel Tsochatzis[7] | Akhilesh Mulay[7] | Jennifer Price[8] | Lucy J. Garvey[9] | Maud Lemoine[9] | Dana Kablawi[1] | Bertrand Lebouche[1] | Marina B. Klein[1] | Luz R. Ballesteros[1] | Christopher Boesecke[5,6] | Filippo Schepis[4] | Sanjay Bhagani[7] | Graham Cooke[9] | Annalisa Berzigotti[10] | Kyoko Hirose[8] | Juan A. Pineda[2] | Agnihotram V. Ramanakumar[11] | Victor De-Ledinghen[3] | Sahar Saeed[12] | Giada Sebastiani[1]

[1]McGill University Health Centre, Montreal, Quebec, Canada

[2]Hospital Universitario de Valme, Seville, Spain

[3]Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France

[4]University of Modena and Reggio Emilia, Modena, Italy

[5]Bonn University Hospital, Bonn, Germany

[6]German Centre for Infection Research (DZIF), partner site Cologne-Bonn, Bonn, Germany

[7]Royal Free London NHS Foundation Trust, London, UK

[8]University of California San Francisco, San Francisco, California, USA

[9]Imperial College Healthcare NHS Trust, London, UK

[10]Bern University Hospital, Bern, Switzerland

[11]Research Institute, McGill University Health Centre, Montreal, Quebec, Canada

[12]Queen's University, Kingston, Ontario, Canada

Correspondence
Giada Sebastiani, Division of Gastroenterology and Hepatology, Chronic Viral Illness Service, Royal Victoria Hospital, McGill University Health Center, 1001 Décarie Blvd. Montreal, QC H4A 3J1, Canada.
Email: giada.sebastiani@mcgill.ca

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Abstract

Background and Aims: People living with HIV (PLWH) are at high risk for advanced chronic liver disease and related adverse outcomes. We aimed to validate the prognostic value of non-invasive scores based on liver stiffness measurement (LSM) and on markers of portal hypertension (PH), namely platelets and spleen diameter, in PLWH.

Methods: We combined data from eight international cohorts of PLWH with available non-invasive scores, including LSM and the composite biomarkers liver

Abbreviations: ALT, alanine aminotransferase; AUROC, area under the receiving operating curve; cACLD, compensated advanced chronic liver disease; CAP, controlled attenuation parameter; CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; LPR, LSM-to-Platelet ratio; LSM, liver stiffness measurement; LSPS, liver stiffness-spleen size-to-platelet ratio score; MAFLD, metabolic dysfunction-associated fatty liver disease; NPV, negative predictive value; PH, portal hypertension; PLWH, people living with HIV; PPV, positive predictive value; PY, person-years; VCTE, vibration-controlled transient elastography.

Amine Benmassaoud, Juan Macias, Sahar Saeed, and Giada Sebastiani equally contributed to this work.

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stiffness-spleen size-to-platelet ratio score (LSPS), LSM-to-Platelet ratio (LPR) and PH risk score. Incidence and predictors of all-cause mortality, any liver-related event and classical hepatic decompensation were determined by survival analysis, controlling for competing risks for the latter two. Non-invasive scores were assessed and compared using area under the receiver operating curve (AUROC).

Results: We included 1695 PLWH (66.8% coinfected with hepatitis C virus). During a median follow-up of 4.7 (interquartile range 2.8–7.7) years, the incidence rates of any liver-related event, all-cause mortality and hepatic decompensation were 13.7 per 1000 persons-year (PY) (95% confidence interval [CI], 11.4–16.3), 13.8 per 1000 PY (95% CI, 11.6–16.4) and 9.9 per 1000 PY (95% CI, 8.1–12.2), respectively. The AUROC of LSM was similar to that of the composite biomarkers, ranging between 0.83 and 0.86 for any liver-related event, 0.79–0.85 for all-cause mortality and 0.87–0.88 for classical hepatic decompensation. All individual non-invasive scores remained independent predictors of clinical outcomes in multivariable analysis.

Conclusions: Non-invasive scores based on LSM, spleen diameter and platelets predict clinical outcomes in PLWH. Composite biomarkers do not achieve higher prognostic performance compared to LSM alone.

KEYWORDS
fibrosis biomarkers, liver-related events, mortality, people living with HIV, portal hypertension

1 | INTRODUCTION

Liver disease is among the leading causes of non-AIDS-related morbidity and mortality in people living with the human immunodeficiency virus (HIV).[1] Complications related to liver disease and portal hypertension (PH) such as ascites formation, variceal bleeding, and hepatic encephalopathy can occur through two distinct pathways in people living with HIV (PLWH).[2,3] The most common pathway emerges in the setting of advanced liver fibrosis and cirrhosis driven by traditional risk factors such as co-infections with the hepatitis C virus (HCV) and hepatitis B (HBV), alcohol abuse, and metabolic dysfunction-associated fatty liver disease (MAFLD).[2,4] MAFLD is a new definition of fatty liver not requiring the exclusion of secondary causes of liver diseases and it may coexist with HCV and HBV.[5] The second pathway develops in the setting of porto-sinusoidal vascular disorder and mitochondrial toxicity, with risk factors including exposure to didanosine, stavudine and zalcitabine, the direct effect of HIV itself, obliterative portal venopathy, and nodular regenerative hyperplasia.[3,6,7] This distinction is important as liver morphology on imaging can be normal, while subtle features of PH such as splenomegaly and/or thrombocytopenia are present.[8] Due to the high prevalence of liver disease in PLWH and the accelerated progression of liver fibrosis, it is imperative to improve the early identification of those at the highest risk of mortality and liver-related complications and initiate appropriate surveillance and preventative interventions.[9–11]

Key points

HIV-infected patients are at high risk for advanced chronic liver disease and portal hypertension. Non-invasive scores based on liver stiffness, spleen diameter and platelets predict clinical outcomes in people living with HIV. Composite biomarkers do not achieve higher prognostic performance compared to liver stiffness alone.

Liver stiffness measurement (LSM) by vibration-controlled transient elastography (TE) is a non-invasive tool that can diagnose advanced liver fibrosis and predict the occurrence of hepatic decompensation and all-cause mortality.[12,13] According to the Baveno VII consensus, LSM ≥ 10 kPa is highly suggestive of compensated advanced chronic liver disease (cACLD), while LSM < 15 kPa and normal platelet count rules-out clinically significant PH and presents with a negligible risk of decompensation.[14,15] Although LSM alone may be useful in PLWH who develop liver-related complications through the classical pathway of fibrosis, it may have suboptimal accuracy in individuals with porto-sinusoidal vascular disorder.[7,16–18] Moreover, LSM cut-off values may be aetiology-specific in PLWH.[19–21] Non-invasive scores such as the Liver Stiffness-Spleen size-to-Platelet ratio Score (LSPS), the LSM-to-Platelet ratio (LPR) and the PH risk score include platelet count and spleen size in combination with LSM. LSM, LSPS

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and PH risk score predict mortality, hepatic decompensation and the presence of clinically significant PH in patients with cACLD, with areas under the receiving operating curve (AUROC) of 0.90, 0.91, 0.93, respectively.[22] The prognostic value of non-invasive scores based on spleen diameter and platelets has not been validated and compared to LSM in PLWH.

This study aimed to evaluate the prognostic value of non-invasive scores based on LSM and on markers of PH, namely platelets and spleen diameter, to identify PLWH at increased risk of liver-related events and all-cause mortality using data from an international cohort collaboration.

2 | PATIENTS AND METHODS

2.1 | Study design and patient population

We conducted a combined retrospective analysis of 8 prospective international cohorts of PLWH undergoing regular liver disease assessment by LSM. The combined cohort of 1695 PLWH included 427 participants from the LIVEr disease in HIV cohort in Montreal, Canada; 584 from the University of Bordeaux, France; 370 patients from the HEPAVIR-Cirrhosis Cohort from 7 hospitals in Andalusia, southern Spain; 212 participants from the Royal Free Hospital in London, UK; 54 participants from the University of Bonn, Germany; 20 patients from Imperial College Healthcare NHS Trust of London, UK; 15 patients from the University of California in San Francisco, US; and 13 patients from the University of Modena and Reggio Emilia, Italy (Table S1). We included PLWH fulfilling the following criteria: (1) >18 years old; (2) confirmed diagnosis of HIV on antiretroviral therapy; (3) at least one reliable VCTE examination; and (4) at least one-year follow-up. We excluded patients with decompensating events, liver transplantation, hepatocellular carcinoma (HCC), or who underwent transjugular intrahepatic portosystemic shunt before baseline (date of LSM).

2.2 | Clinical and biological parameters

Retrospective data on demographic, anthropometric, medical and HIV history, and liver disease information were extracted from existing clinical databases. Undetectable viral load was defined as HIV viral load <50 copies/mL. The upper limit of normal for alanine aminotransferase (ALT) was defined as <45 international units per litre.

2.3 | VCTE examination and non-invasive scores

VCTE examination (Echosens, Paris, France) was performed on a 3-hour fasting patient by an experienced operator at each centre following standard operating procedure.[23] A LSM ≥ 10 kPa and a LSM ≥ 15 kPa were considered suggestive and highly suggestive of cACLD, respectively, while hepatic steatosis was defined as controlled attenuation parameter (CAP) ≥248 dB/m.[14,20,24] Non-invasive scores were calculated as previously described: LPR score, LSM/platelet count × 100; LSPS score, LSM × spleen diameter [cm]/platelet count; PH risk score, −5.953 + 0.188 × LSM + 1.583 × sex [1:male, 0:female] + 26.705 × spleen diameter [cm]/platelet count).[22,25] Higher scores suggested the presence of clinically significant PH.

2.4 | Outcome measures

The primary outcome of interest was the development of any new liver-related event during follow-up, defined as the occurrence of any among a classical hepatic decompensation event, HCC, liver transplantation, or liver-related death. Secondary outcomes of interest included: (i) all-cause mortality; (ii) development of classical hepatic decompensation, defined by the presence of de novo clinically significant ascites, variceal bleeding or overt hepatic encephalopathy (West Haven Grade ≥ II).[26,27] Incident HCC, liver transplantation or death could occur in individuals that did not have hepatic decompensation. Individuals that underwent liver transplantation were censored as alive at the date of their liver transplantation. The time to hepatic decompensation, HCC, liver transplantation, death, and last medical visit were recorded.

2.5 | Statistical methods

The baseline (time zero) was defined as the date of their first LSM after 1 January 2012. Each centre's database was examined from its inception until administrative censoring at the end of 2021. We employed AUROCs to calculate the optimal cut-off by Youden's index for predicting our primary and secondary outcomes of interest by LSM, LPR, LSPS and PH risk score. Prognostic performance was assessed by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), percentage of missed clinical events, along with confidence intervals (CI). To validate the cut-offs in PLWH, a validation set of data was randomly generated for 50% of the sample using a simulation method with 1000 replications, not restricted (or) stratified on any of the outcome/exposure variables (in the random selection). We also conducted a sensitivity analysis to estimate the prognostic performance of the non-invasive scores in patients monoinfected with HIV without viral hepatitis coinfection and in obese PLWH. Discrimination, calibration and changes in reclassification were compared between Model 1 (selected clinical predictors + LSM), Model 2 (selected clinical predictors + LPR), Model 3 (selected clinical predictors + LSPS) and Model 4 (selected clinical predictors + PH risk score) for predicting 10 years risk of the different outcomes. Discrimination was measured with a weighted[28] Harrell's C or concordance index using Stata command–somersd- with a robust jackknife estimator for standard errors.[29] A C-index value of 1 indicates perfect discrimination, while 0.5 means no better than random guessing. Calibration was assessed statistically

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(Hosmer-Lemeshow statistic and the Gronnesby and Borgan test).[30] Incidence rates of any liver-related event, all-cause mortality and classical hepatic decompensation were estimated by dividing the number of participants developing the outcome by the number of person-years (PY) of follow-up and reported as units per 1000 PY with a 95% CI. Incidence count models were used to calculate CIs for incidence rates. Kaplan–Meier plots and log-rank tests were used to illustrate time to outcomes by category of the non-invasive scores according to the cut-off identified by the AUROC analysis. The association between predictors and liver-related events was assessed using univariable and multivariable Cox proportional hazards regression models and reported as hazard ratio (HR) with 95% CI. A priori we selected individual predictors of liver-related events based on clinical relevance. To address the issue of type-1 error, we added false discovery rates to the models. None of the associations were changed. The Fine and Grey method was used to control for competing risks for the outcomes of any liver-related and classical hepatic decompensation. A two-sided level of significance of 0.05 was used. Statistical analyses were performed using STATA 17 (STATA Corp. LP, College Station, Texas, USA).

3 | RESULTS

The baseline characteristics of the whole cohort comprising 1695 PLWH are summarized in Table 1. The XL probe was used in 52 (3%) patients. Overall, 50 patients were excluded for failure or unreliable VCTE, corresponding to a failure rate of 2.9%, which is in line with other studies where XL probe was available. The reasons that caused the failure of VCTE were morbid obesity in 30 patients and marked elevation of ALT (>6× the upper limit of normal) in 20 patients. Overall, the median age was 48 years, and most participants were male and of white ethnicity. The mean number of alcoholic drinks per week was 10. Most PLWH had undetectable HIV viral load. Two hundred sixty-six (16%) patients were overweight (BMI 25–29 kg/m^2), and 128 (8%) were obese (BMI > 30 kg/m^2). ALT was within the upper limit of normal in 755 (45%). The prevalence of cACLD by LSM ≥ 10 kPa and ≥15 kPa was 39% and 28%, respectively, while hepatic steatosis was present in 43% of the subgroup of 647 PLWH with available CAP.

3.1 | Incidence and risk factors of any liver-related event, all-cause mortality and classical hepatic decompensation

During a median follow-up period of 4.7 (interquartile range 2.8–7.7) years, with a 1–17 years range, there was a total of 185 events (Table 2). Classical hepatic decompensation events were the most frequent liver-related events, with ascites being the most common hepatic decompensation event, followed by HCC. The cumulative incidence of any liver-related event, all-cause mortality and classical hepatic decompensation in HIV monoinfected patients vs. HIV/HCV coinfected patients was 2.6% vs. 9%, 1.4% vs. 10%, 2.1 vs. 6.5%, respectively. Compared to patients who did not develop a liver-related event, those who developed it had lower BMI and lower CD4 cell count, longer duration of HIV infection and were less likely to have an undetectable HIV viral load (Table 1). Those who developed any liver-related event also had higher creatinine and lower total cholesterol. They had an abnormal liver profile, including lower albumin and platelets, higher bilirubin, INR and liver transaminases. Historical exposure to didanosine and stavudine was longer in PLWH who developed liver-related events. Finally, spleen diameter was larger and CAP was lower in PLWH who developed any liver-related event. All the baseline non-invasive scores were significantly higher in PLWH who developed clinical outcomes, including any liver-related event, all-cause mortality and classical hepatic decompensation (Table 3).

3.2 | Performance of non-invasive scores to predict any liver-related event, classical hepatic decompensation and all-cause mortality

All non-invasive scores had good AUROCs to predict the occurrence of any liver-related event, ranging between 0.83 and 0.86 (Figure 1). Along the same lines, the non-invasive scores had good performance in predicting all-cause mortality and hepatic decompensation (Table 4). Table 4 reports the optimal cut-offs to predict the outcomes for each non-invasive score, with associated sensitivity, specificity, PPV and NPV. These figures were confirmed in both the whole and the validation cohorts for all non-invasive scores. Moreover, the discrimination and calibration tests showed that there were no significant deviations by observed risk from subgroups of predicted risk estimates, regardless of the number or location of cut-offs (Table 5). Since LSM can overestimate fibrosis and PH in obese patients, we conducted a sensitivity analysis in the subgroup of PLWH with BMI > 30 Kg/m^2.[31] We found that the performance of the LSM-based scores was similar in obese vs. non-obese PLWH (data not shown). In the sensitivity analysis conducted in HIV monoinfected patients, we found that the prognostic performance of all non-invasive scores was excellent and similar to the whole study cohort (Table S2). Interestingly, in HIV monoinfected patients LSM (AUROC 0.84, 95% CI 0.75–0.94) had a lower performance for any liver-related event than LPR (AUROC 0.93, 95% CI 0.87–0.98; $p = 0.006$). Figures 2, S1 and S2 report the Kaplan Meier curves depicting the incidence of any liver-related event, all-cause mortality and classical hepatic decompensation, respectively, stratified by the optimal cut-off values of each non-invasive score identified by the AUROC analysis in the whole cohort. Non-invasive models at optimal cut-offs were associated with the occurrence of any liver-related event after adjusting for age, biological sex, diabetes, detectable HIV viral load, coinfection with viral hepatitis, platelets and ALT (Table 6). All the individual non-invasive scores were also independently associated with all-cause mortality in Cox regression analysis (Table S3). Finally, all the non-invasive scores at optimal cut-offs were independently associated with classical hepatic decompensation in Cox

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TABLE 1 Baseline characteristics of the cohort by outcome status (development of any liver-related event) at the end of follow-up ($n = 1695$).

	Whole cohort ($n = 1695$)	Developed liver event ($n = 121$)	Not developed liver event ($n = 1574$)	p-value
Age (years)	47.7 (42.8–53)	47.8 (42.9–52.1)	47.6 (42.8–53)	0.908
Male sex (%)	1311 (77.4)	97 (80.2)	1214 (77.1)	0.437
Ethnicity (%)				
White	526/724 (72.7)	16/22 (72.7)	510/702 (72.6)	<0.001
Black	143/724 (19.8)	3/22 (13.6)	140/702 (19.9)	
Infection type (%)				
HIV monoinfection	422 (24.9)	11 (9.1)	411 (26.1)	<0.001
HCV coinfection	1133 (66.9)	102 (84.3)	1031 (65.5)	
HBV coinfection	75 (4.4)	4 (3.3)	71 (4.5)	
HBV/HCV coinfection	65 (3.8)	4 (3.3)	61 (3.9)	
Routes of transmission (%)				
IDU	746 (48.4)	29 (25.2)	717 (50.2)	0.278
MSM	308 (18.2)	7 (5.8)	301 (19.3)	
Alcoholic drinks (number per week)	0 (0–7)	0 (0–10)	0 (0–7)	0.431
Hypertension (%)	246 (14.5)	21 (17.4)	225 (14.3)	0.794
Diabetes (%)	161 (9.5)	19 (15.7)	142 (9.0)	0.199
Duration of HIV infection (years)	18 (10.7–25)	21.1 (15.6–26.7)	17.7 (10.1–24.9)	0.001
Undetectable HIV viral load (≤50 copies) (%)	1218 (71.9)	70 (57.9)	1148 (72.9)	<0.001
HCV patients with sustained virological response (% out of 1133)	480 (42.4)	19 (15.7)	461 (44.2)	<0.001
BMI (Kg/m^2)	23.5 (20.9–26.8)	22.1 (19.7–24.2)	23.7 (21–26.9)	0.001
CD4 (cell/μL)	511 (332–734)	341 (206–550)	524 (347–743)	<0.001
Creatinine (mmol/L)	76 (65.0–88.8)	71 (59.2–83.1)	76 (65.4–89.0)	0.002
Platelets (10^9/L)	186 (137–234)	109 (84–165)	190 (144–237)	<0.001
INR	1.02 (1.00–1.10)	1.12 (1.03–1.21)	1.01 (1.00–1.09)	<0.001
Albumin (g/L)	42.5 (39.5–45.0)	38 (34.0–41.5)	43.0 (40.0–45.3)	<0.001
Bilirubin (μmol/L)	11 (8–17.1)	18.64 (12–29.1)	11 (8–16)	<0.001
ALT (IU/L)	50 (30–86)	62 (35–94)	48 (29–85)	0.013
AST (IU/L)	44 (29–70)	76 (49–110)	42 (29–67)	<0.001
Total cholesterol (mmol/L)	4.5 (3.9–5.3)	4.0 (3.3–4.8)	4.6 (3.9–5.3)	<0.001
HDL cholesterol (mmol/L)	1.2 (0.9–1.4)	1.1 (0.8–1.6)	1.2 (1.0–1.4)	0.496
Triglycerides (mmol/L)	1.5 (1.0–2.2)	1.1 (0.9–1.8)	1.5 (1.0–2.2)	0.014
Spleen diameter (cm)	11.6 (10–13.6)	13.25 (12–16.5)	11.5 (10–13.4)	<0.001
Current antiretroviral regimen (%)				
NNRTI	229 (31.6)	5 (22.7)	224 (31.9)	0.476
NRTI	631 (85.0)	19 (86.4)	612 (85.0)	0.846
Protease inhibitors	305 (42.1)	14 (63.6)	291 (41.5)	0.029
Integrase inhibitors	249 (33.6)	9 (39.7)	240 (33.3)	0.459
Total didanosine exposure (mean months, SD)	5.41 (18.3)	27.56 (39.2)	4.63 (16.6)	<0.001
Total stavudine exposure (mean months, SD)	11.14 (26.4)	25.48 (32.5)	10.64 (26.1)	0.002
CAP (dB/m)	238 (202–281)	217 (172–270)	238 (202–283)	0.105

Note: Continuous variables are expressed as median (interquartile range) and categorical variables are expressed as frequencies (%), unless otherwise indicated. The p-values refer to rank-sum tests or χ^2 test between "developed liver event" and "not developed liver event". Data on ethnicity was available for 724 patients. Data on IDU and MSM was available for 1543 and 1550 patients, respectively. Data on time since HIV diagnosis was available for 1114 patients. BMI was available in 1095 patients. Spleen diameter was available for 544 patients. Data on antiretroviral therapy was available for 742 patients. CAP was available for 647 patients.

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; HIV, human immunodeficiency virus; IDU, injection drug use; INR, international normalized ratio; IU, international units; MSM, men having sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PH, portal hypertension; SD, standard deviation.

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TABLE 2 Incidence of any liver-related event, all-cause mortality and classical hepatic decompensation in the whole cohort ($n = 1695$).

	Cases	Incidence rate (per 1000 PY, 95% CI)
Any event	185	20.88 (18.07–24.09)
Any liver event	121	13.66 (11.42–16.32)
All-cause mortality	127	13.83 (11.63–16.43)
Hepatic decompensation	88	9.94 (8.07–12.23)
Ascites	77	8.64 (6.91–10.79)
Hepatic encephalopathy	28	3.08 (2.13–4.46)
Variceal bleeding	23	2.54 (1.69–3.82)
Hepatocellular carcinoma	28	3.08 (2.13–4.46)

Abbreviations: CI, confidence interval; PY, person-year.

regression analysis after adjustments (Table S4). Additionally, in a competing risk analysis, LSM (adjusted HR 13.02, 95% CI 2.35–71.98) and platelet count (adjusted HR 0.13, 95% CI 0.02–0.82) remained independent predictors of hepatic decompensation in the LSM-based model. For all investigated outcomes, there was a progressive increase in HR according to the LSM quartiles (Table S5).

4 | DISCUSSION

The burden of chronic liver diseases and complications related to PH is steadily increasing in ageing PLWH. In recognition of the significant impact of liver diseases in natural history and prognosis of HIV infection, guidelines from the European AIDS Clinical Society recommend screening and risk stratification for liver fibrosis in PLWH with or

TABLE 3 Baseline non-invasive scores values by secondary outcomes status (classical hepatic decompensation and all-cause mortality) ($n = 1695$).

		Any liver-related event		All-cause mortality		Classical hepatic decompensation	
		Developed	Not developed	Developed	Not developed	Developed	Not developed
LSM (kPa)	7.4 (5.1–16)	25.7 (15.9–42.0)	6.9 (5.0–14.5)	20.0 (13.6–32.7)	6.9 (5.0–14.6)	28.7 (18.0–47.6)	7.1 (5.1–14.7)
LPR	3.8 (2.3–11.1)	22.5 (11.0–48.0)	3.5 (2.3–9.0)	17.0 (8.8–34.2)	3.5 (2.3–9.2)	28.1 (13.6–52.9)	3.6 (2.3–9.7)
LSPS	0.5 (0.3–1.6)	3.7 (1.2–6.6)	0.41 (0.2–1.4)	3.0 (1.5–5.4)	0.4 (0.2–1.3)	3.79 (1.6–6.9)	0.4 (0.2–1.4)
PH risk score	−1.3 (−2.2–1.4)	5.1 (0.6–7.0)	−1.5 (−2.2–0.8)	3.9 (1.5–6.4)	−1.5 (−2.2–0.8)	5.3 (2.1–7.5)	−1.4 (−2.2–0.9)

Note: Continuous variables are expressed as median (interquartile range). LPR and LSPS were available for 544 patients.

Abbreviations: LPR, LSM to platelet ratio; LSM, liver stiffness measurement; LSPS, LSM-spleen diameter to platelet ratio; PH, portal hypertension.

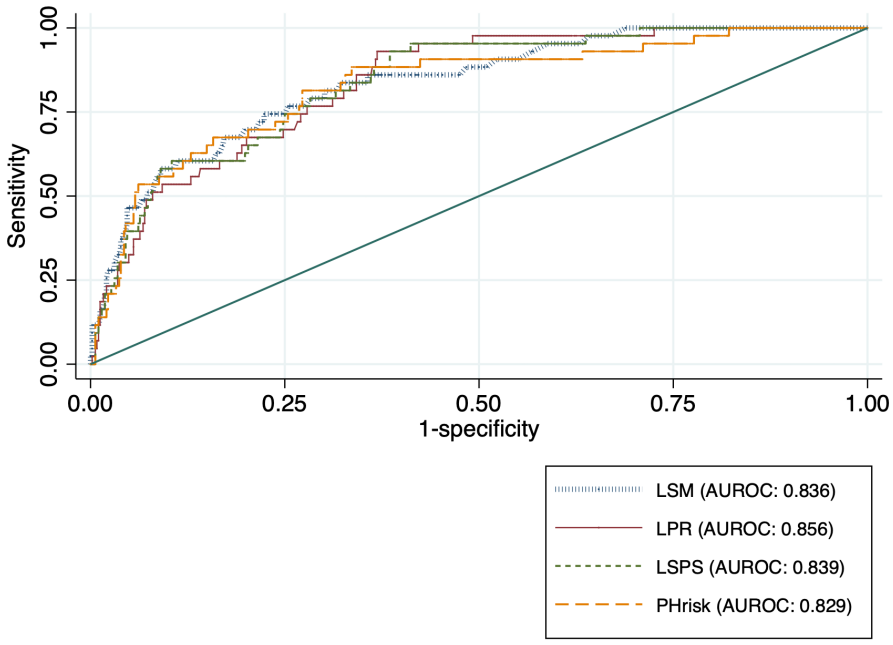

FIGURE 1 Area under the receiver operating characteristics (AUROC) of liver stiffness measurement (LSM), LSM to platelet ratio (LPR), LSM-spleen diameter to platelet ratio (LSPS) and portal hypertension (PH) risk score to predict any liver-related event.

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TABLE 4 Empirical cut-off by Lui of non-invasive tests identified through AUROC analysis for prediction of outcomes in the whole cohort ($n = 1695$) and in the validation cohort ($n = 847$).

	AUROC (95% CI)	Identified cut-off	Sensitivity	Specificity	PPV	NPV
Any liver-related event						
Whole cohort						
LSM (kPa)	0.84 (0.81–0.88)	11.75	0.87	0.63	0.18	0.98
LPR	0.86 (0.83–0.89)	8.62	0.83	0.74	0.20	0.98
LSPS	0.84 (0.78–0.89)	0.61	0.73	0.61	0.18	0.99
PH risk score	0.83 (0.76–0.90)	0.55	0.81	0.73	0.21	0.98
Validation cohort						
LSM (kPa)	0.85 (0.81–0.90)	11.75	0.89	0.69	0.15	0.99
LPR	0.86 (0.81–0.90)	8.62	0.83	0.74	0.16	0.98
LSPS	0.84 (0.74–0.94)	0.61	0.94	0.60	0.14	0.99
PH risk score	0.86 (0.75–0.95)	0.55	0.81	0.70	0.13	0.99
All-cause mortality						
Whole cohort						
LSM (kPa)	0.79 (0.75–0.83)	10.85	0.82	0.67	0.17	0.97
LPR	0.80 (0.76–0.84)	8.62	0.76	0.74	0.19	0.97
LSPS	0.85 (0.81–0.89)	0.88	0.91	0.67	0.18	0.99
PH risk score	0.85 (0.81–0.90)	0.55	0.87	0.73	0.23	0.98
Validation cohort						
LSM (kPa)	0.81 (0.75–0.86)	10.85	0.79	0.74	0.18	0.98
LPR	0.80 (0.75–0.86)	8.62	0.77	0.74	0.20	0.97
LSPS	0.86 (0.80–0.92)	0.88	0.91	0.68	0.21	0.99
PH risk score	0.86 (0.79–0.93)	0.55	0.79	0.78	0.19	0.99
Classical hepatic decompensation						
Whole cohort						
LSM (kPa)	0.87 (0.84–0.91)	15.80	0.84	0.78	0.13	0.99
LPR	0.88 (0.85–0.91)	8.62	0.90	0.73	0.16	0.99
LSPS	0.87 (0.82–0.92)	1.14	0.86	0.72	0.15	0.99
PH risk score	0.87 (0.81–0.93)	0.55	0.89	0.73	0.20	0.99
Validation cohort						
LSM (kPa)	0.93 (0.88–0.98)	15.80	0.88	0.79	0.14	0.99
LPR	0.92 (0.85–0.98)	8.62	0.55	0.93	0.12	0.99
LSPS	0.91 (0.81–0.99)	1.14	0.85	0.68	0.13	0.99
PH risk score	0.91 (0.82–0.99)	0.55	0.78	0.76	0.11	0.99

Note: LPR and LSPS were available for 544 patients.

Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; LPR, LSM to platelet ratio; LSM, liver stiffness measurement; LSPS, LSM-spleen diameter to platelet ratio; NPV, negative predictive value; PH, portal hypertension; PPV, positive predictive value.

without viral hepatitis coinfection.[9] The identification of PLWH with cACLD and associated prognostication is of paramount importance to establish therapeutic interventions, like antiviral therapy and lifestyle modifications for MAFLD, and appropriate surveillance, including screening for HCC and endoscopic signs of PH.[32,33] However, longitudinal studies investigating natural history and prognostic scores for liver diseases in the specific setting of HIV infection are limited, particularly in cohorts including HIV monoinfected patients. Besides, cut-off values of prognostic scores have not been specifically validated in PLWH. The present study confirms that, in individuals with well-controlled HIV infection, non-invasive scores based on LSM, spleen diameter and platelets predict clinical outcomes in PLWH. Thus, even in this population, thrombocytopenia and splenomegaly should trigger an evaluation of liver disease severity and PH. Additionally, we found that composite biomarkers including platelets and spleen did not achieve higher prognostic performance compared to LSM alone.

The close interplay between HIV and other causes of liver injury contributes to the development of cACLD and ultimately

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TABLE 5 Predictive accuracy of non-invasive markers for the primary and the secondary outcomes in the whole cohort ($n = 1695$) and validation cohort ($n = 847$).

	Whole cohort				Validation cohort			
	Model-1	Model-2	Model-3	Model-4	Model-1	Model-2	Model-3	Model-4
Any liver-related event								
Discrimination (Herrel's C index, 95% CI)	0.81 (0.77–0.85)	0.79 (0.74–0.83)	0.80 (0.72–0.88)	0.81 (0.73–0.89)	0.83 (0.77–0.88)	0.81 (0.74–0.86)	0.80 (0.68–0.92)	0.82 (0.70–0.94)
Calibration (*p*-value)								
Hosmer-Lemeshow	0.96	0.42	0.77	0.09	0.43	0.15	0.59	0.07
Gronnesby and Borgan test	0.35	0.73	0.60	0.58	0.32	0.15	0.75	0.17
All-cause mortality								
Discrimination (Herrel's C index, 95% CI)	0.82 (0.78–0.88)	0.81 (0.77–0.85)	0.90 (0.86–0.96)	0.88 (0.83–0.94)	0.83 (0.77–0.88)	0.83 (0.77–0.88)	0.93 (0.89–0.98)	0.92 (0.86–0.98)
Calibration (*p*-value)								
Hosmer-Lemeshow	0.93	0.81	0.98	0.97	0.75	0.65	0.98	0.36
Gronnesby and Borgan test	0.34	0.19	0.13	0.35	0.12	0.16	0.14	0.53
Classical hepatic decompensation								
Discrimination (Herrel's C index, 95% CI)	0.87 (0.83–0.93)	0.85 (0.81–0.89)	0.83 (0.76–0.91)	0.84 (0.77–0.91)	0.88 (0.82–0.93)	0.87 (0.81–0.93)	0.88 (0.80–0.96)	0.89 (0.80–0.98)
Calibration (*p*-value)								
Hosmer-Lemeshow	0.98	0.11	0.49	0.05	0.74	0.57	0.99	0.01
Gronnesby and Borgan test	0.77	0.15	0.25	0.37	0.07	0.88	0.15	0.17

Note: LPR and LSPS were available for 544 patients. Model-1: LSM, age, biological sex, presence of diabetes, presence of detectable HIV viral load, ALT, viral hepatitis co-infection status, and platelet count; Model-2: LPR, age, biological sex, presence of diabetes, presence of detectable HIV viral load, ALT, viral hepatitis co-infection status; Model-3: LSPS, age, biological sex, presence of diabetes, presence of detectable HIV viral load, ALT, viral hepatitis co-infection status; Model-4: PH risk score, age, biological sex, presence of diabetes, presence of detectable HIV viral load, ALT, viral hepatitis co-infection status. Hosmer-Lemeshow is meant for logistic regression-based prediction. For the Gronnesby and Borgan test, tertiles threshold were used for the statistical tests.

Abbreviations: ALT, alanine aminotransferase; LPR, LSM to platelet ratio; LSM, liver stiffness measurement; LSPS, LSM-spleen diameter to platelet ratio; PH, portal hypertension.

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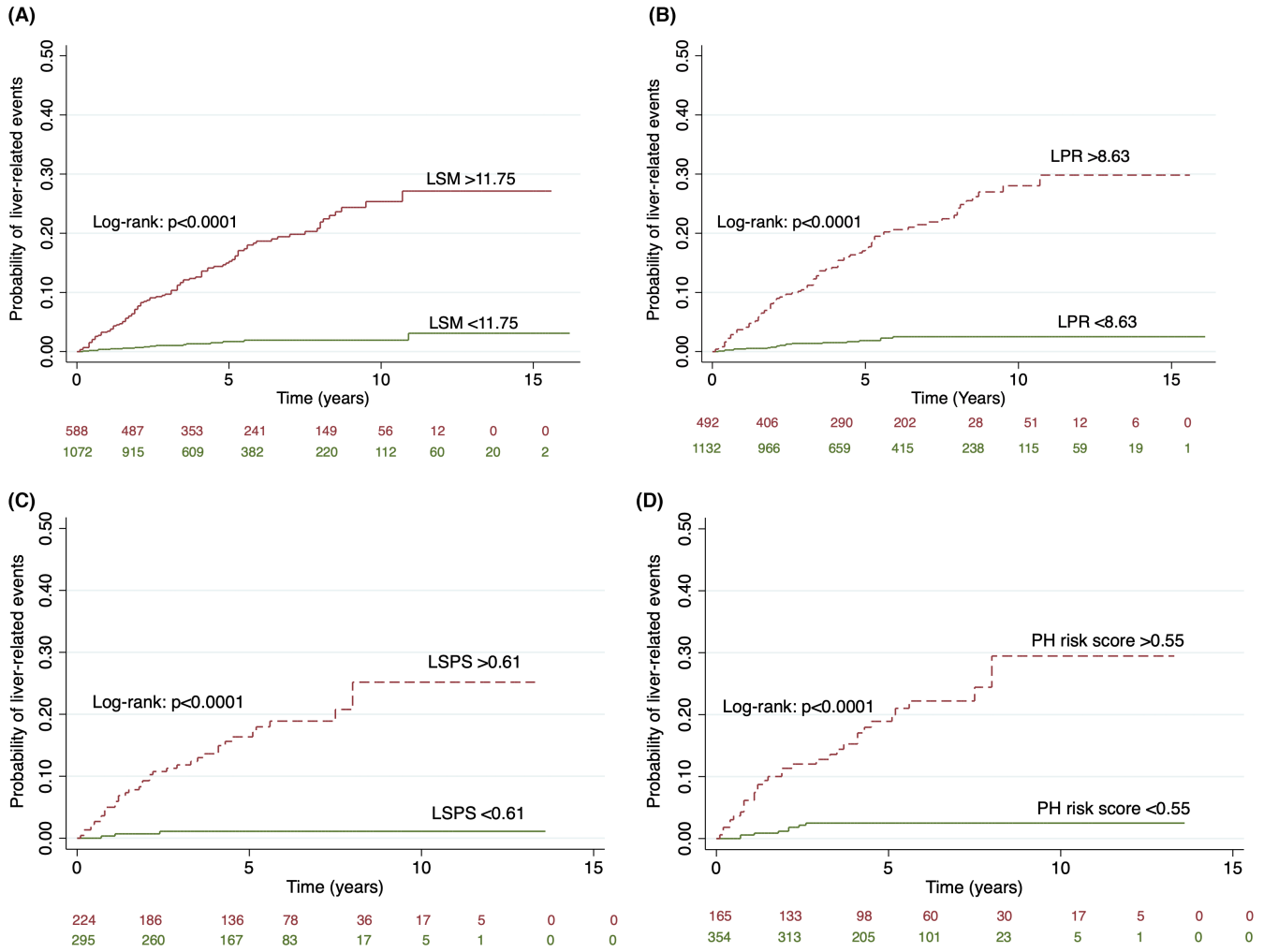

FIGURE 2 Survival curves of incidence of any liver-related event by cut-off of: (A) liver stiffness measurement (LSM); (B) LSM to platelet ratio (LPR); (C) LSM-spleen diameter to platelet ratio (LSPS); (D) portal hypertension (PH) risk score. The *p*-values refer to log-rank test.

complications related to PH such as ascites formation, variceal bleeding and hepatic encephalopathy.[3] Until recently, screening for liver disease severity and PH could not be applied at a population level due to the invasive nature of the available tests, including liver biopsy and measurement of hepatic venous pressure gradient. With the advent of LSM, non-invasive scores have been proposed to identify patients with chronic liver disease at higher risk of clinical outcomes.[12,34] The recent Baveno VII consensus proposed the clinically relevant cut-off value of 10 kPa to rule out cACLD. Moreover, LSM values >15 kPa are highly suggestive of cACLD.[14] Before our study, a knowledge gap existed in the prognostication and risk stratification necessary for the care of PLWH: scores incorporating features of PH, such as platelet count and spleen size combined with LSM, had not been validated and compared to LSM alone in this population.

In our study of 1695 patients and a median follow-up of 4.7 years, PLWH had a significant risk of developing any liver-related event and classical hepatic decompensation, with ascites being the most common event. Previous literature suggested this finding, however, it was either focused on PLWH coinfected with HBV and HCV or had a shorter follow-up period.[18,19,35,36] Our study shows that also HIV monoinfected patients have a significant risk of clinical outcomes, particularly liver-related events. Despite being at risk of hepatic decompensation and HCC, PLWH are often diagnosed at more advanced stages.[37] The limited validation of non-invasive prognostic scores in PLWH might contribute to the lower uptake of surveillance. A challenge specific to PLWH is that clinical markers of PH may be more frequent in the setting of HIV infection and can be due to non-liver-related diseases, including infectious and malignant conditions. Splenomegaly and thrombocytopenia are common clinical findings in PLWH, documented in up to 66% and 35% of cases, respectively.[38,39] The differential diagnosis ranges from other co-incidental viral and parasitic infections to haematological and infiltrative diseases, to PH.[40] In our study, we determined that non-invasive scores based on spleen diameter and/or platelets, namely LPR, LSPS, and PH risk score, have excellent discriminatory capacity to predict the occurrence of any liver-related event, all-cause mortality and classical hepatic decompensation. However, the addition of spleen and/or platelets to LSM did not increase the prognostic performance compared to LSM alone. Porto-sinusoidal vascular disorder may be a relevant contributor to hepatic decompensation in HIV monoinfected patients, which may not be detected by LSM. Since presinusoidal PH may only be detected by platelets, splenomegaly and derived scores, this could

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TABLE 6 Predictors of any liver-related event in univariable and multivariable Cox regression analysis ($n = 1695$).

	Unadjusted model		Adjusted model		
LSM model	**HR (95% CI)**	***p*-value**	**aHR (95% CI)**	***p*-value**	**False discovery rate**
LSM > 11.75 kPa (yes vs no)	11.14 (6.57–18.89)	<0.0001	6.28 (3.26–12.10)	<0.0001	<0.001
Age (per year)			1.00 (0.98–1.04)	0.60	0.933
Male sex (yes vs. no)			0.97 (0.60–1.60)	0.94	0.99
Diabetes (yes vs. no)			0.79 (0.35–1.77)	0.57	0.933
Detectable HIV viral load (yes vs. no)			1.03 (0.94–1.14)	0.51	0.933
Co-infection (yes vs. no)			0.84 (0.65–1.08)	0.17	0.575
Platelets (per log unit)			0.08 (0.03–0.18)	<0.0001	<0.0001
ALT (per IU/L)			0.99 (0.99–1.00)	0.52	0.933
LPR model	**HR (95% CI)**	***p*-value**	**aHR (95% CI)**	***p*-value**	**False discovery rate**
LPR > 8.62 (yes vs. no)	10.66 (6.57–18.89)	<0.0001	9.50 (5.44–16.58)	<0.0001	<0.0001
Age (per year)			1.01 (0.98–1.04)	0.98	0.99
Male sex (yes vs. no)			1.06 (0.65–1.74)	0.65	0.933
Diabetes (yes vs. no)			0.77 (0.36–1.67)	0.36	0.91
Detectable HIV viral load (yes vs. no)			1.04 (0.93–1.14)	0.94	0.99
Co-infection (yes vs. no)			0.97 (0.70–1.19)	0.70	0.933
ALT (per IU/L)			0.99 (0.99–1.00)	0.99	0.99
LSPS model	**HR (95% CI)**	***p*-value**	**aHR (95% CI)**	***p*-value**	**False discovery rate**
LSPS > 0.61 (yes vs. no)	16.16 (4.98–52.41)	<0.0001	5.26 (2.21–12.50)	<0.0001	<0.0001
Age (per year)			0.99 (0.94–1.04)	0.74	0.942
Male sex (yes vs. no)			0.71 (0.32–1.56)	0.39	0.91
Diabetes (yes vs. no)			0.74 (0.27–2.03)	0.56	0.933
Detectable HIV viral load (yes vs. no)			1.24 (0.85–1.82)	0.26	0.742
Co-infection (yes vs. no)			0.77(0.55–1.09)	0.14	0.56
ALT (per IU/L)			0.99 (0.99–1.00)	0.83	0.968
PH risk score model	**HR (95% CI)**	***p*-value**	**aHR (95% CI)**	***p*-value**	**False discovery rate**
PH risk score > 0.55 (yes vs. no)	8.69 (4.00–18.85)	<0.0001	7.06 (2.87–17.34)	<0.0001	<0.0001
Age (per year)			0.99 (0.94–1.04)	0.58	0.933
Diabetes (yes vs. no)			0.81 (0.29–2.22)	0.69	0.933
Detectable HIV viral load (yes vs. no)			1.25 (0.84–1.87)	0.27	0.742
Co-infection (yes vs. no)			0.77 (0.55–1.06)	0.11	0.504
ALT (per IU/L)			0.99 (0.99–1.00)	0.79	0.9593

Note: LPR and LSPS were available for 544 patients.

Abbreviations: aHR, adjusted hazard ratio; ALT, alanine aminotransferase; CI, confidence interval; HR, hazard ratio; LPR, LSM to platelet ratio; LSM, liver stiffness measurement; LSPS, LSM-spleen diameter to platelet ratio; PH, portal hypertension.

explain the higher AUROC of LPR we found in the HIV monoinfected subgroup, in whom sinusoidal PH is comparatively rare.[41] It might be worthwhile to build prospective cohorts with spleen stiffness measurement, which is a direct and dynamic marker of portal pressure and it has been shown to have excellent accuracy in predicting PH and prognosis in patients with cACLD.[42,43] For LSM, we identified in 11 kPa the optimal cut-off to predict any liver-related event, which is very close to the 10 kPa cut-off reported by Baveno VII consensus to suggest cACLD. Similarly, a cut-off of 10 kPa was identified to predict all-cause mortality. Along the same lines, we showed that 15.8 kPa is the ideal cut-off value of LSM to predict hepatic decompensation, with high sensitivity and specificity. This cut-off overlaps with the cut-off of 15 kPa reported by Baveno VII as highly suggestive of cACLD.[14] The application of LSM quartiles showed a progressive increase in specificity to detect clinical outcomes in our cohort. Thus, our study confirms the utility of LSM in this population at high

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risk for cACLD and clinical outcomes. We also identify and validate aetiology-specific cut-offs of LPR, LSPS and PH risk scores in PLWH, which are somewhat lower compared to the HIV-negative populations with chronic liver disease.[12,22]

In multivariable analysis, the non-invasive scores predicted all clinical outcomes, independently of traditional parameters such as age, diabetes and viral hepatitis coinfection status. These findings underline the emerging, relevant role of MAFLD even in patients with HIV monoinfection.[18,44] Interestingly, we did not observe a reduced performance of non-invasive scores in overweight or obese patients, as it has been instead reported in etiologies of cACLD related unrelated to HIV.[31] Lower prevalence of obesity has been reported in PLWH, particularly in HIV/HCV coinfected patients.[45]

Our study has several strengths. First, this is a collaborative effort between 8 academic centres worldwide that care for PLWH, resulting in a large international cohort of 1695 patients with a long follow-up period, ensuring the external validity of our findings. Second, it compared four non-invasive scores head-to-head in their ability to predict clinical outcomes, validating aetiology-specific cut-off values. Our study also has limitations that we wish to acknowledge. First, although our cohort is built from locally-maintained prospective databases, certain clinical variables, including spleen size, have been retrospectively collected which explains why the evaluation of LSPS and PH risk score was only available in a subset of patients. Second, as clinical events were collected retrospectively, there is always a chance that liver-related events would have been missed. However, as patients were followed at tertiary academic centres, this is probably less likely except for patient migration. In addition, we used a time-to-event analysis to mitigate this risk where individuals are censored at their last follow-up. Third, the population was heterogeneous with respect to the causes of liver damage, but this is a reflection of HIV real world: HCV coinfection may still be a driver of clinical outcomes, as there will be some patients who are treated and others who are not for the HCV. The included cohorts are from academic centres, where patients are more likely to be treated (especially since 80% of our study population are men who have sex with men, which is a predictor for direct-acting antiviral treatment). Also, even if all patients would have received antiviral treatment, it is unsure whether we would be able to see already a significant change in long-term outcomes after treatment. Fourth, our cohort might not be representative of all PLWH as these were followed in academic centres and, therefore, could include a high proportion of patients with cACLD and HCV coinfection.

In conclusion, LSM, LPR, LSPS and PH risk scores can help prognosticate PLWH based on dichotomous thresholds. LSM can be reliably used in clinical practice in this population. Splenomegaly and thrombocytopenia could still be seen as subtle indicators of liver disease in individuals with well-controlled HIV infection.[46] The cut-offs identified for LSM are similar to those reported by the Baveno VII consensus. We recommend assessment by other non-invasive scores of PH through aetiology-specific cut-offs. These non-invasive scores may help clinicians caring for individuals with HIV to identify patients at high risk of liver-related events and all-cause mortality and initiate an individualized surveillance strategy. Our data may guide clinical care, advocate for expanded access to VCTE in this population, and lead to personalized medicine approach in patients at higher risk of advanced liver disease.

AUTHOR CONTRIBUTIONS

AB and GS contributed to the conception, study design, data and interpretation of the data and first draft of the manuscript. JM contributed to the conception, study design, data and interpretation of the data. ACG, GG, JM, JKR, KVB, ET, AM, JP, LJG, ML, DK, BL, MBK, CB, FS, BS, GC, AB, KH, JAP and VDL contributed to data and interpretation of data. AVR contributed to the conception, study design, interpretation of the data and statistical analysis. SS contributed to the conception, study design, interpretation of the data and first draft of the manuscript. All authors approved the final version of the article. Part of this work has been presented at the Conference on Retroviruses and Opportunistic Infections (CROI) (US; February 2022).

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CONFLICT OF INTEREST STATEMENT

JAP reports having received consulting fees from Bristol-Myers Squibb, Abbvie, Gilead, Merck Sharp & Dome, and Janssen Cilag; he has received research support from Bristol-Myers Squibb, Abbvie and Gilead, and has received lecture fees from Abbvie, Bristol-Myers Squibb, Janssen Cilag, and Gilead. JM has been an investigator in clinical trials supported by Bristol-Myers Squibb, Gilead and Merck Sharp & Dome; he has received lectures fees from Gilead, Bristol-Myers Squibb, and Merck Sharp & Dome, and consulting fees from Bristol Myers-Squibb, Gilead, and Merck Sharp & Dome. ACG has received research funding and lecture fees from Gilead. GG received a research grant and speaker honoraria from Gilead, ViiV, MERCK and Jansen, and attended advisory boards of Gilead, ViiV and Merck. KVB has received honoraria for lectures for Virology Education and Gilead. CB has received honoraria for lectures and/or consultancies from AbbVie, Gilead, Janssen, MSD, ViiV, and funding from Dt. Leberstiftung, DZIF, Hector Stiftung, NEAT ID. ET advisory boards for Boehringer, Pfizer, NovoNordisk, Alexion and Orphalan, and acted as a speaker for NovoNordisk and Orphalan. GS has acted as a speaker for Merck, Gilead, Abbvie, NovoNordisk, Novartis and Pfizer, served

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as an advisory board member for Pfizer, Merck, NovoNordisk, Gilead and Intercept, and has received unrestricted research funding from Theratec. AB, JM, LJG, SS and FS have nothing to disclose.

DATA AVAILABILITY STATEMENT

According to stipulations of the patient consent form signed by all study participants, ethical restrictions imposed by our Institutional Ethics review boards (Institutional Ethics Review Board Biomedical B Research Ethics Board of the McGill University Health Centre), and legal restrictions imposed by Canadian law regarding clinical trials, anonymized data are available upon reasonable request. Please send data access requests to Sheldon Levy, Biomedical B (BMB) Research Ethics Board (REB) Coordinator Centre for Applied Ethics, 5100, boul. de Maisonneuve Ouest, 5th floor, Office 576, Montréal, Québec, H4A 3T2, Canada.

ETHICS STATEMENT

All patients provided written informed consent for participation in the single cohorts. The Research Ethics Board of the Research Institute of the McGill University Health Centre (study code 14-182-BMD) and local ethics boards approved the study, which was conducted according to the Declaration of Helsinki. This manuscript was prepared according to the STROBE Statement checklist of items.

ORCID

Amine Benmassaoud https://orcid.org/0000-0002-0202-2276
Juan Macias https://orcid.org/0000-0002-4778-790X
Kathrin Van Bremen https://orcid.org/0000-0002-6701-1084
Emmanuel Tsochatzis https://orcid.org/0000-0001-5069-2461
Maud Lemoine https://orcid.org/0000-0002-9011-2991
Filippo Schepis https://orcid.org/0000-0001-6549-5102
Sanjay Bhagani https://orcid.org/0000-0003-2557-4337
Annalisa Berzigotti https://orcid.org/0000-0003-4562-9016
Victor De-Ledinghen https://orcid.org/0000-0001-6414-1951
Giada Sebastiani https://orcid.org/0000-0003-2655-8283

REFERENCES

1. Croxford S, Kitching A, Desai S, et al. Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort. *Lancet Public Health*. 2017;2(1):e35-e46. doi:10.1016/S2468-2667(16)30020-2
2. Rockstroh JK, Mohr R, Behrens G, Spengler U. Liver fibrosis in HIV: which role does HIV itself, long-term drug toxicities and metabolic changes play? *Curr Opin HIV AIDS*. 2014;9(4):365-370. (Research Support, Non-U.S. Gov't) (In eng). doi:10.1097/COH.0000000000000064
3. Kaspar MB, Sterling RK. Mechanisms of liver disease in patients infected with HIV. *BMJ Open Gastroenterol*. 2017;4(1):e000166. doi:10.1136/bmjgast-2017-000166
4. Lake JE, Overton T, Naggie S, et al. Expert panel review on non-alcoholic fatty liver disease in persons with human immunodeficiency virus. *Clin Gastroenterol Hepatol*. 2022;20(2):256-268. doi:10.1016/j.cgh.2020.10.018
5. Fouad Y, Lazarus JV, Negro F, et al. MAFLD considerations as a part of the global hepatitis C elimination effort: an international perspective. *Aliment Pharmacol Ther*. 2021;53(10):1080-1089. doi:10.1111/apt.16346
6. Vispo E, Cevik M, Rockstroh JK, et al. Genetic determinants of idiopathic noncirrhotic portal hypertension in HIV-infected patients. *Clin Infect Dis*. 2013;56(8):1117-1122. doi:10.1093/cid/cit001
7. De Gottardi A, Sempoux C, Berzigotti A. Porto-sinusoidal vascular disorder. *J Hepatol*. 2022;77(4):1124-1135. doi:10.1016/j.jhep.2022.05.033
8. Khanna R, Sarin SK. Non-cirrhotic portal hypertension—diagnosis and management. *J Hepatol*. 2014;60(2):421-441. doi:10.1016/j.jhep.2013.08.013
9. Ryom L, De Miguel R, Cotter AG, et al. Major revision version 11.0 of the European AIDS clinical society guidelines 2021. *HIV Med*. 2022;23(8):849-858. doi:10.1111/hiv.13268
10. Pembroke T, Deschenes M, Lebouche B, et al. Hepatic steatosis progresses faster in HIV mono-infected than HIV/HCV co-infected patients and is associated with liver fibrosis. *J Hepatol*. 2017;67(4):801-808. doi:10.1016/j.jhep.2017.05.011
11. Macias J, Berenguer J, Japon MA, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. *Hepatology*. 2009;50(4):1056-1063. doi:10.1002/hep.23136
12. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. *J Hepatol*. 2017;67(2):399-411. doi:10.1016/j.jhep.2017.02.003
13. Petta S, Sebastiani G, Vigano M, et al. Monitoring occurrence of liver-related events and survival by transient elastography in patients with nonalcoholic fatty liver disease and compensated advanced chronic liver disease. *Clin Gastroenterol Hepatol*. 2021;19(4):806-815 e5. doi:10.1016/j.cgh.2020.06.045
14. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VIIF. Baveno VII—renewing consensus in portal hypertension. *J Hepatol*. 2022;76(4):959-974. doi:10.1016/j.jhep.2021.12.022
15. Corma-Gomez A, Macias J, Morano L, et al. Liver stiffness-based strategies predict absence of variceal bleeding in cirrhotic hepatitis C virus-infected patients with and without human immunodeficiency virus coinfection after sustained Virological response. *Clin Infect Dis*. 2021;72(5):e96-e102. doi:10.1093/cid/ciaa1726
16. Huang R, Gao ZH, Tang A, Sebastiani G, Deschenes M. Transient elastography is an unreliable marker of liver fibrosis in patients with portal vein thrombosis. *Hepatology*. 2018;68(2):783-785. doi:10.1002/hep.29893
17. Vuppalanchi R, Mathur K, Pyko M, Samala N, Chalasani N. Liver stiffness measurements in patients with noncirrhotic portal hypertension-the devil is in the details. *Hepatology*. 2018;68(6):2438-2440. doi:10.1002/hep.30167
18. Benmassaoud A, Nitulescu R, Pembroke T, et al. Liver-related events in human immunodeficiency virus-infected persons with occult cirrhosis. *Clin Infect Dis*. 2019;69(8):1422-1430. doi:10.1093/cid/ciy1082
19. Merchante N, Rivero-Juarez A, Tellez F, et al. Liver stiffness predicts variceal bleeding in HIV/HCV-coinfected patients with compensated cirrhosis. *AIDS*. 2017;31(4):493-500. doi:10.1097/QAD.0000000000001358
20. Merchante N, Saroli Palumbo C, Mazzola G, et al. Prediction of esophageal varices by liver stiffness and platelets in persons with human immunodeficiency virus infection and compensated advanced chronic liver disease. *Clin Infect Dis*. 2020;71(11):2810-2817. doi:10.1093/cid/ciz1181
21. Lemoine M, Assoumou L, De Wit S, et al. Diagnostic accuracy of noninvasive markers of steatosis, NASH, and liver fibrosis in HIV-Monoinfected individuals at risk of nonalcoholic fatty liver disease (NAFLD): results from the ECHAM study. *J Acquir Immune Defic Syndr*. 2019;80(4):e86-e94. doi:10.1097/QAI.0000000000001936

14783231, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/liv.15605 by University Modena, Wiley Online Library on [24/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

22. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology*. 2013;144(1):102-111 e1. (Comparative Study Research Support, Non-U.S. Gov't) (In eng). doi:10.1053/j.gastro.2012.10.001
23. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156(6):1717-1730. doi:10.1053/j.gastro.2019.01.042
24. Duarte M, Ma Y, Noworolski SM, Korn N, Price JC. Controlled attenuation parameter accurately detects liver steatosis in people living with HIV. *AIDS*. 2022;36:2147-2152. doi:10.1097/QAD.0000000000003351
25. Berger A, Ravaioli F, Farcau O, et al. Including ratio of platelets to liver stiffness improves accuracy of screening for esophageal varices that require treatment. *Clin Gastroenterol Hepatol*. 2021;19(4):777-787 e17. doi:10.1016/j.cgh.2020.06.022
26. Engelmann C, Claria J, Szabo G, Bosch J, Bernardi M. Pathophysiology of decompensated cirrhosis: portal hypertension, circulatory dysfunction, inflammation, metabolism and mitochondrial dysfunction. *J Hepatol*. 2021;75(Suppl 1):S49-S66. doi:10.1016/j.jhep.2021.01.002
27. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of hepatic encephalopathy. *J Hepatol*. 2022;77(3):807-824. doi:10.1016/j.jhep.2022.06.001
28. Sanderson J, Thompson SG, White IR, Aspelund T, Pennells L. Derivation and assessment of risk prediction models using case-cohort data. *BMC Med Res Methodol*. 2013;13:113. doi:10.1186/1471-2288-13-113
29. Newsome RB. Comparing the predictive powers of survival models using Harrell's C or Somers' D. *Stata Journal*. 2010;10(3):339-358.
30. Gronnesby JK, Borgan O. A method for checking regression models in survival analysis based on the risk score. *Lifetime Data Anal*. 1996;2(4):315-328. doi:10.1007/BF00127305
31. Mendoza YP, Shengir M, Bosch J, Sebastiani G, Berzigotti A. FIB-4 improves LSM-based prediction of complications in overweight or obese patients with compensated advanced chronic liver disease. *Clin Gastroenterol Hepatol*. 2022;20(10):2396-2398 e3. doi:10.1016/j.cgh.2021.03.007
32. Eslam M, Sanyal AJ, George J, International Consensus P. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*. 2020;158(7):1999-2014 e1. doi:10.1053/j.gastro.2019.11.312
33. European Association for the Study of the Liver. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis—2021 update. *J Hepatol*. 2021;75(3):659-689. doi:10.1016/j.jhep.2021.05.025
34. Shen Y, Wu SD, Wu L, et al. The prognostic role of liver stiffness in patients with chronic liver disease: a systematic review and dose-response meta-analysis. *Hepatol Int*. 2019;13(5):560-572. doi:10.1007/s12072-019-09952-5
35. Corma-Gomez A, Macias J, Tellez F, et al. Kinetics of emergence of liver complications in hepatitis C virus infected patients and advanced fibrosis, with and without HIV-coinfection, after sustained virological response. *AIDS*. 2021;35(13):2119-2127. doi:10.1097/QAD.0000000000002959
36. Merchante N, Rivero-Juarez A, Tellez F, et al. Liver stiffness predicts clinical outcome in human immunodeficiency virus/hepatitis C virus-coinfected patients with compensated liver cirrhosis. *Hepatology*. 2012;56(1):228-238. doi:10.1002/hep.25616
37. Willemse S, Smit C, Sogni P, et al. Low compliance with hepatocellular carcinoma screening guidelines in hepatitis B/C virus co-infected HIV patients with cirrhosis. *J Viral Hepat*. 2019;26(10):1224-1228. doi:10.1111/jvh.13146
38. Furrer H, the Swiss HIV Cohort Study. Prevalence and clinical significance of splenomegaly in asymptomatic human immunodeficiency virus type 1-infected adults. *Clin Infect Dis*. 2000;30(6):943-945. doi:10.1086/313816
39. Getawa S, Aynalem M, Bayleyegn B, Adane T. The global prevalence of thrombocytopenia among HIV-infected adults: a systematic review and meta-analysis. *Int J Infect Dis*. 2021;105:495-504. doi:10.1016/j.ijid.2021.02.118
40. Pozo AL, Godfrey EM, Bowles KM. Splenomegaly: investigation, diagnosis and management. *Blood Rev*. 2009;23(3):105-111. doi:10.1016/j.blre.2008.10.001
41. Kmeid M, Liu X, Ballentine S, Lee H. Idiopathic non-cirrhotic portal hypertension and Porto-sinusoidal vascular disease: review of current data. *Gastroenterology Res*. 2021;14(2):49-65. doi:10.14740/gr1376
42. Colecchia A, Montrone L, Scaioli E, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology*. 2012;143(3):646-654. (Comparative Study) (In eng). doi:10.1053/j.gastro.2012.05.035
43. Colecchia A, Ravaioli F, Marasco G, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. *J Hepatol*. 2018;69(2):308-317. doi:10.1016/j.jhep.2018.04.023
44. Campos-Varela I, Dodge JL, Terrault NA, Brandman D, Price JC. Nonviral liver disease is the leading indication for liver transplant in the United States in persons living with human immunodeficiency virus. *Am J Transplant*. 2021;21(9):3148-3156. doi:10.1111/ajt.16569
45. Hanttu A, Kauppinen KJ, Kivela P, et al. Prevalence of obesity and disturbances in glucose homeostasis in HIV-infected subjects and general population—missed diagnoses of diabetes? *HIV Med*. 2021;22(4):244-253. doi:10.1111/hiv.13009
46. Kablawi D, Alhinai A, Wong P, Deschenes M, Sebastiani G, Benmassaoud A. Splenomegaly is a marker of advanced chronic liver disease and portal hypertension in HIV infection. *HIV Med*. 2022;24:366-371. doi:10.1111/hiv.13390

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