

Noninvasive Risk Stratification After HCV Eradication in Patients With Advanced Chronic Liver Disease

Georg Semmler ^{1,2}, Teresa Binter ¹, Karin Kozbial,¹ Philipp Schwabl ^{1,2}, Stefanie Hametner-Schreil,³ Alberto Zanetto,⁴ Sabrina Gavasso,⁵ David Chromy ^{1,2}, David J.M. Bauer ^{1,2}, Benedikt Simbrunner ^{1,2}, Bernhard Scheiner ^{1,2}, Theresa Bucsics ^{1,2}, Albert F. Stättermayer,^{1,2} Matthias Pinter ^{1,2}, Petra Steindl-Munda ¹, Rainer Schöfl,³ Francesco Paolo Russo ⁴, Paolo Simioni ⁵, Michael Trauner ¹, Peter Ferenci ¹, Thomas Reiberger ^{1,2} and Mattias Mandorfer ^{1,2}

BACKGROUND AND AIMS: Risk stratification after cure from hepatitis C virus (HCV) infection remains a clinical challenge. We investigated the predictive value of noninvasive surrogates of portal hypertension (liver stiffness measurement [LSM] by vibration-controlled transient elastography and von Willebrand factor/platelet count ratio [VITRO]) for development of hepatic decompensation and hepatocellular carcinoma in patients with pretreatment advanced chronic liver disease (ACLD) who achieved HCV cure.

APPROACH AND RESULTS: A total of 276 patients with pretreatment ACLD and information on pretreatment and post-treatment follow-up (FU)-LSM and FU-VITRO were followed for a median of 36.6 months after the end of interferon-free therapy. FU-LSM (area under the receiver operating characteristic curve [AUROC]: 0.875 [95% confidence interval [CI]: 0.796-0.954]) and FU-VITRO (AUROC: 0.925 [95% CI: 0.874-0.977]) showed an excellent predictive performance for hepatic decompensation. Both parameters provided incremental information and were significantly associated with hepatic decompensation in adjusted models. A previously proposed combined approach (FU-LSM < 12.4 kPa and/or FU-VITRO < 0.95) to rule out clinically significant portal hypertension (CSPH, hepatic venous pressure gradient ≥ 10 mm Hg) at FU assigned most

(57.3%) of the patients to the low-risk group; none of these patients developed hepatic decompensation. In contrast, in patients in whom FU-CSPH was ruled in (FU-LSM > 25.3 kPa and/or FU-VITRO > 3.3; 25.0% of patients), the risk of hepatic decompensation at 3 years following treatment was high (17.4%). Patients within the diagnostic gray-zone for FU-CSPH (17.8% of patients) had a very low risk of hepatic decompensation during FU (2.6%). The prognostic value of this algorithm was validated in an internal (n = 86) and external (n = 162) cohort.

CONCLUSION: FU-LSM/FU-VITRO are strongly and independently predictive of posttreatment hepatic decompensation in HCV-induced ACLD. An algorithm combining these noninvasive markers not only rules in or rules out FU-CSPH, but also identifies populations at negligible versus high risk for hepatic decompensation. FU-LSM/FU-VITRO are readily accessible and enable risk stratification after sustained virological response, and thus facilitate personalized management. (HEPATOLOGY 2021;73:1275-1289).

Interferon (IFN)-free therapies for chronic hepatitis C are highly effective, achieving sustained virologic response (SVR) (i.e., HCV cure) in

Abbreviations: ACLD, advanced chronic liver disease; aHR, adjusted hazard ratio; AUROC, area under the receiver operating characteristic curve; BL, baseline; cACLD, compensated ACLD; CHC, chronic hepatitis C; CI, confidence interval; CLD, chronic liver disease; CSPH, clinically significant portal hypertension; CTP, Child-Turcotte-Pugh; dACLD, decompensated ACLD; FU, follow-up; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HVP, hepatic venous pressure gradient; IFN, interferon; IQR, interquartile range; LSM, liver stiffness measurement; MELD, Model for End-Stage Liver Disease; NIT, noninvasive test; NPV, negative predictive value; NSBB, nonselective betablocker; OLT, orthotopic liver transplantation; PH, portal hypertension; PLT, platelet count; PPV, positive predictive value; SVR, sustained virologic response; VCTE, vibration-controlled transient elastography; VITRO, von Willebrand factor antigen/platelet count ratio; VWF, von Willebrand factor.

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almost all patients with advanced chronic liver disease (ACLD).⁽¹⁾ Although SVR ameliorates portal hypertension (PH) in most patients with ACLD treated with IFN-free regimens,⁽²⁻⁵⁾ a considerable proportion still remains at risk for hepatic decompensation.⁽⁶⁻⁸⁾ Thus, risk-stratification concepts to facilitate personalized follow-up (FU) in these patients are urgently needed and currently a matter of debate. Recently, we have shown that posttreatment hepatic venous pressure gradient (HVPG) predicts hepatic decompensation in patients who achieved SVR with a higher discriminatory ability, as compared with pretreatment values.⁽⁹⁾ Patients without posttreatment clinically significant PH (CSPH) (i.e., HVPG values ≤ 9 mm Hg) were protected from hepatic decompensation, whereas the risk was highest in patients with HVPG values ≥ 16 mm Hg. Because HVPG

measurement is limited by its invasiveness and restricted availability, simple noninvasive methods for risk stratification after SVR are needed to facilitate personalized management.

Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) is a well-established indicator of the presence of compensated ACLD (cACLD), CSPH, and varices needing treatment, as reflected by the Baveno VI consensus.⁽¹⁰⁾ Moreover, von Willebrand factor (VWF), a marker for endothelial dysfunction,^(11,12) has been shown to indicate the presence of CSPH in patients with compensated cirrhosis.⁽¹³⁾ In a recent study from our group,⁽¹⁴⁾ the VWF antigen/platelet count ratio (VITRO) showed a numerically better diagnostic performance for posttreatment CSPH than plasma VWF levels alone, which may be explained by the

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ARTICLE INFORMATION:

From the ¹Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; ²Vienna Hepatic Hemodynamic Laboratory, Medical University of Vienna, Vienna, Austria; ³Internal Medicine IV, Ordensklinikum Linz Barmherzige Schwestern, Linz, Austria; ⁴Gastroenterology and Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, Padua University Hospital, Padua, Italy; ⁵General Internal Medicine and Thrombotic and Hemorrhagic Diseases Unit, Department of Medicine, Padua University Hospital, Padua, Italy.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Thomas Reiberger, M.D.
Division of Gastroenterology and Hepatology
Department of Internal Medicine III
Medical University of Vienna

Währinger Gürtel 18-20
1090, Vienna, Austria
E-mail: thomas.reiberger@meduniwien.ac.at
Tel.: +43 1 40400 47440

high diagnostic accuracy of platelet count (PLT) in the post-SVR setting.⁽¹⁵⁾

Of note, the predictive value of plasma VWF levels was independent of HVPG in previous studies, indicating that its prognostic significance reaches beyond the mere association with HVPG.^(11,16) Similarly, changes in LSM have been shown to provide HVPG-independent prognostic information.⁽¹⁷⁾

However, while the prognostic value of LSM by VCTE and VWF in patients with progressive liver disease is well-established, data on their use for risk stratification after SVR are scarce. Therefore, we investigated the prognostic values of pretreatment values, changes in, and posttreatment values of LSM, PLT, VWF, and VITRO in patients with ACLD who achieved SVR to IFN-free therapies.

Patients and Methods

DERIVATION COHORT

A total of 389 patients receiving IFN-free treatment at the Medical University of Vienna with pretreatment ACLD (defined as baseline [BL] LSM \geq 10 kPa, HVPG \geq 6 mm Hg, or advanced fibrosis/cirrhosis on liver histology), who were registered in a local database, were screened for eligibility for this retrospective study based on prospectively collected data (Fig. 1). Sixteen patients were excluded due to concomitant hepatocellular carcinoma (HCC), 1 patient was diagnosed with

porto-sinusoidal vascular disease, 1 patient underwent orthotopic liver transplantation (OLT) during treatment, and 11 patients were lost to FU. Of note, 84 patients were excluded due to missing information on either LSM or VITRO before or after the end of treatment. Finally, 276 patients were included in the derivation cohort. Of these, 80 patients with paired HVPG measurements were included in a previous study investigating the prognostic value of HVPG after SVR.⁽⁹⁾ Importantly, this study did not evaluate the prognostic performance of noninvasive markers.

INTERNAL AND EXTERNAL VALIDATION COHORTS

By querying the laboratory database of the Division of Clinical Virology of the Medical University of Vienna and applying similar inclusion and exclusion criteria (although only FU-LSM/FU-VITRO assessment was required) as in the derivation cohort, 86 additional patients were included in an internal validation cohort.

A total of 162 patients from Padua University Hospital and Ordensklinikum Linz Barmherzige Schwestern who met the inclusion and exclusion criteria of the derivation cohort were included as an external validation cohort. Some of these patients have been included in previously published studies focusing on changes in coagulation after HCV cure⁽¹⁸⁾ as well as the predictive value of VITRO for hepatic decompensation.⁽¹⁹⁾

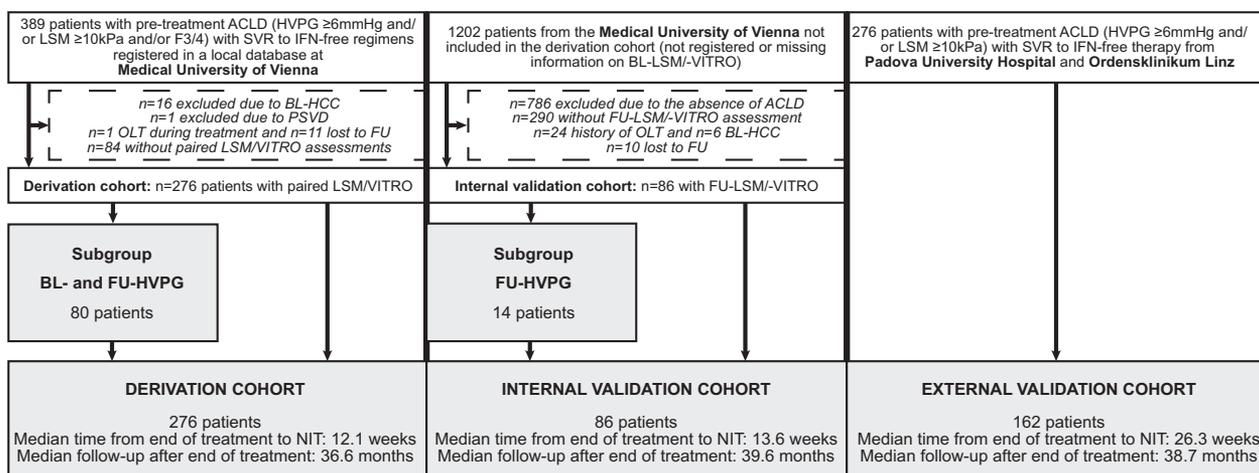


FIG. 1. Study flow chart. Abbreviation: PSVD, porto-sinusoidal vascular disease.

CLINICAL AND LABORATORY PARAMETERS

Clinical and laboratory parameters were evaluated by chart review. Plasma VWF antigen levels were measured by a latex agglutination assay (STA LIATEST VWF; Diagnostica Stago, Asnieres, France). VITRO score was calculated by dividing VWF (%) over PLT ($g \times L^{-1}$), as previously described.⁽¹⁴⁾

HCV THERAPY

All patients were treated with IFN-free therapies. The choice of the regimen was at the physicians' discretion and depended on their availability, reimbursement policies, and national as well as international clinical practice guidelines at the time of treatment initiation.⁽²⁰⁻²⁴⁾ Treatment durations ranged from 8 to 24 weeks.

LIVER STIFFNESS AND HVPG MEASUREMENT

In the derivation cohort, paired measurements of noninvasive markers, and in a subgroup of 80 patients, HVPG, were performed before antiviral therapy as well as at the end of therapy. In the internal validation cohort, noninvasive markers, and - in a subgroup of patients - HVPG, were only performed post-treatment, while in the external validation cohort, only information on noninvasive tests was available. Due to the retrospective design of this study and logistical reasons, the time points were not standardized. VCTE (FibroScan; Echosens, Paris, France) was used for LSM. HVPG measurements were performed by the Vienna Hepatic Hemodynamic Lab at the Medical University of Vienna in accordance with a standardized operating procedure⁽²⁵⁾ and in the absence of nonselective beta-blockers (NSBBs) or nitrates. In patients on NSBBs, treatment was interrupted 5 days before HVPG assessment. CSPH and high-risk PH were defined by HVPG values ≥ 10 mm Hg and ≥ 16 mm Hg, respectively.

All LSM/HVPG measurements were performed after a minimum fasting period of 4 hours.

CLINICAL EVENTS

In patients with cACLD, hepatic decompensation was defined by variceal bleeding, incident ascites, or incident hepatic encephalopathy (HE), whereas in patients with decompensated ACLD (dACLD),

further hepatic decompensation was defined by variceal (re)bleeding, requirement of paracentesis, or development of grade 3/4 HE. Moreover, *de novo* HCC, transjugular intrahepatic portosystemic shunt implantation, and OLT were recorded.

LSM-BASED AND VITRO-BASED RISK STRATIFICATION ALGORITHM

Using a previously described step-wise approach,⁽⁹⁾ patients with a LSM and/or VITRO < 12.4 kPa and < 0.95 , respectively, were assigned to the CSPH ruled-out/low-risk group, while patients with a LSM and/or VITRO > 25.3 kPa and > 3.3 , respectively, were assigned to the CSPH ruled-in/high-risk group. Patients not meeting these criteria were analyzed in the gray-zone group.

STATISTICAL ANALYSES

See the Supporting Information materials.

ETHICS

This study was approved by the ethics committee of the Medical University of Vienna (EK-Nr 1947/2019), Upper Austria (K-49-14), and Padua University Hospital (3103/A0/14). Written informed consent was obtained if the requirement was not waived by the local ethics committee.

Results

PATIENT CHARACTERISTICS OF THE DERIVATION COHORT

A total of 174 (63.0%) male and 102 (37.0%) female patients with a mean age of 56.0 ± 10.6 years were included. A total of 250 patients (90.6%) had cACLD, while 26 (9.4%) had dACLD. BL Child-Turcotte-Pugh (CTP) stage was A in 256 patients (92.8%) and B/C in 20 (7.2%). Overall, 62 patients (22.5%) had varices on gastroscopy. A BL Model for End-Stage Liver Disease (MELD) score was 8.6 ± 2.6 points, BL-LSM was 17.1 kPa (interquartile range [IQR]: 15.6), plasma BL-VWF level was 233% (IQR: 144), and BL-VITRO was 1.69 (IQR: 2.08). When comparing characteristics of patients with hepatic decompensation during

FU (n = 12, 4.3%) to those without (n = 264, 95.7%), varices were significantly more common (n = 10, 83.3% vs. n = 52, 19.7%; $P < 0.001$), patients had a higher BL-MELD score (12.1 ± 2.2 vs. 8.5 ± 2.5 points; $P < 0.001$), and lower serum BL albumin levels (36.2 ± 4.9 vs. 41.4 ± 4.5 g/L; $P < 0.001$). Moreover, patients developing hepatic decompensation had a higher BL-LSM (33.4 [IQR: 28.3] vs. 16.6 [IQR: 15.1] kPa; $P = 0.001$), lower BL-PLT (74 ± 39 vs. 150 ± 68 g/L; $P < 0.001$), higher plasma BL-VWF levels (375% [IQR: 175] vs. 232% [IQR: 133]; $P = 0.003$), and higher BL-VITRO (5.40 [IQR: 5.62] vs. 1.60 [IQR: 1.84]; $P < 0.001$). Importantly, differences in these markers of PH tended to be more pronounced at FU than at BL (FU-LSM: 12.2 kPa [IQR: 13.5] vs. 44.0 kPa [IQR: 44.9]; $P < 0.001$; FU-VITRO: 1.12 [IQR: 1.39] vs. 5.66 [IQR: 6.34]; $P < 0.001$), suggesting that FU values are more discriminative, and therefore more suitable for risk prediction than BL values (Table 1).

The prevalence of components of the metabolic syndrome, hepatic steatosis, and alcohol consumption is shown in Supporting Table S1. Although the metabolic phenotype was comparable between patients with and without hepatic decompensation during FU, alcohol consumption above the sex-specific thresholds was more common in patients who developed post-treatment hepatic decompensation (n = 6, 50% vs. n = 24, 9.1%).

CLINICAL EVENTS DURING FOLLOW-UP IN THE DERIVATION COHORT

Patients were followed for a median of 36.6 (IQR: 22.2) months. The following first decompensating events occurred: variceal bleeding in 2 (0.7%) patients, ascites in 5 (1.8%) patients, and HE in 5 (1.8%) patients. Fourteen (5.1%) patients developed *de novo* HCC, while 4 patients (1.4%) underwent OLT and 11 (4.0%) patients died. Notably, because six (2.2%) deaths were non-liver-related (most commonly due to extrahepatic malignancies), only 5 (1.8%) liver-related deaths occurred. Among these, most patients had been diagnosed with HCC during follow-up (n = 4, 80.0%).

Overall, 12 (4.3%) patients experienced hepatic decompensation before being censored/devolving a competing event, resulting in an incidence rate of 0.96 per 100 patient-years for hepatic decompensation and 1.10 for *de novo* HCC.

NONINVASIVE PREDICTION OF HEPATIC DECOMPENSATION IN THE DERIVATION COHORT

The median time from the end of treatment to the FU assessment of noninvasive tests (NIT) was 12.1 (IQR: 24) weeks (i.e., the time points clustered around SVR12).

Investigating the area under the receiver operating characteristic curve (AUROC) of noninvasive markers to predict hepatic decompensation during FU, FU-VITRO (AUROC = 0.925; 95% confidence interval [CI]: 0.874-0.977), FU-VWF (AUROC = 0.871; 95% CI: 0.757-0.986), FU-LSM (AUROC = 0.875; 95% CI: 0.796-0.954), FU-PLT (AUROC = 0.883; 95% CI: 0.815-0.951), and FU-albumin (AUROC = 0.858; 95% CI: 0.756-0.960) yielded the highest accuracies (Table 2). Interestingly, BL values as well as absolute and relative changes of these parameters did not reach the same diagnostic accuracy (Table 2 and Supporting Fig. S1), confirming that noninvasive markers are more accurate if assessed at FU.

In Cox regression investigating factors associated with hepatic decompensation, FU-VITRO (adjusted hazard ratio [aHR]: 1.044; 95% CI: 1.015-1.072; $P = 0.002$) and FU-LSM (aHR: 1.386; 95% CI: 1.185-1.622; $P < 0.001$) were associated with hepatic decompensation after adjusting for history of hepatic decompensation, FU-MELD score, and serum FU-albumin levels. In addition, they were independently associated with hepatic decompensation, indicating that both variables provide incremental prognostic information (Table 3), although FU-LSM and FU-VITRO showed a positive correlation of moderate strength (Spearman's $\rho = 0.644$; $P < 0.001$).

Notably, these associations remained unchanged when including alcohol consumption above the threshold in the prognostic model (Supporting Table S2), and when adjusting for ascites instead of history of hepatic decompensation in general (Supporting Table S3).

RISK STRATIFICATION FOR PH AND CLINICAL EVENTS DURING FOLLOW-UP BY AN ALGORITHM COMBINING LSM AND VITRO IN THE DERIVATION COHORT

Applying the LSM-based and VITRO-based risk stratification algorithm at BL and FU indicated that

TABLE 1. Characteristics and Comparison of Patients in the Derivation Cohort With and Without Hepatic Decompensation During FU

Patients Characteristics	All Patients, n = 276	No Hepatic Decompensation During FU, n = 264	Hepatic Decompensation During FU, n = 12	P Value
Age, years	56.0 ± 10.6	56.1 ± 10.6	51.6 ± 9.1	0.139
Sex				
Male	174 (63.0%)	166 (62.9%)	8 (66.7%)	1.000
Female	102 (37.0%)	98 (37.1%)	4 (33.3%)	
History of hepatic decompensation	26 (9.4%)	21 (8.0%)	5 (41.7%)	0.003
Variceal bleeding	6 (2.2%)	5 (1.9%)	1 (8.3%)	0.236
Ascites	18 (6.5%)	14 (5.3%)	4 (33.3%)	0.005
HE	3 (1.1%)	3 (1.1%)	0 (0.0%)	1.000
Varices	62 (22.5%)	52 (19.7%)	10 (83.3%)	<0.001
Small	33 (53.2%)	31 (59.6%)	2 (20.0%)	<0.001
Large	29 (46.8%)	21 (40.4%)	8 (80.0%)	
NSBB users	70 (25.4%)	61 (23.1%)	9 (75.0%)	<0.001
BL-CTP, points	5 ± 1	5 ± 1	6 ± 1	0.011
Stage A	256 (92.8%)	247 (93.6%)	9 (75.0%)	0.047
Stage B/C	20 (7.2%)	17 (6.4%)	3 (25.0%)	
Δ CTP, points	0 (0)	0 (0)	0 (1)	0.722
FU-CTP, points	5 ± 1	5 ± 1	6 ± 1	<0.001
BL-MELD, points	8.6 ± 2.6	8.5 ± 2.5	12.1 ± 2.2	<0.001
Δ MELD, points	0 (2)	0 (2)	-0.5 (3)	0.413
FU-MELD, points	8.8 ± 3.3	8.7 ± 3.3	11.6 ± 1.9	0.003
BL-albumin, g × L ⁻¹	41.1 ± 4.6	41.4 ± 4.5	36.2 ± 4.9	<0.001
Absolute Δ albumin, g × L ⁻¹	1.9 (4.5)	1.9 (4.5)	-0.1 (5.3)	0.129
Relative Δ albumin, %	4.4 (11.9)	4.6 (11.9)	-0.3 (15.1)	0.161
FU-albumin, g × L ⁻¹	43.1 ± 4.5	43.4 ± 4.2	36.7 ± 4.9	<0.001
BL-LSM, kPa	17.1 (15.6)	16.6 (15.1)	33.4 (28.3)	0.001
Absolute Δ LSM, kPa	-3.6 (7.4)	-3.6 (7.2)	8.5 (32.3)	0.064
Relative Δ LSM, %	-20.7 (39.2)	-21.2 (37.9)	22.2 (89.5)	0.010
FU-LSM, kPa	12.7 (14.3)	12.2 (13.5)	44.0 (44.9)	<0.001
BL-PLT, g × L ⁻¹	146 ± 69	150 ± 68	74 ± 39	<0.001
Absolute Δ PLT, g × L ⁻¹	9 (28)	10 (27)	-6 (38)	0.021
Relative Δ PLT, %	6.8 (20.8)	7.0 (20.2)	-11.5 (43.9)	0.017
FU-PLT, g × L ⁻¹	158 ± 72	162 ± 71	69 ± 33	<0.001
BL-VWF, %	233 (144)	232 (133)	375 (175)	0.003
Absolute Δ VWF, %	-38 (68)	-41 (71)	2 (66)	0.001
Relative Δ VWF, %	-18.4 (25.2)	-19.3 (25.9)	0.4 (20.1)	<0.001
FU-VWF, %	180 (105)	179 (100)	379 (174)	<0.001
BL-VITRO	1.69 (2.08)	1.60 (1.84)	5.40 (5.62)	<0.001
Absolute Δ VITRO	-0.32 (0.80)	-0.33 (0.80)	0.11 (1.66)	0.003
Relative Δ VITRO, %	-23.3 (32.4)	-25.1 (30.3)	3.7 (40.5)	<0.001
FU-VITRO	1.15 (1.52)	1.12 (1.39)	5.66 (6.34)	<0.001

a considerable proportion of patients who fell into the high-risk or gray-zone groups at BL were reclassified into a lower risk group (Supporting Fig. S2), while progression to a higher risk group was comparatively uncommon.

Of note, the patients of the derivation cohort who underwent paired HVPG measurements (n = 80) had more advanced underlying liver disease at BL (LSM: 23.7 kPa [IQR: 18.0] vs. 17.1 kPa [IQR: 15.6] and VITRO: 2.83 [IQR: 2.95] vs. 1.89 [IQR:

TABLE 2. AUROC Values, Youden's Index–Optimized Cutoffs, and Diagnostic Indices of Potential Predictors of Hepatic Decompensation During FU in the Derivation Cohorts

Parameter	AUROC (95% CI)	Cutoff	Sensitivity	Specificity	PPV	NPV
BL-MELD	0.880 (0.804-0.956)	>9 points*	91.7%	77.3%	15.5%	99.5%
FU-MELD	0.879 (0.817-0.941)	>9 points*	83.3%	79.1%	15.6%	99.0%
BL-albumin	0.772 (0.618-0.927)	<36.9 g × L ⁻¹ *	75.0%	85.2%	18.8%	98.7%
FU-albumin	0.858 (0.756-0.960)	<42.5 g × L ⁻¹ *	91.7%	66.0%	11.0%	99.4%
BL-LSM	0.812 (0.721-0.904)	>24.9 kPa*	83.3%	72.3%	12.0%	99.0%
FU-LSM	0.875 (0.796-0.954)	>12.4 kPa	100%	50.4%	8.4%	100%
		>25.3 kPa	66.7%	80.7%	13.6%	98.2%
BL-PLT	0.837 (0.739-0.935)	<123 g × L ⁻¹ *	91.7%	61.7%	9.8%	99.4%
FU-PLT	0.883 (0.815-0.951)	<111 g × L ⁻¹ *	91.7%	73.9%	13.8%	99.5%
BL-VWF	0.758 (0.604-0.911)	>365%*	66.7%	87.5%	19.5%	98.3%
FU-VWF	0.871 (0.757-0.986)	>221%*	91.7%	71.6%	12.8%	99.5%
BL-VITRO	0.857 (0.762-0.952)	>3.58*	75.0%	85.2%	18.8%	98.7%
FU-VITRO	0.925 (0.874-0.977)	>0.95	100%	42.4%	7.3%	100%
		>3.3	75.0%	88.6%	23.1%	98.7%

*Youden's index–optimized cutoff.

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

TABLE 3. Cox Regression Analyses Investigating Factors Associated With Hepatic Decompensation During FU in the Derivation Cohort

Parameter	Model A			Model B			Model C		
	aHR	95% CI	PValue	aHR	95% CI	PValue	aHR	95% CI	PValue
History of hepatic decompensation	1.710	0.445-6.571	0.435	1.550	0.438-5.491	0.497	—	—	—
FU-MELD, per point	1.090	0.957-1.242	0.193	1.141	1.006-1.293	0.040	—	—	—
FU-albumin, per g × L ⁻¹	0.869	0.808-0.936	<0.001	0.852	0.790-0.919	<0.001	—	—	—
FU-LSM, per kPa	1.044	1.015-1.072	0.002	—	—	—	1.035	1.002-1.069	0.039
FU-VITRO, per point	—	—	—	1.386	1.185-1.622	<0.001	1.312	1.091-1.579	0.004

Note: Model A included FU-LSM and was adjusted for history of hepatic decompensation and indicators of hepatic dysfunction (FU-MELD score and serum FU-albumin levels), whereas model B included FU-VITRO and was adjusted for the same factors. We computed model C, which included FU-LSM and FU-VITRO, to demonstrate that both variables provide independent/incremental prognostic information.

2.08]) and at FU (LSM: 17.3 kPa [IQR: 16.4] vs. 12.7 kPa [IQR: 14.3] and VITRO: 1.82 [IQR: 2.08] vs. 1.15 [IQR: 1.52]), as compared with the overall cohort. Among patients with paired HVPG measurements, those meeting the CSPH ruled-out criteria (n = 29) had a median FU-HVPG of 5 mm Hg (IQR: 4), and the prevalence rates of CSPH and high-risk PH were only 6.9% and 3.4%. Accordingly, FU-CSPH could be ruled out in these patients. In the gray-zone (n = 21), median FU-HVPG was 11 mm Hg (IQR: 4), and 76.2% had CSPH; however, high-risk PH was rare (only 9.5%). Finally, in the CSPH ruled-in group (n = 30; median FU-HVPG 17 mm Hg [IQR: 10]), CSPH

could be ruled in, as the prevalence attained 90.0%. Furthermore, this group was enriched with patients who had high-risk PH (60.0%), despite HCV cure. The between-group differences in FU-HVPG and the prevalence of CSPH and high-risk PH at FU attained statistical significance (Fig. 2).

Because PH is a driver of posttreatment hepatic decompensation, we evaluated whether an LSM-based and VITRO-based algorithm, which has previously been developed to stratify patients according to their risk for posttreatment CSPH, is able to predict posttreatment hepatic decompensation.⁽⁹⁾

When applying the stepwise FU-LSM-based and FU-VITRO-based algorithm to the derivation cohort,

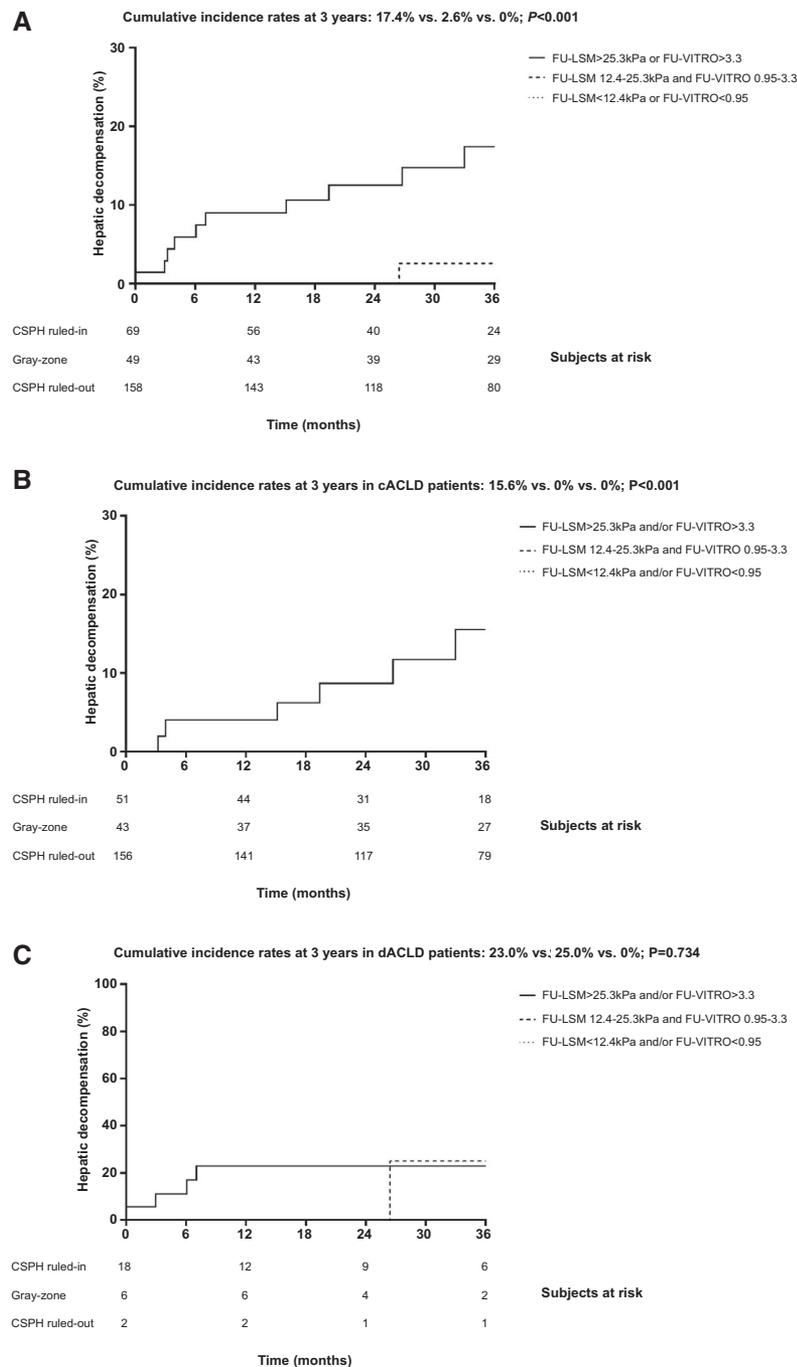


FIG. 2. Kaplan-Meier analyses of hepatic decompensation in the derivation cohort. A, All patients, as well as the subgroups of patients with cACLD (i.e., first hepatic decompensation) (B) and dACLD (i.e., further hepatic decompensation) (C), stratified according to their risk of posttreatment clinically significant portal hypertension (CSPH, HVPG ≥ 10 mm Hg).

FU-LSM < 12.4 kPa and/or FU-VITRO < 0.95 ruled out CSPH at FU in 158 (57.2%) of 159 (57.6%) patients, depending on whether LSM or VITRO was the first step. In 69 (25.0%) of 68 (24.6%) patients,

CSPH was ruled in (FU-LSM > 25.3 kPa and/or FU-VITRO > 3.3), while 49 patients (17.8%) remained in the gray-zone (Table 4). Accordingly, application of LSM or VITRO as a first step yielded very similar results.

TABLE 4. FU-LSM-Based and FU-VITRO-Based Algorithms to Rule In and Rule Out Posttreatment CSPH (HVPG ≥ 10 mm Hg) in the Derivation Cohort

FU-LSM First–FU-VITRO Second		
First Step	FU-LSM	
< 12.4kPa (CSPH ruled-out) 133 (48.2%)	12.4-25.3 kPa (gray-zone) 84 (30.4%)	> 25.3kPa (CSPH ruled-in) 59 (21.4%)
Second Step	FU-VITRO	
< 0.95 (CSPH ruled-out) 25 (9.1%)	0.95-3.3 (gray-zone) 49 (17.8%)	> 3.3 (CSPH ruled-in) 10 (3.6%)
FU-VITRO First–FU-LSM Second		
First Step	FU-VITRO	
< 0.95 (CSPH ruled-in) 112 (40.6%)	0.95-3.3 (gray-zone) 125 (45.3%)	> 3.3 (CSPH ruled-out) 39 (14.1%)
Second Step	FU-LSM	
< 12.4 (CSPH ruled-out) 47 (17.0%)	12.4-25.3 (gray-zone) 49 (17.8%)	> 25.3 (CSPH ruled-in) 29 (10.5%)

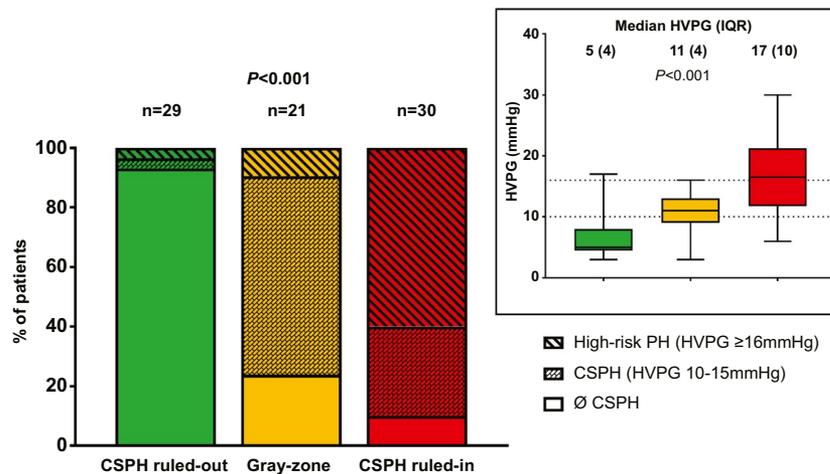


FIG. 3. Prevalence of clinically significant portal hypertension (HVPG ≥ 10 mm Hg) and high-risk portal hypertension (HVPG ≥ 16 mm Hg) and comparison of HVPG levels throughout the risk groups in the derivation cohort, as defined by noninvasive markers.

If patients within the gray-zone were excluded, both approaches (“FU-LSM first–FU-VITRO second” and “FU-VITRO first–FU-LSM second”) had a negative predictive value of 100% and a positive predictive value of 14.5%/14.7% for hepatic decompensation during FU. Patients in whom posttreatment CSPH was ruled out (n = 158, 57.2%) and those in the gray-zone (n = 49, 17.8%) had a significantly lower cumulative incidence of hepatic decompensation at 3 years (0% and 2.6%, respectively) than patients in whom posttreatment CSPH was ruled in (n = 69, 25.0%;

cumulative incidence: 17.4%; *P* < 0.001; Fig. 3A). This finding was confirmed by competing risks analysis, with hepatic decompensation as the event of interest, and HCC development, OLT, as well as death as competing risks, which yielded nearly identical results, as compared with the Kaplan–Meier method/log-rank test (hepatic decompensation at 3 years: 0% vs. 2.4% vs. 16.8%; *P* < 0.001) (Supporting Fig. S3). Of note, stratification by LSM or VITRO as a first step yielded similar results (data not shown), indicating that both approaches can be used interchangeably.

A similar pattern was observed in patients with cACLD (n = 250, 90.6%), with a cumulative incidence of hepatic decompensation at 3 years of 15.6% in patients in whom posttreatment CSPH was ruled in versus 0% in patients in the gray-zone or in whom CSPH was ruled out ($P < 0.001$; Fig. 3B). However, there was a comparable incidence of hepatic decompensation at 3 years in patients with dACLD (n = 26, 9.4%) within the gray-zone and in patients in whom CSPH was ruled in (25.0% and 23.0%, respectively), while no events occurred in the CSPH ruled-out group ($P = 0.734$; Fig. 3C).

A sensitivity analysis restricted to patients with cirrhosis (n = 168), as diagnosed by BL-LSM ≥ 15 kPa or histology, confirmed the discriminatory ability of the FU-LSM-based and FU-VITRO-based risk-stratification algorithm (hepatic decompensation at 3 years: 0% vs. 2.9% vs. 18.4%; $P = 0.001$) (Supporting Fig. S4). Finally, applying other previously proposed highly sensitive/specific FU-LSM cutoffs (13.6⁽²⁶⁾)/21 kPa⁽²⁷⁾ had no relevant effect on the results (Supporting Fig. S5).

INTERNAL VALIDATION

See the Supporting Information materials for information on BL characteristics and FU.

The prognostic performance of FU-LSM (AUROC: 0.896 [95% CI 0.807-0.985]) and FU-VITRO (AUROC: 0.803 [95% CI 0.604-1.000]) for posttreatment hepatic decompensation in the internal validation cohort was very similar to that observed in the derivation cohort. In line with these findings, the rates of hepatic decompensation at 3 years in the different groups of our FU-LSM-based and FU-VITRO-based risk stratification algorithm were as follows: high risk (38.2%) versus gray-zone (0%) versus low risk (0%); $P < 0.001$ (Supporting Fig. S6).

Although the number of patients in the validation cohort who underwent paired HVPG measurements was small (n = 14), we also attempted to replicate our previous findings regarding prevalence of CSPH and high-risk PH at FU. Among patients meeting the noninvasive CSPH ruled-out (i.e., low-risk) criteria (n = 3), median FU-HVPG was 4 mm Hg (IQR: 5), and no patient had CSPH. Accordingly, FU-CSPH could be ruled out in these patients. In the gray-zone (n = 4), median FU-HVPG was 15 mm Hg (IQR: 17), and the prevalence rates of

CPSH and high-risk PH were 75% and 50%. Finally, in the CSPH ruled-in (i.e., high-risk) group (n = 7; median FU-HVPG = 21 mm Hg [IQR: 9]), CSPH could be ruled in, as the prevalence attained 100%. Furthermore, this group was enriched with patients who had high-risk PH (57.1%) after HCV cure. Despite the small number of patients, the between-group differences in HVPG, the prevalence of CSPH, and high-risk PH at FU attained statistical significance (Supporting Fig. S7).

EXTERNAL VALIDATION

See the Supporting Information materials for information on BL characteristics and FU.

In line with the findings in the derivation and the internal validation cohort, FU-LSM of (AUROC: 0.943 [95% CI: 0.886-1.000]) and FU-VITRO of (AUROC: 0.844 [95% CI: 0.758-0.930]) were predictive of hepatic decompensation. The FU-LSM-based and FU-VITRO-based algorithm stratified patients into groups that differed in their risk for hepatic decompensation during FU (high risk [13.4%] vs. gray-zone [4.5%] vs. low risk [0%] [$P < 0.001$] when comparing only high-risk versus low-risk group due to crossing curves) (Supporting Fig. S8).

RECOMPENSATION IN PATIENTS WITH dACLD IN THE DERIVATION COHORT

See the Supporting Information materials.

NONINVASIVE PREDICTION OF DE NOVO HCC AND LIVER-RELATED TRANSPLANT-FREE MORTALITY IN THE DERIVATION COHORT

See the Supporting Information materials.

Discussion

Our study demonstrates that a combination of noninvasive markers of PH (i.e., LSM and VITRO), determined after HCV cure, predicts posttreatment hepatic decompensation in patients with ACLD. Importantly, our noninvasive algorithm is based on

readily accessible parameters that are easily applicable in clinical practice, and thus facilitate risk stratification and personalized therapy.

A number of imaging, laboratory, and functional tests have been shown to correlate with HVPG.⁽²⁸⁾ However, LSM and VWF are particularly promising, as their diagnostic value for CSPH has been confirmed in patients with cACLD (i.e., the main target population),⁽²⁸⁾ and they have been shown to predict outcomes in patients with ACLD, even independently of HVPG.^(11,16,17) Importantly, the diagnostic performance as well as the prognostic ability of these and other noninvasive markers have primarily been studied in progressive liver disease. However, with the advent of etiological therapies, regressive liver disease after the removal of the primary etiological factor (i.e., HCV cure) is becoming increasingly common. Regardless of prevention strategies, the number of individuals who are projected to be treated for and cured from HCV infection worldwide will be around or even considerably higher than 1 million per year for the next decade.⁽²⁹⁾ Because a relevant proportion of patients have pretreatment ACLD and the risk for complications is decreased but not completely abolished⁽⁶⁻⁸⁾ by HCV cure, risk stratification is a key to decrease resource use by individualizing posttreatment management. We have recently established the role of HVPG as a prognostic marker after HCV cure, and although HVPG measurement is unsuitable to guide patient management after SVR on a large scale, our findings highlight the central role of PH.⁽⁹⁾ In contrast to HVPG measurement, LSM and VWF/VITRO are broadly available and easily applicable in clinical routine.

LSM, which has already found its way into the recommendations for the management of PH in 2015,⁽¹⁰⁾ has been used to predict liver-related events following SVR in two recent studies. Corma-Gomez et al.⁽³⁰⁾ reported an independent association of LSM with a composite endpoint of hepatic decompensation, HCC, OLT, and mortality in patients co-infected with HIV/HCV who achieved HCV cure. However, although such a composite endpoint increases statistical power, it negatively affects the granularity of results, as the dynamics of PH do not necessarily relate to HCC risk after HCV cure.⁽⁹⁾ Even more recently, Pons et al.⁽³¹⁾ investigated the risk factors for hepatic decompensation and *de novo* HCC in patients with pretreatment cACLD. They reported an incidence

rate for hepatic decompensation of 0.31/100 patient-years, with hepatic decompensation occurring only in patients with BL-LSM > 20 kPa. Despite the higher incidence of hepatic decompensation (0.96 per 100 patient-years) in our study, *de novo* HCC development was less common (1.10 vs. 1.50/100 patient-years) than in the study by Pons et al. Importantly, differences in incidence rates are likely explained by differences in patient characteristics, as we also included a small proportion of patients with a history of hepatic decompensation, resulting in a higher rate of PH-induced complications, and our patients were considerably younger (56.0 vs. 63.7 years), potentially contributing to the lower incidence of HCC.

In line with a recent study that included a small subgroup of patients following SVR,⁽¹⁹⁾ FU-VITRO showed a consistently good performance for predicting posttreatment hepatic decompensation throughout the study cohorts (AUROC values ranged from 0.803 to 0.925) and an AUROC value that was numerically higher than that of LSM as well as PLT or plasma VWF levels alone in the derivation cohort. Interestingly, VITRO added prognostic information to LSM. This may be explained by the contribution of systemic inflammation (and possibly also endothelial dysfunction and procoagulant imbalance) (i.e., additional factors promoting hepatic decompensation, to plasma VWF levels).^(11,12,16) Based on a previously developed two-step algorithm for ruling in and ruling out posttreatment CSPH,⁽⁹⁾ we stratified patients into three risk groups, which may have important implications for patient management:

1. Patients with FU-LSM < 12.4 kPa and/or FU-VITRO < 0.95 had a CSPH prevalence of <10% (i.e., CSPH ruled-out). Importantly, most patients fulfilled these criteria, and these patients did not develop first or further hepatic decompensation (i.e., low risk of hepatic decompensation). Due to the absence of CSPH, there might be no need for endoscopic surveillance, even in centers that use NSBB in patients with low-risk varices. Moreover, there is no potential for strategies aiming to prevent hepatic decompensation (e.g., NSBB therapy^(32,33)), as these patients are not at a relevant risk.
2. Patients within the diagnostic gray-zone (i.e., patients with FU-LSM and FU-VITRO of 12.4-25.3 kPa and 0.95-3.3, respectively) had a low

probability of hepatic decompensation (2.6% at 3 years), despite three quarters of patients undergoing paired HVPG measurements having CSPH. This may be explained by the very low (<10%) prevalence of high-risk PH (i.e., HVPG \geq 16 mm Hg) in this subgroup and the previously mentioned HVPG-independent prognostic value of LSM and VWF. Surveillance for varices in these patients is clearly warranted, possibly at longer time intervals, than currently recommended.⁽¹⁰⁾

3. In patients with FU-LSM $>$ 25.3 kPa and/or FU-VITRO $>$ 3.3, CSPH was ruled in (prevalence of 90%), and the prevalence of high-risk PH was as high as 60%. This translated into an exceedingly high risk of hepatic decompensation (17.4% at 3 years). Besides variceal surveillance, compensated patients classified as being at high risk based on noninvasive markers may benefit from NSBB treatment to prevent hepatic decompensation.^(32,33)

Moreover, considering that LSM is the most well-established and broadly available elastography technique and that VWF is an inexpensive routine laboratory test,⁽²⁸⁾ our suggested algorithm appears easy to implement. Because the “FU-LSM first” and the “FU-VITRO first” approaches yielded similar results, the sequence of testing can be adopted according to local availability. For instance, using the “FU-VITRO first” approach, most of the patients can be assigned to the low-risk or high-risk group, without the need of VCTE, which may be helpful in settings where VCTE is not readily available.

Of note, the time point of the FU assessment of NIT was not standardized in our study but clustered around SVR12. Accordingly, the predictive value of our risk-stratification algorithm was not critically dependent on the time point of assessment, thereby facilitating its use in clinical routine. Studies performing repeated HVPG measurements within the post-treatment period revealed that the regression of PH may continue beyond the first months after the end of treatment,^(9,34) although CSPH commonly persists 48 weeks after the end of treatment.⁽⁵⁾ An important strength of noninvasive methods for the long-term management of patients is the possibility of repeated assessments, which provides updated information on PH and may even increase their prognostic value. However, despite the relatively short period of time, a considerable proportion of patients had stage

migration from a higher to a lower risk group; this proportion may have further increased, if assessed at a later time point. Accordingly, it should be investigated in future studies whether sequential reassessments of FU-LSM and FU-VITRO further increase the proportion of patients assigned to lower risk groups and improve prognostication.

Although we did not observe an association between features of the metabolic syndrome or hepatic steatosis and posttreatment hepatic decompensation in our study, alcohol consumption was linked to adverse outcomes, highlighting the importance of harm reduction measures.

Apart from PH-related complications, HCC is a main determinant of morbidity and mortality in patients with ACLD who achieved SVR.⁽³⁵⁾ Interestingly, Pons et al.⁽³¹⁾ found FU-albumin and FU-LSM to be independently associated with *de novo* HCC, and therefore developed a model combining these two parameters to predict HCC development during FU. Although our study confirms the ability of serum albumin levels at FU to predict *de novo* HCC (AUROC = 0.786), both BL-LSM and FU-LSM were not predictive, suggesting that the model by Pons et al. requires further validation. Of note, FU examinations were performed around SVR12 (i.e., at a median of 12.1 weeks after end of treatment) in our study, compared with 12 months in the Spanish study, possibly contributing to the partially conflicting results. Interestingly, of all the evaluated variables, VITRO showed the highest AUROC (around 0.8) for *de novo* HCC development in our derivation cohort, and BL-VITRO and FU-VITRO cutoffs of $>$ 2.66 and $>$ 1.82, respectively, stratified patients into groups at low risk and high risk of HCC. These findings are in line with a previous study, reporting that plasma VWF levels are predictive of HCC development, independently of liver fibrosis stage.⁽³⁶⁾ Moreover, VITRO is a noninvasive marker of CSPH, and the latter condition has previously been linked to *de novo* HCC in patients with cirrhosis.⁽³⁷⁾ These promising results indicate that VITRO should be further evaluated as a predictor of HCC development in future studies.

Our study has limitations. First, we combined patients with cACLD and dACLD. However, the concept of cACLD/dACLD has been developed in the setting of progressive disease and will likely be updated with Baveno VII, also considering liver

disease regression/recompensation, which is increasingly common. Patients may recompensate after etiological cure, which is not always clinically evident, as drugs for ascites and/or hepatic encephalopathy are commonly not withdrawn. Moreover, a patient who has already bled may not be at risk for variceal bleeding anymore, due to a decrease of HVPG below the bleeding threshold or even resolution of CSPH. Accordingly, similar to our previous study, we chose to combine patients with cACLD and dACLD for the main analyses and subsequently confirmed the prognostic value of our noninvasive risk stratification algorithm in the substantially larger subgroup of patients with cACLD.⁽⁹⁾ Unfortunately, the number of patients with dACLD with complications other than variceal bleeding was small, which limited the ability of our study to investigate recompensation. Second, not all patients with pretreatment ACLD who underwent antiviral therapy at our center had paired information on LSM/VITRO at BL and FU, and therefore were excluded from the derivation cohort. This could have led to some selection bias, which we tried to reduce by including patients with information on FU-LSM/FU-VITRO in the internal validation cohort, in which we observed very similar results. Third, there were no predefined selection criteria for paired HVPG measurements, and therefore the main decisive factors were the physician's preference/recommendation as well as the patient's willingness. As a result, patients in the derivation cohort who underwent paired HVPG measurements had higher LSM and VITRO at BL and FU, which is indicative of a higher prevalence of CSPH. This may implicate that the application of our algorithm to an unselected ACLD population (i.e., a population comparable to our overall study population) with a lower prevalence of CSPH could also lead to a lower prevalence of CSPH throughout all CSPH risk groups. Although this is unproblematic for the CSPH ruled-out group, it could be of concern for the patients in whom FU-CSPH is ruled in, as it could lead to a prevalence of CSPH lower than 90%. However, this potential limitation is very hard to overcome (or possibly unavoidable), as even a prospectively designed study performing HVPG measurements would be unlikely to recruit an unselected/representative population of patients with ACLD. Fourth, we applied LSM/VITRO cutoffs that were not identified on the basis of their association with the direct clinical

cutoffs provide additional clinically relevant information on the presence or absence of CSPH. Moreover, choosing cutoffs based on their diagnostic indices for hepatic decompensation could have led to overfitting. Finally, the algorithm applying our previously established cutoffs showed an excellent discriminatory ability throughout all assessed cohorts.

In conclusion, FU-LSM and FU-VITRO are strongly and independently predictive of posttreatment hepatic decompensation in patients with ACLD who have achieved SVR using IFN-free therapies. Collectively, our results across the derivation of internal and external validation cohorts indicate that the proposed risk stratification algorithm provides robust information regarding the risk of hepatic decompensation after SVR as well as the extent of PH. In particular, it reliably identified a considerable proportion (overall, 57.2%) of patients with ACLD who are at negligible risk for CSPH and hepatic decompensation and who may be easily managed in a primary/secondary-care setting, given that adequate HCC surveillance is ascertained. This approach could help to take the load off tertiary care centers. At the same time, the FU-LSM-based and FU-VITRO-based algorithm also identified patients who are at high risk of hepatic decompensation, despite etiological cure, and who should be the focus of our clinical and scientific attention. Accordingly, this algorithm enables risk stratification after SVR, and therefore facilitates personalized therapy in this steadily increasing patient population.

Author Contributions: M.M. was responsible for the study concept and design. All authors were responsible for the data acquisition. G.S., T.R., and M.M. were responsible for the analysis, data interpretation, and drafting of the manuscript. All authors were responsible for critical revision of the manuscript for important intellectual content.

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Author names in bold designate shared co-first authorship.

Supporting Information

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