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Article type : Original Articles

Incidence, predictive factors and clinical significance of development of portal vein thrombosis in cirrhosis: a prospective study.

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The authors do not have conflicts of interest to declare.

There was no financial support for this study.

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Abstract

Background & Aims: The role of portal vein thrombosis (PVT) in the natural history of cirrhosis is controversial. There are few prospective studies validating risk factors for development of PVT.

We analyzed the incidence, factors associated with PVT development and its influence on cirrhosis decompensations and orthotopic liver transplant (OLT) free survival.

Methods: In this prospective observational study between January 2014 and March 2019, 445 consecutive patients with chronic liver disease were screened and finally 241 with cirrhosis included. Factors associated with PVT development and its influence on cirrhosis decompensations and OLT free survival by time dependent covariate coding were analyzed.

Results: Majority of patients belonged to Child-Pugh class A 184 (76.3%) and average MELD score was 10±5. Previous cirrhosis decompensations occurred in 125 (52.1%), 63 (26.1%) were on NSBB and 59 (27.2%) had undergone banding for bleeding prophylaxis. Median follow-up was 29 (1–58) months. Cumulative incidence of PVT was 3.7% and 7.6% at 1 and 3 years. Previous decompensation of cirrhosis and and low platelet counts but not NSBB independently predicted development of PVT. During follow-up, 82/236 (34.7%) patients developed cirrhosis decompensations. OLT free survival was 100% and 82.8% at 3 years, with and without PVT respectively. MELD score, but not PVT, independently predicted cirrhosis decompensations (HR 1.14; 95%C.I.:1.09–1.19) and OLT free survival (HR 1.16;95%C.I.:1.11–1.21).

Conclusion: Previous decompensations of cirrhosis and thrombocytopenia predict PVT development in cirrhosis suggesting a pathophysiologic role for severity of portal hypertension. PVT development did not independently predict cirrhosis decompensations or lower OLT free survival.

Keywords: Portal vein thrombosis, diuretics, thrombocytopenia, cirrhosis, OLT free survival

Lay summary:

In this large prospective study involving mostly patients with compensated cirrhosis, previous decompensations of cirrhosis and thrombocytopenia predicted development of portal vein thrombosis (PVT) suggesting a pathophysiologic role of severity of portal hypertension.

PVT though associated with higher risk of decompensation of cirrhosis during follow-up was not an independent predictive factor of decompensations of cirrhosis or of lower orthotopic liver transplant free survival.

Abbreviations

PVT – Portal vein thrombosis

SMV – Superior mesenteric vein

CSPH – Clinically significant portal hypertension

OLT – Orthotopic liver transplant

NSBB – Nonselective beta-blocker

HCC – Hepatocellular carcinoma

TE – Transient elastography

US – Ultrasound

TIPS – Transjugular intra-hepatic portosystemic shunt

BMI – Body mass index

COPD – Chronic obstructive pulmonary disease

PPIs – Proton pump inhibitors

PH – Portal hypertension

CT – Computerized tomography

MRI – Magnetic resonance imaging

SD – Standard deviation

ESLD – End stage liver disease

LMWH – Low molecular weight heparin

LEV – Large esophageal varices

VWF – Von Willebrand factor

Introduction

Portal vein thrombosis (PVT) is defined as thrombosis involving the portal vein which may also involve the splenic or superior mesenteric veins (SMV)[1]. Although considered rare, an autopsy study showed a prevalence of PVT of 1 in 100[2]. PVT prevalence in cirrhosis varies between 1 and 25% with higher prevalence linked to advanced cirrhosis[3,4,5,6,7,8].

Cirrhosis is characterized by rebalanced hemostasis[9]. This rebalanced hemostasis is fragile and dynamic with endothelial dysfunction and bacterial translocation associated with pro-thrombotic effects and bacterial infections or sepsis associated with bleeding[6,10,11,12]. The rebalanced hemostasis explains the higher incidence of PVT, deep vein thrombosis and thromboembolic events in cirrhosis[5,13].

Clinically significant portal hypertension (CSPH) and MELD independently predict higher risk of decompensation of cirrhosis[14]. PVT is associated with higher post orthotopic liver transplant (OLT) mortality but has no effect on wait-list mortality[15] or long term post transplant mortality[3,16,17,18]. The deleterious effect of PVT on peritransplant morbidity and post transplant mortality is related to the extent of PVT and occlusive PVT[15,19] as has also been confirmed in the recent meta-analysis by Zannetto A et al[20]. Development of PVT has been found to be associated with severity of cirrhosis but not with progression of liver disease and there was therefore no evidence of PVT as a cause of decompensation of cirrhosis or

mortality[7]. Recently, nonselective beta-blockers (NSBB) were found to independently predict development of PVT[21]. However, the confidence intervals for this association were wide and the authors could not adequately explain this association specially because there was no association between reduced portal vein flow velocity and heart rate with higher risk of PVT in patients who actually received NSBB[21].

In this prospective observational study we evaluated the incidence and predictors of development of non-tumoral PVT in cirrhosis. We also aimed to determine the clinical implications of PVT, namely its role if any on development of new decompensations of cirrhosis and influence on OLT free survival.

Patients and Methods

Consecutive patients with chronic liver disease were included in this prospective observational study conducted between 1stJanuary 2014 and 30th March 2019. Inclusion criteria included: Age >18 and <75 years, well characterized cirrhosis with compatible clinical, imaging, liver transient elastography (TE) and laboratory values[22]. Exclusion criteria were: anticoagulation at study inclusion; HCC at ultrasound (US) screening; pregnancy; prior liver transplant; prior transjugular intra-hepatic portosystemic shunt (TIPS)/surgical shunt; myeloproliferative diseases; systemic neoplasia; psychomotor handicap. We analyzed clinical etiological features of chronic liver disease, the ultrasound features of chronic liver disease and spleen size, TE, endoscopic and blood laboratory tests of all patients in the study. Non-cirrhotic portal hypertension was systematically eliminated by the analysis of the above-mentioned factors. In fact, two patients both with prior HIV infection, had low transient elastography values (< 10KPa) with one labelled as cryptogenic cirrhosis and the other with chronic viral hepatits B with ongoing treatment with tenofovir. Both had been exposed to first

generation anti HIV drugs and both had prior history of variceal bleed with features of desproportionate portal hypertension with large spleens and preserved liver function. We excluded both these patients.

Studies suggest a prevalence of PVT between 1 and 25% without clear stratification of prevalence according to cirrhosis severity although there is an association with advanced cirrhosis[3,4,5,6,7,8]. The sample size calculated for an estimated incidence of PVT of 10%, patient drop out rate of 10%, confidence interval of 95% and precision of 5% was 280 patients.

Patients had to have US Doppler within 6 months prior to study inclusion without evidence of PVT or HCC. Due to inter and intra-observor and inter equipment variability, the portal vein flow velocity was not considered[23]. Informed consent was obtained from all patients as well as approval from institutional ethics committee.

Baseline evaluation

Clinical data regarding cirrhosis etiology, body mass index (BMI), cardiovascular comorbidities and medications including NSBB, diuretics, statins, antidiabetic agents and proton pump inhibitors (PPIs) were evaluated and their relationship with development of PVT was analyzed. NSBB and diuretics were not considered as time dependent variables. Alcohol intake >60g/day in men and >30g/day in women was registered. Prior endoscopic banding of varices, endoscopic manifestations of portal hypertension (PH) and when available, liver TE values closest to study inclusion were noted.

Follow-up

Patients were followed up regularly and data related to decompensations of cirrhosis, death/OLT till 30th March 2019 noted. Laboratory data were recorded at semestral outpatient visits. Patients with large esophageal and/or gastric varices were managed according to AASLD guidelines and management of complications of cirrhosis were based on international guidelines[24,25,26,27].

Portal vein thrombosis

PVT was suspected where solid endoluminal material was detected in the main trunk of the portal vein and/or its branches with/without extension into the splenic or SMV and confirmed on Doppler study. Patients with suspected PVT underwent triphasic abdominal computed tomography (CT) or magnetic resonance imaging (MRI) to confirm the diagnosis[6,28]. Partial thrombosis was evaluated as non-occlusive endoluminal material involving <50% / >50% of vascular lumen. Occlusive PVT was defined by absence of blood flow in a trombosed segment of the splanchnic circulation. The date of first abdominal imaging study detecting PVT was defined as time zero and used to assess incidence of PVT. The extent of PVT was defined by involvement of portal vein trunk and/or branches, splenic vein and/or SMV thrombosis. PVT within 6 months of HCC detection was considered related to HCC and was not considered for subsequent analysis.

Decompensations of cirrhosis

Patients were evaluated for decompensations of cirrhosis in between outpatient visits upto date of last contact. Decompensations of cirrhosis were defined as variceal bleeding, ascites, hepatic encephalopathy or jaundice. Ascites was defined by presence of signs and symptoms of ascites or free intraperitoneal fluid on US. Jaundice was defined by serum total bilirubin

values of ≥3mg/dL and hepatic encephalopathy by temporospatial desorientation, flapping or both in absence of other possible causes. Subclinical encephalopathy was not investigated. Variceal bleeding was defined according to the Baveno IV and VI criteria[29,30]. Factors at baseline associated with development of any decompensation of cirrhosis were evaluated.

Death or orthotopic liver transplantation

In patients who died or underwent OLT, the main cause of death/OLT was noted. Factors at baseline associated with death/OLT were evaluated.

Statistical analysis

Continuous variables were assessed by Kolmogorov-Smirnov test for normality and expressed as mean±standard deviation (SD) or median with range as applicable. Categorical variables were expressed as counts and percentages. Student´s T test or Mann-Whitney U test for continuous variables and χ^2 or Fisher´s exact test were used for categorical variables as applicable. Follow-up was calculated from the time of study inclusion (1stJanuary 2014) to patient status at last contact (30stMarch 2019) (Alive/death/OLT).

Cumulative incidence of non-tumoral PVT, overall OLT free survival and OLT free survival in patients who did and did not develop non-tumoral PVT was estimated in a competing risks setting where death/OLT competed with the event of interest (PVT). Cox proportional hazards regression model with backward stepwise elimination (significance levels of $p<0.05$ for inclusion and $p\geq0.1$ for exclusion) was used to determine factors at baseline associated with development of non-tumoral PVT, cirrhosis decompensations and OLT free survival. Ninety-five percent confidence intervals (95% CI) were computed. Multivariate models included variables significantly associated with outcome in univariate analysis at a level of significance of $p<0.1$. Time dependent covariate coding for development of non-tumoral PVT was used to assess the impact of PVT on cirrhosis decompensations and OLT free survival.

Data analysis was performed with SPSS, IBM® version 21. P values of <0.05 were considered statistically significant.

Results

Initially, 445 patients with chronic liver disease were evaluated, of which 185 were excluded (Figure 1). Out of the remaining 260 patients, an additional, 19 were excluded either due to inadequate follow-up duration (<6 months) or lack of follow-up imaging studies within the last 12 months. Finally, the study cohort included 241 patients with well characterized cirrhosis and adequate follow-up. Baseline clinical, imaging, endoscopic and laboratory features are highlighted in table 1.

Mean age was 59 ± 10 years and 184 (76.3%) were males. Weight excess or obesity was noted in 157 (65.1%) patients and one or more cardiovascular comorbidities were present in 124 (51.7%) patients. Alcohol with or without chronic hepatitis C or B was a cause of cirrhosis in 150 (62.2%) of patients. Viral hepatitis C or B contributed to cirrhosis in 100 (41.5%) patients and all patients received either direct acting antiviral therapy in case of viral hepatitis C and antiviral therapy when indicated in viral hepatitis B. Majority of patients belonged to Child-Pugh class A 184 (76.3%) and average MELD score was 10 ± 5 points. There was a history of previous decompensation of cirrhosis in 125 (52.1%) and 63 (26.1%) patients were on NSBB for primary or secondary prophylaxis of variceal bleeding. Additionally, 59 (27.2%) patients had undergone endoscopic banding for prophylaxis of variceal bleeding prior to study inclusion. Esophageal/gastric varices were present in 139/221 (62.9%) patients and ascites at US screening was present in 62 (25.8%) patients.

The median follow-up was 29 (1 – 58) months. After study inclusion, four patients died, 3 of these patients, within the same hospitalization after study inclusion, and one additional patient underwent OLT for end stage liver diease (ESLD) within the first 6 months and were

not considered for further evaluation of incidence of non-tumoral PVT, HCC and decompensations of cirrhosis. During follow-up, 6.8% (16/236) patients developed HCC.

Incidence and risk factors for non-tumoral PVT

PVT was detected by abdominal US with Doppler and confirmed with CT scan in 18 patients during follow-up. In three patients, there was concomitant HCC with tumoral invasion of the portal vein. These three patients were not considered for further evaluation. Therefore, 15/233 (6.4%) patients developed non-tumoral PVT. Out of these, only two patients had occlusive PVT. Concomitant portal hypertension complications at the time of diagnosis of PVT were present in 10 (66.7%) patients. All patients had features of acute PVT and the extent of PVT is shown in Supplementary table 1. The large group of patients with chronic liver disease without well defined cirrhosis (n = 82) which were excluded from the study sample were primarily patients with chronic viral hepatitis C with liver transient elastography values (>15KPa) before antiviral therapy and who after antiviral therapy had follow-up liver transient elastography values < 10KPa, platelet count>150 x10^9/L and no unequivocal evidence of cirrhosis or portal hypertension on abdominal ultrasound and/or endoscopy. None of these patients developed PVT.

The cumulative incidence of non-tumoral PVT was 3.7% and 7.6% at 1 and 3 years (Figure 2). Factors at baseline associated with development of non-tumoral PVT were: MELD score, NSBB, need for diuretics, previous decompensation of cirrhosis, presence of esophageal and / or gastric varices, bipolar spleen diameter and thrombocytopenia (Supplementary table 2). Factors associated with development of non-tumoral PVT by Cox univariate regression analysis are shown in supplementary table 3. On multivariate analysis, only previous decompensation of cirrhosis (HR 6.77, 95% C.I. 1.21-37.98, p=0.03) and platelet count (HR 0.97, 95% C.I. 0.96–0.99, p=0.002) independently predicted development of non-tumoral PVT (Table 2).

After PVT detection, anticoagulation was started in 10/15 (66.7%) patients ((varfarin (n = 7), low molecular weight heparin (LMWH) (n = 3)). Anticoagulation was not started in 4 patients due to severe thrombocytopenia and in one patient due to unknown reason. Among the 10 patients who received anticoagulation, 7 had adequate follow-up imaging with PVT recanalization occurring in 5 (71%) (Partial (n = 3); total (n = 2)) patients, no change in 1 patient and PVT progression occurring in 1 patient. Among the 5 patients who did not receive anticoagulation, 4 patients had adequate follow-up imaging, and PVT progression was noted in 3 (75%) and no change in 1 patient. None of the patients who developed PVT died during the study period.

Incidence and risk factors for decompensations of cirrhosis

During follow-up, 82 (34.7%) patients developed decompensation of cirrhosis with ascites in 72 (30.5%), jaundice in 28 (11.9%), hepatic encephalopathy in 21 (8.9%) and variceal bleeding in 8 (3.4%). Two or more decompensations of cirrhosis were registered in 55 (22.8%) of patients during follow-up.

Factors at baseline associated with decompensation of cirrhosis were Child-Pugh and MELD scores, active alcohol intake at study inclusion, psychiatric comorbidities, NSBB, PPIs, need for diuretics, previous decompensations of cirrhosis, presence of esophageal and/gastric varices, bipolar spleen diameter, lower hemoglobin levels, and thrombocytopenia. Antiviral therapy significantly decreased cirrhosis decompensations. (Supplementary table 4).

Factors associated with decompensation of cirrhosis by Cox univariate regression analysis are shown in supplementary table 5. Non-tumoral PVT evaluated as a time dependent variable doubled the risk of decompensation of cirrhosis (HR 2.16; 95% C.I. 1.17–3.97, p=0.014). However, on multivariate analysis, only MELD score (HR 1.14, 95% C.I. 1.09–1.19,

p<0.001); male gender (HR 2.31, 95% C.I. 1.23–4.33, p=0.009); ascites at baseline ultrasound (HR 2.62, 95% C.I. 1.54–4.46, p <0.001), hemoglobin (HR 0.86, 95% C.I. 0.76–0.97, p=0.016) and platelet count (HR 0.99, 95% C.I. 0.99–1, p=0.049 independently predicted decompensation of cirrhosis. Antiviral therapy was associated with a trend for lower risk of decompensations of cirrhosis (HR 0.62, 95% C.I. 0.38–1.03, p=0.063 (Table 2).

Mortality and factors associated with lower OLT free survival

During follow-up, 38/241 (15.7%) patients died. The main cause of death were septic complications in ESLD in 18 patients. Additionally, 7 patients underwent OLT for ESLD (Supplementary table 6). Fifteen patients were lost after at least 12 months of follow-up and these were censored at the date of last contact.

The cumulative OLT free survival was 90.7% and 82.8% at 1 and 3 years (Figure 3). The significantly, better OLT free survival in patients who developed non-tumoral PVT may have been due to the effect of anticoagulant therapy which was started in 10/15 (67.7%) patients. Factors at baseline associated with death/OLT included male gender, alcoholic etiology of cirrhosis, MELD scores, active alcohol intake at study inclusion, need for diuretics, previous decompensation of cirrhosis, ascites at study inclusion, splenomegaly, liver transient elastography values and lower hemoglobin and platelet counts (Supplementary table 7). Factors at baseline associated with death/OLT by univariate Cox regression analysis are shown in supplementary table 8. There was no influence of PVT on OLT free survival.

On multivariate analysis, male gender (HR 3.57, 95% C.I. 1.30–9.84, p=0.014), MELD score (HR 1.16, 95% C.I. 1.11–1.21, p<0.001), alcohol intake (HR 3.05, 95% C.I. 1.59–5.84, p=0.001) and hemoglobin values (HR 0.72, 95% C.I. 0.63–0.83, p<0.001) were independently associated with death/OLT (Table 2).

Discussion

This prospective observational study involving a majority of patients with compensated cirrhosis but with clinical features of CSPH, detected a cumulative incidence of non-tumoral PVT of 3.7% and 7.6% at 1 and 3 years respectively. Previous decompensation of cirrhosis and thromboctyopenia predicted development of non-tumoral PVT. PVT was partially occlusive at diagnosis in 13/15 (86.7%) patients and although associated with, was not an independent predictor of new decompensations of cirrhosis and did not influence OLT free survival.

The cumulative incidence of non-tumoral PVT of 3.7% at 1 year and 7.6% at 3 years is similar to the previously reported incidence of 4.6% at 1 year and 8.2% at 3 years[7] and that of 3.2% in the study by Francoz et al[4]. Additionally, in 86.7% (13/15) patients, PVT was partial, similar to that in the study by Maruyama et al, where *de novo* PVT was partial in 73.8% patients[31] and the french study where 85.5% (101/118) patients had partial PVT[7] and slightly lower than the 95% partial PVT in a large italian multicentre study[5].

The pathophysiology of PVT in cirrhosis is explained by Virchow´s triad: venous stasis, hypercoagulability and endothelial dysfunction[10]. The most plausible explanation for PVT development is reduced portal flow velocity and stagnation of blood in the splanchnic circulation due to PH[3,8,31]. Portal vein blood flow velocity is significantly lower in Child-Pugh B and C compared to Child-Pugh A cirrhosis patients[32]. Grade of ascites and larger spleen size have been reported to predict development of PVT[31]. Zocco et al showed that patients with cirrhosis who developed PVT had significantly lower platelet counts at baseline. In that study, portal vein flow velocity < 15cm/second was the only factor which independently predicted PVT development[8]. However, despite guidelines to decrease inter-observor variability, there is considerable variability in Doppler evaluation of portal flow in

the same patient during longitudinal follow-up as well as in between observors, making it difficult to utilize portal blood flow velocity as a reliable predictor of development of PVT[7,23,33].

We found that severity of cirrhosis and surrogate clinical markers of CSPH are associated with higher risk of development of PVT. Only previous decompensation of cirrhosis and thrombocytopenia independently predicted development of non-tumoral PVT, indirectly reflecting the pathophysiologic role of severity of portal hypertension in the development of PVT. However, these findings have to be interpreted with caution due to the low incidence of PVT in our study.

In several retrospective, cross-sectional and prospective studies, the severity of cirrhosis has been associated with development of PVT[6,7,8,31,34]. Factor VIII levels are elevated in cirrhosis and independently predict development of PVT[35]. Recently, regular treatment with NSBB was found to independently predict higher risk of development of PVT[21]. NSBB may reduce portal blood inflow and pressure which aggravates stagnation of blood in the splanchnic circulation, contributing to PVT development[28]. However, in the study by Nery et al, there was no association between decreased portal blood flow velocity and heart rate and higher risk of developing PVT in patients on NSBB[21]. NSBBs are indicated for prophylaxis of variceal bleeding in patients with large esophageal varices (LEVs) and/or gastric varices, and may only identify patients with greater severity of portal hypertension and thus higher risk of developing PVT. In our study, NSBB, although associated with, was not an independent predicotor of development of PVT.

LEVs have been shown to independently predict PVT development[7]. In our study, LEVs were present in 64 (29%) patients. However, 59 (26.7%) patients had undergone endoscopic banding and 63 (26.1%) were on NSBBs prior to study inclusion, which may explain why,

although there was a significant association, the presence of esophageal and/or gastric varices did not independently predict PVT development. Prior variceal bleeding has been found to independently predict PVT development[4] which was however not confirmed in our study.

During follow-up, 82/236 (34.7%) patients developed decompensations of cirrhosis. PVT although associated with, did not independently predict decompensation of cirrhosis. This may be due to two reasons: (1) In advanced cirrhosis, development of PVT may have little impact on portal pressure or flow due to development of extensive portosystemic collaterals[3]; (2) Two thirds of patients developing *de novo* PVT have partial thrombosis which may not significantly compromise blood supply to the liver[7].

Obesity has been found to independently predict decompensations of cirrhosis[7]. However, we did not find a significant association between BMI and higher risk of decompensation of cirrhosis probably due to shorter follow-up period in our study compared to previous studies[7,36].

Changes in hemostatic balance are pronounced in patients with advanced cirrhosis[9]. Von Willebrand factor (VWF-Ag) and factor VIII/protein C ratio independently predict decompensations and mortality in patients with cirrhosis[37]. The development of intra-hepatic microthrombi could explain aggravation of PH and subsequent decompensation of cirrhosis[38]. In our study, male gender, MELD score, ascites at baseline, lower hemoglobin and thrombocytopenia independently predicted decompensation of cirrhosis confirming that the severity of liver disease and of portal hypertension are the main causes of decompensation of cirrhosis[14].

During follow-up, 38 (15.7%) patients died. Additionally, 7 patients underwent OLT for ESLD. The cumulative OLT free survival was 90.7% at 1 year and 82.8% at 3 years. Non-tumoral PVT did not influence mortality as has been previously reported[3,31,39.] The lack of

effect of PVT on OLT free survival is probably due to the fact that majority of de novo non-tumoral PVT had partial thrombosis[7,31] as well as the fact that anticoagulation was started in majority of these patients. In our study, male gender, MELD score, alcohol intake and lower hemoglobin values independently predicted lower OLT free survival as has been reported[14,22,40,41].

Our study has some limitations. Despite the large number of patients intially evaluated, we did not achieve the estimated sample size. In addition, although 50% of patients had prior decompensations of cirrhosis, only one fourth of patients patients belonged to Child-Pugh class B or C. Additionally, we could not analyze the applicability of portal blood flow velocity measured by US Doppler due to variations in equipment and inter and intra observor evaluations.The relatively short follow-up period and the fact that two thirds of patients in the study belonged to Child-Pugh class A may explain the low incidence of PVT, the high OLT free survival as well as the lack of association of BMI and cardiovascular comorbidities with decompensations of cirrhosis. Despite these limitations, this study has several strengths. This was a large prospective observational study, with the majority of patients having clinical and endoscopic features of CSPH allowing generalization of study results to patients with more advanced cirrhosis. Two thirds of patients had weight excess and obesity with half having one or more cardiovascular comorbidities reflecting the growing importance of obesity and metabolic syndrome in patients with cirrhosis.

In conclusion, in patients with cirrhosis, only previous episode of decompensation of cirrhosis and low platelet count independently predicted increased risk of development of non-tumoral PVT. The majority of patients who develop non-tumoral PVT have partial thrombosis and it is not an independent predictor of cirrhosis decompensation or lower OLT free survival.

Acknowledgements:

Our sincere thanks and appreciation to the following:

Professor Dominique Valla for his expert advice and constructive criticism of this manuscript.

Dr. Teresa Rodrigues for her help in calculation of the sample size and reviewing the data analysis.

Mr. Álvaro Branco for his help in providing patient files in the study.

Ms. Carla Gomes for organizing abdominal doppler ultrasounds of the study patients.

Ms. Angela Afonso, Ms. Susana Ferreira and Ms. Fabiana Rodrigues for managing blood samples of patients in the biobank at the Instituto de Medicina Molecular.

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Table 1. Baseline demographic, clinical and laboratory features of the study sample.

		Study cohort (n = 241)	
		Mean / N	SD / %
Age (years)		59	10
Male gender		184	76.3%
BMI (kg/m2) (n =214)		27.66	4.91
BMI class	18.5 to ≤ 24.9kg/m2	66	29.6%
	≥25 to < 29.9Kg/m2	107	48.0%
	≥ 30kg/m2	50	22.4%
Time from diagnosis of cirrhosis to inclusion in study (months)		59	64
Etiology of cirhosis	Alcohol	104	43.3%
	Alcohol + viral	46	19.2%
	Viral	54	22.5%
	Others	23	9.6%
	NASH	13	5.4%
Child-Pugh score		6	2
Child Pugh class	A	184	76.3%
	B	31	12.9%
	C	26	10.8%
MELD score		10	5
Active alcohol intake at study inclusion		31	13.0%
Any psychiatric comorbidity		47	20.5%
Cardiovascular comorbidities		124	51.7%
Arterial hypertension		78	32.5%
Diabetes mellitus		70	29.2%
Dyslipidemia		42	17.5%
Chronic obstructive pulmonary disease		17	7.0%
Cardiac ischemia		13	5.4%
Concomitant medication		166	73.5%
Nonselective beta blockers		63	26.1%
	Propranolol	51	21.3%
	Carvedilol	12	5.0%
Statins		36	15.1%
Antiviral therapy		94	39.0%
Diuretics		82	34.2%
Antidiabetic agentes		67	27.9%
Proton pump inhibitor		78	32.4%
Previous decompensation of cirrhosis		125	52.1%
Prior variceal bleed		40	32.0%
Prior ascites		107	85.6%
Prior hepatic encephalopathy		29	23.2%
Prior jaudice		22	17.6%
Prior endoscopic banding of varices		59	27.2%

Any esophageal or gastric varices (n=221)		139	62.9%
Esophageal varices		138	62.4%
Size of esophageal varices	**Small**	73	52.5%
	Large	64	46.0%
	Not mentioned	1	.7%
Gastric varices		11	5.0%
Type of gastric varices	**GOV1**	3	27.3%
	GOV2	3	27.3%
	IGV1	5	45.5%
Portal hypertensive gastropathy		96	43.4%
Portal hypertensive gastropathy grade	**Mild**	72	75.0%
	Severe	24	25.0%
Splenomegaly (≥13 cm)		137	57.3%
Spleen bipolar diameter (cm)		13.84	2.46
Ascitis at baseline ultrasound		62	25.8%
Liver transient elastography (Kpa) (n=135)		33.69	19.39
Hemoglobin (g/dL)		13.4	2.0
Platelets x 10^9		117	59
Platelet count <150 x 10^9		180	75.0%
Prothrombin time (Secs)		13.9	2.9
INR		1.2	.2
Glucose (mg/dL)		121	59
Creatinine (mg/dL)		.9	.8
Urea (mg/dL)		40	27
Sodium (mEq/L)		139	4
AST (U/L)		49	40
ALT (U/L)		43	33
GGT (U/L)		130	146
Alkaline phosphatase (U/L)		113	64
Total bilirubin (mg/dL)		1.7	2.7
Direct bilirubin (mg/dL)		.7	.7
Total serum protein (g/dL)		7.2	.8
Serum albumin (g/dL)		3.9	.7
Gama globulin (g/dL)		1.6	.6
Total cholesterol (mg/dL)		153	39
Triglycerides (mg/dL)		101	75

BMI - Body mass index; NASH – Non alcoholic steatohepatitis; GOV 1 - Gastroesophageal varices 1; GOV 2 - Gastroesophageal varices 2; IGV1 - Isolated gastric varices; INR – International normalized ratio

Table 2. Multivariate analysis to determine predictive factors for non-tumoral PVT, decompensations of cirrhosis and death or OLT.

		95.0% CI		
	HR	Lower	Upper	p value
Development of non tumoral PVT				
Previous decompensation of cirrhosis	6.771	1.207	37.977	.030
Platelet count x 10^9	.972	.955	.990	.002
Decompensation of cirrhosis				
Male gender	2.306	1.227	4.332	.009
MELD score	1.137	1.086	1.190	<0.001
Antiviral therapy	.622	.377	1.026	.063
Ascites at baseline ultrasound	2.624	1.544	4.457	<0.001
Hemoglobin (g/dL)	.861	.761	.973	.016
Platelet count x 10^9	.996	.992	1.000	.049
OLT or death				
Male gender	3.574	1.298	9.839	.014
MELD score	1.161	1.110	1.213	<0.001
Active alcohol intake at study inclusion	3.049	1.592	5.837	.001
Hemoglobin (g/dL)	.723	.630	.831	<0.001

CI - Confidence interval; HR - Hazard ratio. PVT - Portal vein thrombosis. OLT - Orthotopic liver transplantation

Fig. 1. Flow chart of patients in the study.

Fig. 2. Incidence of non-tumoral PVT in cirrhosis.

Fig. 3. Overall OLT free survival in patients with cirrhosis.

Figure 1. Flow chart illustrating patients evaluated and finally included in the study.