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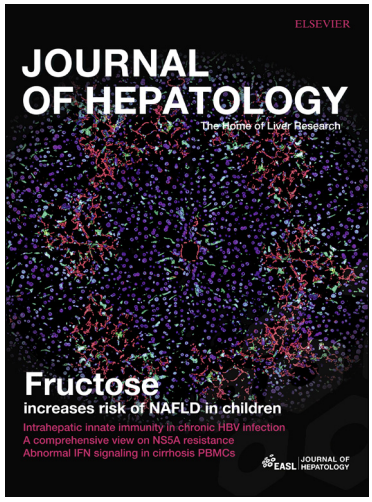

Cardiopulmonary hemodynamics and c-reactive protein as prognostic indicators in compensated and decompensated cirrhosis

Laura Turco, Guadalupe Garcia-Tsao, Ilenia Magnani, Marcello Bianchini, Martina Costetti, Cristian Caporali, Stefano Colopi, Emilio Simonini, Nicola De Maria, Federico Banchelli, Rosario Rossi, Erica Villa, Filippo Schepis

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TITLE PAGE

Title

CARDIOPULMONARY HEMODYNAMICS AND C-REACTIVE PROTEIN AS PROGNOSTIC INDICATORS IN COMPENSATED AND DECOMPENSATED CIRRHOSIS

116 caracthers

Author Names

Laura Turco[1], Guadalupe Garcia-Tsao[1,2], Ilenia Magnani[3], Marcello Bianchini[1], Martina Costetti[1], Cristian Caporali[4], Stefano Colopi[4], Emilio Simonini[4], Nicola De Maria[1], Federico Banchelli[5], Rosario Rossi[3], Erica Villa[1], Filippo Schepis[1].

Affiliation

[1] *Division of Gastroenterology, Azienda Ospedaliero-Universitaria di Modena and University of Modena and Reggio Emilia, Modena, Italy*

[2] *Section of Digestive Diseases, Yale School of Medicine, New Haven, CT, USA; Section of Digestive Diseases, VA Connecticut Healthcare System, West Haven, CT, USA*

[3] *Division of Cardiology, Azienda Ospedaliero-Universitaria di Modena and University of Modena and Reggio Emilia, Modena, Italy*

[4] *Division of Radiology, Azienda Ospedaliero-Universitaria di Modena and University of Modena and Reggio Emilia, Modena, Italy*

[5] *Statistics Unit, Department of Clinical, Diagnostic and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy.*

Corresponding Author

Filippo Schepis, MD

Department of Gastroenterology, University of Modena & Reggio Emilia,

Via del Pozzo 71, Modena, 41100, Italy.

E-mail: filippo.schepis@unimore.it

Telephone number: +39 0594225664

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Author Contribution

Laura Turco: acquisition of data, analysis and interpretation of data, drafting of the manuscript, technical and material support.

Guadalupe Garcia-Tsao: study supervision; interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Ilenia Magnani: acquisition of data; technical and material support.

Marcello Bianchini: acquisition of data.

Martina Costetti: acquisition of data.

Cristian Caporali: acquisition of data.

Stefano Colopi: acquisition of data.

Emilio Simonini: acquisition of data.

Nicola De Maria: acquisition of data.

Federico Banchelli: statistical analysis.

Rosario Rossi: interpretation of data; critical revision of the manuscript for important intellectual content.

Erica Villa: interpretation of data; critical revision of the manuscript for important intellectual content; obtained funding.

Filippo Schepis: study concept and design; acquisition of data; study supervision; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; obtained funding.

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ABSTRACT

Background and Aims: The main stages of cirrhosis (compensated and decompensated) have been substaged based on clinical, endoscopic, and portal pressure (determined by the hepatic venous pressure gradient, HVPG) features. Vasodilatation leading to a hyperdynamic circulatory state is central in the development of a late decompensated stage with inflammation being currently considered a key driver. We aimed to assess hepatic/systemic hemodynamics and inflammation (by C reactive protein, CRP) among the different substages of cirrhosis and to investigate their interrelationship and prognostic relevance.

Methods: Single center, prospective cohort of patients with cirrhosis undergoing *per protocol* hepatic and right-heart catheterization and CRP measurement, classified into recently defined prognostic stages (PS) of compensated (PS1: HVPG ≥6mmHg but <10mmHg; PS2: HVPG ≥10 mmHg without gastroesophageal varices; PS3: patients with gastroesophageal varices) and decompensated (PS4: diuretic-responsive ascites; PS5: refractory ascites) disease. Cardiodynamic states based on cardiac index (L/min/m^2) were created: relatively-hypodynamic (<3.2), normodynamic (3.2-4.2) and hyperdynamic (>4.2).

Results: 238 patients, 151 compensated (PS1=25; PS2=36; PS3=90), 87 decompensated (PS4=48; PS5=39). Mean arterial pressure decreased progressively from PS1 to PS5, cardiac index increased progressively from PS1-to-PS4 but decreased in PS5. HVPG, MELD, and CRP increased progressively from PS1-to-PS5. Among compensated patients, age, HVPG, relatively-hypodynamic/hyperdynamic state and CRP were predictive of decompensation. Among patients with ascites, MELD, relatively-hypodynamic/hyperdynamic state, post-capillary pulmonary hypertension, and CRP were independent predictors of death/liver transplant.

Conclusions: Our study demonstrates that, in addition to known parameters, cardiopulmonary hemodynamics and CRP are predictive of relevant outcomes in patients with both compensated and decompensated cirrhosis.

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LAY SUMMARY

There are two main stages in cirrhosis, compensated and decompensated, each with main relevant outcomes: development of ascites and death, respectively. Major roles of cardiac dysfunction and systemic inflammation in the evolution of the disease have been hypothesized in decompensated patients. In this study, we have shown that these factors were also involved in the progression from compensated to decompensated stage.

INTRODUCTION

Cirrhosis represents the end-stage of chronic liver disease, with a course characterized by a transition from an asymptomatic compensated stage to a symptomatic decompensated stage. [1] These stages have entirely different mortalities and should therefore be considered distinct entities. Decompensation is defined by the development of overt clinical complications of cirrhosis: ascites, variceal hemorrhage (VH), encephalopathy, and jaundice. [1]

Decompensation is mainly driven by portal hypertension (PH), with a portal pressure, as determined by the hepatic venous pressure gradient (HVPG), ≥10 mmHg. [2] Therefore, compensated cirrhosis has been recently sub-staged into mild PH (HVPG >5 but <10 mmHg) and clinically significant portal hypertension (CSPH, HVPG ≥10 mmHg). [2,3] The latter sub-group has in turn been sub-classified into those with or without gastroesophageal varices (GEV) because patients with compensated cirrhosis and GEV have a higher risk of decompensation and death, compared to those without GEV. [4]

The most frequent decompensating event in cirrhosis and the one that carries the highest mortality is ascites. [5,6] Unlike VH and encephalopathy, ascites is a progressive complication that results most directly from a splanchnic venous pooling in the upright posture, which triggers sodium and water retention. [7] Shear stress-induced splanchnic arterial vasodilatation then appears in the supine position as a consequence of blood volume redistribution and cardiac output increase (i.e., vasodilation hypothesis and hyperdynamic circulatory state). [7] Worsening of this state leads to a stage of "further" decompensation, characterized by refractory ascites. [8]

Bacterial or pathogen-associated molecules translocation from the intestinal lumen to the systemic circulation and extraintestinal organs, has been associated with the hyperdynamic circulatory state of advanced experimental and human cirrhosis through an increased production of proinflammatory cytokines. [9-11] A recent paper [12] has de-emphasized the importance of the vasodilation hypothesis in favor of a systemic inflammatory response as the predominant mechanism in decompensated cirrhosis and in acute-on-chronic liver failure (AoCLF), but has recommended the performance of studies assessing the relationship among clinical stages, splanchnic and systemic hemodynamics and systemic inflammation.

The aim of this study was to assess systemic and hepatic hemodynamics and systemic inflammation at each of the five sub-stages of cirrhosis (3 in compensated cirrhosis, [3] 2 in decompensated cirrhosis) and to investigate their relative impact on decompensation (in those with compensated cirrhosis) and death/liver transplant (in those with decompensated cirrhosis).

PATIENTS AND METHODS

The study is a single center cohort study in which consecutive patients evaluated at the Hepatic Hemodynamic Laboratory at the Azienda Ospedaliero-Universitaria in Modena, Italy, between March 2013 and August 2015 were considered for enrolment. Patients referred to this laboratory are those with clinically diagnosed cirrhosis followed at the outpatient Liver Clinics or in the inpatient services (compensated patients were mainly outpatients; about 60% of decompensated patients were recruited while hospitalized for difficult to treat/refractory ascites, pre-OLT workup or hepatic encephalopathy).

Hemodynamic assessment was performed in the setting of two ongoing prospective studies approved by the local Ethics Committee: the first looking at predictors of first decompensation (NCT03084185); the second looking at clinical and molecular predictors of hepatocellular carcinoma (HCC) in both compensated and decompensated patients (NCT03083002). These studies require baseline testing and prospective follow-up. Patients sign consent to participate in the study.

Patients

Inclusion criteria were presence of cirrhosis (based on clinical, biochemical, elastographic, imaging and/or histological criteria) and a HVPG >5 mmHg.

Exclusion criteria were: age below 18 and above 75 years, factors that would impact prognosis and/or hemodynamics (HCC, AoCLF, including alcoholic hepatitis, sepsis or active infections), previous TIPS placement, treatment with non-selective beta-blockers (NSBB) in compensated patients, cholestatic liver disease, active heavy alcohol intake, occlusive portal vein thrombosis, HIV co-infection, coronary artery disease, chronic kidney disease, cirrhosis post-liver transplant, hepatopulmonary syndrome, portopulmonary hypertension, heart failure as defined by an ejection fraction <55%, non-cirrhotic PH, and failure to sign informed consent. All eligible patients underwent hepatic and cardiac hemodynamic assessment. HVPG values, presence of non-cirrhotic PH and portopulmonary hypertension were defined at the time of hemodynamic assessment.

Patients were defined as having compensated cirrhosis in the absence of clinically overt ascites, overt encephalopathy, VH or jaundice. We defined patients as having decompensated cirrhosis in the presence of ascites as this is the most common non-episodic event and the one with the highest mortality. [5-7] Patients with a remote history of VH as the only decompensating event were not considered decompensated because once VH resolves, patients return to a compensated stage. [3]

Patients with overt encephalopathy in the absence of other decompensating events were not seen in this cohort.

Patients with **compensated** cirrhosis were sub-classified into 3 clinical prognostic stages (PS) [3] based on the presence of the following:

1) PS1, mild PH (HVPG >5 mmHg but <10 mmHg)
2) PS2, CSPH (HVPG ≥10 mmHg) without GEV
3) PS3, GEV (by definition, with CSPH).

Patients with **decompensated** cirrhosis were sub-classified into 2 clinical prognostic stages: [13]

4) PS4, diuretic responsive ascites with or without a remote VH or hepatic encephalopathy
5) PS5, refractory ascites, defined according to the International Ascites Club, [14] with or without a remote history of VH or hepatic encephalopathy

Routine Assessments

Routine laboratory tests including liver enzymes/function and cell blood counts were obtained. MELD and Child-Turcotte-Pugh (CTP) scores were calculated. Ultrasound to screen for HCC and portal vein thrombosis was obtained within one month prior to hemodynamic evaluation; upper endoscopy to screen for GEV was performed during the same admission as hemodynamic evaluation.

Hemodynamic Evaluation

Performed after an overnight fast and under mild sedation with intravenous midazolam (0.02 mg/kg). PS5 patients with grade 2-3 ascites underwent large volume paracentesis (LVP) and intravenous albumin [15] the day before the hemodynamic procedure. Most patients with ascites were taking diuretics until the day prior to the procedure. Weight and height were recorded before starting the procedure to calculate the body surface area (BSA). After local anesthesia, a venous introducer was placed in the right internal jugular vein following the Seldinger technique. During the entire procedure, heart rate (HR) and mean arterial pressure (MAP) were measured every five minutes with an automatic sphygmomanometer (Marquette Electronics, Milwaukee, WI).

Cardiopulmonary hemodynamics

Cardiopulmonary pressures were measured under fluoroscopy as already described. [16] Right atrial pressure (RAP), mean pulmonary artery pressure (PAPm) and mean pulmonary artery wedged pressure (PAWP) were recorded electronically (PowerLab, ADI Instruments, Milford, MA, USA) and analyzed using dedicated software (LabChart 7, ADI Instruments, Milford, MA, USA). Cardiac output (CO) was determined by the on-line thermo dilution method (Marquette Electronics, Milwaukee, WI).

Cardiac index (CI = CO/BSA), stroke volume index (SVI = CI/HR), left ventricular stroke work index [LVSWI= SVI x (MAP - PAWP) x 0.0136], systemic vascular resistance index [SVRI = ((MAP–RAP)/CI)*80], pulmonary vascular resistance index [PVRI= [((mPAP - PAWP)/CI)*80] were calculated. Post-capillary pulmonary hypertension (pcPH) due to left ventricular dysfunction was defined as a PAPm ≥25 mmHg associated with a PAWP >15 mmHg. [17,18]

HVPG measurement

After cardiopulmonary parameters were measured, a balloon catheter (Edwards Lifesciences™, Irvine, CA, USA) was introduced into the main right or medium supra-hepatic vein via the inferior vena cava (IVC) for measurements of the wedged hepatic vein pressure (WHVP) and the free hepatic venous pressure (FHVP) as previously described. [16] Permanent tracings were electronically recorded (PowerLab, ADI Instruments, Milford, MA, USA) and analyzed by dedicated software (LabChart 7, ADI Instruments, Milford, MA, USA). The HVPG was obtained by subtracting the FHVP at junction with IVC from the WHVP.

All hemodynamic assessments were performed in triplicate.

Inflammatory marker

C reactive protein (CRP), the most common marker of systemic inflammation, was *per protocol* assessed in sera of all patients by a commercially available test (CRPL3-Cobas-Roche diagnostics) with a lower sensitivity limit of 0.49 mg/dL. Levels ≥0.5 mg/dL were considered abnormal. [19]

Follow up and outcomes

After inclusion, patients were followed at least every 6 months in the clinic. Each visit included physical examination, blood tests and abdominal ultrasound. Follow-up data were gathered up to 36 months from baseline, or until orthotopic liver transplant (OLT) or death. Development of ascites was the main outcome in patients with compensated cirrhosis (PS1, PS2 and PS3), while all-cause mortality/OLT was the main outcome for patients with decompensated cirrhosis (PS4 and PS5).

Statistical Analysis

Continuous variables were expressed as mean ± standard error, while categorical variables as absolute and percentage frequencies. One-way analysis of variance (ANOVA) was conducted to compare continuous variables among prognostic stages. The Tukey test was used to perform multiple comparisons. Two-way ANOVA was used to study the interaction of prognostic stages and cardiodynamic states on main clinical and hemodynamic continuous variables.

Analysis was performed separately for the compensated and decompensated stages.

For the **compensated** stages (PS1, 2 and 3), the relevant outcome was development of ascites evident on physical examination and confirmed by ultrasound. DAA treatment, TIPS, OLT, and death during follow-up were treated as competing events, while patients who were event-free at the day of the last visit were censored.

Comparison of cumulative incidence curves for the probability of developing overt ascites was performed with Gray's test. Multivariable analysis was performed using a backward stepwise Fine & Gray proportional hazards regression model for competing risks analysis, which incorporated age, MELD, albumin, CRP, HVPG, MAP, CI state, pcPH and treatment with non-selective beta-blockers (NSBB). Use of NSBB was defined as a time-varying covariate, which started its effect the day when the maximal tolerated dose was reached.

For the **decompensated** stages (PS4 and 5), the relevant outcomes were death or OLT. TIPS placement or DAA treatment during follow-up were considered as competing events. Comparison of cumulative incidence curves for the probability of death/OLT was performed with Gray's test. Multivariable analysis was performed using a backward stepwise Fine & Gray proportional hazards regression model for competing risks analysis, which incorporated age, refractory ascites (PS5), MELD, CRP, HVPG, MAP, CI state, pcPH and NSBB. Use of NSBB was considered as a time-varying covariate as already stated.

Covariates of multivariable models were selected on the base of both their clinical relevance and adherence to the aim of the study. Backward stepwise selection of covariates was based on their *p* value at each iteration (variables with a significance >0.05 were removed). Proportional hazards assumption of the Fine & Gray models was checked by means of graphical assessment of their weighted Schoenfeld-type residuals. Moreover, we calculated estimates of Akaike Information Criterion (AIC) for the null model (i.e., without covariates), for all univariable models containing independent variables used in the final multivariable models, and for the final multivariable models themselves. Finally, calibration plots by deciles [20] for final competing risks multivariable models (at three years and at one year from baseline for compensated and decompensated patients, respectively) were implemented by the R package "pec" [21] using 100 bootstrap replications.

All statistical analyses were performed at 95% confidence level (p-value <0.05), using R 3.3.2 and SAS Enterprise Guide 6.1.

RESULTS

As shown in Supplementary Figure 1, 798 patients were initially evaluated, 320 were considered eligible and were referred for hepatic and cardiopulmonary hemodynamic assessment. Of these, 238 met inclusion criteria and form the basis of this study. Notably, all patients in PS1 had a liver biopsy showing cirrhosis.

Patient characteristics

Mean age of the whole cohort was 58.4±11.8 years, 66% were male. Main etiologies of cirrhosis were viral hepatitis (50%), alcohol (17%) or both (11%).

At time of enrollment, 151 (63.4%) patients were compensated (no overt ascites, VH or encephalopathy) and 87 (36.6%) were decompensated (ascites in all, remote history of VH in 6, history or presence of encephalopathy in 13). Among patients with compensated cirrhosis, 25 (16%) patients had mild portal hypertension (PS1), 36 (24%) CSPH but no GEV (PS2) and 90 (60%) had GEV (PS3) either present at endoscopy or obliterated via ligation (n=9). Among patients with decompensated cirrhosis, 48 (55%) had diuretic-responsive ascites (PS4) and 39 (45%) had refractory ascites (PS5). Table 1 shows the clinical characteristics by prognostic stage and demonstrates a progressive worsening of liver function (albumin, bilirubin, and INR) and kidney function (creatinine) with each stage. Consequently, MELD and CTP scores increase progressively with each stage.

Hemodynamic changes in the different prognostic stages

As shown in Table 1, there was a progressive higher portal pressure (HVPG) from PS1 to PS5. However, the largest difference in HVPG occurred between patients in PS1 and those in PS2 (mean HVPG 6.4 mmHg to 14.2 mmHg). MAP was progressively lower from PS1 to PS5, while CI was progressively higher from PS1 to PS4 but relatively lower in PS5 (Table 1, Figure 1).

To add granularity to cardiac hemodynamics, data were analyzed using different "cardiodynamic "states": a) hyperdynamic, defined as a CI above the upper limit of normal (>4.2 L/min/m^2); b) normodynamic, defined as a CI between 3.2 (the average in the general population and in our PS1 group) and 4.2 L/min/m^2; and c) relatively hypodynamic, defined as a CI <3.2 L/min/m^2. Using this categorization, the hyperdynamic state appeared as early as stage PS2 (Figure 2). However, at this stage and in all subsequent stages, up to one third of the patients were relatively hypodynamic (Figure 2). Specific clinical and hemodynamic features in these subcategories are reported in Table 2. Importantly, SVI decreased progressively with each prognostic stage in the hypodynamic state. However, when left ventricle performance was expressed as LVSWI (that is in relationship to the

pressure of work), its progressive impairment was observed both in the hypodynamic and hyperdynamic states, while this did not occur in the normodynamic group (Table 2, Supplementary Figure 2).

Post-capillary pulmonary hypertension (pcPH), as an indicator of diastolic left ventricular dysfunction, was observed in patients with CSPH (that is from PS2 to PS5) at every cardiodynamic state (Figure 2). As expected, HVPG was significantly lower in the hypodynamic state at each prognostic stage (Table 2).

No minor/major complications related to both hepatic and cardiac hemodynamic procedures were observed.

Systemic inflammation in the different prognostic stages

C reactive protein increased progressively from PS1 to PS5 with the highest levels observed in PS4 and PS5 (Table 1). Notably, while an abnormal CRP (≥ 0.5 mg/dl) was observed only in 15% of the patients at the earliest stage (PS1), the proportion of patients with abnormal CRP increased progressively with more advanced stages ($p<0.0001$), with 85% of patients at PS5 having an abnormal CRP (Figure 3). CRP levels were not significantly different among the different cardiodynamic states at each prognostic stage (Table 2).

Follow-up and outcomes

Supplementary Table 1 shows the number of outcomes per prognostic stage ignoring the occurrence of competing events.

In the competing risks analysis, in the sample of 151 compensated patients the first event was ascites for 21 (13.9%), DAA for 27 (17.9%), TIPS for 1 (0.7%) and death or OLT for 6 (4.0%). In the sample of 87 decompensated patients, the first event was death or OLT for 31 (35.6%), DAA treatment for 3 (3.4%), and TIPS placement (all for ascites) for 32 (36.8%).

Development of ascites in compensated patients

As shown in Supplementary Figure 3A, the three compensated sub-stages had significantly different cumulative probabilities of developing ascites, with a 36-month probability of 0%, 13.9%±1.1%, and 27.8%±0.6% for PS1, PS2, and PS3, respectively (p=0.031 by Gray test).

Fine & Gray regression analysis revealed that age, HVPG, cardiodynamic state (hyper/relatively hypodynamic), and CRP were independent predictors of decompensation (Table 3) in a mean and median follow-up time of 568 days and 560 days. No evidence of lack of proportional hazards was found (data not shown). Pairwise interactions were tested in the final multivariable model, but none

of them was statistically significant. AIC was equal to 190.4 for the null model, to 187.9, 178.2, 186.5 and 187.6 for the univariable models containing age, HVPG, cardiodynamic state, and CRP, respectively, and was equal to 166.5 for the final multivariable model. The latter had a satisfactory fit according to the calibration plots (Supplementary Figure 4A and 4C). Predictors of ascites development did not change when only compensated patients with CSPH (PS2 and PS3) were analyzed, which adds robustness to our results (Table 3). Figure 4A shows the cumulative risk of decompensation in each cardiodynamic state of patients with CSPH. ROC analysis in these patients (data not shown) identified 16 mmHg and 1.0 mg/dL as the best discriminating cutoffs for HVPG and CRP, respectively.

Mortality in decompensated patients

The 12-month probability of death/OLT was 27.7±0.7 % and 41.0±0.9% in PS4 and PS5, respectively (p=0.223 by Gray test) (Supplementary Figure 3B).

Fine & Gray regression analysis in patients with decompensated cirrhosis revealed that MELD, CRP, cardiodynamic state (hyper/relatively hypodynamic), and pcPH were independent predictors for the risk of death/OLT (Table 3) in a mean and median follow up time of 307 days and 192 days. No evidence of lack of proportional hazards was found (data not shown). Pairwise interactions were tested in the final multivariable model, but none of them was statistically significant. AIC was equal to 262.8 for the null model, to 252.0, 261.4, 259.4 and 259.5 for the univariable models containing MELD, pcPH, cardiodynamic state, and CRP, respectively, and was equal to 242.4 for the final multivariable model. The latter had a satisfactory fit according to the calibration plots (Supplementary Figure 4B and 4D). Figure 4B and C show the 36-month cumulative risk of death/OLT in each cardiodynamic state and in patients with pcPH, respectively. ROC analysis (data not shown) identified 15 and 1.0 mg/dL as the best discriminating cutoffs for MELD and CRP, respectively.

DISCUSSION

This is the first study that characterizes clinical, portal and cardio-systemic hemodynamic states (obtained directly by cardiac and hepatic vein catheterization) and systemic inflammation in different prognostic sub-stages of compensated and decompensated cirrhosis. Importantly, it determines the interrelationship among these parameters and relevant outcomes for the two main stages of cirrhosis, compensated or decompensated.

Compensated Cirrhosis

In patients with **compensated** cirrhosis, those with mild PH (PS1) have normal mean CI and MAP, which become abnormal as early as the CSPH without GEV stage (PS2). In fact, the marked differences in hemodynamic indices between these stages (PS1 and PS2) suggest that there may be intermediate hemodynamically-defined events. As expected, the lowest MAP and highest mean CI occurred in patients with GEV (Table 1 and Figure 1). However, description of mean values of CI among the prognostic stages does not quite depict the hemodynamic variability already present in compensated patients. Indeed, while patients with a hyperdynamic state (CI >4.2 L/min/m^2) appear as early as stage PS2 as recently described, [22] there is a subgroup of patients with CSPH (with or without GEV) that have a relatively hypodynamic state (CI <3.2 L/min/m^2) in the supine position. Patients in this state show significant loss of inotropic performance of the left ventricle from PS1 to PS3. It is conceivable that, when they assume the upright posture, ventricular performance will further deteriorate due to a relative increase in peripheral vascular resistance, leading to sodium and water retention. This detrimental effect of postural change can also affect patients with CI at the highest levels. [23] Because non-selective beta-blockers (NSBB) mainly act via amelioration of the hyperdynamic state and this is absent in patients at PS1, it explains the recent finding that propranolol is less effective in reducing portal pressure in these patients. [22] However, the clinical impact of NSBB in patients with CSPH and hypodynamic features remains to be determined. Together with a progressively greater cardio-circulatory derangement, we observed progressively higher proportion of patients with inflammation as indicated by progressively higher levels of CRP, with the largest increase in PS3. Although a CRP level above 0.5 mg/dl has already been shown to discriminate between cirrhotic and non-cirrhotic patients, [24,25] these findings are rather unexpected as it has been assumed that inflammation occurs in the decompensated stage and contributes to further worsening of an already altered hemodynamic state. In fact, in experimental cirrhosis, only rats with ascites experience bacterial translocation and this phenomenon has been associated with increase in cytokines and worsening of splanchnic vasodilation. [9] Our study suggests that these mechanisms may be in place even at a compensated stage, but this requires further confirmation. It may be that at earlier stages, bacterial products rather than bacteria translocate. [12] These bacterial products and the secondary systemic inflammation may further affect cardiac function particularly in patients with hyper- and relatively hypodynamic circulatory states.

Portal pressure (as determined by the HVPG), cardiodynamic state (relatively hypo- or hyperdynamic), and CRP were predictors of ascites development. While the finding of portal pressure as a main predictor of decompensation in patients with compensated cirrhosis had already been demonstrated in patients without GEV, [26] we prospectively confirmed that HVPG at a cutoff of 16 mmHg predicts decompensation *in patients with CSPH* [27].

Portal hypertension driven inflammation, systemic hemodynamic derangement and cardiac dysfunction may be the pleiotropic target of statins, which have recently been shown to reduce the risk of decompensation and death in patients with cirrhosis. [28,29]

Decompensated Cirrhosis

In patients with **decompensated** cirrhosis, those with ascites still responsive to diuretics (PS4) had the highest mean CI of all stages/substages of cirrhosis, while MAP was the lowest in PS5. In the latter prognostic stage there was an expansion of the group with a relatively hypodynamic circulatory state (Figure 2). It is conceivable that the increased proportion of hypodynamic patients we observed in PS5 is a consequence of a functional shift from the hyperdynamic and normodynamic states due to a primary deterioration of cardiac inotropic activity [30] and/or to paracentesis-induced circulatory dysfunction. [14] Nevertheless, the latter risk is highly decreased by the infusion of albumin [14]. Moreover, LVP should have minimized the risk of overestimating the proportion of patients with a relatively hypodynamic circulation and/or pcPH due to the abdomino-thoracic pressure transmission. On the other end, albumin infusion, by increasing heart preload, should have reduced the risk of underestimating the proportion of patients with underlying preserved systolic function and/or hyperdynamic features.

As shown in compensated cirrhosis, the progression of hemodynamic abnormalities in decompensated cirrhosis was accompanied by an increase in systemic inflammation as determined by CRP levels, with the highest levels (considering all stages of cirrhosis) in patients with refractory ascites. This result supports the hypothesis that inflammation is one of the main drivers of hemodynamic derangement in patients with decompensated cirrhosis. [12,31] Interestingly, even though HVPG was the highest in decompensated cirrhosis, platelet count was higher in these patients than in compensated PS2 and PS3 patients. Because systemic inflammation is accompanied by increased number (and activation) of circulating platelets, [32] we consider that this otherwise inexplicable phenomenon can be explained on the basis of greater inflammation in decompensated cirrhosis.

Regarding mortality, MELD, cardiodynamic state (relatively hypo- or hyperdynamic), pcPH, and CRP resulted independent predictors. MELD is a known strong predictor of death in patients with decompensated cirrhosis [2] and the cutoff of 15 has been associated with post-OLT outcomes. [33] Decompensated cirrhotics in the hypo or hyperdynamic states have further impairment of heart inotropic functional reserve that explains their higher risk of death (Figure 4B and Supplementary Figure 2). [30,34,35] The fact that, in decompensated patients, pcPH is an independent predictor of outcome raises the possibility of severe diastolic dysfunction as a further mechanism of left ventricular impairment in the most advanced stages of cirrhosis. [36] In ascitic patients with hypo/hyperdynamic states and or pcPH the potential detrimental impact of volume/pressure overload of the heart after TIPS and/or OLT should be defined.

Although CRP has been shown to be an independent predictor of death in non-stratified patients (compensated vs. decompensated) with alcoholic cirrhosis [37], this study confirms that CRP predicts death in the short-term in non-septic [31,35,38] decompensated patients with different etiologies. Our finding of CRP as an independent predictor of relevant outcomes in patients with both compensated and decompensated cirrhosis is an indication that inflammation plays a major role in the pathogenesis of the progression of cirrhosis as proposed by Bernardi et al. [12] This evidence supports the use of drugs targeting systemic inflammation both in compensated [28,29,39] and decompensated patients. [35] However, mechanisms that lead to inflammation may be different at the different stages and this requires further examination. As this was an exploratory study, other markers of inflammation or indirect indicators of bacterial translocation were not assessed. For the same reason we did not measure natriuretic peptides and the activity of endogenous vasoactive systems, such as plasma renin activity or plasma concentration of aldosterone and norepinephrine that would be correlated with hemodynamic/inflammatory abnormalities.

In summary, our study demonstrates that portal pressure (HVPG), systemic hemodynamics (CI, MAP), liver function (MELD) and systemic inflammation (CRP) worsen from PS1 to PS5. Although one may argue that some of these findings had been previously shown, we describe them in the context of a concurrent prospective cohort of patients with cirrhosis sub-classified into important prognostic stages and define cutoffs of prognostic indicators. However, the most novel aspect of this study is the description of 3 cardiodynamic states based on cardiac index. Even though, CI increases progressively from PS1 (normal CI) through PS4 and then decreases at PS5 and this was in general described as the hyperdynamic circulatory state of cirrhosis, we find that a significant percentage of patients even in

the compensated stages have a CI that is below the average for normal patients (and for those at PS1 stage). This cardiodynamic classification is relevant because both patients that are "relatively" hypodynamic (CI <3.2 L/min/m^2) and those that are clearly hyperdynamic (CI >4.2 L/min/m^2) have a progressively more altered left ventricular function from PS1 to PS5 (Table 2 and Supplementary Figure 2), deterioration that is not observed in the normodynamic group. This has important prognostic implications as both the hyper and hypodynamic states are independent predictors of relevant outcomes (ascites in compensated patients, death in decompensated patients).

In conclusion, we suggest that the interplay between cardiocirculatory factors and inflammation has an important role in the prognosis of both compensated and decompensated patients with cirrhosis. Given that we had a moderately low events/variables ratio, particularly in compensated patients, our results may be affected by data over-fitting with biased estimates of hazard ratios. Adequately sized external datasets are therefore needed to validate our prognostic models. Moreover, the sequential interaction among bacterial translocation, inflammation, and hemodynamic alterations at different stages of cirrhosis and in different cardiodynamic groups should be dynamically explored. If our results are confirmed, definition of the cardiodynamic state and presence of elevated CRP may help identifying cirrhotic patients at higher risk of ascites development and death.

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FIGURE LEGENDS

Figure 1

Progressive alterations of systemic hemodynamic in the five prognostic stages of cirrhosis.

Asc: ascites; CI: cardiac index; GEV: gastroesophageal varices; HVPG: hepatic venous pressure gradient; MAP: mean arterial pressure; RAsc: refractory ascites.

Figure 2

Cardiodynamic states in the five prognostic stages of cirrhosis.

Asc: ascites; CI: cardiac index; GEV: gastroesophageal varices; HVPG: hepatic venous pressure gradient; pcPH: post-capillary pulmunary hypertension; RAsc: refractory ascites.

Figure 3

Progressive increase of circulating CRP in the five prognostic stages of cirrhosis.

Asc: ascites; CRP: C reactive protein; GEV: gastroesophageal varices; HVPG: hepatic venous pressure gradient; RAsc: refractory ascites.

Represents CRP mean ± SE in patients with CRP ≥ 0.5 mg/dl.

Figure 4

Thirty-six-month cumulative risk of ascites development in compensated patients with CSPH (PS2 and PS3) grouped according to cardiodynamic states (A). Twelve-month cumulative risk of death/OLT in decompensated patients (PS4 and PS5) grouped according to cardiodynamic states (B). Twelve-month cumulative risk of death/OLT in decompensated patients (PS4 and PS5) grouped according to presence of pcPH (C).

CI: cardiac index; CSPH: clinically significant portal hypertension; pcPH: post-capillary pulmonary hypertension; OLT: orthotopic liver transplant; PS: prognostic stage.

Supplementary Figure 1

Flow chart of patients with cirrhosis who were included in the study.

CHF: chronic heart failure; CKD: chronic kidney disease; HCC: hepatocellular carcinoma; HPS: hepato-pulmunary syndrome; HVPG: hepatic venous pressure gradient; LT: liver transplant; NSBB: non-selective beta-blockers; PBC: primary biliary cirrhosis; PH: portal hypertension; PSC: primary

sclerosing cholangitis; PVT: portal vein thrombosis; SBP: spontaneous bacterial peritonitis; TIPS: trans-jugular Intra-hepatic porto-systemic shunt; TJLB: trans-jugular liver biopsy.

Supplementary Figure 2

Inotropic performance of heart left ventricle in the main cardiodynamic states in the five prognostic stages of cirrhosis. A) hyperdynamic, CI >4.2 L/min/m^2; B) normodynamic, CI ≥3.2≤4.2 L/min/m^2, and C) relatively hypodynamic, CI <3.2 L/min/m^2.

Asc: ascites; CI: cardiac index; GEV: gastroesophageal varices; HVPG: hepatic venous pressure gradient; LVSWI: left ventricle stroke work index (normal range: 50-62 g-m/m^2/beat); RAsc: refractory ascites.

Supplementary Figure 3

Thirty-six-month cumulative risk of ascites development in patients, who were compensated at baseline (A). Twelve-month cumulative risk of death/OLT in patients, who presented ascites at baseline (B).

PS: prognostic stage.

Supplementary Figure 4

Calibration plots by deciles of Fine & Gray multivariable prediction models for 3-year risk of ascites (A, C) and 1-year risk of death/OLT (B, D). A and C, the bar plots; B and D, the line plots.

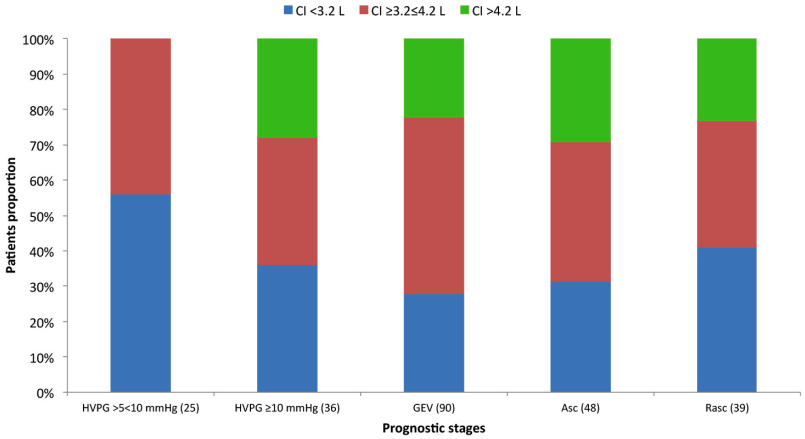
OLT: orthotopic liver transplant.

JHEPAT-D-17-01326R1

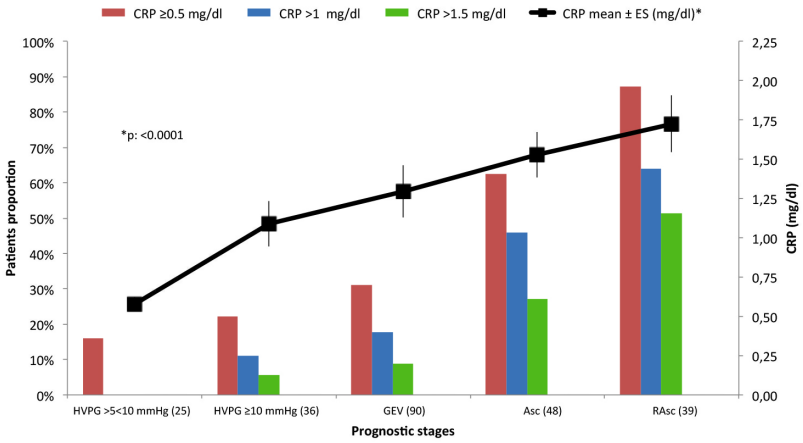
HIGHLIGHTS

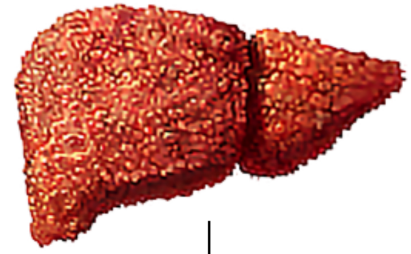
- Description of 3 main cardiodynamic states in different stages of cirrhosis
- Description of elevated serum CRP in both compensated and decompensated patients
- Demonstration of cardiodynamic state and CRP as predictors of disease outcomes

Cardiodynamic states in the five prognostic stages of cirrhosis (CI, cardiac index)



Circulating C reactive protein (CRP) in the five prognostic stages of cirrhosis



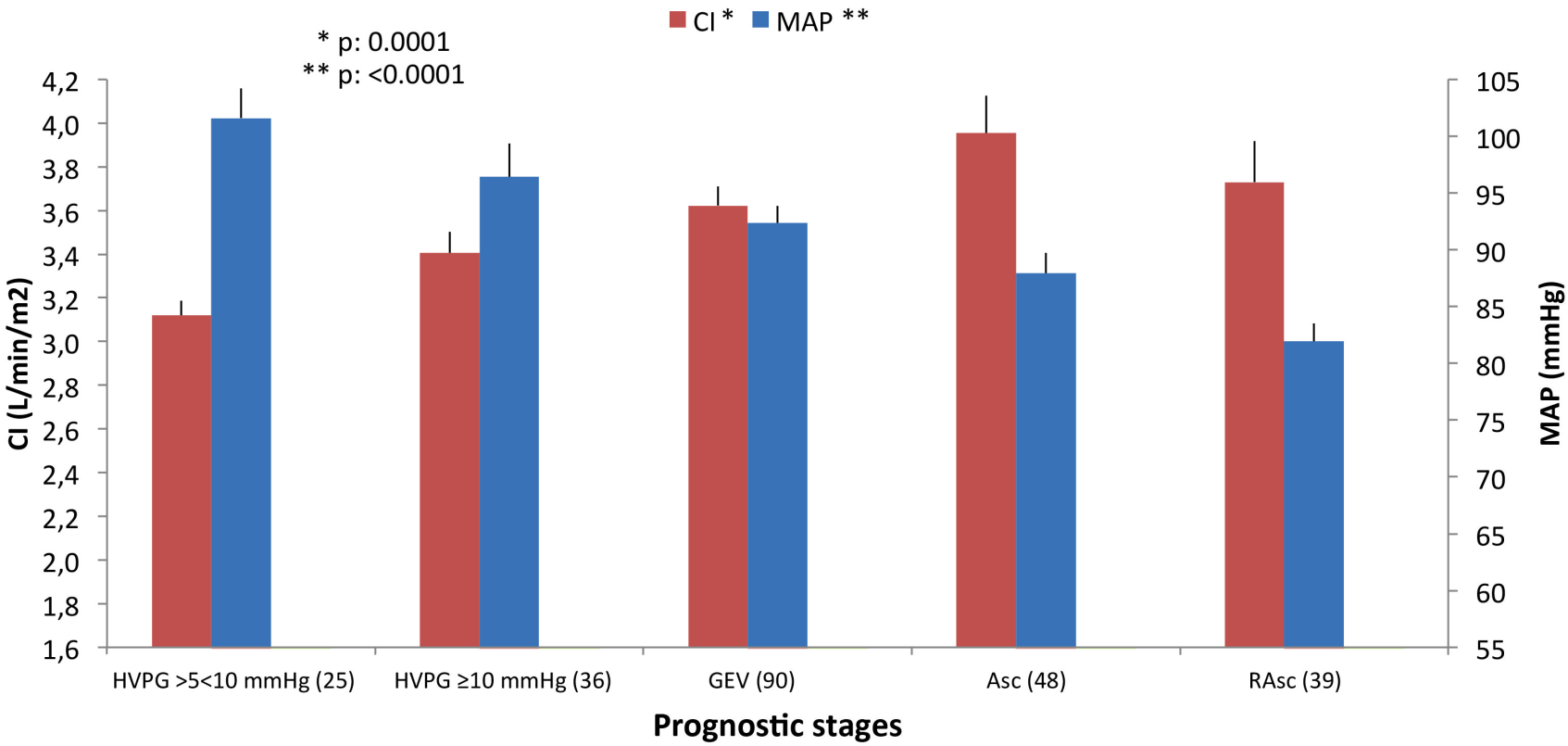


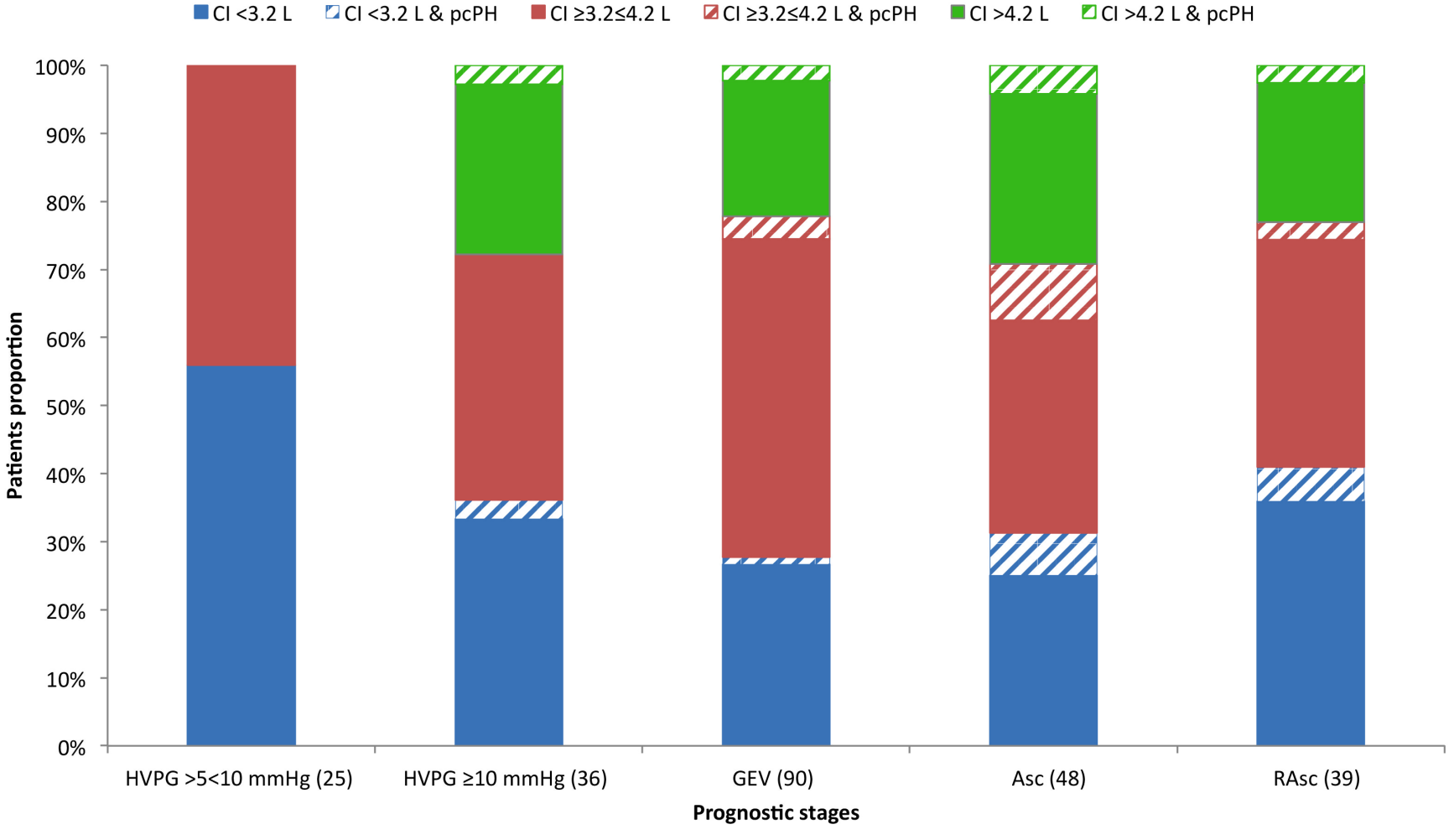
CSPH*

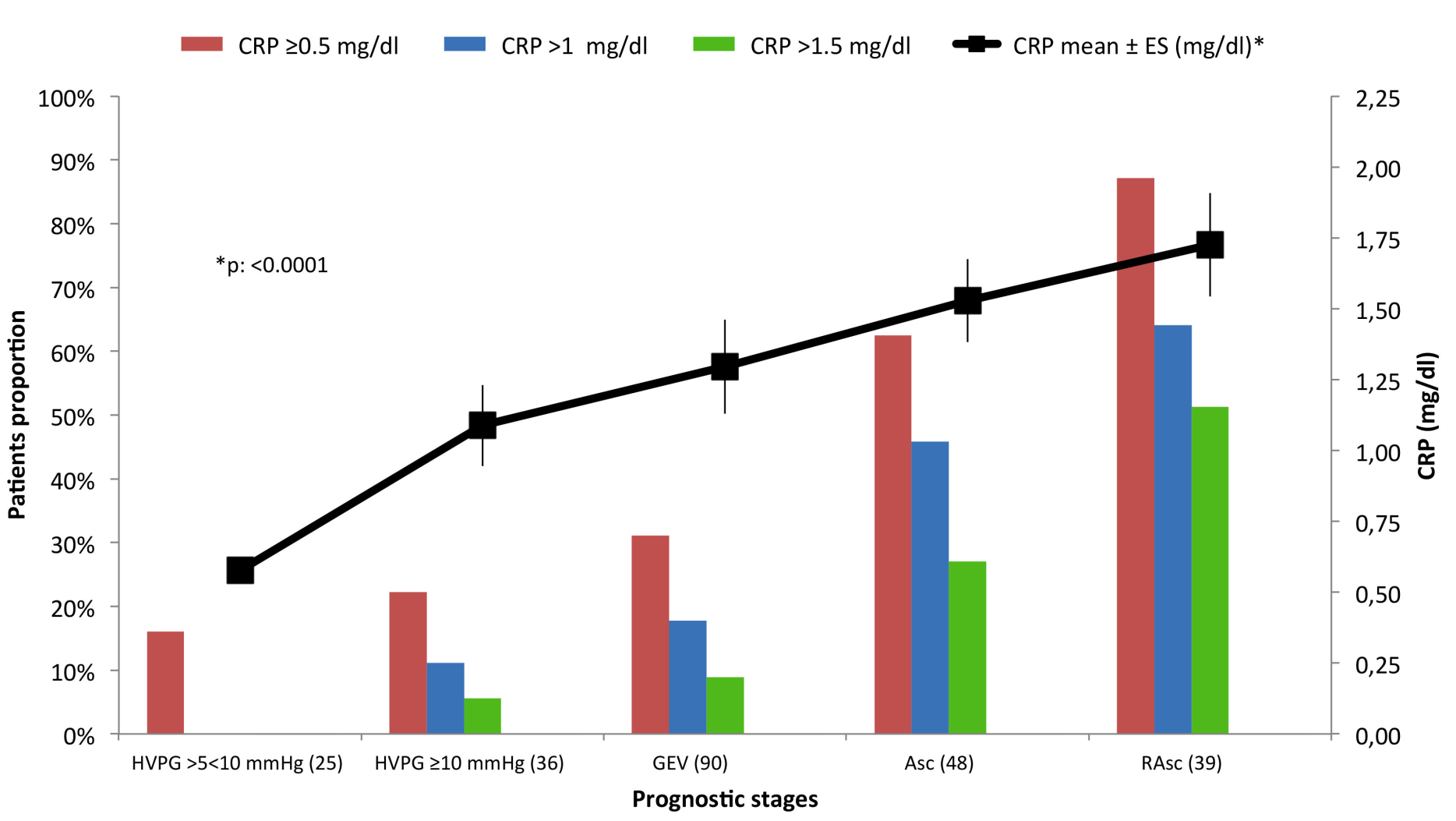
High CRP **Low/High CI**

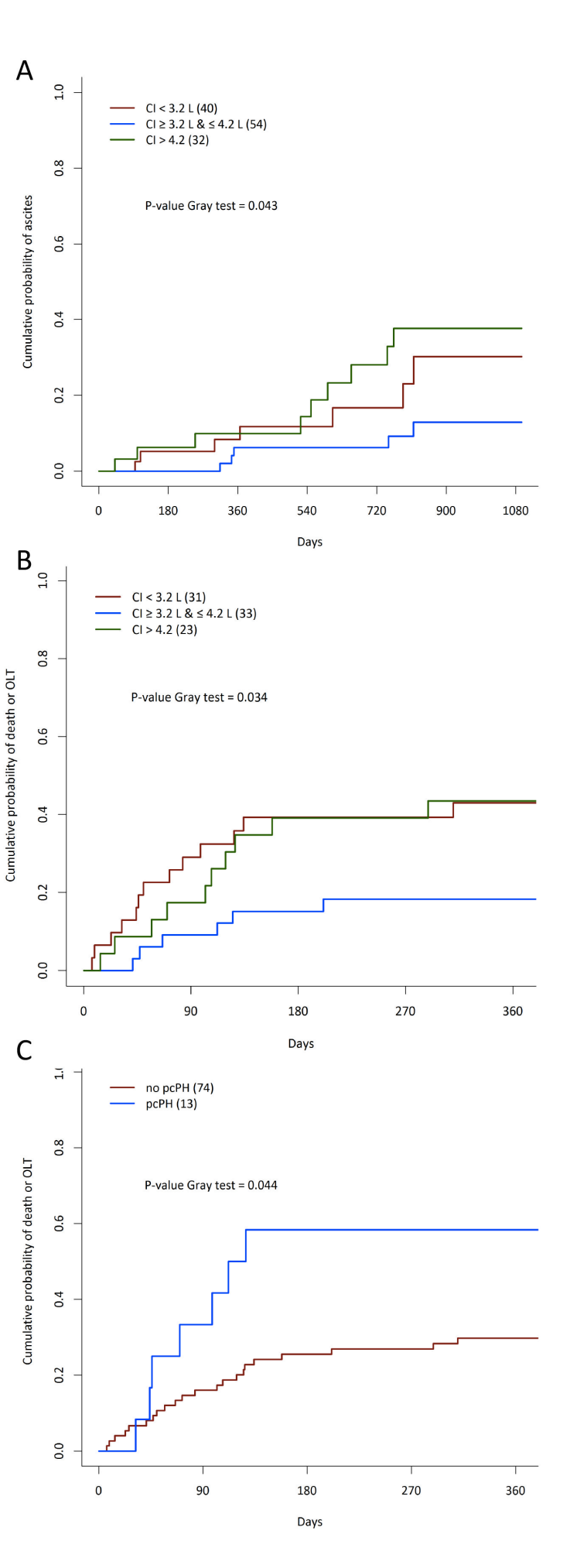
Increased risk of decompensation and death

*clinically significant portal hypertension


CI *
MAP **
* p: 0.0001
** p: <0.0001
CI (L/min/m2)
MAP (mmHg)
4,2
4,0
3,8
3,6
3,4
3,2
3,0
2,8
2,6
2,4
2,2
2,0
1,8
1,6
105
100
95
90
85
80
75
70
65
60
55
HVPG >5<10 mmHg (25)
HVPG ≥10 mmHg (36)
GEV (90)
Asc (48)
RAsc (39)
Prognostic stages


CI <3.2 L
CI <3.2 L & pcPH
CI ≥3.2≤4.2 L
CI ≥3.2≤4.2 L & pcPH
CI >4.2 L
CI >4.2 L & pcPH
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Patients proportion
HVPG >5<10 mmHg (25)
HVPG ≥10 mmHg (36)
GEV (90)
Asc (48)
RAsc (39)
Prognostic stages


CRP ≥0.5 mg/dl
CRP >1 mg/dl
CRP >1.5 mg/dl
CRP mean ± ES (mg/dl)*
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2,25
2,00
1,75
1,50
1,25
1,00
0,75
0,50
0,25
0,00
*p: <0.0001
Patients proportion
CRP (mg/dl)
HVPG >5<10 mmHg (25)
HVPG ≥10 mmHg (36)
GEV (90)
Asc (48)
RAsc (39)
Prognostic stages


A
CI < 3.2 L (40)
CI ≥ 3.2 L & ≤ 4.2 L (54)
CI > 4.2 (32)
P-value Gray test = 0.043
Cumulative probability of ascites
0.0
0.2
0.4
0.6
0.8
1.0
0
180
360
540
720
900
1080
Days
B
CI < 3.2 L (31)
CI ≥ 3.2 L & ≤ 4.2 L (33)
CI > 4.2 (23)
P-value Gray test = 0.034
Cumulative probability of death or OLT
0.0
0.2
0.4
0.6
0.8
1.0
0
90
180
270
360
Days
C
no pcPH (74)
pcPH (13)
P-value Gray test = 0.044
Cumulative probability of death or OLT
0.0
0.2
0.4
0.6
0.8
0
90
180
270
360
Days

JHEPAT-D-17-01326R1

Table 1

Clinical and hemodynamic characteristics of patients at baseline in the five prognostic stages (PS) of cirrhosis.

	PS1 (n=25)	**PS2** (n=36)	**PS3** (n=90)	**PS4** (n=48)	**PS5** (n=39)	***p*** (ANOVA)
Age*	60.43±2.07	60.88±2.30	58.87±1.19	57.91±1.45	57.95±1.83	0.811
Sex – M (%)	17 (68)	24 (66.67)	62 (68.89)	30 (62.5)	24 (61.53)	NA
BMI (kg/m^2)*	26.95±0.83	27.09±0.64	26.89±0.46	24.52±0.57^	24.40±0.62	0.003
Etiology (%)						
Viral	14 (56)	20 (55.56)	52 (57.78)	18 (37.5)	16 (41.03)	
Alcohol	2 (8)	5 (13.89)	11 (12.22)	12 (25)	11 (28.2)	
Alcohol+Viral	3 (12)	3 (8.33)	10 (11.11)	8 (16.67)	3 (7.69)	NA
NASH	5 (20)	5 (13.89)	12 (13.33)	4 (8.33)	2 (5.13)	
Miscellaneous	1 (4)	3 (8.33)	5 (5.56)	6 (12.50)	7 (17.95)	
Patients under NUC for HBV infection (%)	3/3[@] (100)	5/5[@] (100)	5/5[@] (100)	4/4[@] (100)	4/4[@] (100)	NA
Patients under NSBB (%)	0	0	0	6 (12.5)	1 (2.6)	NA
Patients undergoing LVP the day before hemodynamic assessment (%)	0	0	0	0	39 (100)	NA
Ascites removed by LVP (L)*	0	0	0	0	5.77±0.29	NA
Albumin administered after LVP (g)	0	0	0	0	46.17±2.39	NA
GEV (%)						
Varices	0 (0)	0 (0)	81 (90)	36 (75.0)	33 (84.61)	NA
Eradicated	0 (0)	0 (0)	9 (10)	3 (6.25)	0 (0)	

Prior Variceal Bleeding (%)	0 (0)	0 (0)	8 (8.89)	3 (6.25)	3 (7.69)	NA
Encephalopathy (%)						
No overt HE	25 (100)	36 (100)	90 (100)	42 (87.5)	32 (82.05)	NA
Overt HE	0 (0)	0 (0)	0 (0)	5 (10.42)@@	0 (0)	
Prior HE	0 (0)	0 (0)	0 (0)	1 (2.08)	7 (17.95)	
Hemoglobin (g/dl)*	14.14±0.26	13.57±0.30	13.24±0.22§	11.51±0.27^	11.37±0.36	<0.0001
PLT (x10^3/mmc)*	146.60±11.22	97.46±7.53°	90.13±5.16§	101.67±7.98	115.56±11.93	0.00045
AST (UI/l)*	67.52±20.95	56.77±6.12	61.56±4.75	60.52±8.60	41.72±4.68	0.251
INR*	1.10±0.02	1.21±0.02°	1.29±0.02§#	1.42±0.03^	1.50±0.02^^	<0.0001
Bilirubin (mg/dl)*	0.76±0.07	1.12±0.15	1.30±0.10§	2.12± 0.29^	2.39±0.52	0.012
Albumin (g/dl)*	4.11±0.06	3.94±0.05°	3.77±0.05§#	3.34±0.08^	3.17±0.09	<0.0001
Creatinine (mg/dl)*	0.79±0.04	0.80±0.04	0.82±0.03	0.97±0.08^	1.20±0.07^^	<0.0001
MELD*	7.96±0.22	9.50±0.33°	10.47±0.28§#	13.80±0.71^	15.33±0.83	<0.0001
CTP Score*	5.00±0.00	5.13±0.9	5.61±0.12§#	7.54±0.24^	8.41±0.19	<0.0001
CRP (mg/dl)*	0.50±0.01	0.63±0.06	0.81±0.05§#	1.17±0.12^	1.57±0.16^^	<0.0001
WHVP (mmHg)*	15.65±0.53	23.77±0.97°	27.42±0.58§#	30.94±1.05^	32.42±1.11	<0.0001
FHVP (mmHg)*	9.25±0.47	9.65±0.69	10.71±0.42	11.38±0.60	10.68±0.82	0.110
HVPG (mmHg)*	6.39±0.22	14.14±0.59°	16.77±0.40§#	19.55±0.83^	21.52±0.74^^	<0.0001
RAP (mmHg)*	6.58±0.61	6.52±0.58	7.72±0.34	7.70±0.59	6.84± 0.67	0.238
PAPm (mmHg)*	18.79±0.78	17.92±0.90	18.62±0.43	18.97±0.94	15.76±0.83^^	0.020
PAWP (mmHg)*	9.41±0.74	9.26±0.58	10.95±0.39§	11.46±0.79	9.90±0.78	0.053
HR (beats/min)*	66.57±1.86	69.92±2.23	71.58± 1.23§	75.32±1.87^	73.64±1.85	0.032
CI (L/min/m^2)*	3.15±0.07	3.40±0.09°	3.62±0.06§#	3.95±0.17^	3.73±0.19	0.0001
MAP (mmHg)*	101.60±2.61	96.40±2.69	92.36±1.52§	87.60±1.64^	81.95±1.58^^	<0.0001
SVRI (dynes-sec/cm^{-5}/m^2)*	2459.67±76.78	2264.46±59.55°	1962.99±57.68§#	1757.36±82.37^	1744.67±80.93	<0.0001
PVRI (dynes-sec/cm^{-5}/m^2)*	226.35±13.47	192.81±15.66	172.50±8.16§	156.16±9.90	131.84±8.64	<0.0001

SVI (mL/min/m^2)*	47.47±1.32	48.75±1.43	51.25±1.17	52.68±1.90	50.96±2.22	0.318
LVSWI (g-m/m^2/beat)	59.27±2.03	57.15±1.93	56.4±1.57	54.94±2.14	49.62±2.19	0.043

* Data are expressed as mean ± SE

° PS2 vs PS1 p<0.05

§ PS3 vs PS1 p<0.05

PS3 vs PS2 p<0.05

^ PS4 vs PS3 p<0.05

^^ PS5 vs PS4 p<0.05

@ The denominator indicates the total number of HBV infected patients in each PS.

@@ All patients had a grade II (WHC) episode of over HE, which was triggered by diuretics. They were enrolled in the study after recovering from HE.

No changes in the main results were found after removing the 7 decompensated patients under NSBBs at the time of hemodynamic evaluation.

Abbreviations:

BMI, body mass index; CI, cardiac index (range 2.5-4.2 L/min/m2); CTP, Child-Turcotte-Pugh; CRP, C reactive protein; FHVP, free hepatic vein pressure; GEV, gastroesophageal varices; HE, hepatic encephalopathy; HR, heart rate; HVPG, hepatic venous pressure gradient; LVP, large volume paracentesis; LVSWI, left ventricular stroke work index (range 50-62 g-m/m^2/beat); MAP, mean arterial pressure; MELD, model for end stage liver disease; NA, not applicable; NSBB, non selective beta-blockers; NUC, Nucleos(t)Ide Analogs; PAPm, mean pulmonary artery pressure; PAWP, mean pulmonary artery wedged pressure; PLT, platelet count; PVRI, pulmonary vascular resistance index (range 255-285 dynes-sec/cm^{-5}/m^2); RAP, right atrial pressure; SVI, stroke volume index (range 33-47 mL/m^2/beat); SVRI, systemic vascular resistance index (range 1970-2390 dynes-sec/cm^{-5}/m^2); WHC, West Haven criteria; WHVP, wedged hepatic vein pressure.

JHEPAT-D-17-01326R1

Table 2

Two-way ANOVA testing for the effects of prognostic stage (PS, fixed factor) and cardiodynamic state (CS, fixed factor) on main clinical and hemodynamic features.

	CS ($L/min/m^2$)	PS1 (N=14;11;0)	PS2 (N=13;13;10)	PS3 (N=25;45;20)	PS4 (N=15;19;14)	PS5 (N=16;14;9)	Two-way ANOVA		
							PS	CS	PS*CS
Age* (years)	**< 3.2**	61.32 ± 3.13	62.85 ± 3.94	61.77 ± 2.48	63.49 ± 3.11	58.38 ± 3.60	0.773	0.091	0.805
	≥ 3.2 ≤ 4.2	59.30 ± 2.66	60.82 ± 4.43	57.46 ± 1.79	56.97 ± 2.74	61.7 3± 2.17			
	> 4.2	-	55.08 ± 4.33	57.71 ± 1.86	53.92 ± 1.57	52.36 ± 2.62			
MELD*	**< 3.2**	7.71 ± 0.22	8.92 ± 0.43	9.64 ± 0.39	11.79 ± 0.90	15.63 ± 1.14	<0.0001	<0.0001	0.561
	≥ 3.2 ≤ 4.2	8.27 ± 0.41	9.38 ± 0.54	10.81 ± 0.43	14.11 ± 1.05	14.79 ± 1.31			
	> 4.2	-	10.73 ± 1.01	11.75 ± 0.76	15.54 ± 1.65	15.67 ± 2.27			
CRP* (mg/dl)	**< 3.2**	0.50 ± 0.00	0.57 ± 0.05	0.75 ± 0.12	0.90 ± 0.14	1.45 ± 0.29	<0.0001	0.293	0.770
	≥ 3.2 ≤ 4.2	0.52 ± 0.02	0.73 ± 0.16	0.78 ± 0.11	1.18 ± 0.19	1.78 ± 0.46			
	> 4.2	-	0.49 ± 0.00	0.61 ± 0.07	1.44 ± 0.27	1.45 ± 0.15			
HVPG* (mmHg)	**< 3.2**	6.39 ± 0.32	12.24 ± 0.55	15.36 ± 0.69	15.46 ± 1.03	19.51 ± 0.91	<0.0001	<0.0001	0.016
	≥ 3.2 ≤ 4.2	6.40 ± 0.30	15.16 ± 1.37	17.17 ± 0.56	20.05 ± 0.98	23.93 ± 1.08			
	> 4.2	-	15.72 ± 1.08	18.06 ± 0.94	23.23 ± 1.64	21.35 ± 2.07			
HR* (beats/min)	**< 3.2**	62.26 ± 2.87	63.65 ± 2.66	67.27 ± 1.64	70.14 ± 2.55	71.25 ± 2.36	0.019	<0.0001	0.641
	≥ 3.2 ≤ 4.2	70.29 ± 2.34	72.71 ± 2.93	71.49 ± 1.64	73.10 ± 2.85	70.28 ± 2.95			
	> 4.2	-	84.75 ± 4.41	81.82 ± 2.79	84.15 ± 3.40	83.13 ± 3.38			
SVI* ($mL/min/m^2$)	**< 3.2**	46.15 ± 1.92	43.21 ± 1.69	41.28 ± 1.71	39.66 ± 1.68	38.54 ± 1.85	0.067	<0.0001	0.011
	≥ 3.2 ≤ 4.2	49.16 ± 1.73	51.21 ± 1.67	53.46 ± 1.23	53.51 ± 1.99	54.74 ± 2.94			
	> 4.2	-	58.74 ± 3.60	63.47 ± 2.33	65.37 ± 2.70	65.48 ± 3.07			
LVSWI* ($g-m/m^2/beat$)	**< 3.2**	57.46 ± 3.00	52.66 ± 2.52	45.32 ± 2.14	42.37 ± 3.57	38.25 ± 2.02	0.001	<0.0001	0.025
	≥ 3.2 ≤ 4.2	61.58 ± 2.55	59.37 ± 3.71	58.97 ± 1.77	55.19 ± 2.80	55.63 ± 3.10			
	> 4.2	-	72.89 ± 2.92	70.69 ± 2.33	67.58 ± 2.72	60.50 ± 3.25			
MAP*	**< 3.2**	102.21 ± 4.07	99.69 ± 4.28	89.08 ± 2.44	88.00 ± 3.81	80.69 ± 2.79	<0.0001	0.943	0.475

(mmHg)	**≥ 3.2 ≤ 4.2**	100.82 ± 3.11	94.23 ± 5.16	93.63 ± 2.27	85.63 ± 2.59	84.50 ± 2.08			
	> 4.2	-	93.82 ± 4.41	92.75 ± 2.21	90.08 ± 2.88	80.22 ± 3.48			
SVRI* (dynes-sec/cm^{-5}/m^2)	**< 3.2**	2637.10 ± 97.48	2881.16 ± 186.50	2475.29 ± 110.32	2388.55 ± 126.74	2164.05 ± 86.27	<0.0001	<0.0001	0.018
	≥ 3.2 ≤ 4.2	2233.85 ± 85.57	1917.88 ± 125.37	1843.34 ± 53.99	1686.99 ± 47.57	1663.05 ± 86.42			
	> 4.2	-	1386.58 ± 43.35	1364.35 ± 59.02	1215.44 ± 51.94	1088.81 ± 84.55			

*Data are expressed as mean ± SE

No changes in the main results were found after removing the 7 decompensated patients under NSBBs at the time of hemodynamic evaluation.

Abbreviations:

CRP, C reactive protein; HR, heart rate; HVPG, hepatic venous pressure gradient; LVSWI, left ventricular stroke work index (range 50-62 g-m/m^2/beat); MAP, mean arterial pressure; MELD, model for end stage liver disease; NSBB, non-selective beta-blocker; SVI, stroke volume index (range 33-47 mL/m^2/beat); SVRI, systemic vascular resistance index (range 1970-2390 dynes-sec/cm^{-5}/m^2).

Table 3

Fine & Gray proportional hazards regression model for the risk of ascites development in compensated patients and for the risk of death or OLT in decompensated patients.

COMPENSATED PATIENTS							
	Univariable				Multivariable		
Model 1 (PS1, 2 and 3)	**HR**	**95% CI**	**p**		**HR**	**95% CI**	**p**
Age (years)	1.04	1.01 - 1.09	0.026		1.06	1.02 - 1.12	0.009
MELD	1.09	1.01 - 1.18	0.022		-	-	-
Albumin (g/dl)	0.78	0.38 - 1.60	0.500		-	-	-
CRP (mg/dl)	1.69	1.08 - 2.65	0.022		2.50	1.58 - 3.96	<0.0001
HVPG (mmHg)	1.19	1.10 - 1.29	<0.0001		1.17	1.09 - 1.26	<0.0001
MAP (mmHg)	1.01	0.98 - 1.04	0.570		-	-	-
Cardiodynamic state (rHD-HD/ND)	3.16	1.18 - 8.49	0.023		3.29	1.18 - 9.20	0.023
pcPH (present/absent)	0.86	0.14 - 5.15	0.870		-	-	-
NSBB during follow up	0.63	0.27 - 1.49	0.294		-	-	-
	Univariable				Multivariable		
Model 2 (PS2 and 3)	**HR**	**95% CI**	**p**		**HR**	**95% CI**	**p**
Age (years)	1.05	1.01 - 1.09	0.018		1.06	1.02 - 1.11	0.007
MELD	1.07	0.99 - 1.16	0.079		-	-	-
Albumin (g/dl)	0.89	0.44 - 1.78	0.740		-	-	-
CRP (mg/dl)	1.61	1.03 - 2.53	0.037		2.45	1.55 - 3.88	0.0001
HVPG (mmHg)	1.17	1.07 - 1.29	0.001		1.16	1.07 - 1.26	0.0004
MAP (mmHg)	1.01	0.99 - 1.04	0.290		-	-	-
Cardiodynamic state (rHD-HD/ND)	3.06	1.14 - 8.22	0.027		3.31	1.18 - 9.24	0.022
pcPH (present/absent)	0.73	0.12 - 4.43	0.730		-	-	-
NSBB during follow up	0.78	0.33 - 1.82	0.562		-	-	-
DECOMPENSATED PATIENTS							
	Univariable				Multivariable		
Model 1 (PS4 and 5)*	**HR**	**95% CI**	**p**		**HR**	**95% CI**	**p**
Age (years)	1.01	0.98 - 1.05	0.560		-	-	-
Refractory ascites (PS5)	1.47	0.73 - 2.96	0.280		-	-	-
MELD	1.10	1.04 - 1.16	0.001		1.09	1.03 - 1.15	0.002
CRP (mg/dl)	1.46	1.16 - 1.83	0.001		1.73	1.25 - 2.39	0.0009
HVPG (mmHg)	1.02	0.96 - 1.10	0.510		-	-	-
MAP (mmHg)	0.99	0.96 - 1.02	0.450		-	-	-
Cardiodynamic state (rHD-HD/ND)	2.53	1.11 - 5.76	0.027		2.79	1.18 - 6.56	0.018
pcPH (present/absent)	2.38	1.02 - 5.56	0.045		2.55	1.18 - 5.48	0.016
NSBB during follow up	0.72	0.25 - 2.06	0.533		-	-	-

*No changes in the main results were observed after removing the 7 decompensated patients under NSBBs at the time of hemodynamic evaluation.

Abbreviations: CI, confidence interval; CRP, C reactive protein; HD, hyperdynamic (cardiac index >4.2 L/min/m^2); HR, Hazard ratio; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; MELD, model for end stage liver disease; ND, normodynamic (cardiac index ≥3.2≤4.2 L/min/m^2); NSBB, nonselective beta-blockers; OLT, orthotopic liver transplantation; pcPH, post-capillary pulmonary hypertension; PS, prognostic stage; rHD, relatively hypodynamic (cardiac index <3.2 L/min/m^2.