

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Hepatic Venous Pressure Gradient Predicts Clinical Decompensation in Patients With Compensated Cirrhosis

CRISTINA RIPOLL,^{*,‡} ROBERTO GROSZMANN,^{*,‡} GUADALUPE GARCIA-TSAO,^{*,‡} NORMAN GRACE,^{§,||} ANDREW BURROUGHS,[¶] RAMON PLANAS,[#] ANGELS ESCORSELL,^{**} JUAN CARLOS GARCIA-PAGAN,^{**} ROBERT MAKUCH,[‡] DAVID PATCH,[¶] DANIEL S. MATLOFF,^{||} JAIME BOSCH,^{**} and the Portal Hypertension Collaborative Group

^{*}Veterans Affairs CT Healthcare System, West Haven, Connecticut; [‡]Yale University School of Medicine, New Haven, Connecticut; [§]Brigham and Women's Hospital, Boston, Massachusetts; [¶]Faulkner Hospital, Jamaica Plain, Massachusetts; [¶]Royal Free Hospital and School of Medicine, London, United Kingdom; [#]Hospital Germans Trias i Pujol, Badalona, Spain; ^{**}Hospital Clínic i Provincial de Barcelona, Barcelona, Spain

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Background & Aims: Our aim was to identify predictors of clinical decompensation (defined as the development of ascites, variceal hemorrhage [VH], or hepatic encephalopathy [HE]) in patients with compensated cirrhosis and with portal hypertension as determined by the hepatic venous pressure gradient (HVPG).

Methods: We analyzed 213 patients with compensated cirrhosis and portal hypertension but without varices included in a trial evaluating the use of β -blockers in preventing varices. All had baseline laboratory tests and HVPG. Patients were followed prospectively every 3 months until development of varices or VH or end of study. To have complete information, until study termination, about clinical decompensation, medical record review was done. Patients who underwent liver transplantation without decompensation were censored at transplantation. Cox regression models were developed to identify predictors of clinical decompensation. Receiver operating characteristic (ROC) curves were constructed to evaluate diagnostic capacity of HVPG.

Results: Median follow-up time of 51.1 months. Sixty-two (29%) of 213 patients developed decompensation: 46 (21.6%) ascites, 6 (3%) VH, 17 (8%) HE. Ten patients received a transplant and 12 died without clinical decompensation. Median HVPG at baseline was 11 mm Hg (range, 6–25 mm Hg). On multivariate analysis, 3 predictors of decompensation were identified: HVPG (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.05–1.17), model of end-stage liver disease (MELD) (HR, 1.15; 95% CI, 1.03–1.29), and albumin

(HR, 0.37; 95% CI, 0.22–0.62). Diagnostic capacity of HVPG was greater than for MELD or Child–Pugh score. **Conclusions:** HVPG, MELD, and albumin independently predict clinical decompensation in patients with compensated cirrhosis. Patients with an HVPG <10 mm Hg have a 90% probability of not developing clinical decompensation in a median follow-up of 4 years.

A recent systematic review of predictors of death in cirrhosis confirmed the different survival rates between patients with compensated and decompensated cirrhosis and underscored that these are two distinct stages of cirrhosis with different predictors of survival.¹ In fact, in patients with compensated cirrhosis, death does not occur until patients develop complications that characterize the decompensated phase of the disease, that is, ascites, variceal hemorrhage (VH), and encephalopathy. Therefore, it was suggested that in patients with compensated disease prediction of decompensation was more relevant than prediction of survival.

Because most of the complications that characterize decompensation are related to portal hypertension, it would follow that portal pressure would be predictive of decompensation. It is well known that a threshold value of hepatic venous pressure gradient (HVPG) is required for the development of varices and variceal bleeding.² Furthermore, a reduction in HVPG after pharmacologic

Abbreviations used in this paper: CI, confidence interval; HE, hepatic encephalopathy; HR, hazard ratio; HVPG, hepatic venous pressure gradient; MELD, model of end-stage liver disease; RCT, randomized controlled trial; ROC, receiver operating characteristic; VH, variceal hemorrhage.

therapy was identified as a negative predictor of VH and spontaneous bacterial peritonitis.³⁻⁵ However, the role of baseline levels of HVPG in prediction of decompensation in early cirrhosis has not been evaluated.

Therefore, the aim of this study was to evaluate the predictors of clinical decompensation in a homogenous cohort of compensated patients with cirrhosis and portal hypertension without varices and, second, to evaluate the independent role of portal pressure (as determined by HVPG) in predicting clinical decompensation.

Materials and Methods

This study is a nested cohort study within a randomized controlled trial (RCT).⁶ Between August 1993 and March 1999, patients with compensated cirrhosis were enrolled in a prospective RCT designed to evaluate the efficacy of nonselective β -blockers in preventing the development of gastroesophageal varices. Patients were considered for inclusion if they had cirrhosis and portal hypertension (defined by an HVPG of ≥ 6 mm Hg) without gastroesophageal varices and were between the age of 18 and 75 years. The diagnosis of cirrhosis was either biopsy proven or clinically suspected and confirmed by the presence of an HVPG value of ≥ 10 mm Hg. Exclusion criteria included ascites requiring diuretic treatment, hepatocellular carcinoma, splenic or portal vein thrombosis, concurrent illnesses expected to decrease life expectancy to < 1 year, the use of any drug or procedure affecting splanchnic hemodynamics or portal pressure, primary biliary cirrhosis or primary sclerosing cholangitis, contraindication to β -blocker therapy, pregnancy, or alcohol intake during the dose-titration phase. From the 780 patients screened for varices in the RCT, 490 (63%) did not have any. From these patients 277 (57%) were excluded and 213 (43%) patients were finally included in the RCT. The reasons for exclusion are described in the previously published paper.⁶ Patients were randomly assigned to receive placebo or timolol, a nonselective β -blocker. At baseline clinical history, physical examination, blood tests, upper gastrointestinal endoscopy, abdominal ultrasonography, and HVPG measurement were performed. Patients were followed at 1 and 3 months after random assignment and then every 3 months until the primary end point of the study (development of small varices observed in 2 consecutive endoscopies, large varices, or VH), the secondary end point (death or liver transplantation), or until the end of the study in September 2002. During this time period, 84 patients developed the primary end point of the trial, and follow-up was discontinued in the setting of the RCT.⁶

The primary end point of the present study was the development of clinical decompensation defined by the presence of ascites, encephalopathy, or VH. Ascites was

defined by the presence of signs and symptoms suggestive of ascites on physical examination and confirmed on ultrasonography. The presence of free intraperitoneal fluid on ultrasonography not detectable on physical examination or the sole presence of peripheral edema was not considered an end point. HE was defined by the presence of temporospatial disorientation, asterixis, or both in the absence of other possible causes. The presence of subclinical encephalopathy was not investigated. Variceal bleeding was defined according to the Baveno IV criteria.⁷ Patients who received liver transplants because of hepatocellular carcinoma without clinical decompensation previous to the surgery were censored at the time of transplantation. All data about clinical decompensation had been prospectively collected in the RCT, except in 62 patients who developed the primary end point of that trial but had not developed clinical decompensation. Retrospective review of charts of these patients was performed to have complete follow-up about clinical decompensation until the end of the study (September 2002).

Comparisons between patients with and without decompensation were first performed by using univariate Cox analysis. Multivariate analysis with backward stepwise Cox proportional hazards regression analysis was performed with the variables that had attained a P value $< .1$ on univariate analysis. To avoid the common problems of overfitting and colinearity, several different models were created with variables that were statistically significant in univariate analysis ($P < .1$) or that were clinically relevant. The modelling strategy used in this study is based on the reduction in the likelihood ratio ($-2LL$) of the different models developed. The lower the value of $-2LL$, the greater amount of variability of the outcome variable is explained by the model, that is, the better the model. By using this strategy we could evaluate all the potential variables that may have a role in predicting clinical decompensation. Colinearity was assessed with the tolerance value, considering excessive colinearity between variables when the tolerance was < 0.1 . First order two-way interactions between HVPG and the other variables were assessed by introducing in the model the cross-products between HVPG and the other variables; only interactions that would significantly change the predictive capacity would remain in the model. Assessment of proportional hazards was done by introducing a time-dependent variable and graphically. To evaluate the independent role of portal pressure (as determined by HVPG) in predicting clinical decompensation, Cox proportional hazards model was developed. Receiver operating characteristic (ROC) curves were constructed with Child-Pugh score, model of end-stage liver disease (MELD), albumin, and HVPG as predictors of clinical decompensation. The area under each

Table 1. Baseline Characteristics of All Patients and Patients Who Remained Compensated or Developed Decompensation During Follow-Up

	All patients (N = 213)	Remained compensated (n = 151)	Developed decompensation (n = 62)
Men, n (%)	126 (59)	86 (57)	40 (64)
Age (y), median (interquartile range)	54 (46–63)	54 (45–62)	56 (48–64)
Cause of cirrhosis			
Alcoholic, n (%)	51 (24)	36 (24)	15 (24)
Nonalcoholic, n (%)	162 (76)	115 (76)	47 (76)
HCV, n (%)	134 (62)	95 (63)	38 (61)
HBV, n (%)	8 (4)	8 (5)	2 (3)
Cryptogenic, n (%)	10 (5)	4 (3)	6 (10)
Other, n (%)	10 (5)	8 (5)	0 (0)
Child–Pugh score, median (interquartile range)	5 (5–5)	5 (5–5)	5 (5–6)
Child–Pugh class			
A, n (%)	188 (88)	137 (91)	51 (82)
B, n (%)	25 (12)	14 (9)	11 (18)
MELD, median (interquartile range)	8.0 (7.0–10.0)	7.9 (6.8–9.5)	9.0 (7.5–11.1)
Platelets ($\times 10^{-3}/\text{mm}^3$), median (interquartile range)	111 (74–149)	120 (84–150)	88 (66–138)
Total bilirubin (mg/dL), median (interquartile range)	0.9 (0.7–1.4)	0.9 (0.6–1.2)	1.3 (0.8–1.7)
INR, median (interquartile range)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.3)
Albumin	4.0 (3.6–4.3)	4.1 (3.7–4.3)	3.8 (3.4–4.1)
Aspartate aminotransferase (U/L), median (interquartile range)	73 (48–115)	69 (48–109)	84 (48–130)
Alanine aminotransferase (U/L), median (interquartile range)	78 (41–132)	73 (45–117)	88 (40–141)
Serum sodium (mmol/L), median (interquartile range)	140 (139–142)	140 (139–142)	141 (139–142)
Creatinine (mg/dL), median (interquartile range)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.0)
HVPG (mm Hg), median (interquartile range)	11 (8–14)	10 (7.5–13.5)	13 (11–16)
HVPG ≥ 10 mm Hg, n (%)	134 (63)	80 (53)	54 (87)
HVPG responders (n = 147)			
No, n (%)	81 (55)	57 (50)	24 (71)
Yes, n (%)	66 (45)	56 (50)	10 (29)
Hepatocellular carcinoma, n (%)	19 (9)	12 (8)	7 (11)
Follow-up time (mo), median (interquartile range)	51 (33–77)	62 (43–81)	31 (16–57)
Randomly assigned to timolol, n (%)	108 (51)	72 (48)	36 (58)

NOTE. HVPG responders are those in whom HVPG decreased $>10\%$ at 12 months.

HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, model of end-stage liver disease; INR, International Normalized Ratio; HVPG, hepatic venous pressure gradient.

of the curves (c statistic) was estimated. A threshold value of HVPG that distinguished 2 populations with different incidence of clinical decompensation was identified. Kaplan–Meier curves of the 2 populations were constructed and compared with the log-rank test.

Finally, a secondary analysis was performed in the subgroup of patients who had a second hemodynamic study 1 year after inclusion in the RCT. Patients were considered “responders” (independent of whether the patients were taking β -blockers or placebo) if they had a 10% decrease in HVPG from baseline. This cutoff was identified as a predictor of primary end points in the original RCT.⁶ The independent role of hemodynamic response, aside from baseline HVPG, was evaluated with Cox proportional hazards regression analysis.

Statistical significance was considered with a P value of $\leq .05$. Statistical analysis was done with SPSS package 12.0 (SPSS Inc, Chicago, IL). Approval from the local institutional review board was obtained.

Results

Baseline data of the patients is shown in Table 1. From the 213 patients who were included in the original trial,⁶ 62 patients developed clinical decompensation, 12 received a transplant (because of hepatocellular carcinoma), 10 patients died (4 of extrahepatic neoplasia, 4 of bacterial infection, 1 of sudden death, and 1 of mediastinitis after aortic valve replacement surgery) in both cases without having developed previous clinical decompensation, and, finally, 129 patients were alive at the end of follow-up (Figure 1). The median follow-up was 51.1 months (interquartile range, 33–77 months). A significantly greater proportion of patients from the group that had developed the original RCT end point (small varices in 2 consecutive endoscopies, large esophageal varices, or VH) developed clinical decompensation (35/84; 42%) compared with those who did not reach the end point (27/129; 21%) ($P = .002$). Most patients presented with ascites

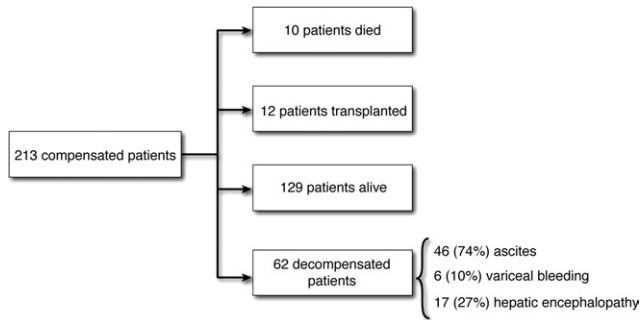


Figure 1. Flow chart showing the outcome of patients included in the study. Patients who died or received a liver transplant did so without developing cirrhosis decompensation.

as their first episode of clinical decompensation (46 patients, 74%) either alone (40 patients) or in combination with other types of clinical decompensation (3 VH, 3 HE). Only 6 patients presented with VH as first clinical decompensation (10%) (2 alone, 3 in combination with ascites, and 1 with HE). Finally 17 patients (27%) had HE during the follow-up, in 13 cases as the only complication (21%) and in the rest of the cases in combination with other types of decompensation (see above). Median HVPG at baseline was 11 mm Hg (interquartile range, 8–14 mm Hg).

As shown in Table 2, on univariate analysis, HVPG, MELD, Child–Pugh score, and its biochemical components, aspartate aminotransferase and platelet count, were significantly more altered in patients who developed decompensation compared with patients who remained compensated. Both groups had a similar proportion of alcoholic liver disease, and a similar proportion of patients randomly assigned to the treatment group (β -blocker or placebo) in the original study.

When all variables significant on univariate analysis were entered in a multivariable model, HVPG (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.05–1.17), MELD [HR, 1.15; 95% CI, 1.03–1.29, and albumin HR, 0.37; 95% CI, 0.22–0.62] remained independent predictors of clinical decompensation (Table 3). No 2-way interactions between HVPG and the other variables were detected.

Different models were developed to avoid colinearity and overfitting (Table 3). The final model (HVPG, MELD, albumin) was chosen according to the reduction in the likelihood ratio. In all models HVPG remained an independent predictor of clinical decompensation. Of interest, the robustness of the quantification of the effect of HVPG on clinical decompensation was emphasized by the similar value of HR obtained in the different models.

ROC curves were constructed to identify the diagnostic capacity of HVPG, MELD, and Child–Pugh score. HVPG had a greater discriminative ability (*c* statistic, 0.71; 95% CI, 0.64–0.78) compared with albumin (*c* statistic, 0.66;

95% CI, 0.58–0.74), MELD (*c* statistic, 0.64; 95% CI, 0.55–0.72), and Child score (*c* statistic, 0.61; 95% CI, 0.52–0.7) (Figure 2).

To identify a threshold value of HVPG to separate different risk populations, it was a priori considered that it would be preferable to identify patients who would not develop decompensation. With this consideration, the threshold HVPG value of 10 mm Hg identified 2 different risk populations for development of clinical decompensation with a 90% negative predictive value. Therefore, compensated patients with a HVPG value <10 mm Hg had a 90% chance of not having any clinical decompensation in a median follow-up of 4 years. Kaplan–Meier curves were constructed in patients with an HVPG \leq 10 mm Hg and \geq 10 mm Hg [unadjusted HR, 5.7; 95% CI, 2.7–12; $P < .001$] (Figure 3). No patient with an HVPG <10 mm Hg developed clinical decompensation during the first 20 months of follow-up. Evaluation of the other 2 variables that had an independent predictive role on multivariable analysis showed that the best cutoff values of both MELD (MELD score = 10; unadjusted HR, 2.3; 95% CI, 1.4–3.9; $P = .001$) and albumin (4 g/dL; unadjusted HR, 2; 95% CI, 1.2–3.3; $P = .007$) had a negative predictive value of 78% and 77%, respectively, lower than that shown for the HVPG (Figure 3).

During follow-up 154 patients had repeat HVPG measurements done 1 year after random assignment. From these patients, 7 had developed clinical decompensation.

Table 2. Univariate Cox Analysis

	Hazard ratio	95% CI	P value
Men	1.271	0.755–2.14	.367
Age	1.011	0.988–1.035	.344
Alcohol cause	1.344	0.751–2.405	.32
Child–Pugh score	1.751	1.341–2.286	<.001
Child–Pugh class	2.748	1.423–5.308	.003
MELD	1.245	1.117–1.387	<.001
Platelets ($\times 10^{-3}/\text{mm}^3$)	0.992	0.987–0.998	.008
Total bilirubin (mg/dL)	1.447	1.174–1.782	.001
INR	14.26	3.14–64.77	.001
Albumin	0.285	0.175–0.464	<.001
Aspartate aminotransferase (U/L)	1.003	1–1.006	.064
Alanine aminotransferase (U/L)	1.001	0.998–1.003	.524
Serum sodium (mmol/L)	1.011	0.936–1.09	.787
Creatinine (mg/dL)	0.598	0.19–1.886	.381
HVPG (mm Hg)	1.132	1.079–1.187	<.001
HVPG \geq 10 mm Hg	3.95	2.286–6.827	<.001
12-mo response	0.571	0.272–1.199	.139
Randomly assigned to timolol	1.371	0.827–2.272	.221

NOTE. All continuous variables were introduced in the univariate model as quantification of the effect.

CI, confidence interval; MELD, model of end-stage liver disease; INR, International Normalized Ratio; HVPG, hepatic venous pressure gradient.

Table 3. Modelling Strategy Used to Avoid Colinearity and Overfitting (62 Events)

Variables introduced	Final model	HR	95% CI	P value	-2LL
HVPG, age, AST, MELD, albumin, platelets, timolol, or placebo	HVPG	1.105	1.046–1.169	.001	531.72
	MELD	1.153	1.032–1.288	.014	
	Albumin	0.368	0.217–0.624	< .0001	
HVPG, age, AST, albumin, INR, total bilirubin, timolol, or placebo	HVPG	1.105	1.046–1.167	.001	534.162
	INR	5.339	1.076–26.486	.05	
	Albumin	0.347	0.205–0.589	< .0001	
HVPG, age, creatinine, AST, CPS, timolol, or placebo	HVPG	1.116	1.061–1.174	< .0001	557.48
	CPS	1.761	1–1.1007	< .0001	
	AST	1.004	1.324–2.342	.052	
HVPG, bilirubin, INR, albumin, AST, MELD, CPS	HVPG	1.105	1.046–1.169	.001	531.72
	MELD	1.153	1.032–1.288	.014	
	Albumin	0.368	0.217–0.624	< .0001	
Albumin, platelets, bilirubin, INR, AST, MELD, CPS, creatinine	Albumin	0.354	0.205–0.612	< .0001	535.58
	Platelets	0.995	0.99–1.001	.08	
	AST	1.004	1–1.007	.035	
	MELD	1.184	1.057–1.327	.004	

NOTE. No one-way interactions were observed. Assumption of proportional hazards was confirmed. All variables were introduced as continuous variables.

HR, hazard ratio; CI, confidence interval; -2LL, likelihood ratio (amount of variability of the outcome explained by the model; the closer to 0, the better the model adjusts to explain the outcome); HVPG, hepatic venous pressure gradient; AST, aspartate aminotransferase; MELD, model of end-stage liver disease; INR, International Normalized Ratio; CPS, Child-Pugh score.

pensation before the second HVPG measurement and were therefore not included in further analysis. Patients were then classified in “responders” (HVPG de-

crease of $\geq 10\%$ from baseline) or “nonresponders.” This subgroup of patients had similar characteristics to the original cohort, except for a longer follow-up (63 vs 51 months, $P < .0001$) (Table 1). When included in the multivariate model with the previously identified variables (baseline HVPG, MELD, albumin), baseline HVPG (HR, 1.15; 95% CI, 1.08–1.23), nonresponders at 12 months (HR, 2.6; 95% CI, 1.1–5.6), and albumin (HR, 0.42; 95% CI, 0.18–0.91) were independent predictors of clinical decompensation. No 2-way interactions were detected. Although patients who were nonresponders had a significantly greater HVPG at baseline (12 mm Hg vs 10.5 mm Hg, $P = .045$), no colinearity between these variables was detected.

Discussion

The natural history of chronic liver disease involves the progression to cirrhosis, first compensated, then to decompensated cirrhosis and ultimately to death. Identification of predictors of decompensation among compensated patients is warranted, because death in cirrhosis is clearly related to the development of decompensation.¹ Even in the compensated phase, 2 stages with different survival rates have been identified: stage 1 without varices and stage 2 with varices.¹

This large prospective cohort study looked specifically at a homogenous group of compensated patients with portal hypertension but without varices (stage 1). In this same group of patients, we had previously shown that an HVPG >10 mm Hg was the strongest predictor of the development of varices, which is not considered a decompensating event. In this study our aim was to identify predictors of clinical decompensation (ascites, VH, or

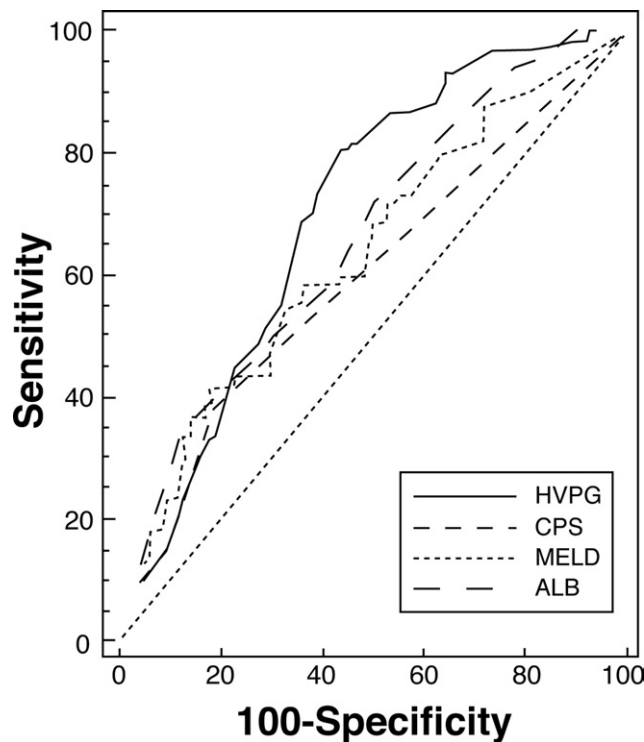


Figure 2. ROC curves for cirrhosis decompensation for the main prognostic factors: HVPG, hepatic venous pressure gradient (c statistic, 0.71; 95% CI, 0.64–0.78); albumin, serum albumin (c statistic, 0.66; 95% CI, 0.58–0.74); MELD, model for end-stage liver disease score (c statistic, 0.64; 95% CI, 0.55–0.72); CPS, Child-Pugh score (c statistic, 0.61; 95% CI, 0.52–0.71).

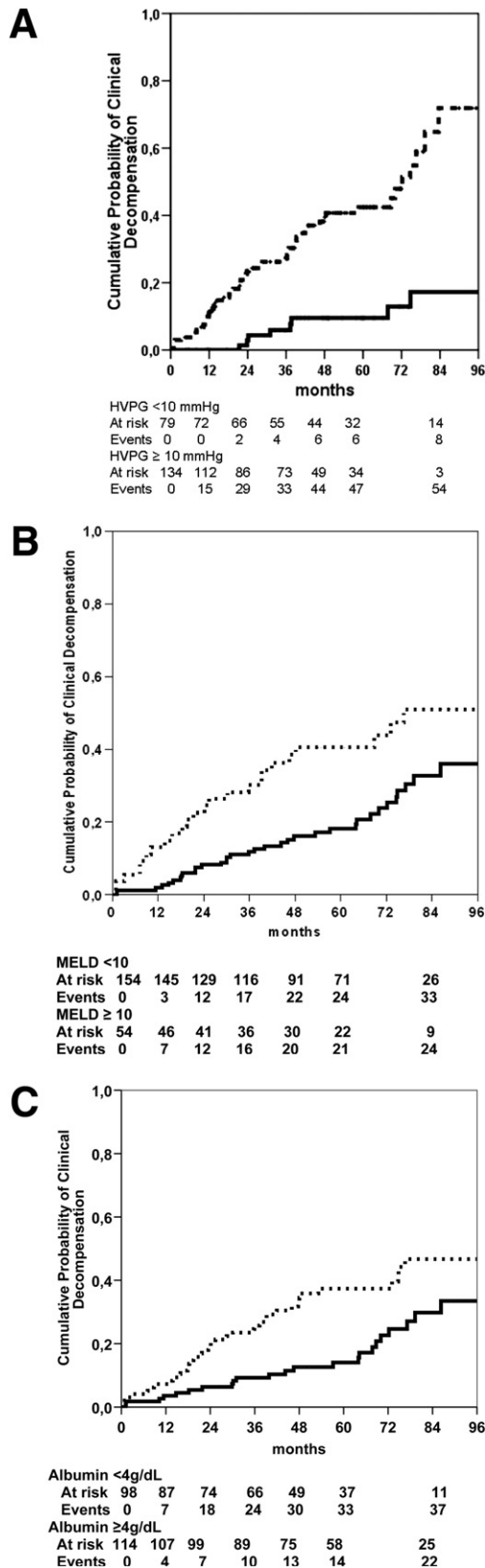


Figure 3. Kaplan–Meier survival curves according to the best cutoff level for (A) HVPG, hepatic venous pressure gradient (best cutoff level is 10 mm Hg); (B) MELD, model for end-stage liver disease (best cutoff score is 10); and (C) serum albumin (best cutoff level is 4 mg/dL). Discontinuous line represents HVPG ≥ 10 mm Hg, MELD ≥ 10 , albumin < 4 g/dL in (A), (B) and (C) respectively.

encephalopathy), and we found that, in a median follow-up of 51.1 months, decompensation occurred in 62 of 213 patients (29%). This relatively high rate of decompensation is most probably related because all patients had portal hypertension (ie, an HVPG of ≥ 6 mm Hg) at baseline. The predictors of clinical decompensation identified in this study (HVPG, albumin, and MELD) are well-known predictors of survival in decompensated patients^{1,8} and are related to the severity of portal hypertension and liver insufficiency. Similar results were shown in a recent study in compensated patients with hepatitis C virus (both stage 1 and stage 2) that identified the presence of esophageal varices and bilirubin as the only independent predictors of clinical decompensation.⁹

HVPG was the most robust predictor of clinical decompensation because it remained an independent predictor across different models. The hazard ratio (ie, the quantification of the effect of HVPG on decompensation prediction) was also similar among the different tested models.

Furthermore, according to the HVPG, 2 different risk populations could be distinguished so that patients with an HVPG value < 10 mm Hg have a 90% chance of not developing clinical decompensation. This further supports the clinical applicability of HVPG measurement because it enables the identification of patients who are unlikely to develop clinical decompensation during the following years. Importantly, in predicting decompensation, it is not only the qualitative value of HVPG that is important (presence or absence of an HVPG ≥ 10 mm Hg), but it is also the quantitative degree of portal hypertension that is relevant because, according to our model, the HVPG has a hazard ratio of 1.11, implying that for each 1 mm Hg increase in HVPG there is an 11% higher risk of clinical decompensation. In this way, a patient with a baseline HVPG of 15 mm Hg has 55% higher chance of developing decompensation compared with a patient with an HVPG of 10 mm Hg, at equivalent MELD and albumin values.

We also provide further evidence on the independent role of a decrease in HVPG in the prediction of clinical decompensation. This effect is independent of baseline HVPG. Previous studies had evaluated the role of a reduction in HVPG in predicting clinical decompensation in patients undergoing primary^{4,10} or secondary prophylaxis.^{3,5} Similar to our results, these studies have shown that being an HVPG nonresponder is independently associated with a greater incidence of portal hypertension-related complications and death.^{3,5,11} The definition of response in our study (decrease of $\geq 10\%$) differs from the traditional criteria (ie, a reduction of $> 20\%$ from baseline or < 12 mm Hg).⁷ However, these criteria were obtained in patients with more severe portal hypertension (large varices with or without VH), whereas our patients had portal hypertension but had not yet developed varices. In fact, several studies have already suggested that, in more

compensated patients, a 10% to 11% threshold is the best cutoff in predicting development of varices or VH⁶ or spontaneous bacterial peritonitis or bacteraemia.⁴

According to the literature, the Child-Pugh score should have been a better predictor in compensated patients and MELD a better predictor in decompensated patients.¹ However, in the present study, MELD, and not Child-Pugh score, is an independent predictor of clinical decompensation in compensated patients. This is probably because the MELD score is composed of laboratory markers that can reflect subtle abnormalities of the liver function. However, one of the setbacks of the MELD score is that it does not include any variable associated to portal hypertensive syndrome.^{12,13} A previous study has evaluated the role of HVPG and MELD score in survival prediction in a population of predominantly decompensated patients with cirrhosis.⁸ In that population group HVPG was independently associated to mortality, although it did not improve the discriminative ability of MELD score. Interestingly, in our study in compensated patients, HVPG gains a predominant role with a greater discriminative ability in the prediction of decompensation, which will ultimately determine survival. This is probably because, in compensated patients, the distribution range of the MELD score is much narrower than in decompensated patients, whereas the HVPG, by virtue of a wider distribution range, provides the most information to predict decompensation.

One limitation of our study is that it constitutes a subanalysis of another study designed for another aim. However, in the original RCT,⁶ data on VH (primary end point) and other decompensating events (secondary end points) were collected prospectively with an a priori definition of each complication so that data collection about complications of cirrhosis was uniform across study centers. Only the 62 patients (29%) who developed varices (and had not developed decompensation) were not followed prospectively until the development of decompensation. The charts of those patients were the only ones that were reviewed retrospectively. Although this review may have introduced some bias, we consider that it is highly unlikely that the development of relevant clinical end points such as ascites, VH, or encephalopathy, requiring specific management, would have been missed and not recorded in the clinical chart, particularly because most of the patients remained under the care of specialists at the same study centers. In fact, we chose not to include jaundice, a complication that has been traditionally considered a decompensating event, in our definition of decompensation. We considered that it would be more difficult to reliably investigate this indicator retrospectively and also because jaundice is often due to an acute-on-chronic illness and thereby would not constitute a "permanent" decompensation. Furthermore, and as expected given a more advanced stage of the disease,¹ patients who developed varices in the original RCT (ie, pro-

gression from stage 1 to stage 2) had a higher rate of clinical decompensation than patients who did not develop varices.

Another possible limitation is related to the study population. The study population was composed of compensated patients with portal hypertension without varices on upper gastrointestinal endoscopy. Therefore, the results can be applied only to this population. Whether the results may be applied to other groups of compensated patients (ie, with varices) remains to be determined. Moreover, cross-validation of the model in a subset of patients of this sample was not done, in order to not reduce the size of the sample and therefore the robustness of the estimates. Further studies will be required to test the model in other datasets and to evaluate more heterogeneous populations (eg, patients with compensated cirrhosis with varices or patients with compensated cirrhosis without varices) with or without portal hypertension.

In conclusion, the results of this large study suggest that in compensated patients with portal hypertension but without varices, HVPG, MELD, and albumin are independent predictors of the development of clinical decompensation which marks a threshold beyond which survival prognosis changes considerably. HVPG is the most robust predictor of clinical decompensation in patients with compensated cirrhosis and portal hypertension without varices.

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Address requests for reprints to: Roberto J. Groszmann, MD, VA CT Healthcare System, Digestive Disease Section/111H, Yale University School of Medicine, 950 Campbell Avenue, West Haven, Connecticut 06516. e-mail: roberto.groszmann@yale.edu; fax: (203) 937-3873.

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