











Non-invasive detection of portal hypertension by enhanced liver fibrosis score in patients with different aetiologies of advanced chronic liver disease

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Handling Editor: Virginia Hernandez-Gea

Abstract

Background and Aims: The enhanced liver fibrosis (ELF) score comprises serum markers of fibrogenesis and matrix remodelling and was developed to detect liver fibrosis, however, it may also be useful for the non-invasive detection of portal hypertension (PHT).

Methods: ELF score and its single components (TIMP1/PIIINP/HA) were analysed in 201 patients with advanced chronic liver disease (ACLD; ie hepatic venous pressure gradient (HVPG) ≥ 6 mm Hg). Patients with pre-/post-hepatic PHT, hepatocellular carcinoma beyond Milan criteria, and history of TIPS implantation or liver transplantation were excluded.

Results: ELF and its single components correlated with HVPG in the overall cohort: ELF: $r = .443$, TIMP1: $r = .368$, PIIINP: $r = .332$, and HA: $r = .419$ (all $P < .001$). The strength of the correlation between ELF and HVPG decreased in higher HVPG strata: 6–9 mm Hg: $r = .569$ ($P = .004$), 10–19 mm Hg: $r = .304$ ($P = .001$) and ≥ 20 mm Hg: $r = -.023$ ($P = .853$).

Area under the receiver operating characteristics (AUROC) of ELF score to detect clinically significant PHT (CSPH; HVPG ≥ 10 mm Hg) was 0.833. Importantly, HA alone yielded an AUROC of 0.828. Detection of CSPH in strictly compensated ACLD (cACLD) patients was less accurate: AUROC: 0.759 ($P < .001$). CSPH was ruled-in by

Abbreviations: ACLD, advanced chronic liver disease; ALD, alcohol-related liver disease; AUROC, area under the receiver operating characteristics; AVB, acute variceal bleeding; cACLD, compensated ACLD; CSPH, clinically significant portal hypertension; CTP, Child-Turcotte-Pugh; dACLD, decompensated ACLD; ELF, enhanced liver fibrosis score; HA, hyaluronic acid; HCV, viral hepatitis C; HRP, high-risk portal hypertension; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; IVD, in vitro diagnostic; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NLR, negative likelihood ratio; NPV, negative predictive value; NSBB, non-selective beta-blockers; PHT, portal hypertension; PIIINP, Amino-terminal propeptide of type III procollagen; PLR, positive likelihood ratio; PLT, platelet; PPV, positive predictive value; TIMP-1, tissue inhibitor matrix metalloproteinase-1; TIPS, transjugular intrahepatic portosystemic shunt; VCTE, vibration-controlled transient elastography.

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ELF ≥ 11.1 with a PPV of 98% (sensitivity: 61%/specificity: 92%/NPV:24%), but CSPH could not be ruled-out.

ELF score had a low AUROC of 0.677 (0.60-0.75; $P < .001$) for the diagnosis of high-risk PHT (HRPH; HVPG ≥ 20 mm Hg) and, thus, HRPH could not be ruled-in by ELF. However, ELF < 10.1 ruled-out HRPH with a NPV of 95% (sensitivity: 97%/specificity: 26%/PPV: 39%).

Conclusion: The ELF score correlates with HVPG at values < 20 mm Hg. An ELF ≥ 11.1 identifies patients with a high probability of CSPH, while an ELF < 10.1 may be used to rule-out HRPH.

KEYWORDS

ACLD, advanced chronic liver disease, cirrhosis, clinically significant portal hypertension, hepatic venous pressure gradient, non-invasive, portal hypertension, prediction

1 | INTRODUCTION

Chronic liver injury causes liver damage that is characterized by necroinflammation and fibrosis, which can ultimately progress towards advanced chronic liver disease (ACLD; ie advanced liver fibrosis and cirrhosis). Perpetual increase in intrahepatic resistance finally results in development of portal hypertension (PHT).¹ Hepatic venous pressure gradient (HVPG) above or equal to 10 mm Hg defines the presence of clinically significant portal hypertension (CSPH) and is assessed by hepatic vein catheterization.² CSPH is an important prerequisite for the development of complications in patients with ACLD. Most importantly, patients with CSPH are at risk of hepatic decompensation and increased mortality.^{2,3}

The enhanced liver fibrosis (ELF) score was firstly described to non-invasively detect fibrosis in patients with non-alcoholic fatty liver disease (NAFLD),⁴ and subsequently validated for viral hepatitis C (HCV)⁵ and is based on combining serum markers of matrix remodelling and fibrosis.⁶ The ELF score includes three single components, ie tissue inhibitor of matrix metalloproteinases (TIMP1), aminoterminal peptide of procollagen type III (PIIINP) and hyaluronic acid (HA).⁵ Ultimately, ELF score cut-offs were proposed for the discrimination of patients with fibrosis from healthy individuals and for staging fibrosis in patients with HCV,^{5,7} non-alcoholic steatohepatitis (NASH),⁸ alcohol-related liver disease (ALD)⁹ and paediatric NAFLD¹⁰ patients. Importantly, multiple studies reported that ELF was a predictor of disease progression and mortality.¹¹⁻¹⁴

Previous studies assessing the ability of ELF score to detect CSPH have produced controversial results.¹⁵⁻¹⁷ In one of these studies, Sandahl et al computed a prediction model for CSPH by combining ELF with serum concentrations of soluble CD163, a serum marker of activated macrophages, which yielded in a higher accuracy in discriminating CSPH from subclinical PHT,¹⁶ as compared to ELF alone. Importantly, both ELF score and histological fibrosis stage as well as HVPG significantly decreased after cure from HCV in patients with PHT suggesting a correlation between the decline in HVPG and fibrosis that may be mirrored by changes

Key points

Patients with liver disease may develop increased pressure in the blood vessels that drain into the liver. This condition is termed portal hypertension (PHT). Invasive catheter measurements must be performed to diagnose PHT. Our study shows that a simple blood test named “enhanced liver fibrosis (ELF) score” can identify patients with a high versus a low likelihood of suffering from PHT.

in ELF score.¹⁷ The varying accuracy of ELF score to predict CSPH in previous studies may derive from considerable differences in the respective study cohorts such as liver disease aetiology, as well as severity of liver disease and of PHT. Finally, previous studies included both compensated and decompensated patients. However, the non-invasive detection of CSPH is particularly relevant in patients with compensated ACLD (cACLD),¹⁸ who have not been analysed separately yet.

The aim of this study was to investigate the performance of ELF score to predict CSPH and high-risk PHT (HRPH; ie HVPG ≥ 20 mm Hg) in a large prospective cohort of patients undergoing HVPG measurements and simultaneous assessment of ELF score.

2 | PATIENTS AND METHODS

2.1 | Study design

A total of 201 patients with clinically stable ACLD undergoing hepatic vein catheterization between January 2017 and August 2019 at the Vienna Hepatic Hemodynamic Lab of the Medical University of Vienna were consecutively included in the prospective Vienna Cirrhosis Study (VICIS) (NCT03267615). Referral to HVPG measurement was based on reasonable suspicion of ACLD as a result of radiological and laboratory

results and/or previous clinical symptoms associated with PHT according to national and international consensus recommendations.^{19,20}

Patients with pre- or post-hepatic causes of PHT, non-cirrhotic PHT, hepatocellular carcinoma beyond Milan criteria, acute decompensation or non-elective hospitalization, liver metastases or a history of transjugular intrahepatic portosystemic shunt (TIPS) implantation or liver transplantation were excluded (Figure S1). Patients receiving concomitant treatment with non-selective beta-blockers were not included in the analysis. More specifically, patients either had never received non-selective beta-blockers (NSBB) or paused NSBB intake at least 5 days before HVPG measurement. Relevant clinical information and laboratory parameters were collected from patients' medical records. cACLD was defined as the absence of decompensating events prior to or at the time point of HVPG measurement, ie ascites, hepatic encephalopathy and variceal bleeding.²¹ Furthermore, vibration-controlled transient elastography (VCTE; Fibroscan®) was performed instantaneously prior to HVPG measurement and considered for analysis when meeting reliability criteria as previously published.²²

2.2 | HVPG measurements

HVPG measurements were performed by trained physicians of the Vienna Hepatic Hemodynamic Lab following a defined standard operating procedure²³ in fasted condition. Briefly, the right internal jugular vein was punctured by ultrasound guidance under local anaesthesia. A catheter introducer set (8.5 F, Arrow International) was inserted using Seldinger technique. The liver vein was cannulated by an angled balloon occlusion catheter (Medical University of Vienna/Medizintechnik Pejcl, Austria).²⁴ Adequate placement and wedge position were verified by X-ray after injection of contrast agent while the balloon was inflated. At least three measurements of free and wedged hepatic vein pressure were performed to assess HVPG. No adverse events requiring medical intervention were recorded for patients included in this study.

2.3 | Analysis of ELF score components

The components of the ELF score (TIMP1, HA, PIIINP) were measured in serum—obtained from the catheter introducer sheath placed in the internal jugular vein during HVPG measurements—by *in vitro* diagnostic CE-certified chemiluminescence immunoassays using the respective assay kits on an Advia Centaur CP analyser (Siemens Healthcare Diagnostics Inc) in an ISO 15189 accredited laboratory at the Department of Laboratory Medicine, Medical University of Vienna. The measurement ranges were for TIMP1 3.5–1300 ng/mL, for HA 1.6–1000 ng/mL, and for PIIINP 0.5–150 ng/mL. The total coefficients of variation according to CLSI Guideline EP5-A2 were ≤ 6.0 , ≤ 7.7 and ≤ 6.5 for TIMP1, HA and PIIINP respectively.

The final score was calculated as previously reported⁵: ELF score = $2.494 + 0.846 \ln(C_{HA}) + 0.735 \ln(C_{PIIINP}) + 0.391 \ln(C_{TIMP1})$.

ELF component measurements were performed by technicians at the department of Laboratory Medicine at the Medical University of Vienna blinded to the clinical and hemodynamic data of the subjects.

2.4 | Statistics

Statistical analyses were performed using IBM SPSS Statistics 26 (IBM) and GraphPad Prism 8 (GraphPad Software). Continuous variables are reported as mean \pm standard error of the mean (SEM) or median and IQR, and categorical variables are presented as numbers (n) and proportions (%) of patients. Comparisons of continuous variables were performed using Student's t-test or Mann-Whitney *U* test, as applicable. Categorical variables were compared with chi-squared or Fisher's exact test, as applicable. Receiver operating characteristic (ROC) curves were used to test the performance of ELF score to detect CSPH. Additionally, we assessed area under the receiver operating characteristics (AUROC), sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, as well as positive (PLR) and negative (NLR) likelihood ratios for the detection of CSPH and HRP. The optimal cut-off values were evaluated by Youden's index (sensitivity + specificity – 1), whereas most inclusive cut-offs achieving a sensitivity or specificity $\geq 90\%$ were chosen for ruling-out and ruling-in CSPH and HRP respectively. Furthermore, exploratory AUROC analyses were performed in subgroups of different disease aetiologies and patients with cACLD. A two-sided $P \leq .05$ was defined to denote statistical significance.

2.5 | Ethics

This study was conducted in accordance with the 1964 Helsinki declaration and its later amendments and approved by the local ethics committee of the Medical University of Vienna (EK1262/2017). All patients gave written informed consent to liver vein catheterizations and provided written consent to be enrolled in the VICIS study (NCT03267615). Study results are reported according to STARD guidelines for diagnostic studies (<https://www.equator-network.org/reporting-guidelines/stard/>).

3 | RESULTS

3.1 | Patient characteristics

The majority of patients in our study cohort were male ($n = 135/201$, 67%), and the prevalence of CSPH and HRP was 88% (177/201) and 32% (65/201) respectively. ALD ($n = 83$, 41%) and viral hepatitis ($n = 40$, 20%) were the most common aetiologies of ACLD. The mean age was 56.8 ± 0.8 years (Table S1). Eighty-five (42%) patients presented with cACLD (including $n = 62$, 73% with CSPH). Most patients (58%) had Child-Turcotte-Pugh (CTP) stage A, while 33% had CTP stage B and 9% had CTP stage C. Median model for end-stage liver disease (MELD) score was 11 (9–14).

Seventy-five (37%) patients had no varices, 64 (32%) had small varices and 56 (28%) had large oesophageal varices, whereas variceal status was unknown in 6 (3%) patients. Seventeen (9%) patients had a history of variceal bleeding, 85 (42%) had a history of or current ascites and 38 (19%) had a history of or current signs of hepatic encephalopathy. Median HVPG was 17 (12-21) mm Hg. Twenty-four (12%) patients had subclinical PHT (PH, ie 6-9 mm Hg), 112 (56%) showed an HVPG between 10 and 19 mm Hg, and 65 (32%) had HRPH.

3.2 | Severity of PHT

Patient characteristics were compared by stratification according to severity of PHT, ie HVPG 6-9 mm Hg, 10-19 mm Hg and ≥ 20 mm Hg (Table 1). Aetiologies of liver disease differed significantly among HVPG groups with a continuous increase in ALD prevalence with

rising severity of PHT (17% among patients with 6-9 mm Hg, 38% with 10-19 mm Hg and 54% with ≥ 20 mm Hg, respectively; $P = .021$).

Expectedly, the proportion of patients with decompensated cirrhosis (dACLD) increased with rising severity of PH (4%, 55% and 82%, respectively; $P < .001$). Consequently, median MELD and CTP score increased with HVPG ($P < .001$). ELF score increased significantly across HVPG strata, with a median ELF of 10.1 (9.6-10.7) in patients with an HVPG of 6-9mm Hg, 11.2 (10.4-12.3) with 10-19mm Hg and 11.8 (11.1-12.8) with ≥ 20 mm Hg ($P < .001$).

3.3 | Patient characteristics according to ELF score tertiles

Similarly, patient characteristics were compared after stratification by ELF score tertiles (T1-T3): T1 was defined as ELF < 10.76 , T2 as

N = 201	HVPG 6-9 mm Hg (n = 24)	HVPG 10-19 mm Hg (n = 112)	HVPG ≥ 20 mm Hg (n = 65)	P-value
Age (y)	52.7 \pm 2.3	56.8 \pm 1.1	58.4 \pm 1.5	0.129
Sex (M, %)	16 (67)	74 (66)	45 (69)	0.910
Etiology (n, %)				
ALD	4 (17)	43 (38)	35 (54)	.021
Viral	8 (33)	21 (19)	11 (17)	
Other	12 (50)	48 (43)	19 (29)	
Decompensation (n, %)	1 (4)	62 (55)	53 (82)	<.001
Varices (n, %)				
None	18 (75)	41 (37)	11 (17)	<.001
Small	3 (13)	25 (22)	23 (35)	
Large	1 (4)	43 (38)	30 (46)	
(Unknown)	2 (8)	3 (3)	1 (1.5)	
Child score (points)	5 (5-5)	6 (5-7)	7 (6-9)	<.001
MELD (points)	8 (7-12)	10 (9-14)	12 (10-15)	<.001
Creatinine (mg/dL)	0.73 (0.63-0.87)	0.77 (0.59-1.02)	0.71 (0.60-0.97)	.847
Sodium (mmol/L)	140 (139-142)	139 (137-141)	137 (134-140)	<.001
Albumin (g/dL)	40.8 (37.3-42.4)	37.2 (33.0-40.7)	36.0 (30.2-39.0)	<.001
INR	1.2 (1.0-1.3)	1.3 (1.2-1.5)	1.4 (1.3-1.6)	<.001
Platelets (g/L)	126 (90-162)	99 (70-137)	96 (57-126)	.056
TE (kPa) ^a	16.3 (11.7-20.4)	27.7 (17.0-43.0)	62.2 (34.8-75.0)	<.001
ELF score (points)	10.1 (9.6-10.7)	11.2 (10.4-12.3)	11.8 (11.1-12.8)	<.001
TIMP1 (ng/mL)	251 (217-301)	297 (244-421)	409 (291-495)	<.001
PIIINP (ng/mL)	11.5 (8.8-16.2)	17.9 (10.8-28.3)	20.6 (13.3-33.1)	<.001
HA (ng/mL)	61.4 (43.4-135.7)	195.1 (106.0-392.4)	284.8 (174.9-505.5)	<.001

TABLE 1 Patient characteristics stratified by severity of portal hypertension

Abbreviations: (ALD) Alcohol-related liver disease; (ELF) enhanced liver fibrosis score; (HA) Hyaluronic acid(HVPG) hepatic venous pressure gradient; (INR) International normalized ratio; (M) male gender; (MELD) Model for end-stage liver disease score; (PIIINP) Amino-terminal propeptide of type III procollagen; (TIMP-1) Tissue inhibitor matrix metalloproteinase-1; (VCTE) vibration-controlled transient elastography.

P-values $< .05$ are indicated in bold.

^aReliable TE results available in n = 21 (87.5%), n = 81 (72.3%) and n = 37 (56.9%) patients respectively.

TABLE 2 Patient characteristics stratified by enhanced liver fibrosis (ELF) scores

N = 201	Tertile 1 (n = 67)	Tertile 2 (n = 67)	Tertile 3 (n = 67)	P-value
	ELF < 10.76	ELF 10.76-11.96	ELF > 11.96	
Age (y)	54.7 ± 1.3	59.0 ± 1.6	56.8 ± 1.3	.107
Sex (M, %)	49 (73)	50 (75)	36 (54)	.016
Etiology (n, %)				
ALD	12 (18)	31 (46)	39 (58)	<.001
Viral	23 (34)	9 (13)	8 (12)	
Other	32 (48)	27 (40)	20 (30)	
Decompensation (n, %)	22 (33)	41 (61)	53 (79)	<.001
Varices (n, %)				
None	31 (46)	16 (24)	23 (34)	.036
Small	11 (16)	24 (36)	16 (24)	
Large	22 (33)	26 (39)	26 (39)	
(Unknown)	3 (5)	1 (1.5)	2 (3)	
HVPG (mm Hg)	12 (9-18)	18 (14-21)	19 (16-21)	<.001
Child score (points)	5 (5-5)	6 (5-7)	8 (6-10)	<.001
MELD (points)	9 (8-12)	10 (9-13)	14 (11-17)	<.001
TE (kPa) ^a	18.8 (14.1-28.1)	30.1 (19.4-46.5)	48.0 (29.5-70.0)	<.001
Creatinine (mg/dL)	0.77 (0.63-0.96)	0.74 (0.59-1.06)	0.67 (0.56-0.90)	.222
Sodium (mmol/L)	140 (138-142)	138 (136-140)	138 (135-140)	.001
Albumin (g/dL)	40.7 (38.7-42.4)	37.1 (33.3-40.1)	31.3 (28.1-35.1)	<.001
INR	1.2 (1.1-1.4)	1.3 (1.2-1.4)	1.5 (1.4-1.7)	<.001
Platelets (g/L)	98 (65-133)	105 (77-141)	101 (76-132)	.258

Abbreviations: ALD, alcohol-related liver disease; ELF, enhanced liver fibrosis score; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; M, male gender; MELD, model for end-stage liver disease score; VCTE, vibration-controlled transient elastography.

P-values < .05 are indicated in bold.

^aReliable TE results available in n = 59 (87.5%), n = 49 (88.1%) and n = 53 (79.1%) patients, respectively.

ELF between 10.76 and 11.96 and T3 as ELF > 11.96. CTP score and MELD increased in patients within higher ELF tertiles, as well as the proportion of patients with decompensation (all $P \leq .001$; Table 2).

Furthermore, HVPG increased significantly across tertiles: median HVPG 12 (9-18) mm Hg in T1, 18 (14-21) mm Hg in T2 and 19 (16-21) mm Hg in T3 ($P < .001$). The presence of varices was significantly different between groups stratified by ELF tertiles in the overall cohort, however, a similar proportion of patients had large varices (33% vs 39% vs 39%, respectively; $P = .036$).

3.4 | Correlation between ELF score and its single components with HVPG

ELF score and its single components correlated with HVPG in the overall cohort (Spearman's Rho 0.443, 0.32-0.55; $P < .001$; Figure 1A-D). Among the single ELF components, HA displayed the strongest correlation with HVPG (Rho 0.419, 0.29-0.53; Table 3, Table S2).

After stratifications according to ACLD aetiology, we specifically analysed correlations in patients with ALD and viral

hepatitis. Median HVPG was higher in ALD than viral hepatitis patients (19 [16-21] mm Hg vs 14 [10-20] mm Hg, respectively; $P = .001$). The correlation coefficients were markedly lower in patients with ALD as compared to viral hepatitis or other aetiologies. PIIINP showed no significant association with HVPG in ALD patients, while TIMP1 did not correlate with HVPG in patients with viral hepatitis.

Similar correlation analyses of the HVPG and ELF were performed in subgroups according to severity of PHT: 6-9 mm Hg, 10-19 mm Hg and ≥ 20 mm Hg respectively. Interestingly, ELF score (Rho = 0.569, $P = .004$), PIIINP (Rho = 0.559; $P = .005$) and HA (Rho = 0.475, $P = .019$) showed the strongest correlation in patients with subclinical PHT. ELF score (Rho = 0.304, $P = .001$) and its single components significantly correlated with HVPG in stratum 10-19 mm Hg, while no ELF parameter (eg ELF Rho = -0.023; $P = .853$) showed a meaningful correlation with HVPG in patients with HRP.

Furthermore, patients were stratified by CTP stage and absence/presence of prior events of hepatic decompensation (Figure 1E,F). No correlation between ELF parameters and HVPG was found in patients with CTP stage B/C. Similarly, ELF showed no significant correlation in decompensated (dACLD) patients. Conversely, all

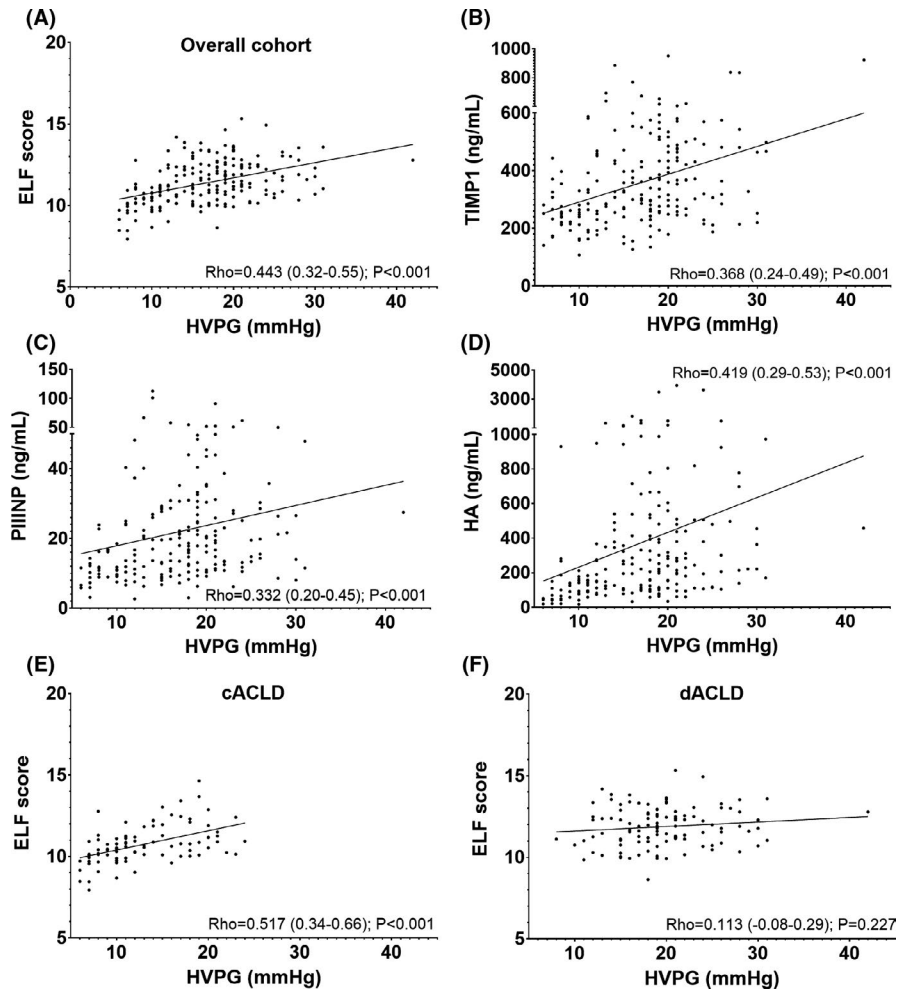


FIGURE 1 Correlation of enhanced liver fibrosis (ELF) score with hepatic venous pressure gradient (HVPG). Abbreviations: cACLD, compensated advanced chronic liver disease; dACLD, decompensated advanced chronic liver disease; ELF, enhanced liver fibrosis score; HA, hyaluronic acid; HVPG, hepatic venous pressure gradient; mm Hg, millimetres of mercury; PIIINP, amino-terminal propeptide of type III procollagen; Rho, Spearman's Rho; TIMP-1, tissue inhibitor matrix metalloproteinase-1

parameters continuously increased with PHT severity in patients within CTP stage A and within cACLD patients. Again, in these patients with persevered liver function, ELF score (Rho = 0.450 for CTP-A and Rho = 0.517 for cACLD; $P < .001$, respectively) and HA (Rho = 0.471 for CTP-A and Rho = 0.535 for cACLD; $P < .001$, respectively) displayed the strongest association with HVPG.

3.5 | Detection of clinically significant PHT by ELF

AUROC analysis was performed to assess whether ELF score and/or its single components accurately detect CSPH (HVPG ≥ 10 mm Hg). In the overall study population, ELF displayed an AUROC of 0.833 (0.75-0.92; $P < .001$, Table 4). CSPH could be ruled-out with an ELF cut-off at <9.7 with 97% sensitivity and 38% specificity. Ruling-in of CSPH with ELF score ≥ 11.1 achieved 61% sensitivity and 92% specificity, with a PPV of 98%. The optimal single ELF cut-off (by Youden's index) was 10.5, yielding 81% sensitivity and 75% specificity and PPV of 96% and NPV of 35% respectively. However, these ELF cut-offs yielded relevant proportions of false-positive and false-negative rates (Table S2).

Among ELF single components, HA achieved the best performance with an AUROC of 0.828 (0.73-0.92; $P < .001$). In contrast,

TIMP1 and PIIINP showed less diagnostic value to detect CSPH: AUROC 0.722 (0.63-0.81; $P < .001$) and 0.748 (0.66-0.83; $P < .001$) respectively (Table S3).

Furthermore, AUROC was analysed by forming subgroups according to ACLD aetiology. In patients with ALD, ELF performed excellent regarding the detection of CSPH with an AUROC 0.978 (0.94-1.00; $P = .001$, Table 4). Ruling-out of CSPH with an ELF score < 9.9 achieved 99% sensitivity, 50% specificity, 98% PPV and 67% NPV. ELF score ≥ 10.3 was the optimal cut-off for ruling-in CSPH (95% sensitivity, 100% specificity, 100% PPV and 50% NPV) in ALD patients. In contrast, ELF was not able to discriminate between subclinical PHT and CSPH in patients with viral hepatitis (AUROC 0.629; $P = .265$).

Finally, we assessed the predictive value for non-invasive CSPH diagnosis in patients with cACLD (Table 2, Figure 2A). In this cohort, ELF AUROC was 0.759 (0.64-0.87; $P < .001$), with an optimal cut-off at 10.5 that detected CSPH with 69% sensitivity, 78% specificity, 90% PPV and 49% NPV. Ruling-in of CSPH in cACLD at an ELF score ≥ 11.1 had 93% PPV with 42% sensitivity and 91% specificity. Moreover, CSPH could be ruled-out in cACLD patients by an ELF cut-off at <9.6 with 97% sensitivity, 26% specificity, 78% PPV and 75% NPV.

In patients with cACLD, HA was the only single parameter suited to detect CSPH, with a slightly but non-significantly better

TABLE 3 Correlation of enhanced liver fibrosis (ELF) score and its single components with hepatic venous pressure gradient (HVPG)

Selection	Parameter	Rho	95%CI	P-value
Overall (N = 201)	ELF	0.443	0.321-0.551	<.001
	TIMP1	0.368	0.238-0.485	<.001
	PIIINP	0.332	0.199-0.453	<.001
	HA	0.419	0.294-0.530	<.001
ALD (N = 83)	ELF	0.281	0.063-0.473	.010
	TIMP1	0.235	0.014-0.434	.033
	PIIINP	0.213	-0.010 to 0.415	.053
	HA	0.283	0.065-0.475	.010
VIRAL (N = 40)	ELF	0.449	0.151-0.673	.004
	TIMP1	0.279	-0.045 to 0.550	.081
	PIIINP	0.328	0.009-0.586	.039
	HA	0.488	0.200-0.699	.001
OTHER (N = 78)	ELF	0.391	0.178-0.569	<.001
	TIMP1	0.323	0.102-0.514	.004
	PIIINP	0.197	-0.034 to 0.407	.084
	HA	0.402	0.191-0.578	<.001
HVPG 6-9 (N = 24)	ELF	0.569	0.203-0.796	.004
	TIMP1	-0.147	-0.529 to 0.284	.493
	PIIINP	0.559	0.189-0.790	.005
	HA	0.475	0.076-0.743	.019
HVPG 10-19 (N = 112)	ELF	0.304	0.120-0.468	.001
	TIMP1	0.247	0.058-0.418	.009
	PIIINP	0.273	0.087-0.441	.004
	HA	0.268	0.081-0.437	.004
HVPG ≥ 20 (N = 65)	ELF	-0.023	-0.273-0.229	.853
	TIMP1	0.020	-0.232 to 0.270	.874
	PIIINP	-0.105	-0.347 to 0.149	.404
	HA	0.021	-0.231 to 0.271	.867
Child-A (N = 116)	ELF	0.450	0.286-0.588	<.001
	TIMP1	0.261	0.077-0.438	.005
	PIIINP	0.237	0.052-0.407	.010
	HA	0.471	0.311-0.605	<.001
Child-B/C (N = 85)	ELF	0.014	-0.206 to 0.233	.896
	TIMP1	0.129	-0.093 to 0.338	.241
	PIIINP	-0.003	-0.222 to 0.216	.979
	HA	-0.009	-0.227 to 0.211	.938
cACLD (N = 85)	ELF	0.517	0.335-0.661	<.001
	TIMP1	0.227	0.062-0.468	.010
	PIIINP	0.291	0.076-0.479	.007
	HA	0.535	0.358-0.675	<.001
dACLD (N = 116)	ELF	0.113	-0.076 to 0.294	.227
	TIMP1	0.186	-0.002 to 0.361	.046
	PIIINP	0.045	-0.144 to 0.231	.633
	HA	0.127	-0.062 to 0.307	.174

Abbreviations: 95%CI, 95% confidence interval; ALD, Alcohol-related liver disease; cACLD, compensated advanced chronic liver disease; dACLD, decompensated advanced chronic liver disease; ELF, enhanced liver fibrosis score; HA, hyaluronic acid; HVPG, hepatic venous pressure gradient; PIIINP, Amino-terminal propeptide of type III procollagen; Rho, Spearman's Rho; TIMP-1, Tissue inhibitor matrix metalloproteinase-1.

P-values < .05 are indicated in bold.

TABLE 4 Diagnostic accuracy of enhanced liver fibrosis (ELF) score and vibration-controlled transient elastography (VCTE) for clinically significant portal hypertension (CSPH) and high-risk portal hypertension (HRPH)

	AUROC	95%CI	P-value	Cut-off	SENS	SPEC	PPV	NPV	PLR	NLR
CSPH—Overall cohort										
ELF	0.833	0.75-0.92	<.001	Youden: 10.5 In: 11.1 Out: 9.7	0.81 0.61 0.97	0.75 0.92 0.38	0.96 0.98 0.92	0.35 0.24 0.6	3.24 7.63 1.56	0.25 0.42 0.08
TE ^a	0.834	0.76-0.91	<.001	Youden: 23.2 In: 23.2 Out: 11.8	0.70 0.70 0.95	0.95 0.95 0.29	0.99 0.99 0.88	0.36 0.36 0.5	14.8 14.8 1.33	0.31 0.31 0.18
CSPH—ALD										
ELF	0.978	0.94-1.00	.001	Youden: 10.3 In: 10.3 Out: 9.9	0.95 0.95 0.99	1 1 0.5	1 1 0.98	0.5 0.5 0.67	— — 1.98	0.05 0.05 0.02
CSPH—VIRAL										
ELF	0.629	0.42-0.84	0.265	—	—	—	—	—	—	—
CSPH—cACLD										
ELF	0.759	0.64-0.87	<.001	Youden: 10.5 In: 11.1 Out: 9.6	0.69 0.42 0.97	0.78 0.91 0.26	0.90 0.93 0.78	0.49 0.37 0.75	3.14 4.67 1.31	0.4 0.64 0.12
TE ^a	0.743	0.62-0.86	.002	Youden: 23.2 In: 23.2 Out: 11.8	0.59 0.59 0.89	0.95 0.95 0.30	0.95 0.95 0.75	0.5 0.5 0.55	11.7 11.7 1.27	0.43 0.43 0.36
HRPH—Overall cohort										
ELF	0.677	0.60-0.75	<.001	Youden: 11.1 In: 13.0 Out: 10.1	0.75 0.18 0.97	0.56 0.9 0.26	0.45 0.48 0.39	0.83 0.7 0.95	1.70 1.80 1.31	0.45 0.91 0.12
TE ^a	0.813	0.74-0.89	<.001	Youden: 27.4 In: 67.1 Out: 27.4	0.92 0.43 0.92	0.59 0.91 0.59	0.45 0.64 0.45	0.95 0.82 0.95	2.23 4.9 2.23	0.14 0.62 0.14

Abbreviations: 95%CI, 95% confidence interval; ALD, alcohol-related liver disease; AUROC, area under the receiver operating characteristics; cACLD, compensated advanced chronic liver disease; CSPH, Clinically significant portal hypertension; ELF, enhanced liver fibrosis score; HRPH, high-risk portal hypertension; NLR, negative likelihood ratio; PLR, positive likelihood ratio; VCTE, vibration-controlled transient elastography.

P-values < .05, PPV and NPV ≥ 0.90, PLR > 7 and NLR < 0.1 are indicated in bold.

^aReliable VCTE results available in n = 139 (69.2%) patients in the overall cohort, and n = 66 (77.6%) patients with cACLD.

performance than ELF score: AUROC 0.787 (0.67-0.90; $P < .001$). Of note, among the single ELF components HA performed reasonable for CSPH prediction in cACLD, however, HA still had limited predictive value for ruling-in and ruling-out CSPH (Table S3 and Paragraph S1).

3.6 | Detection of high-risk PHT by ELF

Similar to AUROC analysis for detection of CSPH, we tested whether ELF and its components accurately detected HRPH (HVPG ≥ 20 mm Hg; Table 4). In the overall cohort, all parameters displayed statistically significant, however, weak potential for

the non-invasive diagnosis of HRPH: AUROC 0.677 (0.60-0.75; $P < .001$) for ELF, 0.673 (0.59-0.75; $P < .001$) for TIMP1, 0.625 (0.55-0.71; $P = .004$) for PIIINP, and 0.663 (0.59-0.74; $P < .001$) for HA (Figure 2B). Non-invasive ruling-in of HRPH by ELF and its single components was suboptimal, however, ruling-out of HRPH by an ELF score < 10.1 yielded a NPV of 95% (39% PPV, 97% sensitivity and 26% specificity).

3.7 | Detection of varices by ELF

Similarly, we performed an exploratory analysis whether ELF was able to detect the presence of any varices or varices needing

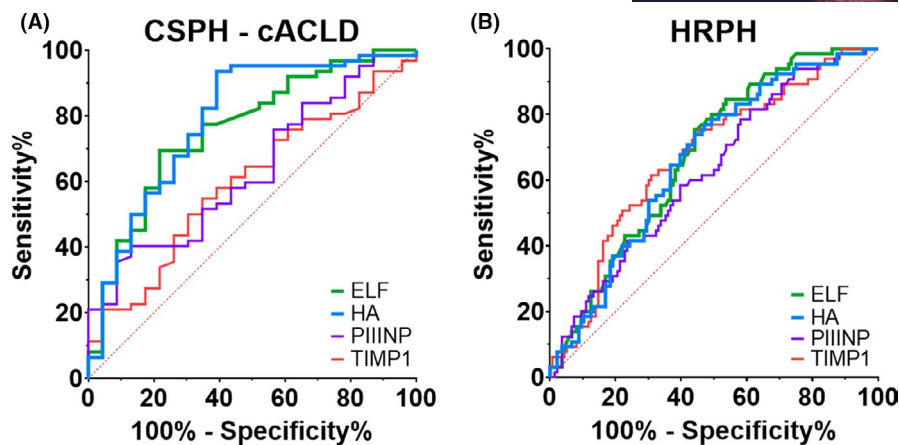


FIGURE 2 Area under the receiver operating characteristics (AUROC) for detection of clinically significant portal hypertension (CSPH) and high-risk portal hypertension (HRPH). (A) CSPH in patients with compensated liver disease (cACLD) and (B) HRPH in the overall cohort. Abbreviations: cACLD, compensated advanced chronic liver disease; CSPH, Clinically significant portal hypertension; ELF, Enhanced liver fibrosis score; HA, Hyaluronic acid; HRP, High-risk portal hypertension; PIIINP, Amino-terminal propeptide of type III procollagen; TIMP-1, Tissue inhibitor matrix metalloproteinase-1

treatment (VNT). Median time span between gastroscopy and hepatic vein catheterization was 0.9 (IQR 0.0-2.6) months, and 55 (27%) patients had gastroscopy on the same day as HVPG/ELF measurement. However, ELF had no value for the detection of any varices or VNT as the AUROCs were only 0.580 ($P = .065$) and 0.552 ($P = .228$) respectively (Figure S2).

3.8 | Diagnostic value of vibration-controlled transient elastography

Reliable VCTE results were obtained in 139 (69%) patients, with a median stiffness of 28.1 (17.6-53.2) kPa. Stratified by PHT severity, median stiffness was 16.3 (11.7-20.4) kPa in patients with HVPG 6-9 mm Hg ($n = 21$, 88%), 27.7 (17.0-43.0) kPa in patients with HVPG 10-19 mm Hg ($n = 81$, 72%) and 62.2 (34.8-75.0) kPa in patients with HVPG ≥ 20 mm Hg ($n = 37$, 57%; $P < .001$ for stiffness comparison between HVPG strata), respectively (Table 1). Correlation between VCTE and ELF was $Rho = 0.591$ (95%CI 0.47-0.69, $P < .001$) and $Rho = 0.668$ (95%CI 0.56-0.75, $P < .001$) between VCTE and HVPG in the overall cohort (Figure S3).

In the overall study cohort, VCTE AUROC was 0.834 (95%CI 0.76-0.91, $P < .001$; Figure S3) for prediction of CSPH, which was nearly identical to ELF (AUROC 0.833). In 66 cACLD patients, VCTE had an AUROC of 0.743 (95% CI 0.62-0.86, $P = .002$), also being comparable to ELF (AUROC 0.759) for diagnosis of CSPH. Ruling-out CSPH by VCTE at <11.8 kPa achieved 94% sensitivity (29% specificity, PPV 88%, NPV 50%) in the overall cohort, and 89% sensitivity but only 55% NPV (30% specificity, 75% PPV) in cACLD patients. CSPH could be ruled-in at >23.2 kPa with 95% specificity (59% sensitivity, 99% PPV, 36% NPV) in the overall cohort, and 95% specificity and 95% PPV (70% sensitivity, 50% NPV) in cACLD.

4 | DISCUSSION

This prospective study of 201 patients undergoing HVPG and simultaneous ELF score measurement is by now the largest analysis investigating whether the ELF score can adequately predict CSPH or HRP in patients with ACLD, while also specifically investigating the diagnostic accuracy of ELF within compensated cirrhosis (cACLD).

ELF score comprises three serum parameters—TIMP1, PIIINP and HA—that reflect fibrosis and matrix remodelling.⁵ While the presence of advanced liver fibrosis is closely linked to the risk of PHT, additional dynamic components determine the severity of PHT and, thus, measurement of HVPG is the current diagnostic gold-standard to detect CSPH.

The identification of non-invasive predictors of CSPH represents an unmet clinical need for patients with cACLD^{18,20} in order to facilitate therapeutic management. However, in patients with cACLD, several serum biomarkers that relate to liver fibrosis and PHT have not been evaluated in the setting of strictly cACLD or have only shown weak-to-moderate associations with HVPG, which limits their diagnostic value.^{25,26}

Since studies have confirmed that ELF score accurately predicts liver fibrosis, ELF depicts an alternative to elastography-based assessment of liver fibrosis, as recently demonstrated for NASH.⁸ However, along with restricted availability in non-tertiary centres, elastography is sometimes limited by obesity and presence of ascites. Not surprisingly, it was also found that ELF single components relate to PHT.²⁷⁻²⁹ Interestingly, Thabut et al demonstrated that correlation of Fibrotest (which comprises five biomarkers related to fibrosis) with HVPG was markedly better (Pearson's $r = .58$) when including patients without PHT, while correlation was weak in patients with HVPG ≥ 6 mm Hg (Pearson's $r = .23$).³⁰ However, the clinical value of this correlation of Fibrotest with HVPG in a population without PHT is limited. In contrast, our study assessed ELF only in patients with an HVPG ≥ 6 mm Hg

and in this setting, the ELF score showed a considerably stronger correlation with HVPG, as previously observed for Fibrotest. Still, we also observed a decrease in the correlation strength between ELF and its single components with increasing HVPG strata. Vizzutti et al reported similar findings for transient elastography, ie a weaker correlation between liver stiffness and HVPG in more pronounced PHT.³¹ Another study that primarily investigated whether quantitative magnetic resonance imaging could predict CSPH that also included patients without PHT, indicated an accurate correlation between ELF and HVPG (Pearson's $r = .758$), but no significant correlation was found in patients with CSPH.³²

Importantly, ELF, Fibrotest and elastography primarily reflect parameters related to hepatic fibrosis, while the development of hyperdynamic circulation that further aggravates PHT in patients with ACLD³³—and especially in decompensated cirrhosis (dACLD)—where the severity of PHT is not sufficiently captured by using fibrosis markers. This pathophysiological explanation was underlined by the lack of correlation between HVPG and ELF in our patients with HRPD.

Considering the diagnostic performance for CSPH screening of other non-invasive fibrosis scores, the Fibrotest had an AUROC of 0.79 for detecting severe PHT (HVPG ≥ 12 mm Hg) in patients with cirrhosis,³⁰ however, again as many as 14% of the included patients did not have PHT. Accordingly, mean/median HVPG was considerably lower³⁰ than in our study.

A previous study (84% CSPH; 58% cACLD) showed that ELF score is able to predict CSPH, however, yielded a low AUROC of 0.68.¹⁵ Conversely, Sandahl et al showed that combining ELF with soluble CD163 achieved an AUROC of 0.91 to predict CSPH in a training cohort and an AUROC of 0.90 in a validation cohort.¹⁶ ELF alone (AUROC 0.88; 90% CSPH) performed slightly better in the study of Sandahl et al as compared to our study (ELF AUROC 0.833; 88% CSPH). Of note, we excluded patients who received concomitant treatment with NSBB at the time of HVPG measurement, while concomitant NSBB therapy was not an exclusion criterium in the study by Sandahl et al. This selection criterium might be relevant since we previously found that liver stiffness (also a marker of “static fibrosis”) and HVPG showed better correlation under NSBB therapy—which is explained by their inhibitory effect on the hyperdynamic circulation as the “dynamic” component or PHT.³⁴

Importantly, ELF was able to rule-in CSPH at a cut-off >11.1 with a PPV of 98%. However, this ELF CSPH cut-off requires validation in independent cohorts, since the related diagnostic indices may have been affected by the high prevalence of CSPH in our study population. Unfortunately, ELF cut-offs for ruling-out CSPH failed to provide clinically meaningful diagnostic value.

Of note, ELF showed an even better diagnostic accuracy for diagnosing CSPH in patients with ALD (AUROC 0.978), as compared to patients with viral hepatitis (AUROC 0.629), while the correlation between ELF and HVPG was considerably weaker in patients with ALD. This counterintuitive observation is explained by more pronounced severity of PHT in ALD patients, who simply had a very high pretest probability of CSPH as compared to viral liver disease. The high AUROC among ALD patients may, thus, be a consequence

of the disproportionately high proportion of easy-to-classify patients with advanced disease in this subgroup. At the same time, there is a “loss-of-correlation” between ELF and HVPG in patients with CSPH (ie the higher HVPG strata), which explains the weaker correlation between ELF and HVPG in ALD patients, in whom CSPH was highly common. Accordingly, the observed differences in AUROC values are primarily a consequence of patient characteristics and should not be interpreted as evidence for aetiology-dependent differences in the diagnostic performance of the test. Thus, differences in discriminative ability of ELF to detect CSPH in patients with ALD or viral liver disease cannot be fully answered by this study, mostly because of the limited number of ALD patients with only subclinical PHT.

While the ELF was of limited accuracy for ruling-in HRPD, an ELF cut-off < 10.1 could, however, rule-out HRPD with a high NPV of 95%. This finding may be useful for clinical decision-making regarding TIPS implantation. For example, early or pre-emptive TIPS implantation has shown favourable impact on patients with acute variceal bleeding (AVB),³⁵ and is currently recommended in patients with AVB if the HVPG is ≥ 20 mm Hg.¹⁹ There also might be clinical applicability of ELF in patients with ascites evaluated for TIPS in order to assess if the refractoriness of ascites is mostly caused by HRPD. However, acute clinical events such as AVB or infections may impact on ELF score via dysregulation of ELF parameters. In our study, patients with acute decompensation and non-elective admission at the time of HVPG measurement were excluded. Therefore, we think that ELF score yields best results for the diagnosis of HRPD (and also for CSPH) if the test is performed under stable conditions without acute decompensation or acute-on-chronic liver failure (ACLF).

Furthermore, liver stiffness measurement by VCTE had similar diagnostic value for prediction of CSPH as compared to ELF both in the overall cohort (AUROC 0.834 and 0.833 respectively) and patients with cACLD (AUROC 0.743 and 0.759 respectively). Previous elastography studies commonly reported better performance of VCTE for cACLD, however, this may be attributed to lower prevalence of CSPH.³⁶⁻³⁸

Importantly, HA performed best in most analyses among all single ELF components, especially in patients with cACLD, which might be explained by its physical-mechanical molecular properties. HA—as an essential component of liver ECM—might correlate more directly with the mechanical component of increased intrahepatic resistance than PIIINP and TIMP1. In contrast, PIIINP in serum was recently discussed to either reflect synthesis or degradation of type III collagen,³⁹ while TIMP1 poses as a regulatory protein for proteinases that are involved in degradation of extracellular matrix.²⁷

Shortcomings of this study include the overrepresentation of patients with CSPH which may have impacted the cut-off for differentiating between subclinical PHT and CSPH. Furthermore, there was a considerable rate of patients with prior decompensation in our study population, in whom the presence of CSPH is highly probable and the clinical relevance of non-invasive tests for CSPH is less meaningful. However, the latter limitation was addressed by an additional analysis in the specific cohort of cACLD patients providing information regarding the diagnostic value of ELF for CSPH in the setting of compensated disease.

In summary, ELF significantly correlates with HVPG and may be used to rule-in CSPH (cut-off > 11.1) and rule-out HRPH (cut-off < 10.1). However, there remains a considerable diagnostic “grey area” where ELF cannot provide a clinically meaningful categorization of PHT severity and HVPG measurements are still necessary to diagnose CSPH.

ETHICS APPROVAL

This study was conducted in accordance with the 1964 Helsinki declaration and its later amendments and approved by the local ethics committee of the Medical University of Vienna (EK1262/2017). All patients gave written informed consent to liver vein catheterizations and provided written consent to be enrolled in the VICIS study (NCT03267615).

CONFLICT OF INTEREST

BeSi received travel support from AbbVie and Gilead. RM received speaker honoraria from Abbott, DiaSorin and Siemens. BeSc received travel support from Abbvie and Gilead. PS received speaking honoraria from Bristol-Myers Squibb and Boehringer-Ingelheim, consulting fees from PharnalN, and travel support from Falk and Phenex Pharmaceuticals. TB received travel support from AbbVie, Bristol-Myers Squibb, and Medis, as well as speaker fees from Bristol-Myers Squibb. DB received travel support from Abbvie and Gilead. MP is an investigator for Bayer, BMS, Lilly and Roche; he received speaker honoraria from Bayer, BMS, Eisai and MSD; he is a consultant for Bayer, BMS, Ipsen, Eisai, Lilly, MSD and Roche; he received travel support from Bayer and BMS. MT received speaker fees from BMS, Falk Foundation, Gilead, Intercept and MSD; advisory board fees from Albireo, BiomX, Boehringer Ingelheim, Falk Pharma GmbH, Genfit, Gilead, Intercept, MSD, Novartis, Phenex and Regulus. He further received travel grants from Abbvie, Falk and Gilead and Intercept and unrestricted research grants from Albireo, Cymabay, Falk, Gilead, Intercept, MSD and Takeda. MM has served as a speaker and/or consultant and/or advisory board member for AbbVie, Bristol-Myers Squibb, Gilead, WL Gore & Associates and Janssen. TR received grant support from Abbvie, Boehringer-Ingelheim, Gilead, MSD, Philips Healthcare and Gore; speaking honoraria from Abbvie, Gilead, Gore, Intercept and Roche, MSD; consulting/advisory board fee from Abbvie, Bayer, Boehringer-Ingelheim, Gilead, MSD and Siemens; and travel support from Boehringer-Ingelheim, Gilead and Roche. AS, EE, RP and AFS declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Simbrunner B, Marculescu R, Scheiner B, et al. Non-invasive detection of portal hypertension by enhanced liver fibrosis score in patients with different aetiologies of advanced chronic liver disease. *Liver Int.* 2020;40:1713-1724. <https://doi.org/10.1111/liv.14498>