Decompensation in advanced nonalcoholic fatty liver disease may occur at lower hepatic venous pressure gradient levels than in patients with viral disease

Decompensation in advanced non-alcoholic fatty liver disease may occur at lower hepatic venous pressure that in viral disease

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Abstract:

Background & Aims: Portal hypertension (PH) is the strongest predictor of hepatic decompensation and death in patients with cirrhosis. However, its discriminatory accuracy in patients with non-alcoholic fatty liver disease (NAFLD) has been challenged as hepatic vein catheterization may not reflect the real portal vein pressure as accurately as in patients with other etiologies. We aimed to evaluate the relationship between HVPG and presence of portal hypertension related decompensation in patients with advanced NAFLD (aNAFLD).

Methods: Multicenter cross-sectional study including 548 patients with advanced NAFLD and 444 with hepatitis C (HCV-RNA-positive; aHCV) who had detailed portal hypertension evaluation (HVPG measurement, gastroscopy, and abdominal imaging). We examined the relationship between etiology, HVPG, and decompensation by logistic regression models. We also compared the proportions of compensated/decompensated patients at different HVPG levels.

Results: Both cohorts, aNAFLD and aHVC, had similar baseline age, gender, CPT, and MELD. Median HVPG was lower in the aNAFLD cohort (13 vs 15 mmHg) despite similar liver function and higher rates of decompensation in aNAFLD group (32% vs 25% p=0.019) than in the aHCV group. For any of the HVPG cutoff analyzed (<10, 10-12 or 12 mmHg) the prevalence of decompensation was higher in the aNAFLD than in the aHCV group.

Conclusion: Patients with aNAFLD have higher prevalence of portal hypertension related decompensation at any value of HVPG as compared to aHCV patients. Longitudinal studies aiming to identify HVPG thresholds able to predict decompensation and long-term outcomes in aNAFLD population are strongly needed.

Keywords: Portal hypertension; NAFLD; HVPG; cirrhosis decompensation; NASH

BACKGROUND & AIMS

Portal hypertension is the stronger predictor of complications and death in patients with cirrhosis as hepatic decompensation develop only after a certain degree of PH has been reached. Evaluation of PH is recommended in patients with advanced chronic liver disease (aCLD) to determine the risk of decompensation, prognosis and to guide management. Hepatic vein catheterization and measurement of hepatic venous pressure gradient (HVPG) is the gold standard technique to measure PH. The prognostic significance of HVPG values and thresholds predicting decompensation has been largely studied. Indeed, clinically significant portal hypertension is defined as an HVPG ≥ 10 mmHg as patients with cirrhosis do not develop in patients with HVPG less than 10 mmHg.[1–5]. However, this cutoff was identified analyzing patients with cirrhosis mainly due to HCV or alcohol and no patients with non-alcoholic fatty liver disease (NAFLD) were included in those studies.[3–5]

Given that NAFLD is the leading chronic liver disease worldwide, it becomes relevant to elucidate whether the stablished values preserve its diagnostic accuracy in NAFLD patients[6]. It has been recently shown that HVPG ≥ 10 mmHg is also able to predict decompensation in NAFLD patients[7,8], although its discriminatory accuracy appears to be much lower than the one reported for other etiologies[3]. Indeed, in the largest study to date evaluating HVPG in NAFLD patients [8] 14% of patients with HVPG <10 mmHg presented PH-related complications (variceal hemorrhage (VH), ascites and hepatic encephalopathy). Moreover, in patients with

decompensated NAFLD cirrhosis HVPG may not reflect the real portal vein pressure as accurately as in patients with HCV cirrhosis[9]. These data suggest that prognostic HVPG thresholds may be different in NAFLD although more studies are needed.

Our hypothesis is that decompensation in aNAFLD may appear at lower HVPG values than in other etiologies. To confirm this, we performed an exploratory study aimed to examine the relationships between portal pressure measurements and the presence hepatic decompensation in patients with advanced NAFLD (aNAFLD) and compare it with the observed in patients with advanced chronic liver disease due to hepatitis C virus (aHCV).

PATIENTS AND METHODS

Study cohort

We performed a multicenter, observational, cross-sectional study in twenty European centers with experience in hepatic hemodynamic procedures. We included all NAFLD patients evaluated in the participating centers who underwent liver catheterization because of clinical suspicion of the presence of portal hypertension from 2014 to 2018. aCLD was defined either histologically by the presence of stage 3 or 4 fibrosis or clinically by presence of portal hypertension (HVPG >5mmHg). aNAFLD diagnosis was made when (i) presence of steatosis plus advanced fibrosis (F3/F4) according to NASH CRN score[10,11]) or (ii) presence of steatosis on imaging plus HVPG >5mmHg +/- unequivocal signs of portal hypertension[12] in the absence of other etiological factors. Patients that presented other concomitant chronic liver disease etiologies were excluded.

As a control group we included a group of patients with virally active (HCV positive viremia) aCLD (aHCV group) and a detailed evaluation of PH. Patients were included before receiving treatment with direct-acting antiviral treatment to avoid the impact of controlling the etiological factor. Only aHCV patients with PH regardless of the presence of decompensation were included. Spain and Vienna provided the aHCV group and details of the cohort can be found elsewhere[13,14].

All the patients from aNAFLD and aHCV cohorts had PH evaluation (HVPG, imaging, upper endoscopy) within a timeframe of maximum 6 months. Patients with an active or previous history of at-risk alcohol consumption (≥140g/week in females and ≥210g/week in males) were excluded to avoid dual etiologies. Other exclusion criteria were prior liver

transplantation, hepatocellular carcinoma outside Milan criteria, sustained viral response in patients with aHCV or non-accurate HVPG measurements, i.e. occlusive portal vein thrombosis, presence of hepatic vein-to-vein communications which precluded from an adequate occlusion of the hepatic vein during catheterization, large-volume paracentesis performed in the previous 24 hours, HVPG calculated with inferior vena cava, hemodynamic instability, infusion of vasoactive drugs or any kind of non-selective betablocker (NSBB) therapy.

Clinical decompensation was defined as previously described including ascites, VH, or hepatic encephalopathy (HE)[3]. For the present study, ascites was only considered if it was grade II or III and HE was considered when it was at least grade 2 according to West-Haven classification[15]. Besides clinical decompensation, we also analyzed the presence of gastroesophageal varices (EV). To avoid the role of subjectivity in interpretation of small varices in the setting of a retrospective study, varices were only considered in the present study when needing treatment, meaning large varices and/or red wall signs (high-risk varices), thereafter called large varices. Patients were considered decompensated when ascites, VH or HE was present at the time of HVPG or reported previous to HVPG.

Portal hypertension evaluation

HVPG was performed by experienced personnel as previously described[16].

All patients had an abdominal imaging technique evaluating portal hypertension (splenomegaly, ascites, presence of portocollateral circulation) either by ultrasound, CT-Scan, or MRI depending on the clinical practice policy of each center. An upper endoscopy evaluating portal hypertension signs (EV) was performed also in all the included patients and we only considered for the present study large or high-risk varices. Routine laboratory tests including liver enzymes, liver function, serum creatinine and cell blood counts were obtained and Model for end-stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) scores were calculated.

Statistical analysis

Continuous normally distributed variables are expressed as means (standard deviation), non-normally distributed as medians (interquartile range), and categorical variables are presented as frequencies (percentages). T-test, Kruskal-Wallis test, and Fisher's exact test were used to

compare baseline characteristics. To examine the relationship between etiology, HVPG, and decompensation, logistic regression models were fitted to each cohort. We also compared the proportions of compensated/decompensated patients at different threshold levels. All tests were 2-sided, and the significance level was established at 5%. Our study adheres to the "Strengthening the reporting of observational studies in epidemiology (STROBE)" statement[17]. All analyses and pre-processing were performed with R 3.6.3 (R Core Team (2020), R Foundation for Statistical Computing, Vienna, Austria).

Ethical Aspects

The ethics committee of all participating centers approved the retrospective collection and analysis of clinical and hemodynamic data for the current study. The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Patient selection and baseline characteristics

From May 2014 to November 2018, a total of 1,212 patients with aNAFLD and aHCV had a complete evaluation of PH including gastroscopy, abdominal imaging and HVPG in the participating centers and were considered for inclusion. 137 were excluded due to NSBB treatment at the time of HVPG (78 in the group of aHCV and 59 in the group of aNAFLD). Additionally, we excluded 83 patients due to inaccurate HVPG measurement (see details in supplementary Figure 1). Finally, we included a total of 548 patients with aNAFLD and 444 with aHCV. Diagnosis of aNAFLD was histological in 418 (76%) and only patients with F3/F4 were included. 301 (72%) presented F4 fibrosis. In 130 patients, histology was not available and diagnosis of aNAFLD was made in the presence of HVPG ≥ 5 mmHg [12]. Among patients with aHCV (all of whom were HCV-RNA positive) diagnosis was histological in 137 (31%) subjects (111 (81%) had F4 and 26 (19%) F3 fibrosis) and clinical criteria (HVPG > 5mmHg) in 307 (69%).

Baseline characteristics of all patients are described in Table 1. Patients included were mainly male (59%) with a median age of 60 years. None of the aNAFLD patients had concomitant alcohol consumption and only 5 patients (1%) in the aHCV consumed alcohol (<140g/week in females and < 210g/week in males). As expected, patients with aNAFLD had higher rates of metabolic syndrome (66% vs 8%, p<0.001), diabetes mellitus (68% vs 18%, p<0.001*)*, hypercholesterolemia (51% vs 8%, p<0.001*)* and arterial hypertension (71% vs 35%, p<0.001*).* aNAFLD patients had a higher body mass index (BMI) and the proportion of obese patients (BMI $\geq$ 30 kg/m^2) was significantly higher in aNAFLD patients (59% vs 25%, p<0.001).

Both aNAFLD and aHCV patients had similar liver function with a median Child-Pugh Turcotte (CPT) score of 5 and a Model for End-stage Liver Disease (MELD) score of 9. However, median HVPG value was significantly lower in patients with aNAFLD compared to aHCV (13 [8-18] vs 15 [11-19] mmHg, p<0.001).

Clinical decompensation

The majority of patients included (71%) had compensated aCLD. The number of decompensated patients was higher in the aNAFLD group (32% aNAFLD vs 25% aHCV; p=0.019), being ascites the most common decompensation (25% aNAFLD vs 18% aHCV; (p=0.008)) (for details see Table 2). Rates of HE and VH were similar in patients with aNAFLD

compared to aHCV (7 and 5%, p=ns; and 10% and 9%, p=ns, respectively). Again, the proportion of patients with large varices at gastroscopy was slightly higher in the aNAFLD group (174 [32%] in aNAFLD vs 119 [27%] in aHCV, p=ns) without reaching statistically significance.

Afterwards, we analyzed the characteristics of patients with clinical decompensation (174 aNAFLD and 110 aHCV) (Table 3). As in the whole cohort, rates of metabolic syndrome and obesity were significantly higher in patients with aNAFLD. Despite having similar liver function, decompensated patients with aNAFLD had lower HVPG values (17 [13-21] mmHg vs 19 [17-22]; mmHg p=0.001) and the presence of abdominal portocollateral shunts (unequivocal sign of portal hypertension) was more frequent in aNAFLD patients (36 vs 24%; p= 0.046).

Clinical decompensation according to classic HVPG thresholds

Table 4 summarizes the presence of clinical decompensation and portal hypertension signs according to HVPG thresholds. Most of the patients in both groups had clinically significant portal hypertension (HVPG ≥10mmHg) and ascites was the most common decompensation. In agreement with previous literature[3,18], none of the aHCV patients with HVPG<10 mmHg had decompensation or presented large varices on gastroscopy. Contrary to what has been reported in other etiologies, 15 (9%) patients with aNAFLD had clinical decompensation and 6 (4%) patients presented large varices with HVPG values below 10 mmHg.

In a continuous approach, the number of decompensated patients for any given value of HVPG was higher in the aNAFLD group compared to the aHCV group (Figure 1a) and similarly for the presence of large varices (Figure 1d). See Figure 1 for further details.

As obesity has been strongly associated with the risk of clinical decompensation in an independent fashion in patients with aCLD[19,20], we evaluated the impact of obesity in our results. To guarantee that the results observed were not due to the higher prevalence of obese patients in the aNAFLD group, we repeated our analysis excluding obese patients. As in the whole cohort, the number of decompensated patients for any given value of HVPG was higher in the aNAFLD group (Supplementary Figure 2) suggesting that NAFLD etiology and not the presence of obesity is associated with higher rate of decompensation. Additionally, we stratified our sample based on the presence of obesity (without considering etiology) and repeated the same analysis. We observed no significant differences (see Supplementary

Figure 3), suggesting that obese and non-obese patients may have similar decompensation prevalence according to HVPG regardless of the etiology.

Another known factor able to interfere with HVPG measurements is the presence of HCC. In our cohort 30 (5,4%) patients in the aNAFLD group and 29 (6.5%) in the aHCV had HCC within Milan criteria. To discard the potential impact of HCC in our results, we repeated the analysis excluding all patients with known HCC (Supplementary Figure 4). Again, the number of decompensated patients for any given value of HVPG was higher in the aNAFLD group suggesting that etiology is the main responsible of the observed differences.

Analysis of aNAFLD patients with HVPG< 10mmHg

Given that clinical decompensation was observed in aNAFLD patients with HVPG below 10 mmHg, and therefore not considered at risk of decompensation following the current guidelines, we evaluated closely this subgroup of patients. When compared with aHCV group (see Supplementary Table 1), both groups had similar liver function as assessed by MELD and CTP scores and renal function but only aNAFLD patients had decompensation (13 ascites, 2 HE and 5 VH). Intriguing, aHCV patients have higher degree of portal hypertension (HVPG 8 [6-9] vs 6 [5-8] p<0.001) and conventional portal hypertension signs were more frequent in the aHVC group (splenomegaly (54% vs 33%; p=0.007) and low platelet count (128 vs 164 x $10^3/\mu L$; p= 0.005), but none of them had decompensation.

Afterwards, we focused on the subgroup of 116 aNAFLD patients with HVPG <10mmHg and comparedcompensated vs decompensated. Patients with decompensation had similar HVPG values that compensated patients (HVPG 6 mmHg). There were no differences in renal function and rates of obesity and metabolic syndrome were lower in the decompensated group. However, decompensated aNAFLD patients presented a more advanced liver disease defined by higher MELD (9 [9-12] vs 7[6-9], respectively; p=0.001) and CTP (6 [6-8] vs 5 [5-5]; p<0.001), higher rate of portosystemic collaterals (25% vs 5%, respectively; p=0.018) and lower platelet count (143 vs 170 x $10^3/\mu L$; p=0.08)), than compensated aNAFLD (Table 5). Ascites was the most frequent decompensating event (all patients except 2), 5 patients had variceal bleeding and 3 hepatic encephalopathy. Supplementary Table 2 provides individual details of decompensated patients.

Discussion

We analyzed the relationships between HVPG and presence of decompensation in a large cohort of patients with aNAFLD (n=548) and compared it with a group of aHCV (n=444). We included patients from 20 European centers with proven expertise in hepatic vein catheterization and rigorous pressure measurement protocols. Our results show that for a similar liver function, NAFLD patients had higher rates of decompensation than aHCV patients HVPG is the strongest predictor of hepatic decompensation in patients with alcohol and viral related cirrhosis and it is well known that patients with cirrhosis do not develop decompensation with HVPG less than 10 mmHg[3–5].However, the reliability of the 10mmHg cut-off for prognostication and clinical decision making in NAFLD patients has been recently questioned[8,21].

Our study shows that indeed, decompensation may arise in aNAFLD despite HVPG<10 mmHg. We found that 15 patients in the aNAFLD group were decompensated and 6 had high-risk varices with HVPG<10 mmHg while in agreement with previous studies none of patients in the aHCV group presented decompensation or high-risk varices with an HVPG<10mmHg[3–5]. Although this subgroup of patients represents only 9% of the population, this finding is clinically relevant as patients thought not to be at risk of decompensation (HVPG<10mmHg) according to the current knowledge in fact decompensate.

As expected, prevalence of decompensation rises in parallel with HVPG increase in the two cohorts. However, for any of the HVPG cutoff analyzed (<10, 10-12 or 12 mmHg) the prevalence of decompensation was higher in the aNAFLD than in the aHCV group suggesting that aNAFLD patients may decompensate at lower HVPG values than aHCV.

Interestingly when comparing only decompensated patients, the aNAFLD group had lower HVPG, higher platelet count and less splenomegaly rates. This suggests that decompensation may occur with less of portal hypertension than the HCV group. In addition, those with decompensated aNAFLD had more porto-systemic collaterals, a well-known finding that can increase wedge pressure and overestimate portal pressure[22–24]. That said, even if HVPG is overestimated in a subgroup of aNAFLD patients, the mean HVPG was still lower than in the aHCV group. This supports the idea the threshold needed to develop decompensation in NAFLD patients may be lower than in aHCV. A closer look at decompensated aNAFLD patients showed that compared with compensated patients they had worse liver function and higher

rate of clinical signs of portal hypertension (ascites, portosystemic collaterals, thrombocytopenia, splenomegaly) despite having similar HVPG. These data suggest that decompensated aNAFLD patients had a more advanced liver disease and degree of portal hypertension than compensated aNAFLD patients that may not be fully captured by HVPG measurement. It is possible that, as happens in patients with refractory complications of portal hypertension[25], HVPG may underestimate the severity of portal hypertension (i.e., the PPG) in patients with aNAFLD. Although it should be evaluated in longitudinal prospective studies, our results suggest that classical HVPG cut-offs established in other etiologies may not adequately predict risk of decompensation in patients with aNAFLD .

Our data indicate that at least a subgroup of patients with NAFLD may have increased intrahepatic resistance at the presinusoidal level (portal tracts/venulae) and therefore not well captured by the WHVP. We can speculate, that systemic metabolic derangements associated with NAFLD may damage the liver endothelium in a different way that HCV does. . Although to be proven, damage of the portal tracts or terminal portal venules due to structural and/or dynamic alterations of liver vasculature during the course of the disease may contribute to presinusoidal portal hypertension and hepatic decompensation. Longitudinal studies aimed to evaluate the precise contribution of vascular alterations to the development of PH decompensation are strongly needed.

BMI has been strongly associated with the risk of clinical decompensation in an independent fashion in patients with aCLD mainly due to alcohol and HCV infection[19,20]. In our cohort, obesity was most frequently found in patients with lower HVPG values and was not associated with higher prevalence of decompensation. Moreover, differences in decompensation rates were maintained for all HVPG thresholds when all obese patients were excluded from the analysis.

The main strength of our study is the inclusion of a large sample size of aNAFLD patients with a thorough evaluation of PH in centers of expertise. HVPG reports were carefully evaluated and we excluded patients with conditions known to influence hepatic pressures.

We recognize limitations of our study, mainly related to its observational retrospective design and its cross-sectional evaluation. Inclusion solely of patients with a complete evaluation of PH and mostly from tertiary centers may have contributed to selection bias. Our study may be lacking patients in both groups (aNAFLD & aHVC) without a clinical suspicion of PH and therefore complete evaluation. However, the enrichment of academic centers with specific

protocols including routinely liver catheterization in the diagnostic work-up of patients with aCLD may have ameliorated this limitation. Finally, the cross-sectional nature of our study in the absence of any intervention or longitudinal follow-up only allows for a descriptive analysis. Therefore, identification of predictive factors responsible for the differences observed is out of the scope of our study. Although aNAFLD patients have a higher prevalence of PH related complications for any given HVPG value, the retrospective nature of this study and the absence of a clear inflection point in the association between HVPG and decompensation prevalence, precluded identification of a reliable threshold able to guide clinical decision-making.

In conclusion, our study suggests that patients with aNAFLD present higher rate of PH related decompensation at any given HVPG value as compared to aHCV patients. Conventional HVPG cutoffs may not identify patients at risk of decompensation in aNAFLD as in aHCV and the most plausible explanation may be an underestimation of the real portal pressure gradient at least in a subgroup of aNAFLD patients. Our results have important implications for future trial designs and open a window for new studies aiming to identify HVPG thresholds to predict decompensation and long-term outcomes in aNAFLD populations.

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Figure Legends

Fig 1. Prevalence of clinical decompensations according to HVPG values categorized by etiology in our sample. a combined outcome defined as the presence of either ascites, hemorrhage, or encephalopathy; **b** prevalence of ascites; **c** prevalence of hepatic encephalopathy; **d** prevalence of hemorrhage; **e**. prevalence of large varices. HVPG expressed in mmHg and prevalence from 0 to 1. For definitions of ascites, hemorrhage, hepatic encephalopathy, and large varices see *Patients and Methods* section. HVPG, hepatic venous pressure gradient.

Supplementary Figure 1. Flow chart of patients included in the study. aNAFLD, advanced non-alcoholic fatty liver disease; aHCV, advanced hepatitis C virus infection; HVPG, hepatic venous pressure gradient; NSBB, non-selective beta blockers; LVP, large volume paracentesis; IVC, inferior vena cava.

Supplementary Figure 2. Prevalence of liver clinical decompensations according to HVPG values categorized by etiology and excluding obese patients from the analysis. a combined outcome defined as the presence of either ascites, hemorrhage, or encephalopathy; **b** prevalence of ascites; **c** prevalence of hepatic encephalopathy; **d** prevalence of hemorrhage; **e**. prevalence of large varices. HVPG expressed in mmHg and prevalence from 0 to 1. For definitions of ascites, hemorrhage, hepatic encephalopathy, and large varices see *Patients and Methods* section. HVPG, hepatic venous pressure gradient.

Supplementary Figure 3. Prevalence of liver clinical decompensations according to HVPG values categorized by the presence of obesity in our sample (regardless of the etiology). a combined outcome defined as the presence of either ascites, hemorrhage, or encephalopathy; **b** prevalence of ascites; **c** prevalence of hepatic encephalopathy; **d** prevalence of hemorrhage; **e**. prevalence of large varices. HVPG expressed in mmHg and prevalence from 0 to 1. For definitions of ascites, hemorrhage, hepatic encephalopathy, and large varices see *Patients and Methods* section. HVPG, hepatic venous pressure gradient.

Supplementary Figure 4. Prevalence of liver clinical decompensations according to HVPG values categorized by etiology and excluding patients with diagnosis of hepatocellular carcinoma from the analysis. a combined outcome defined as the presence of either ascites, hemorrhage, or encephalopathy; **b** prevalence of ascites; **c** prevalence of hepatic encephalopathy; **d** prevalence of hemorrhage; **e**. prevalence of large varices. HVPG expressed in mmHg and prevalence from 0 to 1. For definitions of ascites, hemorrhage, hepatic encephalopathy, and large varices see *Patients and Methods* section. HVPG, hepatic venous pressure gradient.

Abbreviations: BMI: Body mass index; CTP score: Child-Turcotte-Pugh score; FHVP: Free hepatic vein pressure; HE: Hepatic encephalopathy; HV: Hepatic vein; HCV: Hepatitis C virus; aHCV: advanced hepatitis C virus; HVPG: Hepatic venous pressure gradient; LSM: Liver stiffness measurement; NAFLD: Non-alcoholic fatty liver disease; aNAFLD: Advanced Non-alcoholic fatty liver disease; MELD score: Model for end-stage liver disease score; NSBB: Non-selective beta-blocker; PH: Portal Hypertension; VH: variceal hemorrhage; WHVP: wedge hepatic vein pressure

Figure

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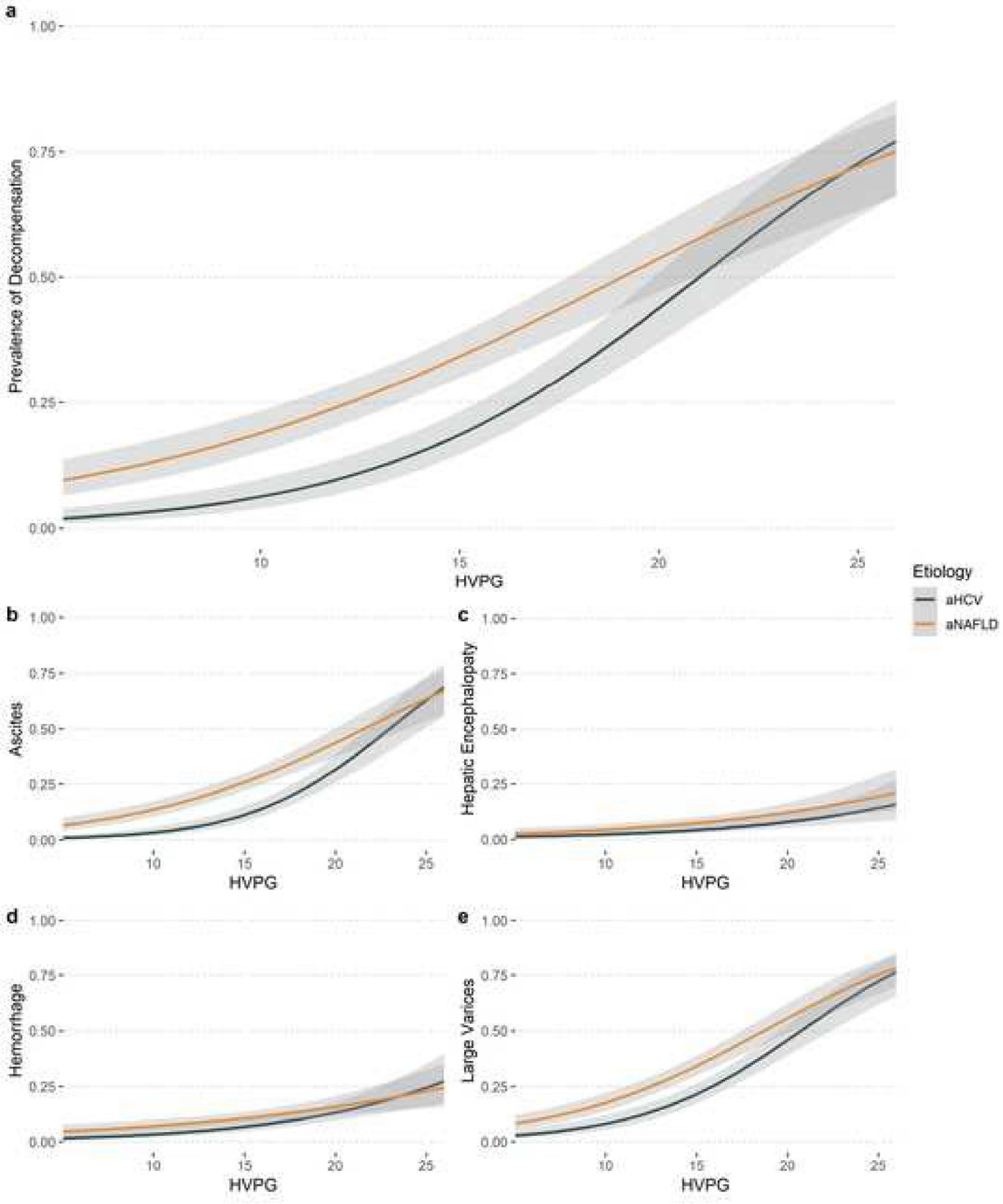

Table 1. Characteristics of all patients included in the study.

	All patients N = 992	aNAFLD n = 548	aHCV patients n = 444	p value
Age, y	60 (53-68)	62 (56-69)	58 (51-67)	<0.001
Sex, female	409 (41)	239 (44)	170 (3)	ns
Obesity	411 (45)	314 (59)	97 (25)	<0.001
Overweight	308 (33)	160 (29)	148 (33)	ns
Normal weight	204 (22)	61 (11)	143 (37)	<0.001
Arterial hypertension	495 (57)	374 (71)	121 (35)	<0.001
Type 2 diabetes mellitus	436 (49)	374 (68)	62 (18)	<0.001
Hypertriglyceridemia	171 (21)	156 (31)	15 (5)	<0.001
Hypercholesterolemia	288 (34)	262 (51)	26 (8)	<0.001
Metabolic syndrome	377 (46)	355 (66)	22 (8)	<0.001
GGT (IU/L)	88 (51-163)	100 (57-184)	76 (47-143)	<0.001
ALT (IU/L)	47 (29-77)	37 (25-52)	69 (40-113)	<0.001
Alkaline phosphatase (IU/L)	105 (77-151)	102 (73-143)	112 (82-168)	0.002
Creatinine (mg/dL)	0.77 (0.65-0.91)	0.80 (0.65-0.97)	0.74 (0.65-0.85)	<0.001
Albumin (g/dL)	3.9 (3.3-4.2)	3.9 (3.3-4.3)	3.8 (3.4-4.2)	ns
INR	1.17 (1.1-1.3)	1.16 (1.1-1.3)	1.18 (1.1-1.3)	0.020
Total bilirubin (mg/dL)	0.95 (0.7-1.4)	0.87 (0.6-1.3)	1.1 (0.78-1.58)	<0.001
Platelets (x $10^3/\mu L$)	108 (74-156)	120 (83-172)	94 (68-128)	<0.001
MELD score	9 (8-11)	9 (7-11)	9 (8-11)	ns
Child-Pugh score	5 (5-6)	5 (5-6)	5 (5-6)	ns
Hepatic venous pressure gradient (mmHg)	14 (10-18)	13 (8-18)	15 (11-19)	<0.001
Right atrium pressure (mmHg)	6 (4-9)	6 (4-8)	7 (5-9)	<0.001
Mean arterial pressure (mmHg)	96 (85-106)	96 (86-107)	96 (85-106)	ns
Histological diagnosis	555 (56)	418 (76)	137 (31)	<0.001

Values are number of patients (percentages) or median (IQR). Non-normally distributed continuous variables were compared using Mann-Whitney *U* test. Categorical variables were reported compared with Chi-squared test.
MELD, model for end-stage liver disease; INR, international normalized ratio; ns, non-significant.

Table 2. Clinical decompensations and characteristics of the whole sample

	All patients n = 992	aNAFLD n = 548	aHCV n = 444	p value
Decompensation[a]	284 (29)	173 (32)	110 (25)	0.019
Ascites	216 (22)	136 (25)	79 (18)	0.008
Hepatic encephalopathy	65 (7)	41 (7)	24 (5)	0.236
Variceal hemorrhage	96 (10)	57 (10)	39 (9)	0.454
Splenomegaly	631 (64)	343 (63)	288 (65)	0.500
Portosystemic collaterals	198 (20)	127 (23)	71 (16)	0.006
Large varices	293 (30)	174 (32)	119 (27)	0.103

Values are number of patients (percentages). Proportions were compared with Chi-squared test.
[a]Decompensation is a combined outcome defined by the presence of either ascites, hepatic encephalopathy and/or variceal hemorrhage.

Table 3. Characteristics of all patients with clinical decompensation categorized according to etiology

	aNAFLD n = 173	aHCV n = 110	p value
Obesity	79 (47)	21 (21)	<0.001
Metabolic syndrome	94 (55)	3 (45)	<0.001
Type 2 diabetes mellitus	109 (63)	16 (19)	<0.001
Arterial hypertension	101 (60)	24 (29)	<0.001
Hypercholesterolemia	72 (44)	3 (4)	<0.001
ALT (IU/L)	30 (21-42)	52 (33-79)	<0.001
GGT (IU/L)	90 (52-155)	60 (37-111)	0.003
Total billirubin (mg/dL)	1.15 (0.72-1.87)	1.4 (1.1-2.2)	0.009
Albumin (g/dL)	3.2 (2.8-3.8)	3.4 (3.1-3.8)	0.076
Alkaline phosphatase (IU/L)	120 (83-156)	108 (85-164)	0.824
Creatinine (mg/dL)	0.90 (0.7-1.14)	0.74 (0.66-0.90)	0.001
Platelets (x $10^3/\mu L$)	115 (79-163)	73 (55-107)	<0.001
MELD score	11 (9-14)	11(9-13)	0.989
Child-Pugh score	7 (6-8)	7 (6-8)	0.232
Hepatic venous pressure gradient (mmHg)	17 (13-21)	19 (17-22)	0.001
Splenomegaly	123 (71)	92 (84)	0.019
Spleen size (cm)	14 (13-18)	16 (14-17)	0.015
Portosystemic collaterals	62 (36)	26 (24)	0.046

Values are number of patients (percentages) or median (IQR). Non-normally distributed continuous variables were compared using Mann-Whitney *U* test. Categorical variables were reported compared with Chi-squared test.
MELD, model for end-stage liver disease; INR, international normalized ratio.

Table 4. Decompensations and clinical characteristics according to HVPG classical thresholds and etiology

	aNAFLD				aHCV			
HVPG threshold	**<10 mmHg n = 166**	**10-12 mmHg n = 78**	**>12 mmHg N = 304**	**p value**	**<10 mmHg n = 57**	**10-12 mmHg n = 94**	**>12 mmHg n = 293**	**p value**
Decompensation[a]	15 (9)	21 (27)	137 (45)	<0.001	0	6 (6)	104 (36)	<0.001
Ascites	13 (8)	12 (15)	111 (37)	<0.001	0	4 (4)	75 (26)	<0.001
Hepatic encephalopathy	3 (2)	4 (5)	34 (11)	0.001	0	1 (1)	23 (8)	0.004
Variceal hemorrhage	5 (3)	8 (10)	44 (15)	0.001	0	2 (2)	37 (13)	<0.001
Hepatocarcinoma	14 (8)	6 (8)	10 (3)	0.037	5 (9)	4 (4)	20 (7)	0.475
Splenomegaly	55 (33)	58 (74)	230 (76)	<0.001	31 (54)	53 (57)	204 (70)	0.013
Portosystemic collaterals	12 (7)	17 (22)	98 (32)	<0.001	3 (5)	10 (11)	58 (20)	0.007
Large varices	6 (4)	21 (27)	147 (48)	<0.001	0	10 (11)	109 (37)	<0.001

Values are number of patients (percentages). Categorical variables were reported compared with Chi-squared test.

[a]Decompensation is a combined outcome defined by the presence of either ascites, hepatic encephalopathy and/or variceal hemorrhage

Table 5. Characteristics of aNAFLD patients with HVPG below 10 mmHg according to the presence or absence of decompensation.

	Compensated n = 151	Decompensated n = 15	p value
Age, y	60 (52-67)	60 (57-71)	0.579
Female	67 (44)	10 (67)	0.168
Obesity	106 (71)	4 (27)	<0.001
Arterial hypertension	113 (77)	7 (47)	0.025
Type 2 diabetes mellitus	98 (65)	9 (60)	0.924
Hypertriglyceridemia	63 (45)	2 (15)	0.048
Hypercholesterolemia	90 (62)	4 (31)	0.029
Metabolic syndrome	115 (77)	5 (36)	0.002
GGT (IU/L)	91 (52-194)	90 (55-184)	0.947
ALT (IU/L)	45 (31-64)	34 (22-49)	0.088
Creatinine (mg/dl)	0.82 (0.69-0.95)	0.66 (0.58-0.99)	0.107
Alkaline phosphatase (IU/L)	82 (64-113)	125 (111-142)	0.008
Albumin (g/dL)	4.2 (3.9-4.4)	3.7 (3.0-4.0)	0.002
INR	1.1 (1.0-1.11)	1.2 (1.2-1.3)	<0.001
Total Billirubin (mg/dl)	0.6 (0.4-0.9)	0.8 (0.5-0.9)	0.384
Platelets (x $10^3/\mu L$)	170 (122-226)	143 (102-167)	0.084
Child-Pugh score	5 (5-5)	6 (6-8)	<0.001
MELD score	7 (6-9)	9 (9-12)	0.001
Hepatic venous pressure gradient (mmHg)	6 (5-8)	6 (6-8)	0.328
Splenomegaly	48 (32)	7 (44)	0.503
Spleen size (cm)	12 (10-14)	12 (11-14)	0.697
Portosystemic collaterals	8 (5)	4 (25)	0.018
Hepatocellular carcinoma	14 (9)	0	0.619

Values are number of patients (percentages) or median (IQR). Non-normally distributed continuous variables were compared using Mann-Whitney *U* test. Categorical variables were reported compared with Chi-squared test.

MELD, model for end-stage liver disease; INR, international normalized ratio.