Size and location of spontaneous portosystemic shunts predict the risk of decompensation in cirrhotic patients

Size and location of spontaneous portosystemic shunts predict the risk of decompensation in cirrhotic patients

Manuscript number: DLD-20-1768

Short title: SPSS predict decompensation

Authors' names: Elton Dajti[1¥], Matteo Renzulli[2¥], Antonio Colecchia[3], Maria Letizia Bacchi-Reggiani[2], Matteo Milandri[2]; Benedetta Rossini[1]; Federico Ravaioli[1]; Giovanni Marasco[1]; Luigina Vanessa Alemanni[1]; Anna Maria Ierardi[4], Gianpaolo Carrafiello[5], Massimo Pinzani[6], Francesco Azzaroli[1], Giuseppe Mazzella[1], Rita Golfieri[2§]; Davide Festi[1§]

Authors' institutions: [1]Department of Medical and Surgical Sciences (DIMEC), University of Bologna; Via Massarenti 9, 40138, Bologna, Italy; [2]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna; Via Massarenti 9, 40138, Bologna, Italy; [3]Unit of Gastroenterology, Borgo Trento University Hospital of Verona; P.le Aristide Stefani 1, 37126, Verona, Italy; [4]Diagnostic and Interventional Radiology, San Paolo Hospital, Milan, Italy; [5]Unit of Radiology, IRCSS Ca' Granda, Policlinico of Milan, Italy; [6]UCL Institute for Liver and Digestive Health and Sheila Sherlock Liver Unit, Royal Free Hospital and UCL, London, UK

Corresponding author: Antonio Colecchia, Unit of Gastroenterology, Borgo Trento University Hospital, Verona, Italy; e-mail: antonio.colecchia@aovr.veneto.it

[¥] Elton Dajti and Matteo Renzulli contributed equally to this work.

[§] Rita Golfieri and Davide Festi contributed equally to this work.

Financial Support: No grants or other financial support.

Conflict of interest statement: The authors declare that they have no conflict of interest.

Abstract

Background: The prognostic role of spontaneous portosystemic shunts (SPSS) has been poorly investigated.

Aims: To evaluate the impact of the presence of SPSS, as well as their characteristics, on the risk of decompensation.

Methods: This is a retrospective cohort study of 235 advanced chronic liver disease (ACLD) patients with available imaging examination, transient elastography, and upper endoscopy. ACLD was defined as liver stiffness measurement (LSM) >10 kPa. Competitive risk analyses were performed to identify the factors associated with the main outcome.

Results: SPSS were reported in 141 (60%) of the patients. Non-viral etiology was independently associated with SPSS presence [Odds-Ratio (OR): 2.743;95%-Interval-of-Confidence (IC):1.129-6.664]. During a follow-up of 37 (20-63) months, SPSS were found predictors of any decompensation type [Subhazard Ratio (SHR):2.264; 95%-IC:1.259-4.071], independently from a history of decompensation or high-risk-varices presence. The risk of complications was higher in patients with large (SHR: 3.775; 95%-IC: 2.016-7.070) and multiple (SHR:3.832; 95%-IC: 2.004-7.330) shunts, and in those with gastrorenal shunts (SHR:2.636; 95%-IC:1.521-4.569).

Conclusions: The presence, size, and number of SPSS predict not only the risk of hepatic encephalopathy but that of any type of decompensation across all stages of cirrhosis. Future studies should explore the possibility of treating shunts to prevent decompensation.

Keywords: portal hypertension; collaterals; hepatic encephalopathy; liver imaging.

Introduction

Portal hypertension (PH) is the primary driver of complications in patients with advanced chronic liver disease (ACLD).[1] Higher values of portal pressure, evaluated by the hepatic venous pressure gradient (HVPG)[2] or its surrogates,[3] can predict the risk of decompensation, such as ascites, variceal bleeding, or hepatic encephalopathy (HE), and other complications. Adequate risk stratification for PH is, therefore, crucial for the prognosis and management of patients with ACLD.[4]

The spontaneous portosystemic shunts (SPSS) represent communications between the portal or splanchnic venous system and the systemic venous system.[5] Their presence is associated with a more severe PH,[6] and has traditionally been conceived as a compensatory mechanism to decompress the portal venous system. However, their presence has been associated with an increased incidence of HE.[7] To date, the prognostic role and the clinical implications of SPSS presence, in terms of risk of decompensation or other PH-related complications, are still poorly understood.

Recently, Simón-Talero et al.[8] reported in a retrospective cohort of cirrhotic patients, the prevalence and characteristics of SPSS, as evaluated by CT-scan or MRI. The authors showed for the first time that patients with SPSS developed events of hepatic decompensation more frequently, and more importantly presented a lower transplant-free survival. However, the relationship between the presence of SPSS, prognostic stages of cirrhosis, and other common surrogates of PH were not explored in this study. Moreover, the clinical role of non-endoluminal gastroesophageal (GEV) varices on the development of PH-related complications was not previously investigated.

The main aim of the present study was to evaluate the prognostic impact of the presence of SPSS, as well as that of their characteristics, on the development of any hepatic decompensation and transplant-free survival in a large and well-characterised cohort of ACLD patients.

Materials and Methods

Study design and population

The present is a retrospective cohort study of consecutive ACLD patients seen at our tertiary centre in the period between January 2014 and December 2017. The inclusion criteria were: 1) presence of ACLD, defined as liver stiffness measurement (LSM) by transient elastography (TE) >10 kPa;[9] 2) availability of an abdominal imaging examination (CT or MRI), esophagogastroduodenoscopy (EGD), biochemical data. Exclusion criteria were 1) time interval >6 months between the imaging, TE evaluation, and upper endoscopy; 2) previous transjugular intrahepatic portosystemic shunt (TIPS) and/or orthotopic liver transplantation (OLT); 3) critical or terminal medical condition.

Clinical data collection

After inclusion in the study, all clinical, endoscopic, and radiologic data were collected. In particular, ACLD etiology, main co-morbidities, history of the previous decompensation and/or HCC, use of non-selective beta-blockers (NSBB) were described for each patient. Liver function scores, such as Model for End-Stage Liver Disease (MELD) and Child-Turcotte Pugh (CTP) were reported. All patients were classified in 5 prognostic stages of cirrhosis and PH, according to D'Amico et al.,[1] namely: I) compensated without esophageal varices (EV); II) compensated with EV; III) decompensated with a first bleeding episode; IV) decompensated with a first non-bleeding episode (i.e. ascites); V) >1 decompensation events.

All patients underwent a standard follow-up in agreement with international recommendations.[10] Every complication of PH, such as ascites, variceal bleeding, HE, spontaneous bacterial peritonitis, and hepato-renal syndrome, was recorded. Other ACLD-related events, such as high-risk varices (HRV) prophylaxes, portal vein thrombosis (PVT) development, HCC development, TIPS placement, OLT, death, and its cause, were also reported. The 31st of December 2018 was considered

to be the end of the follow-up; patients who did not develop the event during the follow-up were censored at the time of death, OLT, or the last visit to the study centre. Data were reported according to STROBE guidelines.

Radiological evaluation

All abdominal radiological examinations, CT and/or MRI, were reviewed by a radiologist with more than fifteen years expertise in liver imaging. All CT and MRI were performed according to the standards of reference, as described in previous papers.[11,12] The presence of SPSS and GEV was reported separately as recently described.[5] No pre-defined cut-off of SPSS diameter was utilised to define large SPSS. Instead, different cut-offs (best-cut-off, rule-in, and rule-out) were calculated and evaluated for the prediction of hepatic decompensation. The total area of SPSS was calculated as previously described.[13]

Other signs of ACLD and PH, such as hepatomegaly, focal liver lesions, portal vein dimension, portal vein thrombosis and its extension, splenomegaly, and presence of ascites, were described for each patient.

TE evaluation

The LSM values were assessed by TE (FibroScan®, Echosens), "M" probe after overnight fasting and after an abdominal US examination, as previously described.[14,15] The LSM cut-off ≥21 kPa was used to rule-in clinically significant portal portal hypertension (CSPH).[9]

Statistical analysis

Categorical data were expressed as numbers (percentages), and continuous variables as medians (and values of the 25% and the 75% percentiles, interquartile range (IQR)). For group comparisons of

categorical and continuous variables, the chi-square test or Mann-Whitney test, and the Mc-Nemar test were used, as appropriate.

The main outcome was the development of any hepatic decompensation. The clinical, biochemical, elastometric, and radiological variables were evaluated using univariate and multivariate competing risk regression models[16] in order to assess the factors associated with the primary outcome; death or OLT were considered as competing events. An index of the time-to-event analysis was considered to be the date of the radiological examination. After evaluation of the multicollinearity, multivariable competing risk regression analyses were carried out on variables that reached $p<0.1$ at univariate analysis. The final multivariate regression model was built from the set of candidate variables by removing the predictors based on p values, in a stepwise manner. The estimated subhazard ratio (SHR) with the 95% CI, the Wald-chi2 tests. Cumulative incidence function (CIF) curves were used to estimate the risk of decompensation during the follow-up.

All p values referred to two-tailed tests of significance. $P<0.05$ was considered significant. The statistical analysis was carried out using Stata/SE (Version 14.0; Stata Corp, Texas, U.S.A.).

Ethics:

This study was conducted in compliance with the Declaration of Helsinki and approved by the local institutional review board (protocol number: 103/2019/Oss/AOUBo).

Results

General and SPSS characteristics in ACLD patients

The flowchart of the study patients is described in **Supplemental Material 1**. Two-hundred and thirty-five patients were included in the final analysis; they were mainly male (70.6%), with compensated cirrhosis (71.6%) of viral etiology (54.5%) HCV-related), median MELD was 9 (8-11). The demographics and clinical data are summarized in **Table 1**.

At least one type of SPSS was present in the majority (141, 60%) of the patients; the median SPSS diameter was 6 mm (4-10 mm). The most common types of shunts were the paraumbilical vein (79, 33.6%), followed by splenorenal (53, 22.6%), inferior epigastric vein (40, 33.6%) and the gastrorenal (24, 10.2%) shunts (**Figure 1A, Supplemental Material 2**).

Patients with and without SPSS differed significantly in etiology (**Figure 1B**); the lowest prevalence was observed in HCV patients (50.8%), whereas 67.4% and 68.8% of the patients with alcohol-related and autoimmune ACLD presented with SPSS, respectively. Moreover, the prevalence of SPSS increased with the severity of liver disease (**Figure 1C**) and the prognostic stage of cirrhosis according to D'Amico ($p= 0.035$). Of note, SPSS prevalence was high also in patients with compensated cirrhosis (92/166, 55.4%), LSM<21 kPa (41/89, 46.1%), or MELD<10 (70/141, 50%).

We conducted a logistic regression analysis of factors associated with SPSS presence: female sex, non-viral etiology, MELD score, LSM ≥21 kPa, and PVT presence were independently associated with SPSS (**Table 2)**.

Risk of hepatic decompensation during follow-up

During a median follow-up of 37 (20-63) months, 70 (29.8%) patients developed at least one episode of decompensation; ascites was the most frequent event (54, 77.1%). **Supplemental Material 3**

summarises the incidence of each clinical event during follow-up, according to SPSS presence. In particular, the cumulative incidence of not only HE but also ascites and variceal bleeding was significantly higher in patients with SPSS (**Figure 2**).

Prediction of hepatic decompensation development

The results of the competing risk univariate analysis for the prediction of decompensation are reported in **Table 3**. In the multivariate analysis, the presence of SPSS was independently associated with hepatic decompensation development (SHR: 2.264, 95%-IC:1.259-4.071); the other predictors found were a history of decompensated cirrhosis (SHR: 8.435, 95%-IC: 5.099-13.955) and presence of high-risk varices (SHR: 2.041, 95%-IC: 1.262-3.304) (**Figure 3A**). Similar results were found when the D'Amico's stages of cirrhosis[1] were included in the model instead of the history of decompensation and the presence of EV (**Supplemental Material 4 & 5**).

Prognostic role of SPSS type and dimension on the risk hepatic decompensation development

Given that 35.3% of the patients presented >1 SPSS, the type of SPSS was not considered as a categorical variable; instead, multivariate models were investigated for each SPSS type, adjusting per relevant factors and predictors found in Table 3. **Table 4** summarises the different unadjusted and adjusted SHR of each SPSS type; among these, only gastrorenal shunts and mesenteric varices consistently and independently predicted the event of decompensation (**Supplemental Material 6**).

Moreover, we found that the risk of decompensation was progressively higher with the increase in SPSS dimensions (**Table 4)**. The best SPSS diameter cut-off was 8 mm (sensitivity 48%, specificity 62%, AUROC 0.55); the rule-in and rule-out cut-offs were, respectively, 4 mm (sensitivity 87%) and 14 mm (specificity 90.8%). The risk of decompensation was higher in patients with SPSS >8 mm (3.755, 95%-IC: 2.106-7.070) vs in small shunts (2.327, 95%-IC: 1.300-4.166) (**Figure 3C**).

However, the performance of this cut-off was very low, as the range of the SPSS diameter in the 54 patients who decompensated was wide (1-33 mm).

Similarly, the risk of decompensation increased with the total number of collaterals present: it was 2.034 (95%-IC: 1.077-3.840) and 3.009 (95%-IC: 1.303-6.948) times higher in patients with 1-2 shunts and >2 shunts, (vs no shunt present), respectively (**Figure 3D**). Alternatively, the total area of SPSS was also found an independent predictor of any type of decompensation (SHR per one mm^3 increase: 1.0005; 95%-IC: 1.0003-1.008) (**Table 4**).

Prediction of OLT or liver-related death in ACLD patients

In **Supplemental Material 7** are shown the results of the univariate and multivariate analysis for the prediction of transplant-free survival. Of note, the presence of SPSS was significantly associated with this outcome only at univariate analysis. Instead, a history of previous decompensation, HCC and higher bilirubin levels decreased independently the transplant-free survival. Interestingly, when each SPSS type was considered separately in adjusted multivariate analysis (**Supplemental Material 8**), gastrorenal shunt was an independent predictor of OLT or liver-related death.

Prevalence, characteristics, and prognostic role of GEV varices at imaging

Supplemental Material 9 summarises the main characteristics of GEV varices evaluated by TC/MRI. Their overall prevalence was 74%, and their presence was associated with a higher risk of decompensation (SHR: 3.122; 95%-IC: 1.270-7.678, p=0.013) (**Supplemental Material 10**). Among GEV, patients with para-esophageal varices and the left gastric vein presented a higher risk of decompensation in multivariate-adjusted models.

Discussion

The present study shows that spontaneous portosystemic shunts, a common finding in patients with advanced chronic liver disease, are associated with a higher risk of not only hepatic encephalopathy but also other events of hepatic decompensation. Furthermore, among collaterals, gastrorenal shunts seem to be associated with worse clinical outcomes.

In our study, SPSS were very common among ACLD patients, as they were found in 141 (60%) of the included subjects; the most prevalent types were the paraumbilical vein (56%) and the splenorenal (37.6%). The observed prevalence was similar to what previously described in a study using CT/MRI,[8] but higher than the one observed in smaller series using ultrasound;[17,18] this difference is most likely due to a lower sensitivity of the latter method to detect these collaterals. As expected, the prevalence of SPSS increased with the worsening of liver function or portal hypertension[6,8]; however, it remained high (46-55%) in the subgroups of patients with compensated cirrhosis, preserved liver function (MELD <10), or LSM <21 kPa, demonstrating for the first time that this feature is widespread also in the early stages of cirrhosis (**Figure 1**).

We investigated the factors associated with SPSS presence, where, besides MELD score and LSM, non-viral etiology, gender, and presence of portal vein thrombosis, were independently associated with a higher risk of SPSS (**Table 2**). Indeed, the role that etiology plays in the formation of collaterals is still unclear.[5] Several authors found that shunts were more common in alcoholic patients,[8,17] but this was initially attributed to a delayed diagnosis of liver disease.[8] In our series, the higher risk of SPSS presence in non-viral etiology was independent of liver function (MELD) or portal pressure (LSM). In our view, this difference could be attributed to the different patterns of fibrogenesis and severity of portal hypertension described in the various liver etiologies.

In our study, we found that SPSS presence was associated with a higher incidence of not only hepatic encephalopathy but also ascites and bleeding (**Figure 2**). Indeed, SPSS presence was associated with a 2.3-fold-increase in the risk of any event of decompensation. The most important aspect is that this result remained significant across all the prognostic stages of cirrhosis according to D'Amico et al.,[1] and independent from the history of decompensation and the presence of high-risk varices and (**Table 3**). Indeed, in the previous studies by the Baveno SPSS Study Group, SPSS presence was the only variable reflecting the portal hypertension grade in the final model predicting transplant-free survival, so it was not clear whether the newly described prognostic role of collaterals was to be attributed simply to more severe portal hypertension found in patients with SPSS, or to an independent effect of their presence. [5] In our study, we demonstrated that SPSS presence adds further prognostic value to these classifications and identifies patients at different risk of complications among both compensated and decompensated cirrhosis.

The relationship between SPSS and the risk of decompensation has been poorly investigated, and the results are controversial. Previous belief was that shunts increased the risk of hepatic encephalopathy, but were protective for the development of varices or ascites;[7,19] however other authors did not confirm this protective effect,[17,20,21] and more recently, two papers by the Baveno VI-SPSS Group showed that patients with shunts were at higher risk of PH-related complications and death.[8,13] From a physiopathological point of view, a possible hypothesis could be that the formation of collateral vessels, initially driven by the increased portal pressure, contributes to a decrease in hepatocyte perfusion, tissue hypoxia, and consequently the promotion of neo-angiogenesis both in the liver and in the splanchnic circulation.[22] This leads to a progressive amplification of the mechanisms causing and maintaining a hyperdynamic splanchnic circulation state,[23] which in turn is responsible for the main complications of portal hypertension. Noteworthy, SPSS were frequent also in patients with LMS values in the "grey zone" between 10-

20 kPa (46%) or in patients in Stage 1 according to D'Amico (47.6%). The presence of SPSS in this population could be explained only if we consider liver cirrhosis as a dynamic disease with different stages and compensatory mechanisms.[24] In the first phase of this pathophysiological functional view of liver disease, SPSS could represent a compensatory measure that reduces portal hypertension and its complications, while in the advanced phase SPSS reduce liver perfusion and can determine liver failure.

Another novel result of our study is that the type, the dimensions, and the number of SPSS are highly relevant for the prediction of the decompensation risk. Regarding SPSS size, the best shunt diameter cut-off to predict decompensation development was 8 mm, therefore SPSS were considered as large according to this value. Noteworthy, we demonstrated for the first time that the risk of any decompensation type increased with the increase in SPSS size and number, as shown in **Figure 3**. Also, the total area of SPSS[13] was validated as an independent predictor of decompensation. Moreover, previous papers have tried to identify associations between SPSS type and the predominant type of decompensation.[25–27] However, none of these studies evaluated whether the global risk of decompensation was different among different types of collaterals. In our cohort, we found, through multivariate models adjusted for known and demonstrated risk factors, that gastrorenal shunts and mesenteric varices were the only types of SPSS consistently associated with an increased risk of decompensation; gastrorenal shunts were even independent predictors of transplantation or liver-related death. If confirmed in other studies, our data suggest that not all SPSS are the same in terms of prognostic significance. This is even more relevant when considering and selecting shunts to treat for the prevention of rebleeding or (further) decompensation. In the last years, several studies have shown that radiological procedures, such as balloon-occluded retrograde transvenous obliteration, are safe in treating recurrent hepatic encephalopathy.[28] Recently, a novel technique, such as the clip-assisted endoscopic cyanoacrylate injection, was shown safe and efficient

in the treatment of gastric varices with gastrorenal shunts.[29] Interestingly, some authors have observed an improvement in liver function after embolisation,[30,31] most likely due to an improvement in liver perfusion, even in patients without gastric varices.[31] Therefore, future studies should address the possibility of embolizing SPSS in selected patients to prevent PH-related complications in cirrhotic patients.

Lastly, this is the first study to describe the prevalence and the characteristics of non-luminal gastroesophageal varices. In particularly para-esophageal varices and left gastric vein, were also found predictors of hepatic decompensation. (**Supplemental Material 9 & 10**).

The main limitations of the study are its retrospective and monocentric nature, the relatively small number of patients and liver imaging revision was made by a single radiologist. Moreover, the most common etiology in our cohort was viral, so the association between shunt presence and each cause of liver disease could not be conclusively evaluated. On the plus side, differently from previous reports,[8] liver disease was fully characterised in our patients, including medical history, endoscopic, and imaging data.

In conclusion, cirrhotic patients with large, multiple, and gastrorenal shunts are at higher risk of complications. Therefore, the presence, type, and dimension SPSS, which are common since the early stages of cirrhosis, should be actively searched and reported in patients undergoing radiological examinations, as they are highly relevant from a prognostic point of view. Their presence reflects a dysfunctional compensatory mechanism, that, while inefficient in decreasing portal pressure, it increases the risk of decompensation in both compensated and decompensated cirrhosis. Future prospective studies need to explore SPSS treatment as a new target to prevent the complications of portal hypertension in cirrhotic patients.

Reference List:

[1] D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39:1180–93. doi:10.1111/apt.12721.

[2] Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol 2009;6:573–82. doi:10.1038/nrgastro.2009.149.

[3] Colecchia A, Colli A, Casazza G, Mandolesi D, Schiumerini R, Reggiani LB, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: A prospective study. J Hepatol 2014;60:1158–64. doi:10.1016/j.jhep.2014.02.024.

[4] Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases 2017;65:310–35. doi:10.1002/hep.28906.

[5] Guillaume M, Bureau C. Should the Presence of Spontaneous Portosystemic Shunts Be Implemented to the Model for End-Stage Liver Disease Score for a Better Prediction of Outcome? Gastroenterology 2018;154:1569–71. doi:10.1053/j.gastro.2018.03.035.

[6] Berzigotti A, Rossi V, Tiani C, Pierpaoli L, Zappoli P, Riili A, et al. Prognostic value of a single HVPG measurement and Doppler-ultrasound evaluation in patients with cirrhosis and portal hypertension. J Gastroenterol 2011;46:687–95. doi:10.1007/s00535-010-0360-z.

[7] Riggio O, Efrati C, Catalano C, Pediconi F, Mecarelli O, Accornero N, et al. High prevalence of spontaneous portal-systemic shunts in persistent hepatic encephalopathy: A

case-control study. Hepatology 2005;42:1158–65. doi:10.1002/hep.20905.

[8] Simón-Talero M, Roccarina D, Martínez J, Lampichler K, Baiges A, Low G, et al. Association Between Portosystemic Shunts and Increased Complications and Mortality in Patients With Cirrhosis. Gastroenterology 2018;154:1694-1705.e4. doi:10.1053/j.gastro.2018.01.028.

[9] de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743–52. doi:10.1016/j.jhep.2015.05.022.

[10] Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406–60. doi:10.1016/j.jhep.2018.03.024.

[11] Renzulli M, Biselli M, Brocchi S, Granito A, Vasuri F, Tovoli F, et al. New hallmark of hepatocellular carcinoma, early hepatocellular carcinoma and high-grade dysplastic nodules on Gd-EOB-DTPA MRI in patients with cirrhosis: a new diagnostic algorithm. Gut 2018;67:1674–82. doi:10.1136/gutjnl-2017-315384.

[12] Tovoli F, Renzulli M, Negrini G, Brocchi S, Ferrarini A, Andreone A, et al. Inter-operator variability and source of errors in tumour response assessment for hepatocellular carcinoma treated with sorafenib. Eur Radiol 2018;28:3611–20. doi:10.1007/s00330-018-5393-3.

[13] Praktiknjo M, Simón-Talero M, Römer J, Roccarina D, Martínez J, Lampichler K, et al. Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis. J Hepatol 2020;72:1140–50. doi:10.1016/j.jhep.2019.12.021.

[14] Colecchia A, Ravaioli F, Marasco G, Colli A, Dajti E, Di Biase AR, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. J Hepatol 2018. doi:10.1016/j.jhep.2018.04.023.

[15] Dajti E, Ravaioli F, Colecchia A, Marasco G, Bacchi Reggiani ML, Colli A, et al. Spleen Stiffness Measurements Predict the Risk of Hepatic Decompensation After Direct-Acting Antivirals in HCV Cirrhotic Patients. Ultraschall Der Medizin - Eur J Ultrasound 2020. doi:10.1055/a-1205-0367.

[16] D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, et al. Clinical states of cirrhosis and competing risks. J Hepatol 2018;68:563–76. doi:10.1016/j.jhep.2017.10.020.

[17] Lipinski M, Saborowski M, Heidrich B, Attia D, Kasten P, Manns MP, et al. Clinical characteristics of patients with liver cirrhosis and spontaneous portosystemic shunts detected by ultrasound in a tertiary care and transplantation centre. Scand J Gastroenterol 2018;53:1107–13. doi:10.1080/00365521.2018.1498913.

[18] Berzigotti A, Merkel C, Magalotti D, Tiani C, Gaiani S, Sacerdoti D, et al. New abdominal collaterals at ultrasound: a clue of progression of portal hypertension. Dig Liver Dis 2008;40:62–7. doi:10.1016/j.dld.2007.08.011.

[19] Ohnishi K, Sato S, Saito M, Terabayashi H, Nakayama T, Saito M, et al. Clinical and portal hemodynamic features in cirrhotic patients having a large spontaneous splenorenal and/or gastrorenal shunt. Am J Gastroenterol 1986;81:450–5.

[20] Aseni P, Beati C, Brambilla G, Bertini M, Belli L. Does large spontaneous portal systemic shunt in cirrhosis protect from the risk of gastroesophageal bleeding? J Clin Gastroenterol 1986;8:235–8. doi:10.1097/00004836-198606000-00006.

[21] Saks K, Jensen KK, McLouth J, Hum J, Ahn J, Zaman A, et al. Influence of spontaneous splenorenal shunts on clinical outcomes in decompensated cirrhosis and after liver transplantation. Hepatol Commun 2018;2:437–44. doi:10.1002/hep4.1157.

[22] Fernandez M, Mejias M, Angermayr B, Garcia-Pagan JC, Rodés J, Bosch J. Inhibition of VEGF receptor-2 decreases the development of hyperdynamic splanchnic circulation and portal-systemic collateral vessels in portal hypertensive rats. J Hepatol 2005;43:98–103. doi:10.1016/j.jhep.2005.02.022.

[23] Fernández M, Semela D, Bruix J, Colle I, Pinzani M, Bosch J. Angiogenesis in liver disease. J Hepatol 2009;50:604–20. doi:10.1016/j.jhep.2008.12.011.

[24] Vidal-González J, Quiroga S, Simón-Talero M, Genescà J. Spontaneous portosystemic shunts in liver cirrhosis: new approaches to an old problem. Therap Adv Gastroenterol 2020;13. doi:10.1177/1756284820961287.

[25] Del Piccolo F, Sacerdoti D, Amodio P, Bombonato G, Bolognesi M, Mapelli D, et al. Central nervous system alterations in liver cirrhosis: the role of portal-systemic shunt and portal hypoperfusion. Metab Brain Dis 2003;18:51–62.

[26] Moubarak E, Bouvier A, Boursier J, Lebigot J, Ridereau-Zins C, Thouveny F, et al. Portosystemic collateral vessels in liver cirrhosis: a three-dimensional MDCT pictorial review. Abdom Imaging 2012;37:746–66. doi:10.1007/s00261-011-9811-0.

[27] Philips CA, Rajesh S, Augustine P, Padsalgi G, Ahamed R. Portosystemic shunts and refractory hepatic encephalopathy: patient selection and current options. Hepat Med 2019;11:23–34. doi:10.2147/HMER.S169024.

[28] Nardelli S, Gioia S, Ridola L, Riggio O. Radiological Intervention for Shunt Related

Encephalopathy. J Clin Exp Hepatol 2018;8:452–9. doi:10.1016/j.jceh.2018.04.008.

[29] Zhang M, Li P, Mou H, Shi Y, Tuo B, Jin S, et al. Clip-assisted endoscopic cyanoacrylate injection for gastric varices with a gastrorenal shunt: a multicenter study. Endoscopy 2019. doi:10.1055/a-0977-3022.

[30] Ishikawa T, Sasaki R, Nishimura T, Matsuda T, Maeda M, Iwamoto T, et al. Comparison of patients with hepatic encephalopathy and those with gastric varices before and after balloon-occluded retrograde transvenous obliteration. Hepatol Res 2018;48:1020–30. doi:10.1111/hepr.13199.

[31] Nakazawa M, Imai Y, Uchiya H, Ando S, Sugawara K, Nakayama N, et al. Balloon-occluded retrograde transvenous obliteration as a procedure to improve liver function in patients with decompensated cirrhosis. JGH Open an Open Access J Gastroenterol Hepatol 2017;1:127–33. doi:10.1002/jgh3.12020.

Table and Figure Legends

Table 1 – Characteristics of the patients included in the study

Table 2 – Factors associated with SPSS presence in ACLD patients

Table 3 – Predictors of hepatic decompensation in a cohort of ACLD patients

Table 4 – Prognostic role of SPSS type and dimensions on hepatic decompensation development

Figure 1 – Prevalence of SPSS according to A) SPSS type; B) etiology; C) liver disease severity

Figure 1A summarizes the prevalence of each SPSS type in our cohort of patients with chronic liver disease. In Figure 1B it is reported the prevalence of any type of SPSS in the main etiologies of liver disease (viral, non-alcoholic fatty liver disease, alcohol, autoimmune). Figure 1C depicts the prevalence of SPSS according to the severity of liver dysfunction (according to MELD Score), the presence of a history of decompensation, and the values of liver stiffness measurements (LSM >21 kPa).

Figure 2 – Cumulative incidence function curves according to SPSS presence for A) any hepatic decompensation; B) hepatic encephalopathy; C) variceal bleeding; D) ascites

The presence of SPSS can stratify the risk and identify the patients at higher risk of decompensation, not only defined as any type of decompensation (1A) but also when each type of decompensation event was considered separately (2B-2D).

Figure 3 – Cumulative incidence function curves for hepatic decompensation risk according to A) the presence of SPSS and history of decompensation; B) the presence of SPSS and presence of HRV; C) SPSS dimensions; D) SPSS number

The presence of SPSS, prior decompensation, and high-risk esophageal varices were identified as independent predictors of hepatic decompensation in our cohort; accordingly, the risk of decompensation was stratified and depicted according to these variables in figure 3A and 3B. Moreover, both SPSS diameter (3C) and number (3D) are highly relevant when predicting the risk of decompensation, even when adjusting for age, gender, MELD, prior decompensation, presence of esophageal varices.

Figure 1 – Prevalence of SPSS according to A) SPSS type; B) etiology; C) liver disease severity

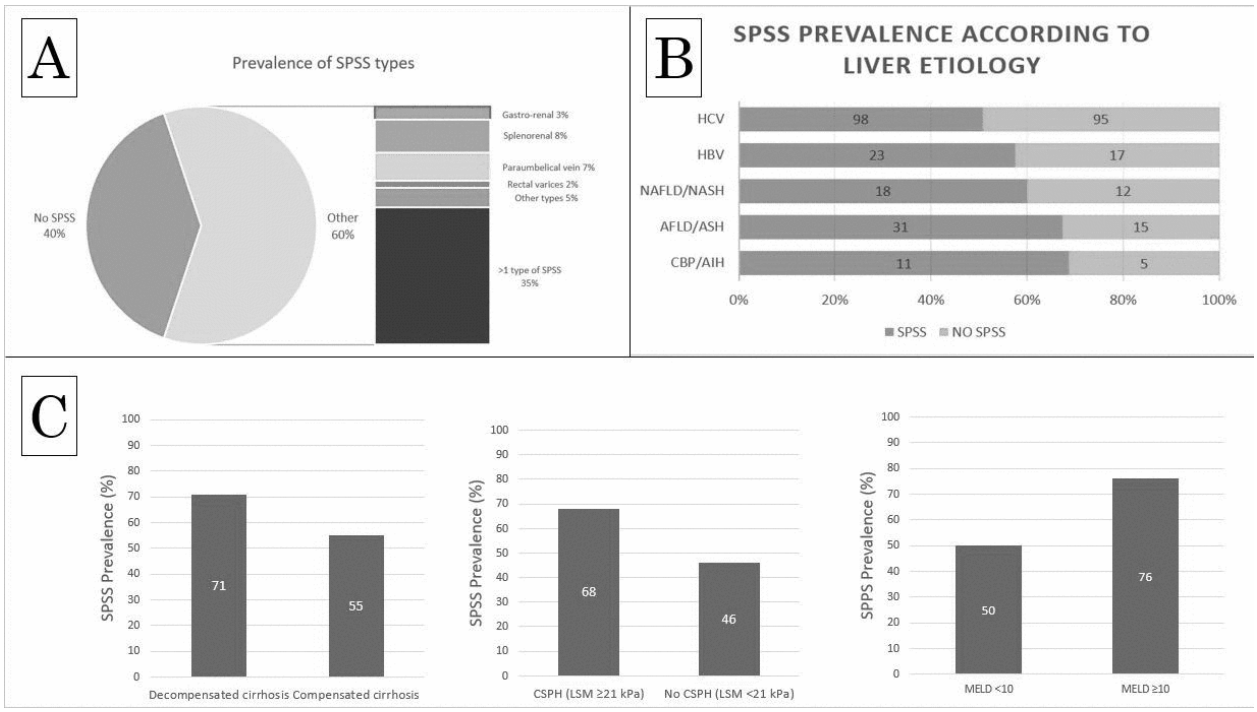
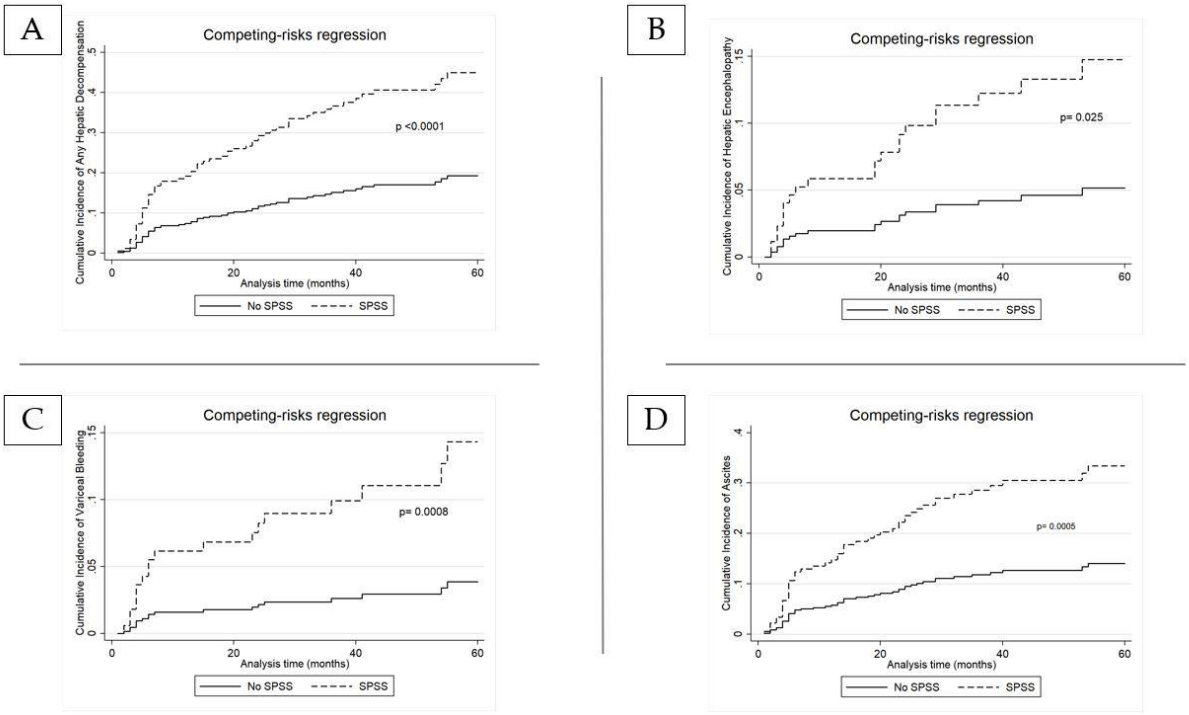


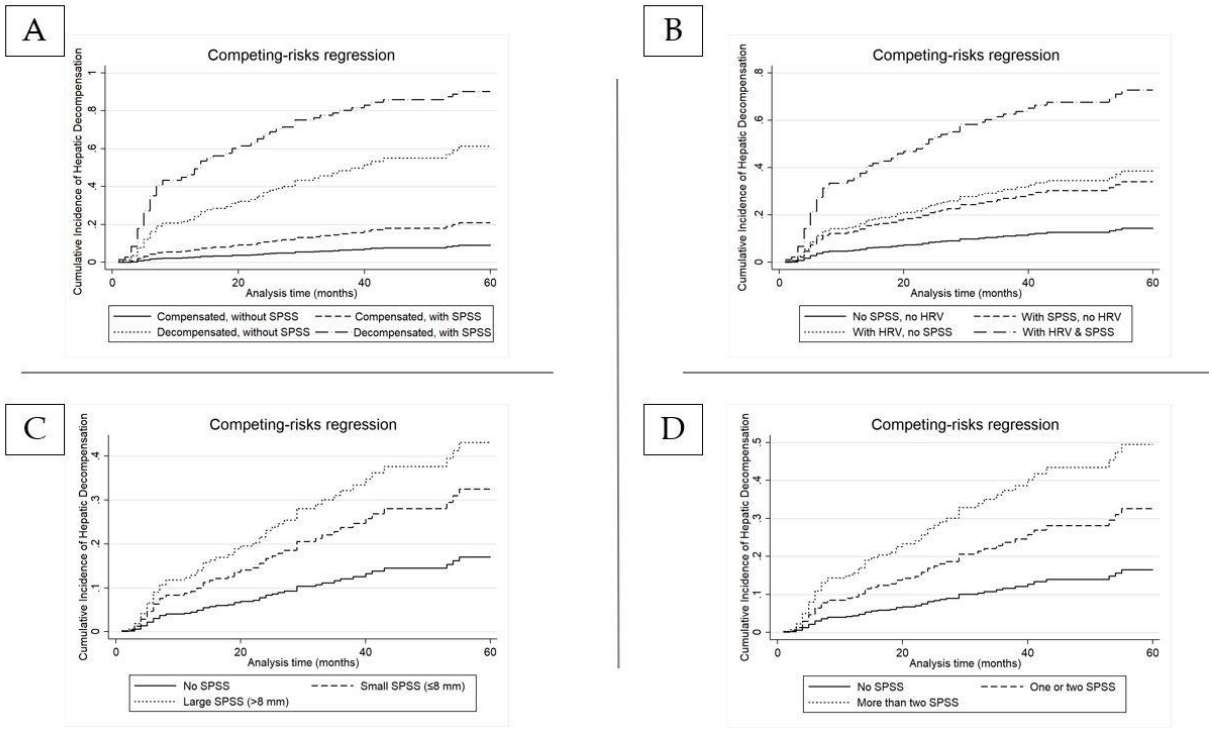
Figure 1A summarizes the prevalence of each SPSS type in our cohort of patients with chronic liver disease. In Figure 1B it is reported the prevalence of any type of SPSS in the main etiologies of liver disease (viral, non-alcoholic fatty liver disease, alcohol, autoimmune). Figure 1C depicts the prevalence of SPSS according to the severity of liver dysfunction (according to MELD Score), the presence of a history of decompensation, and the values of liver stiffness measurements (LSM >21 kPa).

Figure 2 – Cumulative incidence function curves according to SPSS presence for A) any hepatic decompensation; B) hepatic encephalopathy; C) variceal bleeding; D) ascites



The presence of SPSS can stratify the risk and identify the patients at higher risk of decompensation, not only defined as any type of decompensation (1A) but also when each type of decompensation event was considered separately (2B-2D).

Figure 3 – Cumulative incidence function curves for hepatic decompensation risk according to A) the presence of SPSS and history of decompensation; B) the presence of SPSS and presence of HRV; C) SPSS dimensions; D) SPSS number



The presence of SPSS, prior decompensation, and high-risk esophageal varices were identified as independent predictors of hepatic decompensation in our cohort; accordingly, the risk of decompensation was stratified and depicted according to these variables in figure 3A and 3B. Moreover, both SPSS diameter (3C) and number (3D) are highly relevant when predicting the risk of decompensation, even when adjusting for age, gender, MELD, prior decompensation, presence of esophageal varices.

Manuscript number: DLD-20-1768

Table 1 – Characteristics of the patients included in the study

Variables	All patients (n=235)	Patients with SPSS (n=141)	Patients without SPSS (n=94)	P-value
Age	64 (57-76)	64 (57-76)	66 (57-75)	0.844
Sex (male)	166 (70.64%)	90 (63.83%)	76 (80.85%)	**0.005**
ACLD Etiology				**0.046**
HCV	128 (54.47%)	65 (46.10%)	63 (67.02%)	
HBV	11 (4.68%)	8 (5.67%)	3 (3.19%)	
NAFLD	10 (4.26%)	7 (8.7%)	3 (2.5%)	
ALD	8 (3.4%)	8 (5.76%)	0 (0%)	
PBC	8 (3.4%)	6 (4.26%)	2 (2.13%)	
AIH	2 (0.85%)	2 (1.42%)	0 (0%)	
> 1 cause of ACLD	61 (25.96%)	40 (28.37%)	21 (22.34%)	
Other etiology	7 (2.98%)	5 (3.55%)	2 (2.13%)	
Co-morbidities				
HIV co-infection	9 (4.4%)	6 (4.8%)	3 (3.8%)	0.725
Diabetes mellitus	69 (29.87%)	45 (32.37%)	24 (26.09%)	0.307
Arterial hypertension	50 (21.55%)	29 (20.71%)	21 (22.83%)	0.702
Stage of Cirrhosis				**0.035**
Stage I	63 (26.81%)	30 (21.28%)	33 (35.11%)	
Stage II	103 (43.83%)	62 (43.97%)	41 (43.62%)	
Stage III	11 (4.83%)	10 (7.09%)	1 (1.06%)	
Stage IV	29 (12.34%)	18 (12.77%)	11 (11.70%)	
Stage V	29 (12.34%)	21 (14.89%)	8 (8.51%)	
ACLD History				
Decompensated cirrhosis	69 (29.36%)	49 (34.75%)	20 (28.99%)	**0.026**
Variceal bleeding	27 (11.49%)	22 (15.60%)	5 (5.32%)	**0.015**
Ascites	46 (19.57%)	33 (23.40%)	13 (13.86%)	0.070
Hepatic encephalopathy	12 (5.11%)	9 (6.38%)	3 (3.19%)	0.276
Spontaneous bacterial peritonitis	4 (1.70%)	2 (1.42%)	2 (2.13%)	0.681
Hepatorenal syndrome	6 (2.55%)	5 (3.55%)	1 (1.06%)	0.237
Previous EV ligation	32 (13.62%)	26 (18.44%)	6 (6.38%)	**0.008**
Use of NSBB	57 (24.26%)	42 (29.79%)	15 (15.96%)	**0.015**
History of HCC	75 (31.91%)	49 (34.75%)	26 (27.66%)	0.253
Laboratory Test				
AST (U/L)	50 (34-81)	51 (35-81)	46 (33-81)	0.870
ALT (U/L)	44 (29-78)	42 (26-70)	46 (32-88)	0.097
Platelets (cells x10^9/L)	100 (69-134)	88 (63-123)	114.5 (86-145.5)	**0.001**
Albumin (g/dL)	3.8 (3.7-4)	3.8 (3.6-4)	3.8 (3.79-4)	0.261
Bilirubin (mg/dL)	0.95 (0.7-1.43)	1.1 (0.8-1.65)	0.805 (0.64-1.05)	**<0.0001**
INR	1.17 (1.09-1.26)	1.21 (1.11-1.29)	1.14 (1.07-1.21)	**<0.0001**
Creatinine (mg/dL)	0.8 (0.72-0.91)	0.8 (0.7-0.8)	0.8 (0.76-0.96)	**0.037**
MELD score	9 (8-11)	10 (8-11)	8 (7-9)	**0.0001**

Child-Pugh score	5 (5-6)	6 (5-6)	5 (5-6)	0.124
Child-Pugh class B	37 (15.74%)	23 (16.31%)	14 (14.89%)	0.770
TE evaluation				
LSM (kPa)	23.6 (16.6-33.8)	25.7 (19.5-34.8)	20.6 (14.8-31.2)	**0.0008**
LSM ≥21 kPa (%)	146 (62.13%)	100 (70.92%)	46 (48.94%)	**0.001**
Upper endoscopy				
EV presence	164 (69.79%)	107 (75.89%)	57 (60.64%)	**0.013**
EV grade				**0.020**
Grade 1	114 (69.51%)	69 (64.49%)	45 (78.95%)	
Grade 2	39 (23.78%)	28 (26.17%)	11 (19.30%)	
Grade 3	11 (6.71%)	10 (9.35%)	1 (1.75%)	
Red signs	23 (14.02%)	19 (17.76%)	4 (7.02%)	0.059
High-risk varices	53 (32.72%)	39 (36.7%)	14 (25%)	0.128
Radiological evaluation				
Hepatomegaly	186 (79.15%)	113 (80.14%)	73 (77.66%)	0.646
HCC	41 (17.45%)	27 (19.15%)	14 (14.89%)	0.400
Number of nodules	1 (1-2)	1 (1-2)	1 (1-2)	0.519
Maximal diameter (cm)	2.2 (1.1-4.5)	2.7 (1.2-4.9)	2 (1-3)	0.242
Dilated portal vein	161 (68.51%)	101 (71.63%)	60 (63.83%)	0.207
Portal Vein Thrombosis	23 (9.79%)	20 (14.18%)	3 (3.19%)	**0.005**
Occlusion <50%	14 (63.64%)	12 (63.16%)	2 (66.67%)	
Occlusion >50%	3 (13.64%)	2 (15.79%)	0 (0%)	
Occlusion complete	5 (22.73%)	4 (21.05%)	1 (33.33%)	
Splenomegaly	194 (82.55%)	120 (85.11%)	74 (78.72%)	0.207
Ascites	67 (28.51%)	44 (31.21%)	23 (24.47%)	0.262

ACLD: advanced chronic liver disease; AIH: autoimmune hepatitis; ALD: alcohol-related liver disease; ALT: alanine transaminase; AST: aspartate transaminase; EV: esophageal varices; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; INR: international normalized ratio; LSM: liver stiffness measurement; MELD: Model for end-stage-liver-disease; NAFLD: non-alcoholic fatty liver disease; NSBB: non-selective beta-blocker; PBC: primary biliary cholangitis; SPSS: spontaneous portosystemic shunts; TE: transient elastography.

Table 2 – Factors associated with SPSS presence in ACLD patients

Variables	Univariate analysis		Multivariate analysis	
	OR (95%-IC)	**P-value**	**OR (95%-IC)**	**P-value**
Sex (female)	2.393 (1.290-4.439)	0.006	2.568 (1.316-5.013)	0.006
Non-viral etiology	2.466 (1.148-5.299)	0.021	2.325 (1.021-5.291)	0.044
Decompensated cirrhosis	1.971 (1.078-3.603)	0.028		
Stage of cirrhosis	1.277 (1.037-1.573)	0.021		
Previous EV ligation	3.316 (1.308-8.405)	0.012		
Use of NSBB	2.234 (1.55-4.321)	0.017		
Platelets (cells $x10^9$/L)	0.995 (0.990-0.999)	0.027		
Bilirubin (mg/dl)	2.632 (1.555-4.454)	<0.0001		
MELD score	1.206 (1.073-1.356)	0.002	1.163 (1.026-1.320)	0.019
LSM (kPa)	1.032 (1.009-1.055)	0.006		
LSM ≥21 kPa	2.545 (1.478-4.384)	0.001	2.584 (1.425-4.686)	0.002
EV presence	2.043 (1.160-3.597)	0.013		
Portal vein thrombosis	6.858 (2.012-23.376)	0.002	5.177 (1.468-18.257)	0.011
			LR-chi2= 45.11	
			AUROC=0.750	

ACLD: advanced chronic liver disease; AUROC: area under ROC curve; EV: esophageal varices; HCV: hepatitis C virus; LR: likelihood ratio; MELD: model for end-stage liver disease; NSBB: non-selective beta-blockers; OR: odds ratio; SPSS: spontaneous portosystemic shunts.

Table 3 – Predictors of hepatic decompensation in a cohort of ACLD patients

	Univariate Analysis		Multivariate analysis	
Variables	**SHR (95% IC)**	**P-value**	**SHR (95% IC)**	**P-value**
ACLD Etiology				
HCV	0.567 (0.353-0.912)	0.019		
ALD	2.623 (1.580-4.352)	<0.0001		
ACLD history				
Decompensated cirrhosis	9.882 (6.038-18.176)	<0.0001	8.435 (5.099-13.955)	<0.0001
Previous EV ligation	4.181 (2.638-6.626)	<0.0001		
Use of NSBB	3.003 (1.898-4.750)	<0.0001		
Radiological Data				
SPSS presence	2.749 (1.599-4.726)	<0.0001	2.264 (1.259-4.071)	0.006
Portal vein diameter (mm)	3.224 (2.113-4.919)	<0.0001		
Portal vein thrombosis	2.812 (1.656-4.773)	<0.0001		
Ascites	3.863 (2.440-6.113)	<0.0001		
Upper endoscopy				
Presence of EV	5.154 (2.236-11.880)	<0.0001		
Grade of EV	2.110 (1.660-2.682)	<0.0001		
Red signs	3.465 (2.114-5.680)	<0.0001		
High-risk varices	3.188 (2.027-5.014)	<0.0001	2.041 (1.262-3.304)	0.004
Laboratory Test				
AST (U/L)	0.994 (0.989-0.999)	0.045		
ALT (U/L)	0.993 (0.988-0.999)	0.019		
Albumin (g/dL)	1.036 (1.016-1.506)	<0.001		
Bilirubin (mg/dL)	1.157	0.053		

	(0.998-1.341)			
MELD score	1.105 (1.041-1.172)	0.001		
Child-Pugh score	1.716 (1.372-2.146)	<0.0001		
TE evaluation				
LSM (kPa)	1.026 (1.012-1.041)	<0.0001		
LSM ≥21 kPa (%)	1.934 (1.145-3.266)	0.014		
			Wald-chi2= 129.05	

ACLD: advanced chronic liver disease; ALD: alcohol-related liver disease; ALT: alanine transaminase; AST: aspartate transaminase; EV: esophageal varices; HCV: hepatitis C virus; LSM: liver stiffness measurement; MELD: Model for end-stage-liver-disease; NSBB: non-selective beta-blocker; SPSS: spontaneous portosystemic shunts; SHR: subhazard ratio; TE: transient elastography.

Table 4 – Prognostic role of SPSS type and dimensions on hepatic decompensation development

SPSS type	**Unadjusted SHR (95% IC)**	**P-value**	**Model 1[#] Adjusted SHR (95% IC)**	**P-value**	**Model 2[§] Adjusted SHR (95% IC)**	**P-value**
Gastrorenal	2.478 (1.431-4.324)	**0.001**	2.447 (1.374-4.259)	**0.002**	2.636 (1.521-4.569)	**0.001**
Splenorenal	1.636 (0.987-2.713)	0.056	1.388 (0.813-2.369)	0.230	1.490 (0.862-2.575)	0.153
Mesenteric Varices	3.837 (1.897-7.762)	**<0.0001**	3.259 (1.583-6.712)	**0.001**	2.622 (1.435-4.789)	**0.002**
Meso (SMV)- caval	1.741 (0.490-6.183)	0.391	1.798 (0.494-6.540)	0.373	1.997 (1.103-3.615)	**0.022**
Paraumbilical Vein	1.635 (1.037-2.577)	**0.034**	1.503 (0.920-2.454)	0.104	0.906 (0.560-1.465)	0.687
Inferor epigastric vein	1.515 (0.868-2.644)	0.143	1.265 (0.701-2.284)	0.435	0.805 (0.464-1.397)	0.441
Rectal Varices	2.575 (1.367-4.849)	**0.003**	2.128 (1.006-4.503)	**0.048**	1.373 (0.709-2.659)	0.348
Mesorenal	1.237 (0.148-10.305)	0.844	1.079 (0.136-8.570)	0.943	1.743 (0.412-7.382)	0.450
Uterine Varices/ Gonadic Vein	1.809 (0.979-3.341)	0.058	1.600 (0.773-3.314)	0.206	1.242 (0.607-2.542)	0.553
Other	1.218 (0.547-2.712)	0.629	1.148 (0.484-2.721)	0.754	1.229 (0.594-2.544)	0.578
SPSS diameter	**Unadjusted SHR (95% IC)**	**P-value**	**Model 1[#] Adjusted SHR (95% IC)**	**P-value**	**Model 2[§] Adjusted SHR (95% IC)**	**P-value**
0-8 mm	2.327 (1.300-4.166)	**0.004**	2.322 (1.290-4.179)	**0.005**	2.033 (1.065-3.882)	**0.032**

>8 mm	3.775 (2.016-7.070)	**<0.0001**	3.238 (1.675-6.260)	**<0.0001**	2.795 (1.333-5.862)	**0.007**
SPSS number	**Unadjusted SHR (95% IC)**	**P-value**	**Model 1[#] Adjusted SHR (95% IC)**	**P-value**	**Model 2[§] Adjusted SHR (95% IC)**	**P-value**
One or two shunts	2.412 (1.360-4.276)	**0.003**	2.408 (1.353-4.284)	**0.003**	2.034 (1.077-3.840)	**0.029**
>2 shunts	3.832 (2.004-7.330)	**<0.0001**	3.343 (1.612-6.932)	**0.001**	3.009 (1.303-6.948)	**0.010**
Total shunt area	**Unadjusted SHR (95% IC)**	**P-value**	**Model 1[#] Adjusted SHR (95% IC)**	**P-value**	**Model 2[§] Adjusted SHR (95% IC)**	**P-value**
SPSS area (mm^2)	1.0007 (1.0004-1.0010)	**<0.0001**	1.0006 (1.0003-1.0010)	**<0.0001**	1.0005 (1.0003-1.008)	**<0.0001**

[#]Adjusted for age, gender, MELD score.

[§]Adjusted for age, gender, MELD score, decompensated cirrhosis, presence of high-risk varices.

MELD: model for end-stage liver disease; SHR: subhazard ratio; SMV: superior mesenteric vein; SPSS: spontaneous portosystemic shunt.

Manuscript number: DLD-20-1768

Supplemental Material Legend

Supplemental Material 1 - Flowchart of the patients' selection in our study

Supplemental Material 2 – Characteristics of SPSS in a cohort of ACLD patients

Supplemental Material 3 – Frequency of clinical events during follow-up according to SPSS presence

Supplemental Material 4 – Predictive role of SPSS presence independently from each prognostic stage of cirrhosis according to D'Amico

Supplemental Material 5 - Cumulative incidence function curves for hepatic decompensation risk according to prognostic stages of cirrhosis

Supplemental Material 6 - Coronal CT images demonstrate gastrorenal shunt (arrow in A), mesenteric varices (arrow in B) and meso-caval shunts (arrows in C).

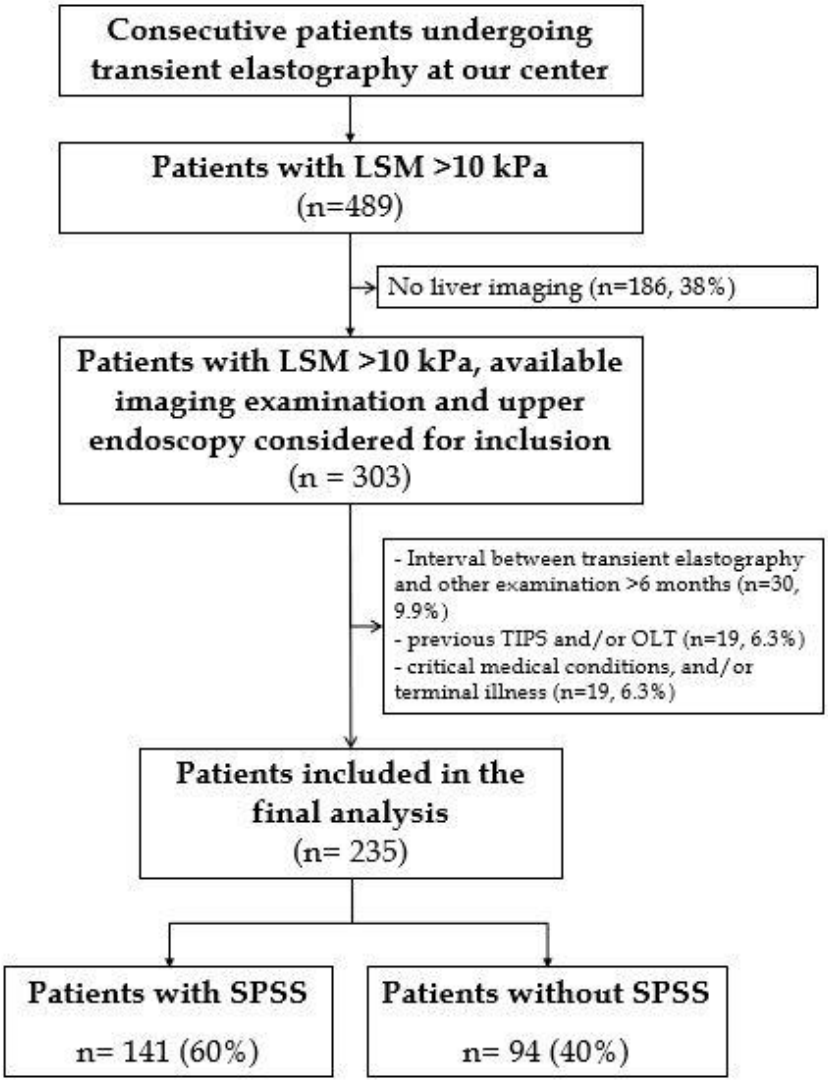
Supplemental Material 7 – Predictors of transplant-free survival in a cohort of ACLD patients

Supplemental Material 8 – Prognostic role of type and dimension of SPSS on the prediction of OLT or liver-related mortality

Supplemental Material 9 – Characteristics and prognostic role of gastroesophageal varices presence at imaging examination

Supplemental Material 10 – Cumulative incidence curves according to GEV presence for any hepatic decompensation

Supplemental Material 1 – Flowchart of the patients' selection in our study



Supplemental Material 2 – Characteristics of SPSS in a cohort of ACLD patients

SPSS type	**Number / Total of patients with SPSS (%)**	**Median diameter (mm)**
Any SPSS type	141	6 (4-10)
Gastrorenal	24 (17.02%)	7 (5-8)
Splenorenal	53 (37.59%)	7 (5-12)
Mesenteric Varices	11 (7.80%)	4 (4-5)
Meso (SMV)- caval	7 (4.96%)	8 (5-9)
Paraumbilical Vein	79 (56.04%)	4 (3-7)
Inferor epigastric vein	40 (28.37%)	5 (3-8)
Rectal Varices	15 (10.64%)	4 (3-4)
Mesorenal	3 (2.13%)	7 (2-9)
Uterine Varices/ Gonadic Vein	21 (14.89%)	6 (4-6)
Other	21 (14.89%)	6 (4-10)
>1 type of SPSS	83 (58.87%)	N/A

SMV: superior mesenteric vein; SPSS: spontaneous portosystemic shunt;

Supplemental Material 3 – Frequency of clinical events during follow-up according to SPSS presence

Clinical Event	**All patients (n=235)**	**Patients with SPSS (n=141)**	**Patients without SPSS (n=94)**	**P-value**
Number of hospitalizations	1 (0-1)	1 (0-1)	1 (0-1)	**0.053**
Hepatic decompensation	70 (29.79%)	54 (38.30%)	16 (17.02%)	**<0.0001**
Ascites	54 (22.98%)	42 (29.79%)	12 (12.77%)	**0.002**
Variceal bleeding	19 (8.09%)	16 (11.35%)	3 (3.19%)	**0.025**
Hepatic encephalopathy	21 (8.94%)	17 (12.06%)	4 (4.26%)	**0.040**
Spontaneous bacterial peritonitis	9 (3.83%)	8 (5.67%)	1 (1.06%)	0.071
Hepatorenal syndrome	5 (2.13%)	4 (2.84%)	1 (1.06%)	0.356
EV ligation	65 (27.66%)	51 (36.17%)	14 (14.89%)	**<0.0001**
Portal vein thrombosis	33 (14.04%)	25 (17.73%)	8 (8.51%)	**0.046**
Hepatocellular carcinoma	73 (31.06%)	48 (34.04%)	25 (26.60%)	0.227
Other Neoplasia	19 (8.09%)	9 (6.38%)	10 (10.64%)	0.241
TIPS	5 (2.13%)	3 (2.13%)	2 (2,13%)	1.000
Liver transplantation	25 (10.64%)	17 (12.06%)	8 (8.51%)	0.388
Death	31 (13.19%)	22 (15.60%)	9 (9.57%)	0.181

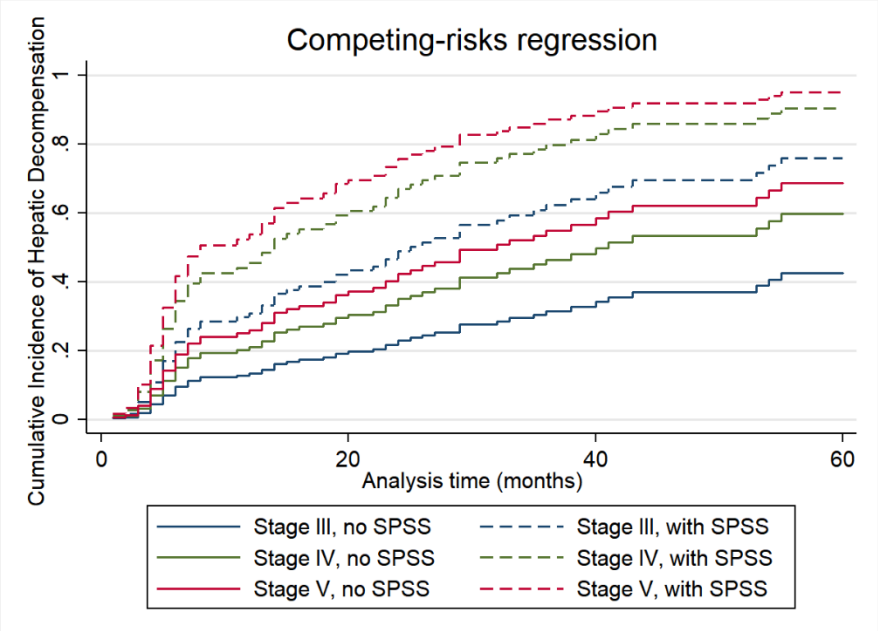
EV: esophageal varices; SPSS: spontaneous porto-systemic shunt; TIPS: transjugular portosystemic shunt

Supplemental Material 4 – Predictive role of SPSS presence for the prediction of decompensation is independent from each prognostic stage of cirrhosis according to D'Amico

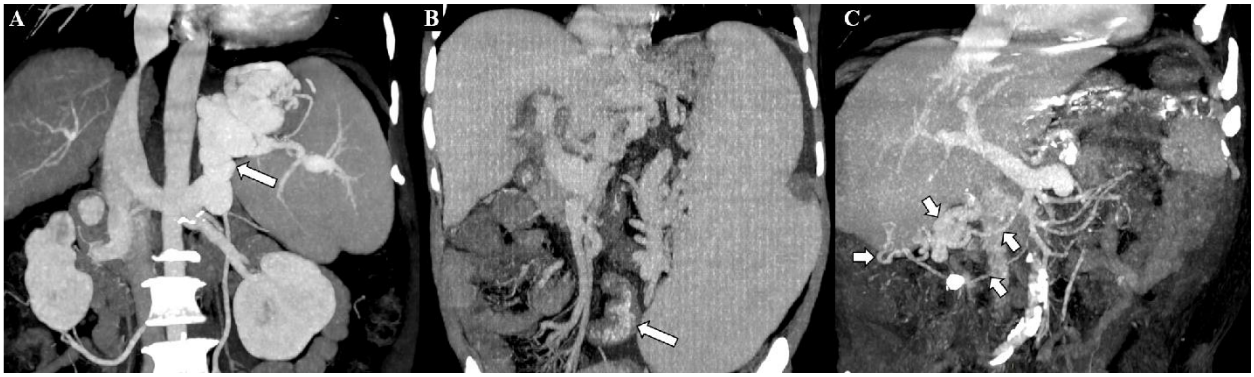
	Multivariate analysis Wald-chi2=103.77	
Variables	**SHR (95% IC)**	**P-value**
Radiological Data		
SPSS presence	2.476 (1.391-4.407)	0.002
Cirrhosis Prognostic stage		
Stage of Cirrhosis (vs stage I)	1	
Stage II	3.396 (1.006-11.466)	0.049
Stage III	14.674 (3.686-58.418)	<0.0001
Stage IV	23.323 (6.643-81.887)	<0.0001
Stage V	30.103 (9.239-98.084)	<0.0001

IC: interval of confidence; SHR: subhazard ratio; SPSS: spontaneous portosystemic shunts

Supplemental Material 5 - Cumulative incidence function curves for hepatic decompensation risk according to prognostic stages of cirrhosis



Supplemental Material 6 - Coronal CT images demonstrate gastrorenal shunt (arrow in A), mesenteric varices (arrow in B) and meso-caval shunts (arrows in C).



Supplemental Material 7 – Predictors of transplant-free survival in a cohort of ACLD patients

	Univariate analysis		Multivariate analysis	
Variables	**SHR (95%IC)**	**P-value**	**SHR (95%IC)**	**P-value**
Age	0.981 (0.962-1.000)	0.050		
ALD	1.911 (1.014-3.603)	**0.045**		
ACLD History				
Decompensated cirrhosis	2.328 (1.336-4.055)	**0.003**	2.362 (1.356-4.115)	**0.002**
Previous HCC	2.307 (1.326-4.013)	**0.003**	2.742 (1.619-4.643)	**<0.0001**
Previous EV ligation	1.737 (0.903-3.343)	0.098		
Stage of cirrhosis	1.376 (1.129-1.677)	**0.002**		
Laboratory Test				
Albumin (g/dL)	0.493 (0.233-1.044)	0.065		
Bilirubin (mg/dL)	1.373 (1.268-1.487)	**<0.001**	1.338 (1.214-1.475)	**<0.0001**
MELD score	1.099 (1.015-1.190)	**0.020**		
Child-Pugh score	1.432 (1.098-1.869)	**0.008**		
Child-Pugh Class B	2.721 (1.485-4.984)	**0.001**		
TE evaluation				
LSM (kPa)	1.025 (1.006-1.044)	**0.010**		
Radiological Data				
SPSS presence	1.863 (1.003-3.457)	**0.049**		
Portal vein thrombosis	2.391 (1.200-4.766)	**0.013**		
Ascites	1.752 (0.985-3.116)	0.056		
			Wald-chi2= 97.4	

ACLD: advanced chronic liver disease; ALD: alcohol-related liver disease; HCC: hepatocellular carcinoma; LSM: liver stiffness measurement; MELD: Model for end-stage-liver-disease; SPSS: spontaneous portosystemic shunts; SHR: subhazard ratio; TE: transient elastography.

Supplemental Material 8 – Prognostic role of type and dimension of SPSS on the prediction of OLT or liver-related mortality

SPSS type	**Unadjusted SHR (95% IC)**	**P-value**	**Model 1[#] Adjusted SHR (95% IC)**	**P-value**	**Model 2[§] Adjusted SHR (95% IC)**	**P-value**
Gastrorenal	2.553 (1.280-5.091)	**0.008**	2.706 (1.386-5.283)	**0.004**	2.275 (1.127-4.592)	**0.022**
Splenorenal	1.330 (0.691-2.560)	0.393	1.104 (0.540-2.257)	0.786	1.104 (0.561-2.174)	0.775
Mesenteric Varices	2.150 (0.724-6.388)	0.168	1.484 (0.439-5.025)	0.525	1.054 (0.284-3.908)	0.937
Meso (SMV)- caval	1.698 (0.359-8.030)	0.504	1.821 (0.378-8.774)	0.455	2.746 (0.677-11.129)	0.157
Paraumbilical Vein	1.279 (0.724-2.259)	0.396	1.231 (0.707-2.143)	0.463	1.043 (0.579-1.877)	0.889
Inferor epigastric vein	1.915 (1.033-3.550)	**0.039**	1.735 (0.944-3.190)	0.076	1.435 (0.775-2.656)	0.250
Rectal Varices	2.218 (0.830-5.926)	0.112	1.902 (0.717-5.048)	0.197	1.906 (0.664-5.470)	0.231
Mesorenal	1.564 (0.246-9.934)	0.636	1.288 (0.186-8.915)	0.797	1.457 (0.265-8.002)	0.665
Uterine Varices/ Gonadic Vein	1.676 (0.694-4.050)	0.251	1.651 (0.681-4.002)	0.267	1.225 (0.459-3.266)	0.686
Other	1.264 (0.519-3.077)	0.606	1.294 (0.513-3.263)	0.586	1.251 (0.452-3.467)	0.666
SPSS diameter	**Unadjusted SHR (95% IC)**	**P-value**	**Model 1[#] Adjusted SHR (95% IC)**	**P-value**	**Model 2[§] Adjusted SHR (95% IC)**	**P-value**
0-8 mm	1.939 (1.007-3.733)	**0.047**	1.962 (1.035-3.719)	**0.039**	1.671 (0.842-3.214)	0.142
>8 mm	1.715 (1.007-3.733)	0.183	1.386 (1.628-3.059)	0.419	1.175 (0.555-2.488)	0.674

SHR: subhazard ratio; SMV: superior mesenteric vein; SPSS: spontaneous portosystemic shunts; TE: transient elastography.

Supplemental Material 9 – Characteristics and prognostic role of gastro-esophageal varices presence at imaging examination

PREDICTION OF HEPATIC DECOMPENSATION								
GEV type	**Number (%)**	**Diameter (mm)**	**Unadjusted SHR (95% IC)**	**P-value**	**Model 1[#] Adjusted SHR (95% IC)**	**P-value**	**Model 2[§] Adjusted SHR (95% IC)**	**P-value**
Any GEV	174 (74%)	4 (3-5)	3.074 (1.520-6.215)	**0.002**	2.6777 (1.304-4.497)	**0.007**	3.122 (1.270-7.678)	**0.013**
Para-esophageal Varices	90 (38.30%)	4 (3-6)	3.019 (1.890-4.825)	**<0.0001**	2.735 (1.661-4.503)	**<0.0001**	2.606 (1.548-4.389)	**<0.0001**
Esophageal Varices	102 (43.4%)	3 (2-4)	3.290 (2.019-5.360)	**<0.0001**	3.029 (1.815-5.056)	**<0.0001**	2.319 (1.324-4.059)	**0.003**
Posterior Gastric Vein	56 (23.83%)	4 (3-4)	1.365 (0.825-2.258)	0.225	1.256 (0.753-2.094)	0.383	0.923 (0.566-1.505)	0.747
Short Gastric Vein	56 (23.83%)	3 (3-4)	1.345 (0.808-2.237)	0.254	1.322 (0.790-2.213)	0.288	1.437 (0.817-2.527)	0.208
Left Gastric Vein	101 (42.9%)	5 (4-7)	1.931 (1.212-3.076)	**0.006**	1.722 (1.055-2.810)	**0.030**	1.705 (1.036-2.807)	**0.036**

[#]Adjusted for age, gender, MELD score.

[§]Adjusted for age, gender, MELD score, decompensated cirrhosis, presence of high-risk varices.

Supplemental Material 10 – Cumulative incidence curves according to GEV presence for any hepatic decompensation