Research Article
Cirrhosis and Liver Failure

JOURNAL
OF HEPATOLOGY

Hepatic venous pressure gradient predicts risk of hepatic decompensation and liver-related mortality in patients with MASLD

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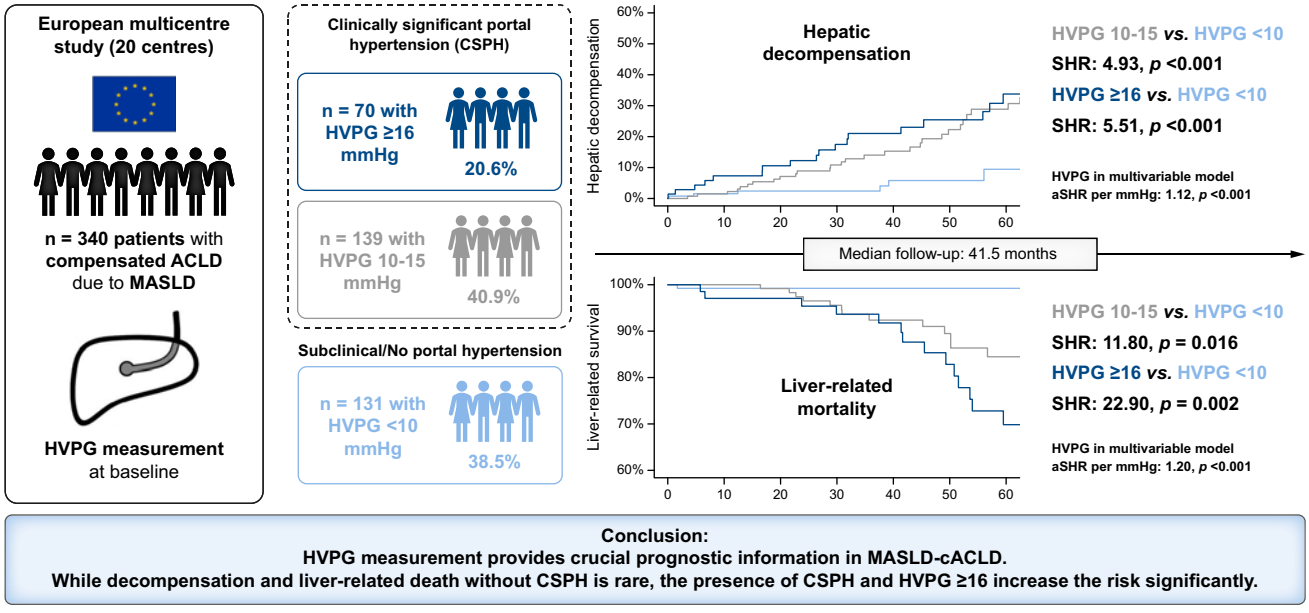
Graphical abstract



Highlights

- HVPG measurement can identify patients with MASLD-cACLD at risk of liver-related events.
- CSPH drives decompensation and liver-related death in MASLD-cACLD.
- The risk of liver-related events in MASLD-cACLD without CSPH is low.
- HVPG can facilitate risk-stratification and treatment decisions in MASLD-cACLD.

Impact and implications

While the incidence of compensated advanced chronic liver disease (cACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing worldwide, insights into the impact of clinically significant portal hypertension (CSPH) on the risk of liver-related events in MASLD-cACLD remain limited. Based on the findings of this European multicentre study including 340 MASLD-cACLD patients, we could show that increasing HVPG values and the presence of CSPH in particular were associated with a significantly higher risk of first hepatic decompensation and liver-related mortality. In contrast, the short-term incidence of decompensation in patients with MASLD-cACLD without CSPH was low and the risk of liver-mortality remained negligible. Thus, HVPG measurements can provide important prognostic information for individualised risk stratification in MASLD-cACLD and may help facilitate the study of novel and promising treatment possibilities for MASLD.

https://doi.org/10.1016/j.jhep.2024.05.033
 J. Hepatol. 2024, 81, 827–836

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Hepatic venous pressure gradient predicts risk of hepatic decompensation and liver-related mortality in patients with MASLD

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Journal of Hepatology **2024**. vol. 81 | 827–836

Background & Aims: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of advanced chronic liver disease (ACLD). Portal hypertension drives hepatic decompensation and is best diagnosed by hepatic venous pressure gradient (HVPG) measurement. Here, we investigate the prognostic value of HVPG in MASLD-related compensated ACLD (MASLD-cACLD).

Methods: This European multicentre study included patients with MASLD-cACLD characterised by HVPG at baseline. Hepatic decompensation (variceal bleeding/ascites/hepatic encephalopathy) and liver-related mortality were considered the primary events of interest.

Results: A total of 340 patients with MASLD-cACLD (56.2% male; median age 62 [55-68] years, median MELD 8 [7-9], 71.2% with diabetes) were included. Clinically significant portal hypertension (CSPH: *i.e.,* HVPG ≥10 mmHg) was found in 209 patients (61.5%). During a median follow-up of 41.5 (27.5-65.8) months, 65 patients developed hepatic decompensation with a cumulative incidence of 10.0% after 2 years (2Y) and 30.7% after 5 years (5Y) in those with MASLD-cACLD with CSPH, compared to 2.4% after 2Y and 9.4% after 5Y in patients without CSPH. Variceal bleeding did not occur without CSPH. CSPH (subdistribution hazard ratio [SHR] 5.13; p <0.001) was associated with an increased decompensation risk and a higher HVPG remained an independent risk factor in the multivariable model (adjusted SHR per mmHg: 1.12, p <0.001). Liver-related mortality occurred in 37 patients at a cumulative incidence of 3.3% after 2Y and 21.4% after 5Y in CSPH. Without CSPH, the incidence after 5Y was 0.8%. Accordingly, a higher HVPG was also independently associated with a higher risk of liver-related death (adjusted SHR per mmHg: 1.20, p <0.001).

Conclusion: HVPG measurement is of high prognostic value in MASLD-cACLD. In patients with MASLD-cACLD without CSPH, the short-term risk of decompensation is very low and liver-related mortality is rare, while the presence of CSPH substantially increases the risk of both.

Introduction

Clinically significant portal hypertension (CSPH) is the main driver of hepatic decompensation in patients with compensated cirrhosis[1–3] and its severity defines distinct prognostic stages.[4] Importantly, CSPH, for which hepatic venous pressure gradient (HVPG) measurement is the diagnostic gold standard, precedes the development of varices and portal hypertension-related complications.[1] Thus, once CSPH has developed, patients are at a substantially increased risk of developing variceal bleeding, ascites, hepatic encephalopathy and liver-related death.[1,4] In a landmark study by D'Amico *et al.*,[5] which included 377 patients with compensated cirrhosis, mainly due

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https://doi.org/10.1016/j.jhep.2024.05.033

to alcohol and viral hepatitis, a cumulative incidence of 33% for ascites and 10% for variceal bleeding during 20 years of follow-up has been reported. Additional studies in similar populations have also shown that development of ascites (18-27%) is the most frequent first decompensation event, followed by variceal bleeding (9.5-18%) and hepatic encephalopathy (2-7%).[4,6]

However, comparable data regarding the natural history and impact of CSPH on first hepatic decompensation in patients with advanced chronic liver disease (ACLD) due to metabolic dysfunction-associated steatotic liver disease (MASLD) remain limited. Nevertheless, these insights would be of high clinical relevance, as 25% of patients with MASLD may already show clinical signs of CSPH at the time of diagnosis.[7] Results from the 'negative' simtuzumab trial with 258 patients with compensated MASLD and histological F4 cirrhosis reported that liver-related events were close to 3-fold more frequent in patients with CSPH.[8] A more recent study by Sanyal *et al.*[9] showed that hepatic decompensation is driven by histological fibrosis severity with a decompensation rate of 2.69 per 100 person-years for those with histological F4 cirrhosis, and virtually no events observed in patients with stages F0–F2. However, no data on the impact of CSPH were reported in this study.[9]

Intriguingly, lower levels of both HVPG and wedged hepatic venous pressure (WHVP) have been found in patients with MASLD at each fibrosis stage when compared to patients with ACLD due to HCV infection.[10] Moreover, a large cross-sectional multicentre study showed a higher prevalence of decompensating events at lower HVPG levels in MASLD than in HCV.[11] In line with this observation, MASLD was suggested to cause – at least subclinical – portal hypertension even in the absence of cirrhosis.[7,12,13] Nevertheless, CSPH in patients with MASLD was almost exclusively found in those with advanced fibrosis.[13] Hepatic steatosis *per se* also seems to only have a marginal impact on portal hypertension severity, particularly once cirrhosis develops.[14] Overall, these controversial findings underline the need for more granular data on the clinical value of HVPG in patients with MASLD-related ACLD.[15]

Thus, the aims of our study were (i) to assess the predictive value of HVPG for the development of hepatic decompensation and liver-related mortality in patients with MASLD-related compensated ACLD (MASLD-cACLD) and (ii) to investigate the incidence of hepatic decompensation and liver-related mortality in distinct HVPG strata.

Patients and methods

Study population

Patients from 20 European centres undergoing HVPG measurement were retrospectively screened for MASLD until Q3/2022. The diagnosis of MASLD was established (i) by liver biopsy showing MASLD histology or (ii) by the treating clinician based on features of the metabolic syndrome and exclusion of other liver disease aetiologies. Only strictly compensated patients with either HVPG values ≥6 mmHg (indicating portal hypertension) and/or a reliable liver stiffness measurement ≥15 kPa (defining ACLD[3]) were included. Exclusion criteria at baseline were (i) presence or history of any hepatic decompensation event (ascites, overt hepatic encephalopathy, variceal bleeding), (ii) Child-Pugh stage ≥B8, (iii) diagnosis of hepatocellular carcinoma (HCC), (iv) portal vein thrombosis (PVT), (v) missing or insufficient follow-up data.

Clinical characteristics, laboratory parameters and clinical follow-up

The date of the first recorded HVPG measurement defined the date of study inclusion (*i.e.*, baseline). Demographic, laboratory/clinical parameters, Child-Pugh score, MELD (model for end-stage liver disease), varices, liver histology (if available), metabolic comorbidities, cardiovascular disease, diagnosis of HCC/PVT and co-medication (*e.g.*, non-selective beta-blockers [NSBBs], statins, metformin, diuretics, and encephalopathy medication) were recorded. During clinical follow-up, the following events were considered the primary events of interest: (i) first occurrence of hepatic decompensation and (ii) liver-related death. For the purpose of this study, first hepatic decompensation was defined by either (i) development of ascites requiring diagnostic/therapeutic paracentesis, (ii) hospital admission for overt hepatic encephalopathy, (iii) acute variceal bleeding or (iv) liver-related death in patients without any other prior documented decompensation event. Death was considered liver-related if it arose as a direct consequence of the progression of the underlying liver disease or was considered to be directly related to the underlying liver disease.

In addition to the primary events of interest, we investigated the incidence of major adverse cardiovascular events (MACEs), HCC (based on unequivocal histological and/or radiological findings) and PVT, as well as incident liver transplantation.

The intake of relevant co-medication (NSBBs, statins, rifaximin) during follow-up was recorded semiquantitatively and patients were classified according to their intake of the respective medication as either 'never' (*i.e.*, 0-10% of the time), 'almost never' (10-50% of the time), 'almost always' (50%-90% of the time) and 'always' (90-100% of the time).

Measurement of the HVPG and VCTE-LSM

Measurement of HVPG was performed according to the standards at the respective study centres, as previously described.[11,16] Measurements within this study were performed as part of the clinical routine assessment of CSPH in patients with cACLD, given the absence of contraindications or lack of consent. CSPH was defined as an HVPG ≥10 mmHg, severe portal hypertension as HVPG ≥16 mmHg. Vibration-controlled transient elastography liver stiffness measurement (VCTE-LSM) was performed, and only patients meeting the VCTE-LSM quality criteria[17] (*i.e.*, ≥10 measurements and an IQR/Median <30% when VCTE-LSM ≥7.1 kPa) were included in the analysis.

Statistical analysis

All statistical analyses were conducted using R 4.2.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Categorical variables are reported as n (%) of patients with the certain characteristic. Pearson's Chi-squared or Fisher's exact tests were used to compare differences in proportions of a certain characteristic between groups. Continuous variables are reported as median (IQR). The presence of a normal distribution was analysed via a visual inspection of density plots and the Shapiro-Wilk test. Group comparisons of continuous data were conducted using an independent samples t-test or a Mann-Whitney *U* test, as applicable. For multiple group

comparisons, a one-way analysis of variance or a Kruskal-Wallis test was conducted, as applicable.

The impact of HVPG on first hepatic decompensation, liver-related death and secondary outcomes was assessed in uni- and multivariable Fine and Gray competing risk regression models[18] and illustrated using cumulative incidence plots. In order to accurately analyse multicentric data, the centre ID of each participating institution was included as a clustering covariate in all multivariable models. The R-package used for all multivariable models was 'crrSC: Competing Risks Regression for Stratified and Clustered Data; https://cran.r-project.org/web/packages/crrSC/'. In addition to HVPG, multivariable models investigating first hepatic decompensation and liver-related death also included age, sex, BMI, the severity of liver dysfunction (*i.e.*, MELD and albumin) and the presence of diabetes. The proportionality of hazards for HVPG in the calculated competing risk models for first hepatic decompensation and liver-related mortality was analysed using modified weighted Schoenfeld residuals (calculated by R package 'crrSC'). Further details on the statistical models used for clustered data analysis and the applied goodness-of-fit test have been described by Zhou *et al.*[19,20] Due to the limited number of cardiovascular events, the respective multivariable models only included HVPG, BMI, MELD, the presence of diabetes and coronary disease.

With regard to competing events, non-liver-related death and liver transplantation, as well as the occurrence of HCC and PVT, were considered competing events within the analysis of hepatic decompensation. For the analysis of liver-related mortality, non-liver-related death and liver transplantation were considered competing events. For the analysis of HCC and PVT occurrence, all-cause death and liver transplantation were considered competing events. For MACE, non-cardiovascular-associated death and liver transplantation were considered competing events. All patients entered the model at the time of HVPG measurement. Of note, six patients experienced liver-related death due to infection or sepsis without a prior documented episode of ascites/variceal bleeding/hepatic encephalopathy. As liver-related death without prior hepatic decompensation is highly unlikely, particularly in the setting of severe infection or sepsis, these events were considered 'any hepatic decompensation' in the models investigating first hepatic decompensation.

The comparison of the predictive capacity of VCTE-LSM, FIB-4 and HVPG was calculated based on time-dependent AUROCs using the R-package 'timeROC: Time-dependent ROC Curve and AUC for Censored Survival Data; https://cran.r-project.org/web/packages/timeROC/' and accounting for competing events. Further details on the methodology are provided in the original work of Blanche *et al.*,[21] on which this package is based. The median follow-up time was calculated using the reverse Kaplan-Meier method. Two-sided p values <0.05 were considered statistically significant.

Ethics

This study was approved by the local ethics committees of the respective centres and performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and its later amendments.

Results

Patient characteristics

Overall, 340 patients with MASLD-cACLD were included in the study. The number of patients from each participating centre is shown in Table S1. One hundred and ninety-one (56.2%) were male with a median age of 62 (55-68) years and a median BMI of 31.7 (28.0-35.7) kg/m^2. A liver biopsy was performed in 282 (82.9%) patients. Of all included patients, 320 (94.1%) had an HVPG ≥6 mmHg and 155 of them also had an LSM-VCTE ≥15 kPa, confirming cACLD. Only 20 (5.9%) patients were included based on LSM-VCTE ≥15 kPa alone.

Metabolic risk factors were common, with diabetes in 71.2%, arterial hypertension in 74.2%, hypertriglyceridemia in 32.4%, and hypercholesterolemia in 52.2%. Regarding disease severity, 328 (96.5%) patients were classified as Child-Pugh stage A and 12 (3.5%) as Child-Pugh stage B7. CSPH was present in 209 patients (61.5%), including 139 patients with an HVPG of 10-15 mmHg (40.9% of the cohort; HVPG 10-15) and 70 patients with severe portal hypertension and an HVPG ≥16 mmHg (20.6% of the cohort; PH16). High-risk varices at baseline were present in 6.9% (n = 8) of patients with HVPG <10 mmHg (HVPG <10) compared to 27.8% (n = 37) with HVPG 10-15 and 61.8% (n = 42) with PH16 (p <0.001). Characteristics of the eight patients without CSPH who presented with high-risk varices are shown in Table S2.

Patients in the HVPG10-15 and PH16 groups also had a significantly higher MELD (p <0.001), higher bilirubin (p <0.001) and international normalized ratio (p <0.001), as well as lower albumin (p <0.001) and platelet count (p <0.001) compared to the HVPG <10 group. Interestingly, patients with more severe portal hypertension (HVPG 10-15/PH16) had a lower median BMI (p = 0.048) and a lower prevalence of hypertriglyceridemia (p = 0.008). The distribution of other metabolic comorbidities was not different. A detailed description of all baseline characteristics is provided in Table 1.

Incidence of first hepatic decompensation and liver-related mortality

During a median follow-up of 41.5 (27.5-65.8) months, 65 patients experienced first hepatic decompensation. The cumulative incidence of first hepatic decompensation was 2.4% in HVPG <10, 8.9% in HVPG 10-15 and 12.2% in PH16 after 2 years and increased to 9.4% in HVPG <10, 28.9% in HVPG 10-15 and 33.8% in PH16 after 5 years. Cumulative incidences of specific decompensating events stratified by the severity of portal hypertension are shown in Table 2 and Fig. 1. A figure additionally including all competing events is shown in Fig. S1. Detailed characteristics of the six patients with a baseline HVPG <10 mmHg experiencing hepatic decompensation are shown in Table S3.

During follow-up, 53 patients died, with 37 of those deaths (69.8%) being considered liver related. The cumulative incidence of liver-related death was 0.8% in HVPG <10, 2.6% in HVPG 10-15, and 4.6% in PH16 after 2 years and increased to 0.8% in HVPG <10, 15.5% in HVPG 10-15 and 30.2% in PH16 after 5 years.

When analysing patients according to the presence of CSPH (Table S4), the cumulative incidence of first hepatic decompensation in patients with MASLD and CSPH was 10.0% after 2 years and increased to 30.7% after 5 years.

Table 1. Patient baseline characteristics stratified by severity of portal hypertension.

	All patients (n = 340)	HVPG <10 mmHg (n = 131)	HVPG 10-15 mmHg (n = 139)	HVPG ≥16 mmHg (n = 70)	*p* value
Sex, male	191 (56.2%)	77 (58.8%)	73 (52.5%)	41 (58.6%)	0.528
Age, years	62 (55-68)	60 (53-66)	64 (57-70)	63 (58-67)	**0.029**
BMI, kg/m^2	31.7 (28.0-35.7)	32.5 (28.6-38.7)	31.5 (28.0-35.0)	31.2 (28.0-33.9)	**0.048**
Diabetes	242 (71.2%)	90 (68.7%)	98 (70.5%)	54 (77.1%)	0.441
Arterial hypertension	247 (74.2%)[7]	93 (72.1%)	101 (74.8%)	53 (76.8%)	0.752
Hypertriglyceridemia	95 (32.4%)[47]	48 (42.5%)	34 (28.8%)	13 (21.0%)	**0.008**
Hypercholesterolemia	164 (52.2%)[26]	72 (58.5%)	60 (48.4%)	32 (47.8%)	0.199
MAP, mmHg	101 (92-111)[79]	102 (93-111)	101 (91-111)	100 (93-110)	0.924
Child-Pugh stage					**0.005**
A5/A6	328 (96.5%)	131 (100%)	130 (93.5%)	67 (95.7%)	
B7	12 (3.5%)	0 (0%)	9 (6.5%)	3 (4.3%)	
MELD	8 (7-9)[10]	7 (6-9)	8 (7-9)	9 (8-10)	**<0.001**
High-risk varices	87 (27.4%)[23]	8 (6.9%)	37 (27.8%)	42 (61.8%)	**<0.001**
Bilirubin, mg/dl	0.75 (0.57-1.08)	0.67 (0.45-0.90)	0.80 (0.60-1.10)	0.89 (0.69-1.40)	**<0.001**
Albumin, g/L	4.1 (3.8-4.3)[4]	4.2 (3.9-4.5)	4.0 (3.8-4.2)	3.9 (3.7-4.3)	**<0.001**
Creatinine, mg/dl	0.78 (0.65-0.91)[2]	0.81 (0.69-0.94)	0.73 (0.62-0.90)	0.79 (0.64-0.87)	**0.009**
INR	1.10 (1.03-1.20)[9]	1.05 (1.00-1.13)	1.15 (1.06-1.24)	1.20 (1.10-1.26)	**<0.001**
Platelet count, G/L	126 (89-177)[10]	172 (127-221)	116 (86-161)	91 (66-116)	**<0.001**
AST, IU/L	43 (32-57)[6]	41 (30-53)	44 (34-60)	44 (34-57)	0.065
ALT, IU/L	42 (28-58)[6]	43 (31-67)	42 (28-57)	37 (27-54)	0.122
GGT, IU/L	106 (63-210)[17]	90 (58-172)	111 (63-185)	132 (74-273)	**0.022**
FIB-4	3.28 (2.23-5.08)[18]	2.33 (1.42-3.07)	3.63 (2.59-5.52)	5.20 (3.45-6.88)	**<0.001**
Thrombocytopenia (<150 G/L)	205 (62.1%)	49 (39.5%)	94 (69.1%)	62 (88.6%)	**<0.001**
VCTE-LSM, kPa	22.8 (15.7-34.0)[123]	17.2 (15.3-23.6)	26.0 (16.8-37.3)	32.4 (22.2-45.3)	**<0.001**
VCTE-LSM ≥20 kPa	126 (58.1%)	28 (34.6%)	66 (68.0%)	32 (82.1%)	**<0.001**
VCTE-LSM ≥25 kPa	94 (43.3%)	17 (21.0%)	52 (53.6%)	25 (64.1%)	**<0.001**
Baveno VII CSPH criteria	112 (53.1%)[129]	19 (24.7%)	62 (65.3%)	31 (79.5%)	**<0.001**
Histological fibrosis stage					**<0.001**
F2 fibrosis	11 (3.9%)	8 (6.7%)	3 (2.6%)	0 (0.0%)	
F3 fibrosis	66 (23.4%)	38 (31.9%)	23 (20.0%)	5 (10.4%)	
F4 fibrosis	190 (67.4%)	62 (52.1%)	85 (73.9%)	43 (89.6%)	

Data presented as n (%) or median (IQR). Continuous variables were compared using a one-way analysis of variance or a Kruskal-Wallis test, depending on the presence of a normal distribution. Categorical variables were compared using the Pearson's Chi-squared test or Fisher's exact test. Missing data are noted in superscript. Liver biopsy results available in 282 patients. Baveno VII non-invasive CSPH rule-in criteria: LSM ≥25 kPa or LSM 20-25 kPa + PLT <150 G/L. CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MAP, mean arterial pressure; MELD, model for end-stage liver disease; PLT, platelet count; VCTE-LSM, vibration-controlled transient elastography liver stiffness measurement. *p* values in bold indicate statistical significance.

Risk factors for hepatic decompensation and liver-related mortality

When analysing risk factors for first decompensation, HVPG (per mmHg; adjusted subdistribution hazard ratio [aSHR] 1.12, 95% CI 1.07-1.18, *p* <0.001) emerged as the key independent factor associated with the development of decompensation (Table 3A, Fig. 2A,B and S2).

When liver-related death was considered as the outcome of interest, HVPG (per mmHg; aSHR 1.20, 95% CI 1.17-1.24, *p* <0.001) and albumin (per g/L; aSHR 0.33, 95% CI 0.21-0.53, *p* <0.001) remained independent risk factors (Table 3B, Fig. 2C,D).

With regard to intake of relevant co-medications during follow-up, both NSBBs and rifaximin were prescribed more frequently in patients with more severe portal hypertension (Table S5). Specifically, while only 7.8% (n = 10) in the HVPG <10 group were classified to have 'always' been on NSBB therapy during the study period, the percentage increased to 27.5% (n = 38) in HVPG 10-15 and 50.0% (n = 34) in PH16 (*p* <0.001). Similarly, the percentage of patients who were classified to have 'always' been on rifaximin was significantly lower in HVPG <10 (0%, n = 0) when compared to HVPG 10-15 (2.2%, n = 3) or PH16 (4.3%, n = 3) (*p* <0.001). As for statins, there was no difference in the intake in different HVPG strata. Importantly, neither the inclusion of NSBBs, statins or rifaximin intake in additional multivariable outcome models altered the significant association between a higher HVPG and an increased risk of hepatic decompensation or liver-related mortality (Table S6).

Non-invasive tests for the prediction of hepatic decompensation

The value of VCTE-LSM and FIB-4 as non-invasive predictors of decompensation during follow-up was analysed and compared to HVPG based on time-dependent AUROCs. In order to provide comparable results, this analysis was only conducted in the 202 patients for whom all three variables (*i.e.*, HVPG, VCTE-LSM, FIB-4) were available. Furthermore, considering that decompensation within the first year of follow-up only occurred in three patients within this subgroup, the predictive value of HVPG, VCTE-LSM and FIB-4 was not compared for this time period (*i.e.*, the analysis focused on years 2-5).

Interestingly, while FIB-4 consistently showed the highest AUROC for the prediction of hepatic decompensation, VCTE-LSM performed numerically worse than both HVPG and FIB-4 in our MASLD-cACLD cohort (Fig. S3, Table S7). Following univariable analysis limited to the subgroup of patients with all three variables available, both VCTE-LSM (SHR 1.02, 95% CI 1.00-1.04, *p* = 0.048) and FIB-4 (SHR 1.07, 95% CI 1.05-1.10,

Table 2. Cumulative incidence and number of events of ascites, hepatic encephalopathy, variceal bleeding, any hepatic decompensation, liver-related mortality and cardiovascular events stratified by severity of portal hypertension.

	All (n = 340)		HVPG <10 mmHg (n = 131)		HVPG 10-15 mmHg (n = 139)		HVPG ≥16 mmHg (n = 70)	
	CI	Events	CI	Events	CI	Events	CI	Events
Ascites								
6 months	0.9%	n = 3	1.5%	n = 2	0.7%	n = 1	0.0%	n = 0
1 year	1.2%	n = 4	1.5%	n = 2	0.7%	n = 1	1.5%	n = 1
2 years	2.2%	n = 7	2.4%	n = 3	1.5%	n = 2	3.1%	n = 2
5 years	9.0%	n = 17	7.8%	n = 5	8.8%	n = 7	10.0%	n = 5
Hepatic encephalopathy								
6 months	0.0%	n = 0	0.0%	n = 0	0.0%	n = 0	0.0%	n = 0
1 year	0.0%	n = 0	0.0%	n = 0	0.0%	n = 0	0.0%	n = 0
2 years	1.8%	n = 5	0.0%	n = 0	2.6%	n = 3	3.3%	n = 2
5 years	7.8%	n = 14	1.7%	n = 1	11.4%	n = 9	7.7%	n = 4
Variceal bleeding								
6 months	1.2%	n = 4	0.0%	n = 0	0.7%	n = 1	4.3%	n = 3
1 year	1.8%	n = 6	0.0%	n = 0	1.5%	n = 2	5.8%	n = 4
2 years	2.8%	n = 9	0.0%	n = 0	3.9%	n = 5	5.8%	n = 4
5 years	4.9%	n = 14	0.0%	n = 0	5.9%	n = 7	11.0%	n = 7
Any hepatic decompensation								
6 months	2.1%	n = 7	1.5%	n = 2	1.5%	n = 2	4.3%	n = 3
1 year	3.0%	n = 10	1.5%	n = 2	2.2%	n = 3	7.3%	n = 5
2 years	7.2%	n = 22	2.4%	n = 3	8.9%	n = 11	12.2%	n = 8
5 years	24.4%	n = 50	9.4%	n = 6	28.9%	n = 26	33.8%	n = 18
Liver-related mortality								
6 months	0.6%	n = 2	0.8%	n = 1	0.0%	n = 0	1.5%	n = 1
1 year	0.9%	n = 3	0.8%	n = 1	0.0%	n = 0	2.9%	n = 2
2 years	2.4%	n = 7	0.8%	n = 1	2.6%	n = 3	4.6%	n = 3
5 years	15.6%	n = 28	0.8%	n = 1	15.5%	n = 13	30.2%	n = 14
Cardiovascular events								
6 months	1.2%	n = 4	0.0%	n = 0	2.9%	n = 4	0.0%	n = 0
1 year	1.8%	n = 6	0.8%	n = 1	3.7%	n = 5	0.0%	n = 0
2 years	3.5%	n = 11	1.7%	n = 2	4.5%	n = 6	4.9%	n = 3
5 years	9.9%	n = 20	3.0%	n = 3	12.6%	n = 11	12.2%	n = 6

Incidences of ascites, hepatic encephalopathy and variceal bleeding refer to the respective event as first decompensation event. n = 6 patients experienced liver-related death (infection/sepsis) without prior documented ascites/variceal bleeding/hepatic encephalopathy (n = 5 within 5 years) – this was considered 'any hepatic decompensation'. CI, cumulative incidence; HVPG, hepatic venous pressure gradient.

p <0.001) were significantly associated with the risk of first hepatic decompensation. Nevertheless, only FIB-4 remained independently associated with hepatic decompensation following multivariable analysis (aSHR 1.06, 95% CI 1.03-1.09, *p* <0.001; Table S8). Subsequently, we investigated the concordance between HVPG, VCTE-LSM and FIB-4 cut-offs used for establishing an increased risk of decompensation. Interestingly, of all patients within this subgroup who eventually

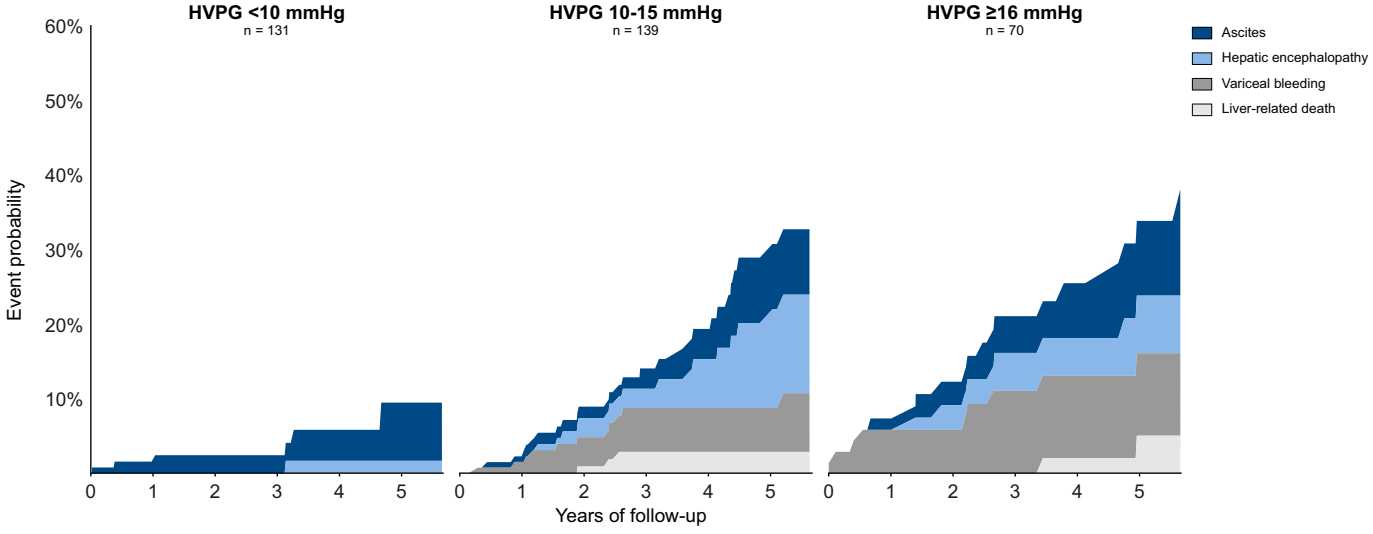

Fig. 1. Stacked cumulative incidence curves for the respective first decompensation event during follow-up, stratified according to severity of portal hypertension. HVPG, hepatic venous pressure gradient.

Table 3. Risk factors for hepatic decompensation and liver-related mortality in patients with MASLD-cACLD.

	Univariable analysis			Multivariable analysis		
Decompensation	**SHR**	**95% CI**	***p* value**	**aSHR**	**95% CI**	***p* value**
Age (per year)	1.01	0.98-1.04	0.604	1.00	0.98-1.02	0.965
Sex (male)	0.89	0.56-1.44	0.646	0.92	0.61-1.38	0.687
BMI (per kg/m^2)	0.96	0.92-1.01	0.099	0.97	0.94-1.00	0.069
MELD (per point)	1.10	1.04-1.16	**<0.001**	1.06	0.97-1.16	0.218
Albumin (per g/L)	0.52	0.30-0.92	**0.025**	0.71	0.40-1.25	0.239
Diabetes (yes)	0.83	0.50-1.35	0.444	0.83	0.49-1.40	0.479
HVPG (mmHg)	1.15	1.09-1.20	**<0.001**	1.12	1.07-1.18	**<0.001**
HVPG strata						
<10 mmHg	Reference					
10-15 mmHg	4.93	2.08-11.70	**<0.001**			
≥16 mmHg	5.51	2.20-13.80	**<0.001**			
Liver-related mortality	**Univariable analysis**			**Multivariable analysis**		
	SHR	**95% CI**	***p* value**	**aSHR**	**95% CI**	***p* value**
Age (per year)	1.03	0.99-1.08	0.175	1.03	0.99-1.08	0.106
Sex (male)	2.26	1.09-4.70	**0.029**	3.16	0.76-13.04	0.112
BMI (per kg/m^2)	0.96	0.89-1.04	0.353	0.98	0.94-1.03	0.386
MELD (per point)	1.13	1.06-1.21	**<0.001**	1.03	0.96-1.10	0.406
Albumin (per g/L)	0.32	0.15-0.71	**0.005**	0.33	0.21-0.53	**<0.001**
Diabetes (*vs.* no diabetes)	0.52	0.28-0.98	**0.044**	0.64	0.31-1.31	0.220
HVPG (per mmHg)	1.17	1.12-1.21	**<0.001**	1.20	1.17-1.24	**<0.001**
HVPG strata						
<10 mmHg	Reference					
10-15 mmHg	11.80	1.57-88.70	**0.016**			
≥16 mmHg	22.90	3.10-169.00	**0.002**			

Uni- and multivariable Fine and Gray competing risk regression models. HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease. *p* values in bold indicate statistical significance.

decompensated (n = 32/202), 29 patients (90.6%) presented with an HVPG ≥10 mmHg (*i.e.*, CSPH) and 27 (84.4%) with a FIB-4 above 2.67. Importantly, all 27 patients with a FIB-4 above 2.67 also had CSPH. In contrast, only 16 patients who decompensated (50.0%) showed a VCTE-LSM ≥25 kPa and for four patients, VCTE-LSM at baseline was even <15 kPa. Of note, despite the presence of VCTE-LSM <15 kPa, these four patients not only had CSPH and a FIB-4 >2.67, but also splenomegaly, oesophageal varices, and thrombocytopenia.

In addition to analysing the role of VCTE-LSM and FIB-4, further models including the presence of varices, collaterals, thrombocytopenia and splenomegaly as surrogates of portal hypertension were conducted (Table S9). The prevalence of these parameters stratified by the severity of portal hypertension is shown in Table S10. The presence of varices and thrombocytopenia were both associated with a significantly higher risk of first hepatic decompensation, yet this was not true for the presence of collaterals or splenomegaly.

Incidence and risk factors for cardiovascular events in patients with MASLD-cACLD

The cumulative incidence of MACEs during follow-up in the overall cohort was 1.2% after 6 months, 1.8% after 1 year, 3.5% after 2 years and 9.9% after 5 years. In order to identify risk factors for MACEs, we performed multivariable analyses accounting for different metabolic and hepatic cofactors. Interestingly, while the severity of portal hypertension was associated with the risk of MACEs within the univariable analysis, the presence of coronary artery disease emerged as the primary factor associated with MACEs in the multivariable models (Table S11, Fig. S4). Both a higher BMI and diabetes were not independently associated with MACEs in our cohort.

Incidence and risk factors for HCC and PVT in patients with MASLD-cACLD

During follow-up, HCC occurred in 30 patients, with a cumulative incidence of 0.9% in HVPG <10, 4.6% in HVPG10-15 and 3.1% in PH16 after 2 years and 2.5%, 16.0% and 13.7% after 5 years, respectively (Tables S12A and 13A, Fig. S5). When investigating the impact of HVPG on HCC incidence, both CSPH (*vs.* no CSPH; SHR 2.28, 95% CI 0.85-6.09, $p = 0.101$) as well as HVPG10-15 (*vs.* HVPG <10; SHR 2.32, 95% CI 0.83-6.47, $p = 0.109$) and PH16 (*vs.* HVPG <10; SHR 2.21, 95% CI 0.73-6.67, $p = 0.161$) were associated with a numerically higher risk of HCC occurrence.

PVT occurred in 25 patients during the follow-up period, with a cumulative incidence of 0.8% in HVPG <10, 3.3% in HVPG10-15 and 0.0% in PH16 after 2 years and 0.8%, 10.0% and 14.8% after 5 years, respectively (Tables S12B and S13B, Fig. S6). When investigating the impact of HVPG on PVT incidence, both CSPH (*vs.* no CSPH; SHR 5.41, 95% CI 1.26-23.20, $p = 0.023$) as well as HVPG10-15 (*vs.* HVPG <10; SHR 5.63, 95% CI 1.29-24.60, $p = 0.022$) and PH16 (*vs.* HVPG <10; SHR 5.05, 95% CI 1.03-24.60, $p = 0.045$) were associated with a significantly higher risk of PVT.

Discussion

In this large multicentre study, we evaluated the impact of portal hypertension on the risk of first hepatic decompensation and liver-related mortality in 340 patients with MASLD-

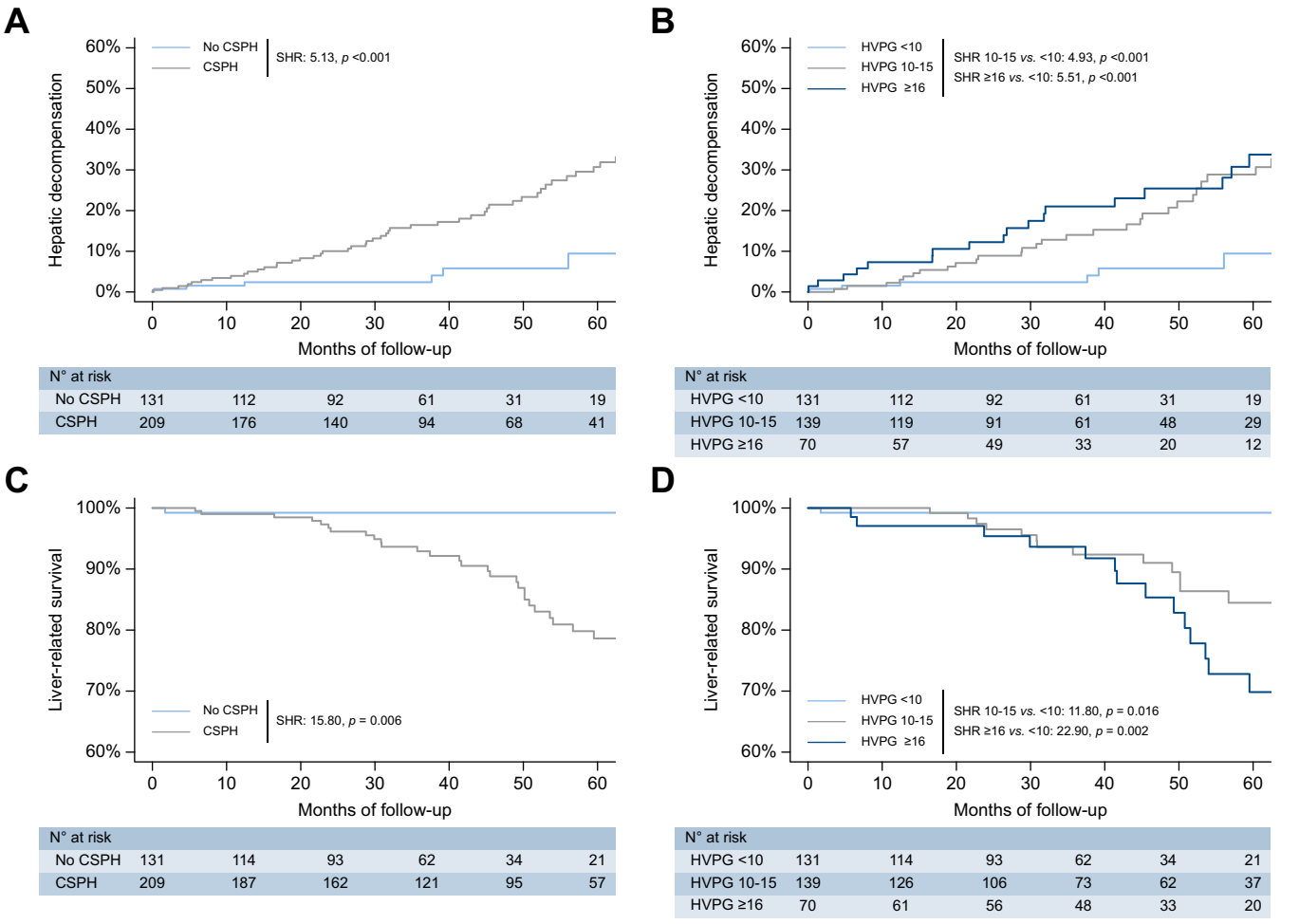

Fig. 2. Cumulative incidence of hepatic decompensation and liver-related mortality. Cumulative incidence of hepatic decompensation according to (A) presence/absence of CSPH and (B) HVPG strata. Cumulative incidence of liver-related mortality according to (C) presence/absence of CSPH and (D) HVPG strata. Reported SHRs and *p* values based on univariable Fine and Gray competing risk analyses. CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; SHR, subdistribution hazard ratio.

associated cACLD. We used the diagnostic gold standard HVPG to assess the severity of portal hypertension and to stratify our patients according to the presence/absence of CSPH and high-risk portal hypertension (HVPG ≥16 mmHg). Our study demonstrates that higher HVPG values are associated with an increased risk of hepatic decompensation and liver-related death in patients with MASLD-cACLD. Importantly, this association remained true even after accounting for age, sex, relevant comorbidities or co-medications and the severity of liver disease. Overall, our data fill an important knowledge gap on the prognostic role of HVPG in MASLD, as previous studies that have identified CSPH as a risk factor for decompensation mostly focused on other liver disease aetiologies.[2,22,23] Specifically, per mmHg HVPG increase, we observed a 12% and 20% increased subdistribution hazard for hepatic decompensation and liver-related mortality, respectively. Interestingly, in the simtuzumab trial that also included HVPG measurements, a similar risk was attributed to portal hypertension severity, with a 15% increased risk of liver-related events per mmHg HVPG increase.[8]

Our study also reports cumulative incidence rates for key liver-related events occurring in MASLD-cACLD. These are not only important for risk stratification in daily clinical practice but are also valuable for designing trials in patients with MASLD-cACLD. At 5 years of follow-up, the cumulative incidence of first hepatic decompensation in patients with CSPH was 30.7%: 9.2% for ascites, 10.0% for hepatic encephalopathy and 7.7% for variceal bleeding. When comparing our results to the available literature, a similar decompensation pattern has been observed in a large prospective study by Sanyal *et al.*[9] Nevertheless, the clinical spectrum of decompensation in MASLD-cACLD, as observed in our and other cohorts,[9] are slightly different to other liver disease aetiologies, for which the cumulative incidence rates were highest for ascites (18-27%), followed by variceal bleeding (9.5-18%) and hepatic encephalopathy (2-7%).[4–6]

Notably, while most events occurred in patients with CSPH, decompensation, albeit at a markedly lower rate, also occurred in patients with MASLD and HVPG <10 mmHg, which might imply an underestimation of portal hypertension severity by

HVPG in MASLD-cACLD.[24,25] In line with this hypothesis, it has been shown that decompensation in HVPG <10 mmHg occurred in 9% of patients with MASLD, yet not in patients with HCV.[11] Furthermore, a previous study showed lower HVPG values in patients with MASLD when compared to patients with HCV within similar stages of fibrosis[10] and hepatic decompensation was reported to occur at lower HVPG thresholds in MASLD than HCV.[11] Accordingly, WHVP did not reflect portal pressure measured during transjugular intrahepatic portosystemic shunt procedures as accurately in MASLD cirrhosis, when compared to alcohol- or HCV-related cirrhosis.[26] Importantly, only patients with decompensated MASLD cirrhosis were included in the latter study[26] and similar data in MASLD-cACLD are not available. The fact that HVPG seems to underestimate portal pressure in MASLD cirrhosis is further suggested by the presence of (high-risk) oesophageal varices in a few patients without CSPH in our cohort. In summary, previous observations, combined with the findings of our analyses, support the hypothesis of a presinusoidal component of portal hypertension in MASLD.[7,26]

Nevertheless, it must also be considered that, in our study, only two patients without CSPH developed hepatic decompensation within the first year of follow-up, with a respective HVPG of 7 and 9 mmHg at baseline. Thus, one may also argue that the progression of MASLD and portal hypertension or the occurrence of a concomitant infection, which was observed in one of the two abovementioned patients, could explain the occurrence of decompensation in these patients. Variceal bleeding, however, did not occur in any patient without CSPH. When compared to previous studies including other aetiologies, similarly low rates of decompensation in patients with HPVG <10 mmHg have been reported,[2,27] yet events did not occur before 20 months of follow-up.[2] Overall, these observations warrant further studies and might lead to adapted risk stratification (HVPG- and aetiology-based) in order to effectively prevent hepatic decompensation, *e.g*. via early implementation of NSBB therapy as suggested by current guidelines.[3]

Interestingly, while HVPG was associated with an increased risk of MACEs during follow-up within the univariable analysis, the presence of coronary artery disease emerged as the primary risk factor in our multivariable models.

The widely available non-invasive fibrosis markers FIB-4 and VCTE-LSM were also predictive of hepatic outcomes in our cohort, although VCTE-LSM seemed to perform worse than HVPG. This contrasts with the findings of a recent study,[28] which notably also included patients without advanced disease, who are easy to classify in terms of decompensation risk. In line with this consideration, the time-dependent AUROCs shown within this study decreased from the derivation to the validation cohort, with the latter showing more advanced disease. Furthermore, it has to be acknowledged that the number of events that occurred within the first years of follow-up in our study, particularly in the analysed subgroup, was limited and that the performance of VCTE-LSM increased steadily during long-term follow-up, thus warranting a careful interpretation of our findings. Notably, the possibility of longitudinally monitoring individual patients with MASLD by non-invasive VCTE-LSM[29] or lab-based models[30] may increase its prognostic value, as this approach is not as feasible for HVPG measurements due to the (minimally) invasive nature.

While our findings are based on a large number of well-characterised patients from multiple European centres with expertise in HVPG measurement, some limitations need to be considered: First, data were collected retrospectively. Nevertheless, outcome data from a MASLD-cACLD cohort of this size, who were characterised by HVPG, is scarce and we recruited a well-powered cohort of 340 patients from multiple haemodynamic centres. Second, as HVPG is not widely available and is mostly performed based on the clinical suspicion of ACLD or portal hypertension, this cohort represents tertiary care and might have been prone to selection bias. Nevertheless, selection occurred in multiple centres outside a specific research/trial setting and thus reflects routine (tertiary care) practice. Third, while we accounted for potential disease-modifying co-medication in additional multivariable models, the prescription/intake of these therapies represents a surrogate for a more severe underlying disease (*i.e.*, statins for dyslipidaemia, NSBBs for CSPH/varices and rifaximin for a perceived higher risk of encephalopathy). Thus, future randomised-controlled trials are required to investigate their role in MASLD. Lastly, liver biopsy was not available in all patients (available in 82.9%). However, in the remaining patients, MASLD was diagnosed after ruling out other relevant aetiologies by expert hepatologists,[31] which widely reflects current clinical practice outside of pharmaceutical trials.

Importantly, it remains to be shown whether changes in HVPG over time are of prognostic value in MASLD-cACLD and whether these changes in HVPG reflect benefits of liver-directed therapies (*e.g.* anti-diabetic drugs), as previously shown for aetiological treatment in HCV-induced ACLD.[32,33] In the simtuzumab trial, the absence of <20% reduction in HVPG or a decrease to HVPG <10 mmHg was associated with a significantly higher risk of liver-related events.[8] Furthermore, comparing cirrhosis regressors *vs*. non-regressors, the former showed a higher reduction in HVPG.[34] Importantly, a small but clinically relevant study has shown that HVPG response to NSBB therapy suggests protection from bleeding.[35] In addition to NSBBs, therapies aimed at reducing portal pressure in pre-clinical MASLD (cirrhosis) models have shown promising results[36–39] and are currently being tested in clinical trials involving patients with compensated MASLD cirrhosis.[40,41] Another approach that has recently been shown to exert beneficial effects regarding non-alcoholic steatohepatitis resolution and improvement in liver fibrosis, including in patients with advanced F3 fibrosis, is the liver-directed, thyroid hormone receptor beta-selective agonist resmetirom.[42] Thus, HVPG-driven studies may help clarify whether resmetirom can also improve portal hypertension and clinical outcomes in patients with more advanced disease stages. Overall, given these promising results on the predictive value of HVPG in MASLD-cACLD, prospective studies are warranted to assess the impact of aetiological (MASLD-directed) and non-aetiological (CSPH- or fibrosis-directed) therapies on portal hypertension severity and hepatic decompensation in MASLD.

In conclusion, HVPG measurement is of strong prognostic value in patients with MASLD-associated cACLD. In patients

with MASLD without CSPH, the short-term risk of hepatic decompensation is very low and liver-related mortality is rare. In contrast, the presence of CSPH raises the risk of hepatic decompensation to 10% within 2 years and 31% within 5 years, which increases further if HVPG rises to values ≥16 mmHg. Thus, HVPG can not only provide important prognostic information for individualised risk stratification and treatment decisions in patients with MASLD-cACLD but may also be a valuable parameter for identifying suitable patients for therapeutic trials in MASLD-related cirrhosis.

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Abbreviations

ACLD, advanced chronic liver disease; aSHR, adjusted subdistribution hazard ratio; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; MACE, major adverse cardiovascular events; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; NSBB, non-selective beta-blocker; PVT, portal vein thrombosis; SHR, subdistribution hazard ratio; VCTE-LSM, vibration-controlled transient elastography liver stiffness measurement; WHVP, wedged hepatic venous pressure.

Financial support

No financial support was received for this study.

Conflict of interest

R.PAT., BS.HOF., G.SEM., A.BAG., I.LUZ., V.HER., I.GRA., JC.GAR., D.SAL., F.INU, F.SCH., L.MOG., PE.RAT., E.LLO., L.TEL., A.ALB., JI.FOR., A.PUE., G.TOS., M.PRI., A.ZIP., E.VUI., A.BER., MG.TAR., V.TAR., B.PRO., C.JAN., M.PRAK., W.GU, L.IBA., J.RIV., JM.PER., E.ALV., C.VIL., H.LAR., C.BUR., W.LAL., A.ARD. and H.MAS. declare no conflicts of interest. W.KWA.: Co-inventor of a patent on the use lipopigment imaging for disease filed by MIT/MGH; travel grant from Norgine; speakers fee from PanNASH initiative. J.TRE.: Speaking and/or consulting fees from Versantis, Gore, Boehringer-Ingelheim, Falk, Grifols, Genfit and CSL Behring. R.BAN.: Speaking honoraries from Abbvie, Gilead, Gore; consulting/advisory board fee from Abbvie, Intercept, MSD. J.GEN.: Consulting/advisory board fee from Boehringer-Ingelheim. T.VAN.: Recipient of a senior clinical research mandate from the Fund for Scientific Research (FWO) Flanders (18B2821N); advisory committees or review panels for Janssen Pharmaceuticals, Gilead Sciences, Abbvie, BMS, WL Gore; grant/research support from Gilead Sciences, Roche, BMS; speaking and teaching support from Gilead Sciences, BMS. M.TRA.: Consulting for Abbvie, Albireo, BMS, BI, Falk, Gilead, Genfit, Hightide, Intercept, Janssen, MSD, Novartis, Phenex, Pliant, Regulus, Siemens, Shire; grants from Albireo, Alnylam, Cymabay, Falk, Gilead, Intercept, MSD, Takeda, Ultragenyx; speakers bureau for BMS, Falk, Gilead, Intercept, MSD, Roche, Madrigal; co-inventor patent on medical use of nor UDCA. M.MAN.: Speaker and/or consultant and/or advisory board member for AbbVie, Bristol-Myers Squibb, Collective Acumen, Gilead and W. L. Gore & Associates. S.FRA.: Senior clinical research mandate from the Fund for Scientific Research (FWO) Flanders (1802154N); advisor and/or lecturer for Roche, Gilead, Abbvie, Bayer, BMS, MSD, Janssen, Actelion, Astellas, Genfit, Inventiva, Intercept, Genentech, Galmed, Promethera, Coherus and NGM Bio. T.REI.: Grant support from Abbvie, Boehringer-Ingelheim, Gilead, MSD, Philips Healthcare, Gore; speaking honoraria from Abbvie, Gilead, Gore, Intercept, Roche, MSD; consulting/advisory board fee from Abbvie, Bayer, Boehringer-Ingelheim, Gilead, Intercept, MSD, Siemens; travel support from Boehringer-Ingelheim, Gilead and Roche.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Research design (R.P., W.K., S.F., T.R.), data acquisition (all authors), data analysis (R.P., BS.H., M.M., T.R.), critical revision (all authors). R.P., BS.H. and T.R. drafted the manuscript. All authors approved the final version of this manuscript.

Data availability statement

Data and results are available upon reasonable request to the corresponding author.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2024.05.033.

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Author names in bold designate shared co-first authorship

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Keywords: portal hypertension; MASLD; hepatic venous pressure gradient; hepatic decompensation; advanced chronic liver disease.
Received 7 December 2023; received in revised form 2 May 2024; accepted 22 May 2024; available online 31 May 2024