UNIVERSIDADE DE LISBOA

Faculdade de Medicina

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Tese especialmente elaborada para obtenção de grau de Doutor em Medicina, especialidade em Gastrenterologia

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Abstract

Cirrhosis is considered a hipercoagulable state and there is strong evidence that the incidence of nontumoral portal vein thrombosis (PVT) increases in advanced cirrhosis. There is conflicting data regarding the impact of PVT on the natural history of cirrhosis. The safety of anticoagulation especially in patients with advanced cirrhosis and PVT is unclear. The impact of anticoagulation in patients with cirrhosis and PVT on orthotopic liver transplant (OLT) free survival is controversial.

There is scant data regarding natural history of gastroesophageal varices in patients with chronic noncirrhotic nontumoral PVT (NCNTPVT), which are usually managed as in cirrhosis. There is no evidence regarding efficacy of this policy.

In the first study of this thesis, a cohort of 241 patients with cirrhosis without PVT at study inclusion were evaluated prospectively and we found that prior decompensation of cirrhosis and thrombocytopenia independently predicted development of PVT. PVT did not independently predict higher risk of cirrhosis decompensations and lower OLT free survival.

In the second study, a retrospective analysis of a prospective cohort of 178 patients with chronic NCNTPVT, we found that the course of esophagogastric varices appears to be similar to that in cirrhosis.

In the third study, a retrospective analysis of 80 patients with cirrhosis with nontumoral PVT, although anticoagulation did not improve OLT free survival of the entire study cohort, it was associated with significantly higher survival in advanced cirrhosis. Anticoagulation was safe, significantly increased PVT recanalization and should be maintained to avoid rethrombosis.

In conclusion, prior decompensation of cirrhosis and thrombocytopenia predicted higher risk of developing PVT. PVT did not independently influence cirrhosis decompensations or OLT free survival. Anticoagulation appears to improve OLT free survival only in advanced cirrhosis. In chronic NCNTPVT using the same therapeutic approach as for cirrhosis was associated with a low risk of bleeding and death.

Keywords: Cirrhosis; portal vein thrombosis; prognosis; anticoagulation; varices

Resumo

A cirrose caracteriza-se por um estado de hipercoagulabilidade. A incidência de trombose da veia porta (TVP) aumenta na cirrose avançada. O impacto da TVP na história natural de cirrose não é claro. A segurança de anticoagulação na cirrose avançada e TVP não é clara e o seu impacto na sobrevida livre de transplante hepático ortotopico (THO) na cirrose avançada e TVP é controverso.

Em doentes com trombose da veia porta não-cirrótica e não-tumoral (TVPNCNT) crónica, existe escassa evidência sobre a história natural de varizes esófagogastricas que são habitualmente manejadas como na cirrose. Não existe evidência relativa à eficácia desta estratégia.

No primeiro estudo desta tese, uma coorte de 241 doentes com cirrose sem TVP foi seguida prospectivamente e verificamos que a descompensação prévia de cirrose e trombocitopenia foram factores independentes predizentes de desenvolvimento de TVP. A TVP não foi factor predizente independente de descompensações de cirrose ou de sobrevida livre de THO.

No segundo estudo, uma análise retrospectiva duma coorte prospectiva de 178 doentes com TVPNCNT crónica, verificamos que o curso natural de varizes esofagogástricas é semelhante ao de doentes com cirrose.

No terceiro estudo, uma análise retrospectiva de 80 doentes com cirrose e TVP não-tumoral, constatamos que a anticoagulação, embora não melhorasse a sobrevida global livre de THO, associou-se a melhoria de sobrevida apenas em doentes com cirrose avançada. A anticoagulação aumentou significativamente a recanalização da TVP e deverá ser mantida para prevenir a retrombose.

Em conclusão, a descompensação prévia de cirrose e trombocitopenia predizem independentemente, maior risco de desenvolvimento de TVP. A TVP não influenciou independentemente, descompensações de cirrose ou a sobrevida livre de THO. A anticoagulação foi segura e aparenta melhorar a sobrevida livre de THO na cirrose avançada. Na TVPNCNT crónica a mesma estratégia terapêutica como na cirrose associou-se a um baixo risco de hemorragia e mortalidade.

Palavras chave: Cirrose; trombose da veia porta; prognóstico; anticoagulação; varizes.

Resumo alargado da tese

A trombose da veia porta (TVP) define-se pela presença dum trombo dentro do tronco e/ou ramos intra-hepáticos da veia porta que poderá estender-se até à veia esplénica e/ou à veia mesentérica superior. O desenvolvimento da TVP na cirrose é explicada pela tríade de Virchow: a estase de fluxo venoso na circulação esplâncnica, a lesão Endothelial e a hipercoagulabilidade. Na cirrose, a diminuição da síntese de fatores procoagulantes e anticoagulantes e a sequestração de plaquetas no baço, resulta num reequilíbrio de hemostase. O grau de desequilíbrio hemostático aumenta com a gravidade da cirrose avaliada pelo escore de Child-Pugh. A cirrose é um fator de risco importante para o desenvolvimento de TVP, que ocorre em 2–26% dos doentes em lista para transplante hepático (TH). Os fatores de risco mais relevantes para o desenvolvimento de TVP são a gravidade de cirrose e a diminuição do fluxo sanguíneo na veia porta.

A anticoagulação e o "Transjugular Intra-hepatic Portosystemic Shunt" (TIPS) são as principais estratégias terapêuticas no manejo de doentes com cirrose que desenvolvem TVP em particular os que são candidatos a TH. A taxa de recanalização de TVP é significativamente melhor em doentes que recebem anticoagulação comparada com aqueles que não a recebem.

A incidência de trombose da veia porta não-cirrótica e não-tumoral (TVPNCNT) varia entre 1,75 e 3,8 por 100.000 habitantes em mulheres e homens respetivamente. Os fatores de risco para tromboses venosas são detetados em 75% dos doentes com TVPNCNT. A recanalização espontânea de TVP ocorre raramente. Na TVP aguda, está recomendada a anticoagulação precoce dentro de 30 dias do diagnóstico para se obter recanalização da veia porta que poderá ocorrer em até 45% dos doentes. Em doentes sem cirrose, a endoscopia para rastreio de varizes deverá ser efetuada a 3 meses e a um ano após o diagnóstico de TVP aguda, uma vez que as varizes poderão desenvolver-se no período de um mês em doentes sem recanalização de TVP. A mortalidade relacionada com hemorragia por varizes, em doentes com TVPNCNT crónica, é significativamente mais baixa devido à função hepática preservada nesses doentes. A evidência sobre a eficácia da profilaxia primária e secundária da hemorragia por varizes em doentes com TVPNCNT crónica é escassa e é por isso que as recomendações para doentes com cirrose são seguidas empiricamente nestes doentes.

O primeiro estudo desta tese, apresentado no Capítulo 3, teve como objetivo primário, avaliar, em doentes com cirrose, a incidência e significado clínico de desenvolvimento de TVP em termos de descompensações de cirrose e sobrevida livre de TH.

Foram avaliados 445 doentes consecutivos com doença hepática crónica e finalmente incluídos 241 com cirrose seguidos prospectivamente com ecografia abdominal com doppler semestralmente para rastreio de carcinoma hepatocelular e TVP. Neste estudo prospetivo observacional avaliamos a incidência e fatores predizentes de desenvolvimento de TVP e a sua influência nas descompensações de cirrose e sobrevida livre de TH.

A maioria dos doentes, 184(76,3%) pertencia a classe A de Child-Pugh. A média de escore de MELD foi de 10±5 pontos. A média de idade foi de 59±10 anos, sendo 184(76,3%) homens. Verificaram-se descompensações prévias de cirrose em 125(52,1%) doentes, estando 63(26,1%) sob beta bloqueadores

não seletivos e 59(27,2%) submetidos a laqueação elástica para profilaxia de rotura de varizes. Verificaram-se presença de varizes esofágicas em 138/221(62,4%) e ascite em 62(25,8%) doentes, na altura de inclusão no estudo. A mediana de seguimento foi de 29(1–58) meses. A incidência cumulativa de TVP não-tumoral foi de 3,7% e 7,6% a 1 e a 3 anos. O desenvolvimento de TVP associou-se independentemente a descompensações prévias de cirrose e trombocitopenia mas não a beta bloqueadores não seletivos. Durante o seguimento, 82/236(34,7%) doentes desenvolveram descompensações de cirrose. A sobrevida livre de TH foi de 100% e 82,8% a 3 anos em doentes com e sem TVP respectivamente. O escore MELD foi o único fator independente predizente de descompensações de cirrose (HR 1,14; 95% I.C.:1,09–1,19) e sobrevida livre de TH (HR 1,16; 95% I.C.:1,11–1,21).

Assim, concluímos que a descompensação prévia de cirrose e trombocitopenia são fatores independentes predizentes de maior risco de desenvolvimento de TVP na cirrose. A TVP não foi um fator independente predizente de descompensações de cirrose ou de sobrevida livre de TH o que poderá ser explicado pelo facto de mais de 2/3 dos doentes que desenvolveram TVP terem trombose parcial na altura de diagnóstico.

No segundo estudo apresentado no Capítulo 4, avaliamos a história natural de varizes gastroesofágicas numa grande coorte de doentes com TVPNCNT crónica.

Avaliamos, retrospetivamente, numa coorte prospetiva de 178 doentes com TVPNCNT crónica, a incidência de varizes de novo em doentes sem varizes em endoscopia basal, a taxa de crescimento de varizes esofágicas pequenas (VEPs) detetadas na endoscopia basal e a eficácia de profilaxia primária e secundária de rotura de varizes em doentes com varizes esofágicas grandes (VEGs) e/ou varizes gástricas (VGs). Finalmente, avaliamos o prognóstico de doentes com TVPNCNT crónica.

O tempo mediano de seguimento foi de 49(1–598) meses. A hemorragia por rotura de varizes foi a manifestação inicial em 27(15%) doentes. A endoscopia inicial nos restantes 151 doentes revelou: ausência de varizes em 52(34%), VEPs em 28(19%), VEGs em 60(40%) e VGs sem VEGs em 11(7%). A ascite e esplenomegalia foram fatores independentes predizentes de presença de varizes. Em doentes sem varizes, a probabilidade de desenvolverem varizes foi de 2%, 22% e 22% a 1, 3 e 5 anos. Em doentes com VEPs, a taxa de crescimento para VEGs foi de 13%, 40% e 54% a 1, 3 e 5 anos. Em doentes com VEGs sob profilaxia primária, a probabilidade de hemorragia foi de 9%, 20% e 32% a 1, 3 e 5 anos respetivamente. 9(5%) doentes faleceram após um tempo mediano de 51(8–280) meses, apenas um deles por hemorragia por rotura de varizes.

Assim, concluímos que o curso de varizes na TVPNCNT crónica é semelhante ao dos doentes com cirrose. A mesma abordagem terapêutica como em doentes com cirrose associa-se a um baixo risco de hemorragia e mortalidade.

Os aspetos inovadores deste estudo prendem-se com:

(1) Um seguimento endoscópico efetuado de forma relativamente estandardizada em doentes sem varizes ou com VEPs;

(2) A profilaxia primária e secundária de rotura de varizes aplicada de forma relativamente uniforme em quase todos os doentes com indicação para o fazer;

(3) Um estudo etiológico de fatores trombóticos na maioria dos doentes e terapêutica anticoagulante administrada de forma uniformizada.

No Capítulo 5 apresentamos o estudo em que avaliamos retrospetivamente uma coorte prospetiva de 80 doentes consecutivos com cirrose e TVP não-tumoral e comparamos o efeito de anticoagulação na recanalização de TVP e sobrevida livre de TH em doentes que receberam anticoagulação comparado com aqueles que não receberam.

O escore médio de MELD na altura de diagnóstico de TVP foi de 15±7. Verificamos a presença de complicações relacionadas com hipertensão portal em 65(81,3%) doentes na altura do diagnóstico de TVP. A trombose isolada do tronco/ramos da veia porta foi documentada em 53(66,3%) doentes. A anticoagulação foi iniciada em 37 doentes. Em 17(45,9%) doentes, a anticoagulação foi terminada por diferentes motivos, sendo que em 4(10,8%) doentes por episódios de hemorragia. Não ocorreram episódios de hemorragia por rotura de varizes em doentes sob anticoagulação. Em 6/17(35,2%) doentes, a anticoagulação foi reiniciada por retromboses. Em 67 doentes com adequada avaliação imagiológica durante o seguimento, a anticoagulação aumentou significativamente a taxa de recanalização de TVP comparado com os doentes que não receberam anticoagulação (51,4%(18/35) vs 6/32(18,8%), p=0,005). A sobrevida livre de TH após uma mediana de seguimento de 25(1–146) meses foi de 32(40%). Embora não se tenha verificado efeito significativo de anticoagulação na sobrevida global livre de TH, doentes com escores de MELD ≥15 que receberam anticoagulação tiveram melhor sobrevida livre de TH comparado com aqueles que não receberam anticoagulação (p=0,011). MELD na altura de detecção de TVP foi um factor independente predizente de recanalização de TVP (HR 1,11, 95%C.I.1,01–1,21,p=0,027) e de risco de mortalidade ou necessidade de transplante hepático (HR 1,12, 95%C.I.1,05–1,19,p<0,001).

Assim, concluímos neste estudo que embora a terapêutica anticoagulante não tenha melhorado a sobrevida global livre de TH, ela melhorou significativamente a sobrevida livre de TH em doentes com cirrose avançada (Child-Pugh B e C). A anticoagulação também melhorou significativamente a taxa de recanalização de TVP e deverá ser mantida após recanalização de TVP para evitar retromboses. Confirmamos que a anticoagulação é segura em doentes com cirrose sob adequada profilaxia primária e secundária de rotura de varizes.

No Capítulo 6, o capítulo final, discutimos e contextualizamos os resultados dos três estudos clínicos em relação ao conhecimento atual e apresentamos os contributos desta tese, apresentando as perspetivas em relação ao desenvolvimento futuro de investigação nesta área.

Em conclusão, de acordo com os nossos estudos, a incidência de TVP é relativamente baixa na cirrose compensada e não parece influenciar descompensações de cirrose e sobrevida, livre de TH. Na TVP não-cirrótica e não-tumoral crónica, o curso natural de varizes é semelhante ao de doentes com cirrose. A anticoagulação na TVP na cirrose é segura com melhoria da sobrevida livre de TH na cirrose avançada.

Dreams are extremely important.

If you don't imagine it you will not achieve it!

Chinese proverb

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Abbreviations

ADAMTS	A Disintegrin and Metalloproteinase with Thrombospondin motifs
AT	Anticoagulant therapy
BMI	Body mass index
BRTO	Balloon occluded retrograde transvenous obliteration
COPD	Chronic obstructive pulmonary disease
CSPH	Clinically significant portal hypertension
CT	Computerized tomography
EBL	Endoscopic band ligation
EIS	Endoscopic injection sclerotherapy
ESLD	End stage liver disease
ETP	Endogenous thrombin potential
EVs	Esophageal varices
FFP	Fresh frozen plasma
GIB	Gastrointestinal bleeding
GOV	Gastroesophageal varix
GOV1	Gastroesophageal varices type 1
GOV2	Gastroesophageal varices type 2
GP VI	Glycoprotein VI
GVs	Gastric varices
HCC	Hepatocellular carcinoma
HVPG	Hepatic venous pressure gradient
IGV	Isolated gastric varices
INR	International normalized ratio
KM	Kaplan Meier
LEVs	Large esophageal varices
LMWH	Low molecular weight heparin
LT	Liver transplantation
MELD	Model for end stage liver disease
MP	Microparticles
MRI	Magnetic resonance imaging
NASH	Non alcoholic steatohepatitis
NCNTPVT	Noncirrhotic nontumoral portal vein thrombosis
NSBB	Non selective beta blockers
OLT	Orthotopic liver transplant
PH	Portal hypertension
PPIs	Proton pump inhibitors
PT	Prothrombin time
PV	Portal vein
PVT	Portal vein thrombosis
RFA	Radiofrequency ablation
SD	Standard deviation
SEVs	Small esophageal varices
SMV	Superior mesenteric vein
SV	Splenic vein
TACE	Transcathether arterial chemoembolization
TE	Transient elastography
TE index	Time/Endoscopy index.
TF	Tissue factor
TIPS	Transjugular intra-hepatic portosystemic shunt
UGIB	Upper gastrointestinal bleeding
US	Ultrasound
VKA	Vitamin K antagonists
VWF	von Willebrand factor

CHAPTER 1 INTRODUCTION

1.1. Hemostatic imbalances in cirrhosis

1.1.1. Hemostasis in cirrhosis and tests for its evaluation

Until recently, cirrhosis was considered a "natural anticoagulative state" on the basis of frequently found reduction in platelet counts and prolonged prothrombin time and this was thought to be responsible for the frequent bleeding episodes that these patients have. However, it is now known that this bleeding tendency observed in end stage liver disease (ESLD) is indeed due to hemodynamic alterations secondary to portal hypertension, endothelial dysfunction and the presence of endogenous heparin like substances due to bacterial infections and also due to renal failure that these patients develop (1).

Prothrombin time (PT) only assesses thrombin generated in plasma by procoagulant drivers but not the thrombin inhibited by anticoagulant drivers (1) (2) (3) (4). Neither the International Normalized Ratio (INR) or other classical coagulation tests adequately predict the risk of gastrointestinal or procedure related bleeding (1) (5). By contrast, thrombin generation assay expressed as endogenous thrombin potential (ETP) comprehensively assesses the coagulation system because the degree of thrombin formation and disappearance is influenced by both procoagulant and anticoagulant factors (2) (3). In this test, tissue factor (TF) and phospholipids are added at much smaller concentrations mimicking coagulation in vivo and Protein C activation in vivo is optimized by the presence of the endothelial receptor thrombomodulin (2). Thrombin generation is maintained or even increased in patients with cirrhosis and platelet counts above 75 x 10^9/L, due to simultaneous decrease in coagulation inhibitors (Protein C, protein S and antithrombin) and an increase in procoagulant factor VIII (37). Despite thrombocytopenia in patients with cirrhosis, platelets are qualitatively able to support thrombin generation in vitro provided that their count is between 50 – 60 x 10^9/L (2). Consequently, more than a hypocoagulative state, patients with cirrhosis may have a hypercoagulative state that could explain, at least in part, why patients with cirrhosis have increased risk of venous thromboembolism (59).

1.1.2. Imbalances in procoagulant and anticoagulant factors

The abnormal coagulation profile in patients with cirrhosis is due to decreased synthesis of procoagulant and anticoagulant factors and sequestration of platelets in the spleen resulting in a rebalanced hemostasis (2) (6) (16).

Increased thrombin and fibrin generation as well as fibrinolysis suggest defective clearance rather than ongoing activation of platelets, coagulation and fibrinolysis (4). Plasma levels of natural anticoagulants namely antithrombin, protein C and factor XI tend to decrease with increasing severity of cirrhosis (5). In the context of thrombocytopenia, factor VIII and Von Willebrand Factor (VWF) levels increase and ADAMTS-13 (A Disintegrin and Metalloproteinase with Thrombospondin motifs) decrease as a compensatory mechanism (1) (6). Ultimately, plasma from patients with cirrhosis tends to have a procoagulant imbalance due to resistance to invitro anticoagulant action of thrombomodulin which

is attributed to high plasma levels of factor VIII and low protein C (2) (60) (61). This degree of hemostatic imbalance increases with the severity of cirrhosis as assessed by the Child-Pugh score (1).

Thrombin generation measured by ETP is increased in patients with cirrhosis compared to healthy controls and this is significantly higher in patients belonging to Child-Pugh classes B and C compared to class A (60). In the study by Fimognari F et al, factor VIII levels and D-Dimer levels were significantly higher in Child-Pugh C compared to Child-Pugh A and B patients (62). Among patients who developed portal vein thrombosis (PVT), D-Dimer levels were significantly higher and Factor VIII levels significantly lower probably due to consumption by thrombosis compared to those who did not develop PVT (62).

The VWF-Ag and factor VIII to protein C ratio independently predict new onset ascites, variceal bleeding and mortality in cirrhosis (63). High factor VIII levels have also been shown to be independently associated with increased risk of extra-hepatic PVT (64). In addition, among patients with cirrhosis who develop PVT, expression of monocyte TF was found to be increased compared to that in cirrhotic patients without PVT as well as controls without cirrhosis (65). This may be useful since Factor VII and TF form a complex to activate factor X, which is responsible for conversion of prothrombin to thrombin resulting in abundant formation of fibrin and clotting (65).

In the past, cirrhosis and the consequent changes in coagulation were considered to be irreversible. However, recently, direct acting anti-viral therapy in patients with cirrhosis due to viral hepatitis C has been found to increase levels of individual procoagulant and anticoagulant factors, thus improving the stability of hemostatic balance (66).

1.1.3. Thrombocytopenia and compensatory mechanisms

Cirrhosis is associated with thrombocytopenia and not only platelet number but also their function is reduced when platelet count is <50 x 10^9/L (2). Low platelet count in patients with cirrhosis is due to several factors: 1) increased splenic pooling; 2) shortened life span due to increased splenic destruction; 3) increased antibody mediated splenic destruction; 4) relative bone marrow insufficiency and 5) decreased thrombopoietin secretion (4) (37).

Markedly elevated levels of VWF contribute to induction of primary hemostasis and compensate for thrombocytopenia in cirrhosis (2). Platelets adhere to damaged vessel walls interacting with multimeric adhesive protein VWF promoting aggregation and formation of primary hemostatic plug (2). In addition, platelets support other coagulation factors on their surfaces facilitating thrombin generation (2). Levels of ADAMTS 13, a plasma metalloprotease that limits VWF effect on platelets are reduced in cirrhosis while VWF levels are substantially increased which counterbalances the deleterious effects of low platelet numbers and function on hemostasis (1) (4).

Glycoprotein VI (GPVI) is a marker of platelet activation and the GPVI/platelet ratio was found to be significantly higher in patients with cirrhosis compared to those without cirrhosis (67). Additionally, in the same study, VWF levels were significantly higher in patients with cirrhosis compared to those without cirrhosis (67). Both higher GPVI/platelet ratio and VWF levels have been shown to be significantly associated with development of PVT after hepatotectomy or splenectomy (67).

1.1.4. Infections and their role in fibrinolysis and thrombosis

Fibrinolysis regulates digestion of fibrin clots and hyperfibrinolysis is clinically evident by laboratory testing in 5 – 10% patients with cirrhosis and bleeding events (2). Infections have been shown to be a trigger for variceal bleeding via endotoxins which stimulate myofibroblasts increasing intra-hepatic resistance and portal pressure and simultaneously inhibiting platelet aggregation trough release of prostacyclin and nitric oxide (68). Additionally, infections have been shown to increase endogenous heparinoids impairing coagulation in patients with cirrhosis (68).

Features of accelerated intravascular coagulation and fibrinolysis (increased levels of D-dimers, thrombin-antithrombin complexes, fibrinopeptide A and soluble fibrin and shortened clot lysis time) can be found in patients with cirrhosis which may be related to endotoxemia which commonly occurs in patients with cirrhosis (37). Small bowel overgrowth and increased intestinal permeability lead to endotoxemia with increased bacterial translocation and risk of bacterial infection (69). Endotoxins or cytokines can release heparinoids from the vascular endothelium in a dose dependent manner and additionally mast cell activation due to bacterial infection can also release heparin (3). Peripheral and portal levels of endotexemia are correlated with the severity of liver disease (69).

1.2. Virchow's triad and development of portal vein thrombosis in cirrhosis

The development of PVT in patients with cirrhosis can be explained by the Virchow's triad. The stasis of venous flow in the splanchnic circulation, damaged endothelium and hypercoagulability are the three factors contributing to development of venous thrombosis in patients with cirrhosis (3) (7) (8). The relative deficiency of procoagulant and anticoagulant factors in patients with cirrhosis contributes to a fragile hemostatic balance which may tip to hemorrhage or thrombosis depending on the prevailing risk factors (1).

1.2.1. Acquired prothrombotic factors

Thrombocytopenia in the context of hypersplenism secondary to portal hypertension has been shown to be a predictor of development of PVT in some studies while others have not confirmed this finding (13) (70). The degree of thrombocytopenia is crucial in the ability of the hemostatic system to support thrombin formation (71). As mentioned previously, thrombin generation has been found to be intact in patients with liver disease and there may even be a prothrombotic tendency as seen by greater thrombin burst in patients with acute decompensation of cirrhosis (71).

1.2.2. Blood flow velocity and turbulence

The development of collateral vessels has been found to be a significant predictor of development of PVT in virus-induced cirrhosis (15). The development of abdominal venous collaterals has been found to be independently associated with a hepatic venous pressure gradient (HVPG) values of ≥ 16mmHg (72) suggesting underlying clinically significant portal hypertension. A decreased portal vein flow velocity below 15 cm/sec has been found to have an independent role in the development

of PVT suggesting that stasis of blood in the splanchnic circulation specially in patients with advanced cirrhosis is a major risk factor for development of PVT (16) (37).

1.2.3. Inflammation and vascular Endothelial changes

Vascular endothelial cells are regulators of the inflammatory response forming a physical barrier for blood cells (73). They regulate vascular permeability, intravascular coagulation, vascular tone and blood pressure as well as release hormones and other soluble mediators such as cytokines that initiate and regulate inflammation (73).

Inflammation affects plasma levels of procoagulants. Factor VIII is an acute phase reactant and its concentration rises in the presence of inflammation (64). Continuous low grade activation of vascular Endothelial cells results in continous release of hemostatic proteins such as VWF whose levels are often elevated in patients with liver disease (4). Although, plasma D-dimer may rise in infections, values >16mg/mL have been shown to predict the development of PVT (70).

Cytokines are involved in development of venous thrombosis (73). P-selectin, an adhesion molecule, has been shown to facilitate leucoctye accumulation and adhesion to endothelium for subsequent platelet accumulation and its levels are increased in patients with venous thrombosis (73). Matrix metalloproteases are important during venous thrombosis resolution and may impact vessel wall fibrosis and are crucial in acute and chronic thrombosis pathophysiology (73).

The activation of the coagulation system within the liver vascular network may play a role in the development and progression of the fibrotic process mainly mediated by thrombin via protease activated receptors (1). Factor Xa has been shown to promote hepatic stellate cell contractility and activation (74). The inhibition of coagulation with a Factor Xa inhibitor in mice significantly reduced murine liver fibrosis (74).

Based on the above mentioned pathophysiologic mechanisms, inflammation is thought to contribute to development of obliterative microthrombi in the portal and hepatic veins leading to tissue ischemia, cell death and fibrosis trough parenchymal extinction (1) (75). These pathophysiological changes responsible for development of portal vein thrombosis in cirrhosis are summarized in Figure 1.

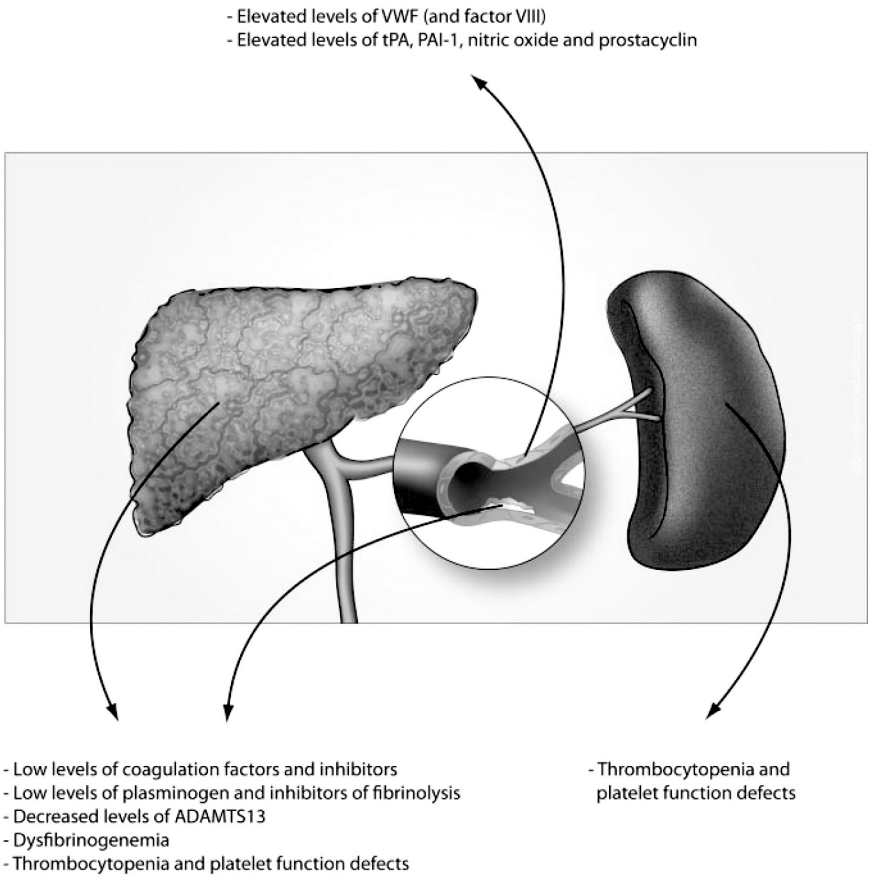

Fig. 1 Pathophysiology of portal vein thrombosis in cirrhosis
in Lisman, Porte «Rebalanced Hemostasis in Liver Disease» Blood Journal, Vol. 116, No. 6, 2010 p. 879
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1.3. Portal vein thrombosis in cirrhosis

1.3.1. Incidence and clinical predictors of development of PVT in cirrhosis

PVT is defined as the development of a thrombus within the main portal vein (PV) and/or intra-hepatic portal branches which can extend into the splenic vein (SV) and/or superior mesenteric vein (SMV) (9). Cirrhosis is a major risk factor for development of PVT (10), with a reported prevalence of PVT of 2 – 26% in patients awaiting liver transplantation (LT) (8) (11) (12). In a prospective study in patients with cirrhosis on liver transplant list, the prevalence of PVT was 8.4% (21/251 patients) at the time of listing for LT and the incidence of de novo PVT at the time of LT was 7.4% (17/230 patients) during a mean follow-up of 12.1 months (13). More recently, a large prospective observational study in Child-Pugh A and B patients with cirrhosis, showed a 5 year cumulative incidence of PVT of 10.7% (23).

The most important risk factors for development of PVT are probably the severity of liver disease and reduced blood flow in the portal vein (9) (11). Additionally, increased blood flow volume in the largest collateral vessel were found to independently predict development of PVT (15). Local factors associated with development of PVT include portal venous endothelial injury (Ex splenectomy, hepatectomy, surgical shunts and other intra-abdominal surgeries) and inflammatory conditions (Ex Pancreatitis, cholecystitis, appendicitis and other intra-abdominal infections) (9). Low platelet count has been found to be an independent predictor of development of PVT in cirrhosis (13) (16).

1.3.2. Diagnosis of PVT in cirrhosis and exclusion of hepatocelular carcinoma

The diagnostic sensitivity and specificity for detection of PVT by abdominal color Doppler ultrasound varies from 66 to 100% depending on the expertise of the examiner and the extent of PVT (11). PVT in patients with advanced cirrhosis is usually asymptomatic at diagnosis and is usually detected during systematic imaging for hepatocellular carcinoma (HCC) prior to LT (8) (17). While, PVT may not preclude transplantation in patients with HCC, macroscopic vascular invasion by the tumor is a definite contraindication (8). High alpha-fetoprotein level, endovascular obstruction adjacent to the tumor, enlargement of the vessel by the endovascular material, disruption of the vessel wall and enhancement of the intravascular material at the arterial phase on imaging with CT scan or contrast enhanced ultrasound are consistent with tumor invasion (76) (77) (78). Patients diagnosed with PVT by abdominal Doppler US should be assessed with cross-sectional imaging (CT or MRI) to confirm as well as stage the extent of thrombosis and exclude HCC (3).

1.4. Clinical implications of nontumoral portal vein thrombosis in cirrhosis

1.4.1. Nontumoral PVT in cirrhosis and its influence on cirrhosis decompensations, progression of liver disease and mortality

There is controversy regarding the role of PVT in development of complications of cirrhosis and its influence on progression of liver disease and mortality. In patients with cirrhosis and variceal bleeding, although some studies have not shown a link between PVT and higher variceal rebleeding and mortality (18), others suggest that PVT is associated with significantly higher variceal rebleeding rates (19) (20), recurrence of varices after eradication of esophageal varices by band ligation (21) and higher short and long term mortality (20) (22). The largest prospective study evaluating incidence and clinical significance of development of PVT in patients with cirrhosis showed that development of PVT was not associated with progression of liver disease (23). This may be due to the fact that more than two thirds of patients who develop PVT have partial thrombosis at the time of detection of PVT which may be not sufficient to compromise blood flow to the liver (23). A prospective study evaluating prophylactic anticoagulation in patients with advanced cirrhosis (Child-Pugh B and C – 10 points) showed a significant decrease in the incidence of PVT and a lower incidence of decompensations of cirrhosis and mortality in patients who received AT compared to those who did not which suggests that anticoagulation in patients with cirrhosis may have benefits beyond prevention of development of macroscopic PVT (79).

1.4.2. Nontumoral PVT in patients on LT list

Anticoagulation and transjugular intra-hepatic portosystemic shunt (TIPS) are the main management strategies in patients listed for orthotopic liver transplantation (OLT) who develop PVT, with anticoagulation achieving complete recanalization rates of up to 40% (11). PVT does not increase waitlist mortality but occlusive thrombosis is a risk factor for early post LT mortality (9) (11) (12) (24) (25). However, PVT is not considered a MELD exception and patients with PVT do not receive extra points while on LT waitlist (26) (27). Extensive PVT with involvement of the superior mesenteric vein in LT

candidates is associated with longer operative times, greater consumption of blood products and complex surgical techniques (12).

The extent and degree of luminal occlusion in patients with PVT determines surgical technique (9) (11). The Yerdel classification of PVT (Figure 2) has prognostic importance in patients undergoing LT: grade 1, thrombus at the main PV affecting < 50% of the lumen with/without minimal extension into SMV; grade II, thrombus at PV affecting > 50% including complete thrombosis with or without extension into the SMV; grade III, complete PVT plus thrombosis extending to the proximal SMV with patent distal SMV; grade IV, complete PVT plus complete thrombosis of the SMV (11). In patients with grade I to III PVT, resection of the short affected PVT segment and removal of PVT by eversion thrombectomy is done (11). In grade IV PVT patients, the PV can be anastomosed to a patent splanchnic tributary for example the coronary vein or a large collateral vein measuring ≥ 2 cm (9) (11).

PVT prior to LT is a risk factor for PVT recurrence after LT (11). Post LT PVT is associated with reduced graft and patient survival after LT and can severely limit future re-transplantation (11). Prophylactic anticoagulation with LMWH during at least 3 months has been recommended to prevent post LT PVT especially in patients with cavoportal hemitransposition, renoportal anastomosis and living donor LT (11).

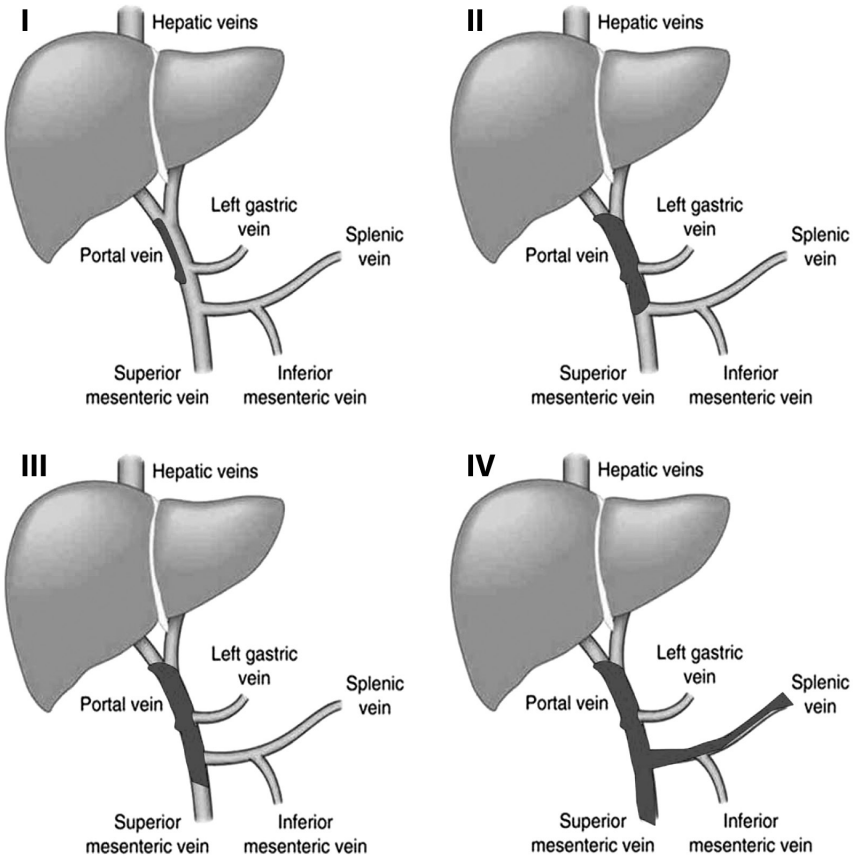

Fig. 2 Yerdel classification of portal vein thrombosis
in Chen et al. «Nontumoral Portal Vein Thrombosis in Patients Awaiting Liver Transplantation» Liver Transplantation, Vol. 22, No. 3, 2016 p. 357.
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1.5. Anticoagulation in patients with cirrhosis and nontumoral portal vein thrombosis

1.5.1. Rationale for anticoagulation in patients with cirrhosis and nontumoral PVT

The aim of anticoagulation in patients with cirrhosis and PVT is to recanalize the PV and in patients candidates for LT, if recanalization is not possible, to prevent extension of thrombosis and allow use of a splanchnic vein to restore physiological blood flow to the allograft (3) (8). Despite increasing awareness that cirrhosis is a prothrombotic state, patients with cirrhosis who develop PVT are less likely to receive anticoagulation probably due to the fear of bleeding risk (80).

Most of the studies evaluating anticoagulation in patients with cirrhosis and PVT are retrospective with small sample sizes and with majority of patients having non occlusive PVT (11). However, anticoagulation significantly improves recanalization rates, which range between 37 and 93% and decreases rates of thrombosis progression which range between 0 to 15% in the meta-analysis by Qi Xingshum et al (40). Doses of enoxaparin 1 mg/kg every 12 hours have been shown to have comparable efficacy in terms of recanalization of PVT compared to enoxaparin 1.5 mg/kg/day with a lower incidence of injection site hemorrhage, epistaxis or hematuria (11). However this is associated with the inconvenience of the requirement for daily subcutaneous injections of low molecular weight heparin (LMWH) (8). Empirical dose reductions (≥50% of therapeutic dose, based on individiual risk assessment) in the presence of additional risk factors for bleeding have been suggested (39).

Vitamin K antagonists (VKA) are most commonly used for long term anticoagulation with the inconvenience of regular monitoring of INR which additionally does not correlate well with the degree of anticoagulation in patients with cirrhosis (11). In patients with prolonged baseline INR, it may be difficult to determine if a given dose of VKA ensures adequate anticoagulation and it may also be difficult to determine appropriate INR target for dose adjustment (8). This may explain the higher rates of complete PVT recanalization rates in patients receiving LMWH compared to warfarin (36).

Thrombin inhibitors and inhibitors of activated factor X such as dabigatran and rivaroxaban have the advantage of oral administration, mechanism of action independent of anti-thrombin and the absence of need for laboratory monitoring (8). Direct acting oral anticoagulants have been used in patients with cirrhosis belonging to Child-Pugh A and B with similar bleeding risk as VKAs and LMWH (81) (82).

Prior to starting anticoagulation, screening for varices by endoscopy and initiation of primary and secondary prophylaxis of variceal bleeding should be performed (3) (8) (11).

1.5.2. Anticoagulation and nontumoral PVT recanalization and progression in cirrhosis

Between 30 and 70% of patients with cirrhosis and partial PVT may have spontaneous recanalization (9) (15) (23) (28) (29) (30). Anticoagulation is associated with significantly higher PVT recanalization rates which range between 36% and 82% (7) (8) (31) (32) (35), compared to that in patients with cirrhosis and PVT who did not receive anticoagulation (33) (34). Additionally, the rate of complete PVT recanalization is significantly higher in patients who receive anticoagulation compared to those who do not (53% vs 33%, p=0.002) (34). Shorter duration between diagnosis of PVT and initiation of anti-

coagulation (32) and prolonging anticoagulation beyond 6 months has been associated with higher PVT recanalization rates in patients with cirrhosis (35) (83).

The rate of progression of PVT was shown to be significantly lower in patients receiving anticoagulation compared to those who did not (9% vs 33%, p <0.0001) (34). Among patients candidates for LT who fail to recanalize or have progression of PVT with anticoagulation or have contraindications for anticoagulation, TIPS may achieve complete PVT recanalization through mechanical thrombectomy (8) and prevent rethrombosis by restoring portal blood flow through the creation of a low resistance shunt (8). However, marked impairment of liver function which is a feature of patients candidates for LT may be a contraindication for TIPS (8). Failure of TIPS placement can occur and is due to inability to identify intrahepatic portal vein branches, transformation of portal vein into a fibrous cord and extension of PVT into the SMV (8). Concomitant anticoagulation in patients receiving TIPS is only recommended in those patients with underlying prothrombotic conditions (8). In the absence of patency of the PV and/or SMV, non-anatomical techniques (renoportal anastomosis or cavoportal hemitransposition) can be performed but these techniques do not reverse portal hypertension completely and are associated with higher morbidity and mortality (8).

1.5.3. Rethrombosis rates after nontumoral PVT recanalization in cirrhosis

Rethrombosis rates range between 38% and 62.5%, after stopping anticoagulant therapy (AT) following successful PVT recanalization (3) (7) (30) (32) (35). PV rethrombosis may be due to persistent stagnation of blood in the splanchnic circulation due to underlying cirrhosis which contributes to development of PVT (32). Therefore, in general, AT is recommended to be maintained indefinitely in patients with persisting or permanent risk factors (39) which is the underlying portal hypertension in patients with cirrhosis. In the absence of prothrombotic states that persist after LT, there is no justification for long term AT after LT in patients with PVT prior to LT provided portal flow has been restored through conventional end-to-end portal anastomosis (8).

1.5.4. Anticoagulation in nontumoral PVT in cirrhosis, portal vein recanalization and progression of liver disease

There is conflicting data regarding the effect of AT on decompensation events in patients with cirrhosis and PVT. No differences in the rate of decompensations of cirrhosis have been noted in patients with partial or complete recanalization of PVT compared to those without any recanalization with anticoagulation (23) (30). More recently, in the study by Kwon J et al, patients with cirrhosis and PVT who were given LMWH and had partial or complete recanalization of the PVT, had higher platelet count and lower bilirubin levels after 6 months of AT with LMWH compared to those without response to anticoagulation, suggesting a potentially beneficial effect of anticoagulation in improving liver function (7). Recently, in a large retrospective study, anticoagulation in patients with cirrhosis and PVT was found to be an independent factor predicting better OLT free survival (35). However, only 13% of patients in this study belonged to Child-Pugh class C and patients belonging to Child-Pugh class A were significantly more likely to be given anticoagulation compared to patients belonging to Child-Pugh class C (35).

1.5.5. Safety of anticoagulation in cirrhosis

Bleeding related to AT is higher in patients with cirrhosis compared to that in patients without cirrhosis (36). This is thought to be related to defective hemostasis (37) and/or portal hypertension in the context of cirrhosis rather than due to the associated PVT as was shown in the study by La Mura et al (38). Platelet counts < 50 x 10^9/L are associated with significantly higher bleeding risk in patients with cirrhosis on AT (3) (32). In general, AT is not started in these patients or if started, LMWH dose is reduced by 50% or more in patients with extensive and occlusive PVT (39).

The presence of esophageal varices significantly increases the major bleeding risk (HR 5.4; 95% CI 1.14 – 21.1, p=0.015) justifying appropriate prophylaxis of variceal bleeding with non-selective beta blockers (NSBB) or endoscopic banding prior to starting AT (84). Adverse events related to AT include cerebral hemorrhage, lower gastrointestinal bleeding (GIB), oral bleeding, obscure GIB, vaginal bleeding and surgical wound hemorrhage (11). Bleeding events related to AT have been reported in 10 – 14.3% patients (7). In the study by Kwon J et al involving 91 patients with cirrhosis treated with LMWH, 59 of whom with HCC treated with radiofrequency abalation (RFA) or trans-cathether arterial chemoembolization (TACE), two deaths were reported and these were attributed to duodenal variceal bleeding and intracraneal bleed in the context of AT, highlighting the potential risks of anticoagulation (7). Features of advanced cirrhosis such as low albumin and a history of variceal bleeding have been shown to be independent predictors of bleeding on AT (7).

There are however several studies suggesting that AT in patients with cirrhosis and PVT is safe and with a low rate of complications when adequate prophylaxis of variceal bleeding is undertaken prior to anticoagulation (9) (31) (32) (85). In a meta-analysis by Qi Xingshun et al, the incidence of AT related bleeding varied between 0 and 18% (40). However, many of the studies are retrospective and have small sample sizes which increases the risk of bias (9) (31). Exclusion criteria for AT include advanced age, multiple comorbidities (including advanced cardiac and pulmonary disease), advanced HCC, recent history of GIB, history of multiple falls and inability to monitor anticoagulation (31). In the meta-analysis by Loffredo et al, there was no difference in the proportions of patients with major or minor bleeding between groups that did and did not recieve anticoagulants (11% for both groups) (34). In a subgroup of patients from 4 studies from the same meta-analysis, the rate of spontaneous variceal bleeding reported was significantly lower in patients recieving AT compared to those without (2% vs 12%, p=0.04) (34) In a large multicentre observational study of AT in splanchnic vein thrombosis which included patients with cirrhosis, the case fatality rate for major bleeding events in patients recieving anticoagulation was 0% which supports the utility and safety of anticoagulation in these patients in the absence of absolute contraindications (36). Additionally, recent data suggests that there is no significant difference in the incidence of all cause bleeding and major bleeding in chronic liver disease patients treated with direct acting oral anticoagulants compared to those on warfarin (86).

1.6. Noncirrhotic nontumoral portal vein thrombosis – Incidence, etiology and management

The age standardised incidence of PVT unrelated to cirrhosis was 1.75 and 3.8 per 100,000 inhabitants in females and males respectively (44). Risk factors for venous thrombosis are detected in 75% of patients with PVT without underlying liver disease (45). One or several prothrombotic conditions are identified in up to 60% of patients with a local risk factor in 30 – 40% patients (41) (45) (46). Myeloproliferative disorders are the most common etiologic factors of noncirrhotic nontumoral PVT (NCNTPVT) (47). Local risk factors include inflammatory conditions affecting intraperitoneal organs and surgery (48).

There are two potential mechanisms which account for the usual absence of deleterious consequences of PVT on liver function. This includes the arterial "buffer" response which is the immediate vasodilatation of hepatic arterial bed in response to decreased portal vein flow and the rapid development of collateral veins bypassing the thrombosed segment of the portal vein (46) (87) . Ischemia of the intestine occurs when PVT extends into the mesenteric veins and the mesenteric venous arches and is associated with a mortality risk of up to 60% (46) (49).

Abdominal Doppler US of the portal venous system has a diagnostic sensitivity and specificity of more than 95% in diagnosis of PVT and is the initial investigation of choice (49) (88) (89) (90). Ultrasound features suggesting acute PVT include presence of a hypoechogenic thrombus and dilation of the portal vein in the absence of collaterals, while signs of chronicity are the presence of a cavernoma which are a set of collateral veins, splenomegaly and a fibrous remnant of the original portal vein (48) (91). Contrast enhanced ultrasound with Doppler allows for differentiation between benign and malignant PVT (92). CT and/or MRI are required to determine the exact extent of thrombosis in the portosplenic mesenteric axis as well as to rule out bowel infarction and possible causes of PVT such as malignancy and chronic pancreatitis (41) (49) (93). A normal liver transient elastography value helps differentiate cirrhotic from noncirrhotic PVT and in case of doubt, liver biopsy rules out liver disease (41).

Spontaneous recanalization of PVT rarely occurs (41) (46) (49) (50). In patients with acute PVT, early AT within 30 days of diagnosis is recommended to achieve thrombus recanalization (41) (49). AT has been shown to achieve PVT recanalization in up to 45% of patients with acute PVT (45) (50) (51). No additional recanalization was noted beyond the first 6 months of AT (45) (49). In patients with portal cavernoma or chronic NCNTPVT, AT is aimed at preventing progression and recurrence of PVT (41) (49). Patients are less likely to be put on AT if they present with variceal bleeding (56). Anticoagulation is recommended for at least 6 months and then continued if an underlying thrombophilia is detected (46). Long term AT is recommended in patients with genetic or acquired prothrombotic disorder, recurrent episodes of thrombosis or family history of vein thrombosis (41). The duration of AT has been independently associated with lower risk of thrombotic events in patients with PVT (36). Ascites and splenic vein thrombosis at the time of detection of PVT and more than one prothrombotic disorder predict lack of recanalization (41) (45).

1.7. Chronic noncirrhotic nontumoral portal vein thrombosis, portal hypertension complications and prognosis

Portal cavernoma is used interchangeably with chronic NCNTPVT and is the second most frequent cause of portal hypertension in adults and the commonest cause of pre-hepatic portal hypertension (41) (89) (92). Portoportal collaterals allow hepatopetal flow but are insufficient in effectively bypassing the entire splenomesenteric blood inflow and result in clinically significant pre-hepatic portal hypertension wherein liver function and structure is preserved (41) (93). Varices may develop within one month after detection of acute PVT with majority of patients who do not achieve PVT recanalization going on to develop gastroesophageal varices during follow-up (41) (50). In addition, patients may develop portal cavernoma cholangiopathy, hypersplenism and neurocognitive dysfunction (93) (94). Patients with chronic NCNTPVT have a hyperdynamic circulation due to elevated nitrous oxide levels with increased splenic blood flow and moderate to massive splenomegaly (89). Changes in liver morphology including atrophy and regenerative nodular hyperplasia may occur due to ischemia and compensatory arterial vasodilatation (95) (96).

The initial episode of PVT is often paucisymptomatic or asymptomatic and often NCNTPVT is diagnosed in the context of portal hypertension related complications including thrombocytopenia, splenomegaly, variceal bleeding and rarely jaundice or incidentally during imaging for unrelated motives (41) (51). Ruptured varices may belong to the portosystemic collateral circulation (esophagus and gastric fundus) or to the portal cavernoma (gastric antrum and the duodenum) (46).

Ascites develops in 13 to 21% of patients with PVT and usually occurs after a bleeding episode and is related to hypoalbuminemia or in late stages, to parenchymal extinction (89) (94) (97). Ascites may develop in the context of chronic NCNTPVT in patients with preserved liver function and is usually easy to control (41). Some authors have suggested that ascites may develop due to liver dysfunction due to prolonged reduction in portal blood flow and/or development of portal cavernoma related cholangiopathy (97). Ascites in these patients has been shown to be an independent factor predictive of higher mortality (52) (56) (90).

Mortality related to variceal bleeding in patients with chronic NCNTPVT is significantly lower than in patients with cirrhosis due to preserved liver function in these patients (51) (52) (53) (54) (55). Mortality is primarily related to medical conditions which are often the cause of PVT rather than variceal bleeding (46) (49). One and 5 year survival rates among patients with chronic NCNTPVT has been reported to range between 85.7 to 95%% and 82.1% to 89% (53) (56). NSBB and AT are associated with improved survival while ascites and hyperbilirubinemia are associated with reduced survival (49) (56) (98). Neither variceal bleeding or myeloproliferative disorders influence survival (53).

1.8. Natural history of varices and variceal bleeding in chronic noncirrhotic nontumoral portal vein thrombosis

Upper gastrointestinal endoscopy shows esophageal and/or gastric varices in 20 to 55% patients with chronic NCNTPVT and these are usually large (41) (49). Since varices may develop within one month after acute PVT, screening endoscopy for varices should be performed within 3 months after

diagnosis of acute PVT (41). Among patients without varices at baseline, a repeat endoscopy should be performed at 1 year after diagnosis of acute PVT in patients without recanalization of PVT as they are at risk of developing varices due to underlying portal hypertension (41). Gastric and ectopic varices in the duodenum and anorectal regions are significantly more common in patients with chronic NCNTPVT compared to those with cirrhosis (41) (42) (43). In the study by Amitrano et al, 42 patients had upper gastrointestinal endoscopy performed every 1 to 2 years and in this sub group of patients, 20 patients without varices at the time of detection of chronic NCNTPVT did not develop varices while 3 out of 8 patients with small esophageal varices (SEVs) went on to develop large esophageal varices (LEVs) during follow-up (51).

Variceal bleeding is more common in children than in adults but is still the most frequent clinical manifestation in adults (41) (52) (99). In a large study involving 135 patients with chronic NCNTPVT, the incidence of gastrointestinal bleeding was 12.5 per 100 patient-years (55). LEVs but not AT were found to predict bleeding in patients with portal cavernoma (46) (49) (55). Neither spleen size or portal pressure seem to be correlated with incidence or severity of variceal bleeding (89). Howeever, in patients with chronic NCNTPVT resulting in portal hypertension, spleen stiffness is high and a value more than 42.8KPa has reasonable accuracy in differentiating patients with a history of bleeding from varices from those without (100) highlighting potential utility of transient elastography of the spleen in stratifying risk of variceal bleeding in these patients.

There is scant data regarding the efficacy of primary and secondary prophylaxis of variceal bleeding in patients with chronic NCNTPVT and therefore recommendations from patients with cirrhosis are followed in these patients (41) (49) (56). Either endoscopic banding or NSBB are recommended for primary prophylaxis of variceal bleeding (41) (57). Esophageal variceal bleeding events should be managed as in patients with cirrhosis with vasopressors, endoscopic band ligation and antibiotics (41) (57). Patients bleeding from gastric fundal varices may require endoscopic therapy with cyanocrylate injection (58).

In a study, after management of primary esophageal variceal bleed, 46% (18/39) of patients had recurrent variceal bleeding, without there having been identified predictive factors of rebleeding (56). Previous gastrointestinal bleed and fundal varices have been found to be predictive of new hemorragic events during follow-up in patients with chronic NCNTPVT (49) (51) (58). Banding of esophageal varices has been shown to be effective to prevent rebleeding while there is scarcity of data regarding role of NSBB either as monotherapy or combined with endoscopic therapy to prevent rebleeding (41) (49) (56). In a small proportion (8 – 12%) of patients with NCNTPVT, medical and endoscopic treatment fails to control variceal bleeding and in these patients, surgical shunt procedures, TIPS or balloon-occluded retrograde transvenous obliteration (BRTO) are performed (58) (89) (101) (102).

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CHAPTER 2 OBJECTIVES OF THE THESIS

In patients with cirrhosis, slow and turbulent blood flow in the portal vein secondary to portal hypertension is thought to be the main etiologic factor for the development of portal vein thrombosis (PVT). In addition, in these patients, there is a fragile balance between procoagulant and anticoagulant factors which may be tipped to hemorrhage or thrombosis depending on the prevailing risk factors. Low grade endotoxemia in patients with cirrhosis is thought to contribute to development of microthrombotic events which result in parenchymal extinction and progression of cirrhosis. These changes are more frequent in advanced cirrhosis (Child-Pugh B and C) which may explain the higher incidence and prevalence of PVT in these patient groups. However, there is controversy regarding the clinical significance of PVT in cirrhosis and its influence on its natural history.

Among patients with cirrhosis and nontumoral PVT, especially those who are candidates for liver transplantation, the development of PVT may increase morbidity and mortality at 1 year post liver transplantation. Patients with cirrhosis who develop PVT often do not receive anticoagulation due to fears of increased bleeding risk and the misconception by some physicians that these patients are already "naturally" anticoagulated. However, anticoagulation in patients with cirrhosis has been shown to be safe in those receiving adequate primary and secondary prophylaxis of variceal bleeding. Anticoagulation significantly improves recanalization in PVT and may improve OLT free survival in patients as has recently been shown. However, most of the studies evaluating anticoagulation in patients with cirrhosis and PVT have been conducted in study samples wherein majority of patients had compensated cirrhosis.

In patients with chronic noncirrhotic nontumoral portal vein thrombosis (NCNTPVT) one of the main complications related to portal hypertension is variceal bleeding. These patients have significantly better prognosis compared to variceal bleeding in patients with cirrhosis. However there is scant information regarding how best to manage those patients who develop portal hypertension with regard to endoscopic screening for varices and as well as primary and secondary prophylaxis of variceal bleeding.

The aim of this thesis is to contribute to a better understanding of the clinical significance of PVT and clinical situations related to it in patients with and without cirrhosis. For this purpose we conducted three clinical studies, two of them in patients with cirrhosis and one in patients with chronic NCNTPVT.

In the first study (Chapter 3), which was a prospective observational study involving 241 patients with cirrhosis and without PVT at baseline, the primary aim was to evaluate the incidence and factors predicting development of PVT as well as its influence on decompensations of cirrhosis and OLT free survival. In addition, we sought to determine factors predicting decompensations of cirrhosis and OLT free survival.

In the second study (Chapter 4), in which we retrospectively evaluated a prospective cohort of 178 patients with chronic NCNTPVT, the primary aim was to determine the incidence of new varices in

patients without varices at baseline endoscopy; to ascertain the rate of growth of small esophageal varices detected at screening endoscopy and evaluate the efficacy of primary and secondary prophylaxis of variceal bleeding in patients with large esophageal and or gastric varices. In addition we also sought to determine the prognosis of patients with chronic NCNTPVT.

Finally, in the third study (Chapter 5), in which we retrospectively evaluated a prospective cohort of 80 patients with cirrhosis, majority of whom with advanced cirrhosis with nontumoral PVT, the primary aim was to determine the effect of anticoagulation on PVT recanalization and OLT free survival in patients who actually received anticoagulation compared to those who did not. In addition, we also sought to determine the safety of anticoagulation in patients with cirrhosis with regard to bleeding events and in those patients who stopped anticoagulation, we determined the incidence of rethrombosis.

The results of these studies were published in the following manuscripts:

1. **Incidence and clinical significance of development of portal vein thrombosis in cirrhosis: a prospective study.**

   Carlos Noronha Ferreira, Rui Tato Marinho, Helena Cortez-Pinto, Paula Ferreira, Margarida Sobral Dias, Mariana Vasconcelos, Paula Alexandrino, Fátima Serejo, Ana Júlia Pedro, Afonso Gonçalves, Sónia Palma, Inês Leite, Daniela Reis, Filipe Damião, Ana Valente, Leonor Xavier Brito, Cilenia Baldaia, Narcisa Fatela, Fernando Ramalho, José Velosa. Accepted for publication, Liver International 2019, April 25th.

2. **Natural history and management of esophagogastric varices in chronic noncirrhotic, nontumoral portal vein thrombosis.**

   Carlos Noronha Ferreira, Susana Seijo, Aurelie Plessier, Gilberto Silva-Junior, Fanny Turon, Pierre-Emmanuel Rautou, Anna Baiges, Christophe Bureau, Jaime Bosch, Virginia Hernández-Gea, Dominique Valla, Juan-Carlos García-Pagan. Hepatology 2016 May; 63(5):1640-50

3. **Anticoagulation in cirrhosis and portal vein thrombosis is safe and improves prognosis in advanced cirrhosis.**

   Carlos Noronha Ferreira, Daniela Reis, Helena Cortez-Pinto, Rui Tato Marinho, Afonso Gonçalves, Sónia Palma, Inês Leite, Tiago Rodrigues, Ana Júlia Pedro, Paula Alexandrino, Fátima Serejo, Margarida Sobral Dias, Paula Ferreira, Mariana Vasconcelos, Filipe Damião, Leonor Xavier Brito, Cilenia Baldaia, Narcisa Fatela, Fernando Ramalho, José Velosa. Accepted for publication, Dig Dis Sci. 2019 Mar 9

CHAPTER 3 INCIDENCE, PREDICTIVE FACTORS AND CLINICAL SIGNIFICANCE OF DEVELOPMENT OF PORTAL VEIN THROMBOSIS IN CIRRHOSIS:A PROSPECTIVE 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 mortality/OLT (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

3.1. 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 nontumoral 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.

3.2. Patients and Methods

Consecutive patients with chronic liver disease were included in this prospective observational study conducted between 1st January 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 and etiological features of chronic liver disease, the ultrasound features of chronic liver disease and spleen size, transient elastography, 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 both low transient elastography values (< 10KPa) with one labelled as cryptogenic cirrhosis and the other with chronic viral hepatits B on 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.

3.2.1. 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.

3.2.2. 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).

3.2.2.1 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.

3.2.2.2 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.

3.2.2.3 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.

3.2.3. 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 $\chi 2$ or Fisher´s exact test were used for categorical variables as applicable. Follow-up was calculated from the time of study inclusion (1st January 2014) to patient status at last contact (30th March 2019) (Alive/death/OLT).

Cumulative incidence of nontumoral PVT, overall OLT free survival and OLT free survival in patients who did and did not develop nontumoral 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 nontumoral 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 nontumoral 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.

Table 3.1 Baseline demographic. clinical and laboratory features of patients 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%
Statin		36	15.1%
Antiviral therapy		94	39.0%
Diuretics		82	34.2%
Antidiabetic agents		67	27.9%
Proton pump inhibitor		78	32.4%
Prior 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; GOV 1 - Gastroesophageal varices 1; GOV 2 - Gastroesophageal varices 2; IGV1 - Isolated gastric varices

3.3. Results

Initially, 445 patients with chronic liver disease were evaluated, of which 185 were excluded (Figure 3.1). 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.

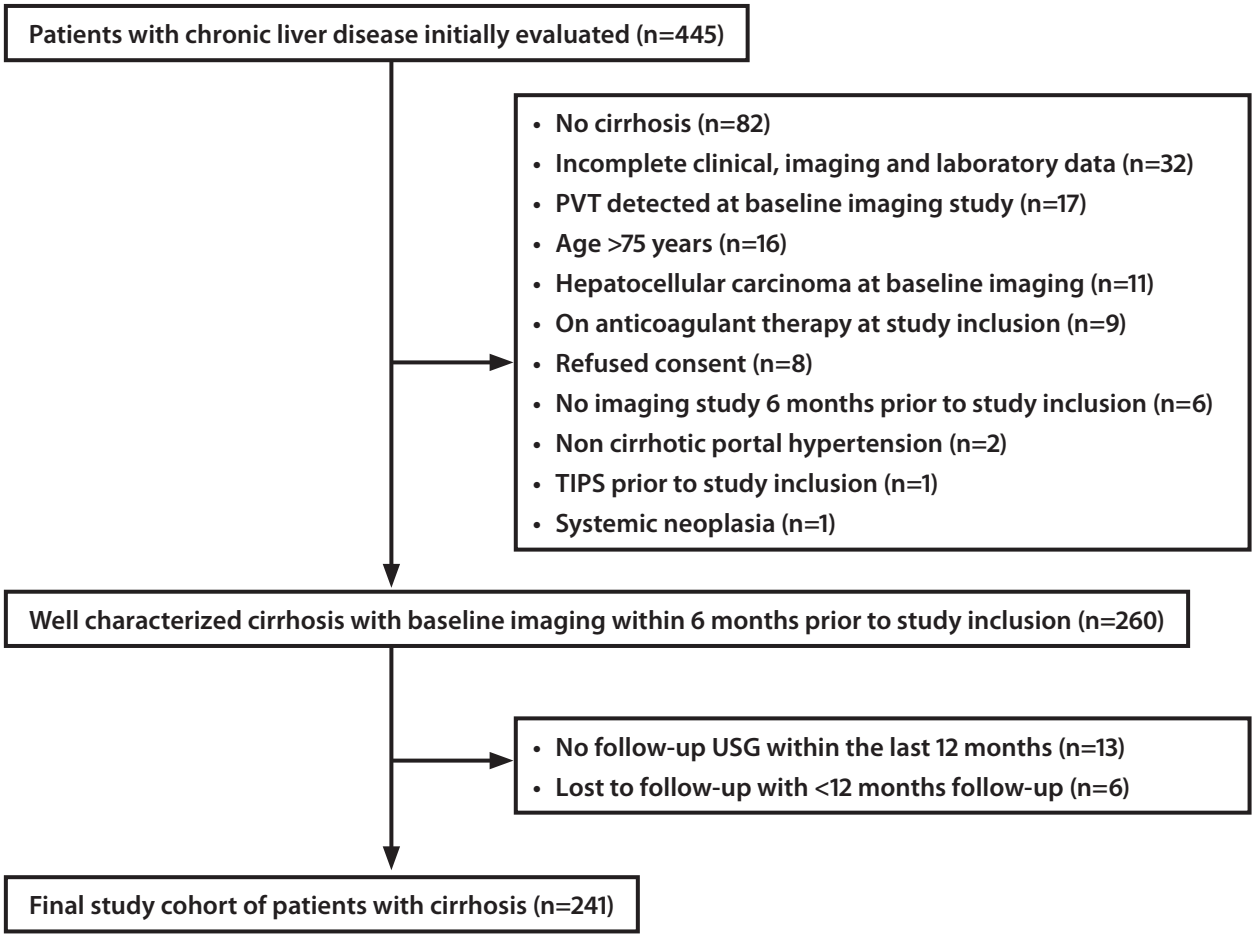

Figure 3.1 Flow chart illustrating patients evaluated and finally included in the study.

Baseline clinical, imaging, endoscopic and laboratory features are highlighted in table 3.1.

Mean age was 59 ± 10 years and 184 (76.3%) were males. Weight excess or obesity was noted in 157 (73.4%) 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 nontumoral PVT, HCC and decompensations of cirrhosis. During follow-up, 6.8% (16/236) patients developed HCC.

3.3.1. Incidence and risk factors for nontumoral 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 nontumoral PVT. Out of these, only two patients had occlusive PVT and 10 (66.7%) patients had concomitant portal hypertension complications at the time of diagnosis of PVT. All patients had features of acute PVT and the extent of PVT is shown in Supplementary table 3.1. The large group of patients with chronic liver disease without clear cut 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 / portal hypertension on abdominal ultrasound and/or endoscopy. None of these patients developed PVT.

The cumulative incidence of nontumoral PVT was 3.7% and 7.6% at 1 and 3 years (Figure 3.2). Factors at baseline associated with development of nontumoral 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 3.2). Factors associated with development of nontumoral PVT by Cox univariate regression analysis are shown in supplementary table 3.3. 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 nontumoral PVT (Table 3.2).

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.

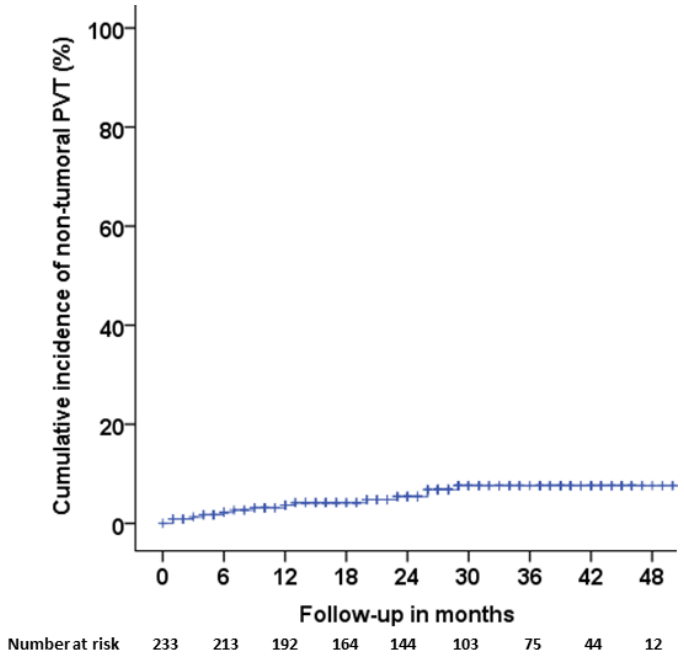

Figure 3.2 Incidence of nontumoral PVT in patients with cirrhosis.

Table 3.2 Multivariate analysis to determine predictive factors for nontumoral PVT decompensations of cirrhosis and death or OLT.

		95% CI		
	HR	**Lower**	**Upper**	**p value**
Development of non tumoral PVT				
Prior decompensation of cirrhosis	6.771	1.207	37.977	0.030
Platelet count x 10^9	.972	.955	.990	.002
Decompensation of cirrhosis				
Male gender	2.306	1.227	4.332	0.009
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	0.001
Hemoglobin (g/dL)	.723	.630	.831	<0.001

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

3.3.2. 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 3.4).

Factors associated with decompensation of cirrhosis by Cox univariate regression analysis are shown in supplementary table 3.5. Nontumoral 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 counts (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 3.2).

3.3.3. 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 3.6). 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 3.3). The significantly, better OLT free survival in patients who developed nontumoral 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 3.7). Factors at baseline associated with death/OLT by univariate Cox regression analysis are shown in supplementary table 3.8. 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 3.2).

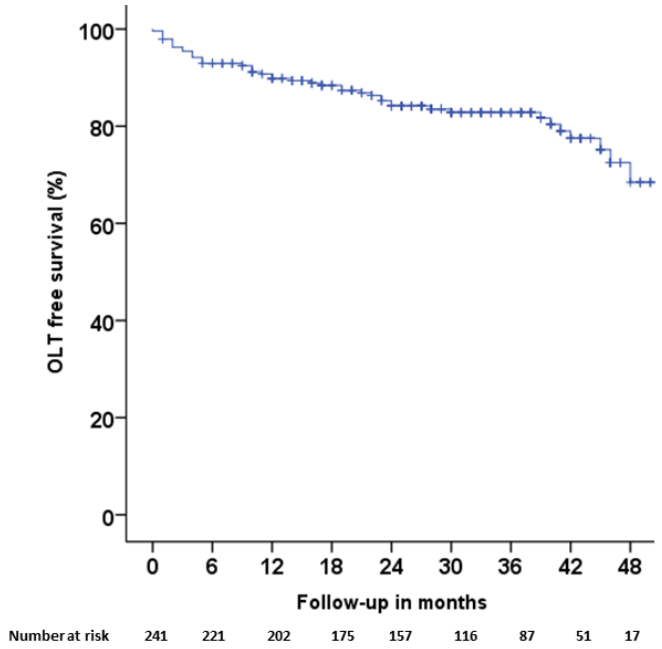

Figure 3.3 Overall OLT free survival in patients with cirrhosis.

3.4. Discussion

This prospective observational study involving a majority of patients with compensated cirrhosis but with clinical features of CSPH, detected a cumulative incidence of nontumoral PVT of 3.7% and 7.6% at 1 and 3 years respectively. Previous decompensation of cirrhosis and thromboctyopenia predicted development of nontumoral 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 nontumoral 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 nontumoral 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 hyperten-

sion 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. Nontumoral 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 nontumoral 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 third 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 hav-

ing 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 nontumoral PVT. The majority of patients who develop nontumoral PVT have partial thrombosis and it is not an independent predictor of cirrhosis decompensation or lower OLT free survival.

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Supplementary Data

Supplementary table 3.1
Clinical features, extent of Nontumoral PVT and degree of luminal occlusion at diagnosis.

No.	Etiology of cirrhosis	Child-Pugh class	PHT complications at diagnosis	PV trunk	PV left branch	PV right branch	Splenic vein	SMV
1	Alcohol	B	Yes	Partial >50%	Total	Partial <50%	No	No
2	Alcohol	A	Yes	No	Partial >50%	No	No	No
3	VHC	A	Yes	Total	Partial >50%	Partial <50%	NM	NM
4	Alcohol + VHC	C	Yes	Total	No	No	No	NM
5	Wilson´s disease	B	No	Partial <50%	Partial <50%	No	Total	No
6	Alcohol	A	No	Partial <50%	No	No	No	No
7	VHC	A	No	Partial >50%	No	No	Partial <50%	No
8	Alcohol	B	No	No	No	Partial <50%	No	NM
9	Alcohol	B	Yes	Partial <50%	No	No	No	No
10	Alcohol + VHC	A	Yes	Partial <50%	No	No	No	Partial >50%
11	Alcohol	A	Yes	No	No	Partial >50%	No	No
12	Alcohol	C	Yes	Partial <50%	No	No	No	NM
13	Cryptogenic	A	No	Partial >50%	No	No	No	No
14	VHB	A	Yes	Partial >50%	No	No	No	No
15	Alcohol	B	Yes	No	No	No	Partial <50%	Partial <50%

PHT - Portal hypertension; PV – Portal vein; VHC – Viral hepatitis C; VHB – Viral hepatitis B; NM – Not mentioned

Supplementary table 3.2

Comparing baseline features of patients who did and did not develop nontumoral PVT

		Developed PVT				
		No (n=218)		Yes (n=15)		
		Mean / N	SD / %	Mean / N	SD / %	p value
Age (years)		59	10	63	8	0.203
Male gender		166	76.1%	12	80.0%	1
BMI (kg/m2) (n = 214)		27.70	4.97	27.83	4.23	0.773
BMI class	18.5 ≤ 24.9kg/m^2	59	29.1%	5	35.7%	0.638
	≥ 25 < 29.9Kg/m^2	99	48.8%	5	35.7%	
	≥30kg/m^2	45	22.2%	4	28.6%	
Time from diagnosis of cirrhosis to study inclusion (months)		58	62	87	86	0.073
Etiolology of cirrhosis	Alcohol	91	41.7%	8	57.1%	0.603
	Alcohol + viral	43	19.7%	2	14.3%	
	Viral	52	23.9%	2	14.3%	
	Others	19	8.7%	2	14.3%	
	NASH	13	6.0%	0	0.0%	
Child-Pugh score		6	2	6	2	0.258
Child-Pugh class	A	171	78.4%	11	73.3%	0.587
	B	25	11.5%	3	20.0%	
	C	22	10.1%	1	6.7%	
MELD score		10	5	11	3	0.019
Active alchohol intake at study inclusion		29	13.5%	0	0.0%	0.227
Any psychiatric comorbidity		43	20.9%	3	20.0%	1
Cardiovascular comorbidities		114	52.5%	7	46.7%	0.66
Non selective beta blockers		52	23.9%	9	60.0%	0.004
Statins		34	15.7%	1	6.7%	0.707
Antiviral therapy		90	41.3%	4	26.7%	0.415
Diuretics		68	31.3%	9	60.0%	0.043
Antidiabetic therapy		61	28.1%	5	33.3%	0.768
Proton pump inhibitor		70	32.1%	6	40.0%	0.573
Previous decompensation of cirrhosis		105	48.4%	12	80.0%	0.018
Prior variceal bleed		34	32.4%	4	33.3%	1
Prior ascites		90	85.7%	11	91.7%	1
Prior hepatic encephalopathy		21	20.0%	4	33.3%	0.282
Prior jaudice		20	19.0%	0	0.0%	0.216
Any prior endoscopic banding of varices		51	25.8%	6	42.9%	0.21
Any esophageal or gastric varices (n= 221)		122	60.7%	13	92.9%	0.016
Esophageal varices		121	60.2%	13	92.9%	0.015
Gastric varices		8	4.0%	2	14.3%	0.077
Portal hypertensive gastropathy		82	40.8%	12	85.7%	0.005
Splenomegaly		119	55.1%	14	93.3%	0.014
Bipolar spleen diameter (cm)		13.58	2.28	17.33	2.35	<0.001
Ascitis at baseline ultrasound		52	24.0%	6	40.0%	0.214
Liver transient elastography values (KPa) (n = 135)		32.96	18.96	56.70	22.25	0.022
Hemoglobin (g/dL)		13.5	2.0	13.6	1.8	0.962
Platelets x 10^9		122	58	67	29	<0.001
Platelet count <150 x 10^9		158	72.8%	15	100.0%	0.014

SD – Standard deviation; BMI Body mass index

Supplementary table 3.3
Cox regression analysis to determine factors associated with development of nontumoral PVT.

		95% CI		
	HR	**Lower**	**Upper**	**p value**
Age (years)	1.045	.984	1.110	0.15
Male gender	1.446	.403	5.189	0.572
BMI (Kg/m2)	1.003	.903	1.114	0.956
Time since diagnosis of cirrhosis to study inclusion (months)	1.005	.999	1.011	0.14
Etiology of cirrhosis (Alcohol / Non-alcohol related)	1.477	.504	4.329	0.477
Child-Pugh score	1.163	.896	1.510	0.256
MELD score	1.123	1.02	1.235	0.018
Active alcohol intake at study inclusion	.042	.000	53.667	0.384
Psychiatric comorbidities	.670	.171	2.634	0.567
Cardiovascular comorbidities	.796	.288	2.205	0.661
Nonselective beta blockers	4.631	1.643	13.053	0.004
Statins	.415	.055	3.154	0.395
Antiviral therapy	.482	.153	1.517	0.212
Diuretics	4.331	1.529	12.266	0.006
Previous decompensation of cirrhosis	5.031	1.414	17.904	0.013
Prior variceal bleed	.921	.277	3.064	0.893
Prior ascites	2.183	0.281	16.942	0.455
Prior hepatic encephalopathy	2.202	.662	7.324	0.198
Prior jaundice	.039	.000	36.666	0.352
Any prior endoscopic banding of varices	2.098	.726	6.066	0.171
Any esophageal or gastric varices	8.708	1.138	66.661	0.037
Splenomegaly (> 13 cm)	11.330	1.490	86.210	0.019
Ascites at baseline ultrasound	2.761	.977	7.801	0.055
Liver transient elastography KPa	1.048	.998	1.100	0.06
Hemoglobin (g/dL)	.996	.768	1.291	0.974
Platelet count x10^9	.970	.954	.986	<0.001
Platelet count < 150 x 10^9	32.862	.256	4213.384	0.158

HR – Hazard ratio; CI – Confidence interval; BMI – Body mass index

Supplementary table 3.4

Comparing baseline features of patients with and without decompensations of cirrhosis during follow-up.

		Any decompensation of cirrhosis				
		No (n=154)		Yes (n=82)		
		Mean / N	SD / %	Mean/N	SD / %	p value
Age (years)		59	9	60	10	0.198
Male gender		114	74.0%	67	81.7%	0.184
BMI (kg/m2) (n = 219)		27.95	5.05	27.29	4.64	0.285
BMI class	18.5 to ≤ 24.9kg/m2	42	29.4%	22	28.9%	0.875
	≥ 25 to < 29.9Kg/m2	67	46.9%	38	50.0%	
	≥30kg/m2	34	23.8%	16	21.1%	
Time from diagnosis of cirrhosis to study inclusion (months)		58	60	62	71	0.944
Etiolology of cirrhosis	Alcohol	58	37.7%	43	53.1%	0.067
	Alcohol + viral	28	18.2%	18	22.2%	
	Viral	42	27.3%	12	14.8%	
	Others	16	10.4%	5	6.2%	
	NASH	10	6.5%	3	3.7%	
Child-Pugh score		5	1	7	2	<0.001
Child-Pugh class	A	142	92.2%	41	50.0%	<0.001
	B	8	5.2%	22	26.8%	
	C	4	2.6%	19	23.2%	
MELD score		9	4	13	5	<0.001
Active alchohol intake at study inclusion		12	7.9%	18	22.0%	0.002
Any psychiatric comorbidity		38	26.0%	8	10.3%	0.005
Cardiovascular comorbidities		84	54.9%	38	46.3%	0.211
Non selective beta blockers		30	19.5%	31	37.8%	0.002
Statins		25	16.3%	10	12.3%	0.415
Antiviral therapy		67	43.5%	27	32.9%	0.114
Diuretics		28	18.3%	50	61.0%	<0.001
Antidiabetic therapy		44	28.8%	22	26.8%	0.754
Proton pump inhibitor		41	26.6%	37	45.1%	0.004
Previous decompensation of cirrhosis		55	35.9%	65	79.3%	<0.001
Prior variceal bleed		22	40.0%	17	26.2%	0.107
Prior ascites		43	78.2%	59	90.8%	.054
Prior hepatic encephalopathy		10	18.2%	17	26.2%	0.297
Prior jaudice		10	18.2%	11	16.9%	0.857
Any prior endoscopic banding of varices		33	23.9%	25	32.9%	0.157
Any esophageal or gastric varices		79	56.4%	57	74.0%	0.01
Esophageal varices		78	55.7%	57	74.0%	0.008
Gastric varices		6	4.3%	5	6.5%	0.526
Portal hypertensive gastropathy		54	38.6%	41	53.2%	0.045
Splenomegaly		77	50.7%	57	69.5%	0.01
Bipolar spleen diameter (cm)		13.29	2.33	14.69	2.47	0.001
Ascitis at baseline ultrasound		15	9.8%	43	52.4%	<0.001
Liver transient elastography values (KPa) (n = 135)		30.66	17.97	42.79	20.66	0.002
Hb (g/dL)		13.9	1.8	12.7	2.2	<0.001
Platelets x 10^9		128	61	99	49	<0.001
Platelet count <150 x 10^9		106	69.3%	70	85.4%	0.007

OLT - Orthotopic liver transplantation; N - Number; SD - Standard deviation; BMI - Body Mass Index

Supplementary table 3.5
Cox regression analysis to determine factors associated with any decompensation of cirrhosis.

		95% CI		
	HR	Lower	Upper	p value
Age (years)	1.013	.990	1.037	0.284
Male gender	1.615	.920	2.834	0.095
BMI (Kg/m2)	.980	.935	1.028	0.416
Etiology of cirrhosis (Alcohol / Non alcohol)	2.125	1.293	3.491	0.003
Active alcohol intake at study inclusion	2.935	1.732	4.976	<0.001
Psychiatric comorbidity	.329	.156	.693	0.003
Cardiovascular comorbidities	.834	.539	1.292	0.417
Nonselective beta blockers	1.532	.979	2.399	0.062
Statins	1.143	.586	2.229	0.696
Antiviral therapy	.690	.434	1.096	0.116
Diuretics	3.687	2.361	5.757	<0.001
Antidiabetic therapy	.972	.596	1.587	0.91
Proton pump inhibitors	1.790	1.155	2.773	0.009
Previous decompensation of cirrhosis	4.370	2.560	7.460	<0.001
Prior variceal bleed	.758	.434	1.324	0.329
Prior ascites	1.951	.841	4.525	0.12
Prior hepatic encephalopathy	1.151	.653	2.029	0.626
Prior jaundice	1.348	.701	2.593	0.37
Prior endoscopic banding of varices	1.495	.923	2.421	0.102
Any esophageal and / or gastric varices	1.682	1.009	2.805	0.046
Splenomegaly (> 13 cm)	1.575	.983	2.523	0.059
Ascites at baseline ultrasound	4.63	2.99	7.17	<0.001
Liver transient elastography (KPa)	1.021	1.003	1.038	0.019
Hemoglobin (g/dL)	.785	.712	.865	<0.001
Platelet count x 10^9	.995	.990	.999	0.015
Platelet count <150 x 10^9	1.959	1.061	3.618	0.032
Portal vein thrombosis (Time dependent)	2.156	1.171	3.969	0.014

HR - Hazard ratio; CI - Confidence interval; BMI - Body mass index

Supplementary table 3.6
Causes of death or orthotopic liver transplantation.

Outcomes		Number (N)
Death		**38**
	Sepsis	18
	ESLD	9
	HCC	8
	Variceal bleed	1
	Cardiac failure	1
	Lung cancer	1
Orthotopic liver transplantation	ESLD	**7**
Total		**45**

ESLD – End stage liver disease; HCC – Hepatocelular carcinoma.

Supplementary table 3.7

Comparing baseline features of patients who died or underwent orthotopic liver transplantation compared to those who did not.

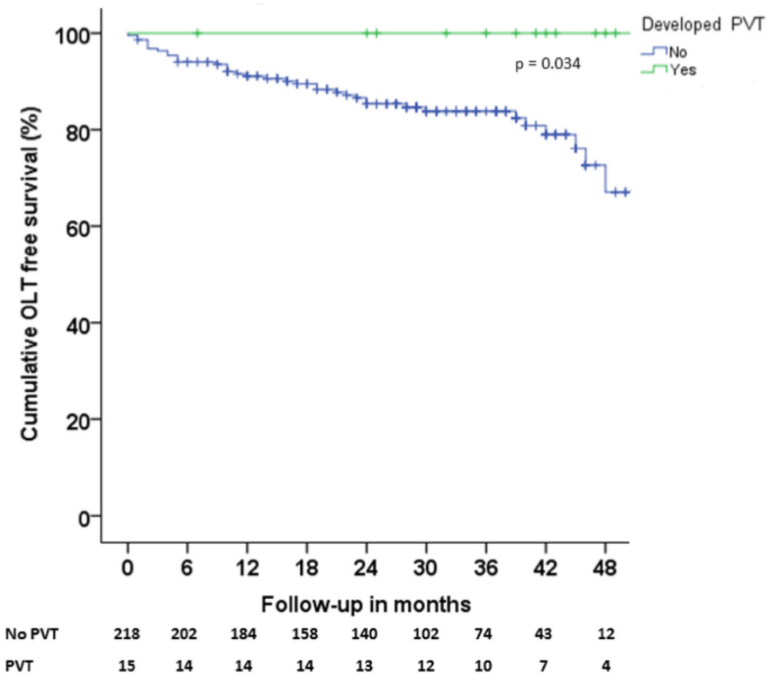
		OLT or death				
		No (n = 196)		Yes (n= 45))		
		Mean/N	SD/%	Mean/N	SD/%	p-value
Age (years)		59	10	59	9	0.999
Male gender		144	73.5%	40	88.9%	0.028
Body mass index (BMI) (kg/m2) (n=214)		27.88	4.88	26.64	4.98	0.048
BMI class	18.5 ≤ to 24.9kg/m2	52	28.3%	14	35.9%	0.261
	≥ 25 to < 29.9Kg/m2	87	47.3%	20	51.3%	
	≥30kg/m2	45	24.5%	5	12.8%	
Time from cirrhosis diagnosis to study inclusion (months)		59	62	58	70	0.518
Etiolology of cirrhosis	Alcohol	78	40.0%	26	57.8%	0.04
	Alcohol + viral	37	19.0%	9	20.0%	
	Viral	50	25.6%	4	8.9%	
	Others	21	10.8%	2	4.4%	
	NASH	9	4.6%	4	8.9%	
Child-Pugh score		6	1	8	3	<0.001
Child-Pugh class	A	165	84.2%	19	42.2%	<0.001
	B	23	11.7%	8	17.8%	
	C	8	4.1%	18	40.0%	
MELD score		9	3	16	8	<0.001
Active alcohol intake at study inclusion		15	7.8%	16	35.6%	<0.001
Any psychiatric comorbidity		41	21.9%	6	14.3%	0.268
Comorbidities		98	50.3%	26	57.8%	0.363
Nonselective beta blockers		51	26.0%	12	26.7%	0.929
Statin		28	14.4%	8	18.2%	0.522
Antiviral_therapy		84	42.9%	10	22.2%	0.01
Diuretics		55	28.2%	27	60.0%	<0.001
Antidiabetic agents		54	27.7%	13	28.9%	0.872
Proton pump inhibitor		59	30.1%	19	42.2%	0.117
Previous decompensation of cirrhosis		88	45.1%	37	82.2%	<0.001
Prior variceal bleed		30	34.1%	10	27.0%	0.44
Prior ascites		74	84.1%	33	89.2%	0.459
Prior hepatic encephalopathy		18	20.5%	11	29.7%	0.262
Prior jaudice		12	13.6%	10	27.0%	0.073
Any prior endoscopic banding of varices		48	27.1%	11	27.5%	0.961
Any esophageal or gastric varices		109	60.9%	30	71.4%	0.203
Esophageal varices		108	60.3%	30	71.4%	0.182
Gastric varices		8	4.5%	3	7.1%	0.441
Portal hypertensive gastropathy		73	40.8%	23	54.8%	0.051
Splenomegaly		106	54.6%	31	68.9%	0.047
Bipolar spleen diameter (cm)		13.72	2.61	14.28	1.77	0.081
Ascitis at baseline ultrasound		37	19.0%	25	55.6%	<0.001
Liver transient elastography KPa (n = 135)		32.17	18.44	50.97	22.83	0.004
Hemoglobin (g/dL)		13.8	1.8	11.9	2.2	<0.001
Platelets x 10^9		122	60	95	50	0.007
Platelets <150 x 10^9		143	73.3%	37	82.2%	0.215

OLT - Orthotopic liver transplantation; N - Number; SD - Standard deviation; BMI - Body Mass Index

Supplementary table 3.8
Cox regression analysis to determine factors associated with death or OLT.

		95% CI		
	HR	**Lower**	**Upper**	**p value**
Age (years)	1.000	.970	1.032	0.984
Male gender	2.652	1.046	6.727	0.04
BMI (kg/m2)	.948	.880	1.021	0.157
Time since diagnosis cirrhosis before study inclusion	.999	.994	1.004	0.618
Etiology of cirrhosis (Alcohol / Non alcohol)	2.413	1.194	4.875	0.014
Child Pugh score	1.575	1.413	1.755	<0.001
MELD score	1.192	1.148	1.237	<0.001
Active alcohol intake at study inclusion	4.971	2.681	9.215	<0.001
Psychiatric comorbidity	.555	.232	1.332	0.187
Cardiovascular comorbidities	1.309	.723	2.367	0.374
Nonselective beta blockers	0.949	0.489	1.84	0.877
Statins	1.526	.706	3.302	0.283
Antiviral therapy	.404	.200	.817	0.012
Diuretics	3.537	1.943	6.436	<0.001
Antidiabetic therapy	1.054	.553	2.009	0.873
Proton pump inhibitors	1.598	.884	2.889	0.121
Previous decompensation of cirrhosis	5.011	2.332	10.769	<0.001
Prior variceal bleed	.729	.352	1.508	0.394
Prior ascites	1.626	.576	4.594	0.359
Prior hepatic encephalopathy	1.629	.804	3.300	0.175
Prior jaundice	2.193	1.059	4.539	0.034
Prior endocopic banding of varices	1.060	.529	2.124	0.87
Any esophageal and / or gastric varices	1.494	.765	2.920	0.24
Ascites at baseline ultrasound	4.834	2.671	8.746	<0.001
Liver transient elastography (KPa)	1.039	1.010	1.068	0.007
Hemoglobin (g/dL)	.701	.620	.793	<0.001
Platelet count x 10^9	.992	.986	.999	0.015
Platelet count < 150 x 10^9	1.547	0.72	3.323	0.264
Portal vein thrombosis (Time dependent)	0.038	0	11.792	0.264

HR - Hazard ratio; CI - Confidence interval; BMI - Body mass index



Supplementary Figure 3.1 Nontumoral PVT is not associated with poorer OLT free survival compared to patients without PVT.

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CHAPTER 4 NATURAL HISTORY AND MANAGEMENT OF ESOPHAGOGASTRIC VARICES IN CHRONIC NONCIRRHOTIC NONTUMORAL PORTAL VEIN THROMBOSIS

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Abstract

Background and aims: In patients with chronic non-cirrhotic nontumoral portal vein thrombosis (PVT), the usually recommended strategy for endoscopic screening and management of varices is the same as in cirrhosis. However, the efficacy of this policy in patients with PVT is unknown. We aimed at assessing the course of gastroesophageal varices in a large cohort of patients with chronic PVT.

Methods: Patients prospectively registered in 2 referral centres for vascular liver disorders were eligible for the study. End-points evaluated were development and growth of varices, and the incidence and outcome of portal hypertension related bleeding.

Results: 178 patients with chronic PVT were included. Median follow-up was 49 (1–598) months. Variceal bleeding was the initial manifestation in 27 (15%) patients. Initial endoscopy in the remaining 151 patients showed: no varices in 52 (34%), small esophageal varices (SEVs) in 28 (19%), large esophageal varices (LEVs) in 60 (40%), and gastric varices (GVs) without LEVs in 11 (7%). Ascites and splenomegaly were independent predictors for presence of varices. In patients without varices, the probability of developing varices was 2%, 22% and 22% at 1, 3 and 5 years. In those with SEVs, growth to LEV was observed in 13%, 40% and 54% at 1, 3 and 5 year. In patients with LEVs on primary prophylaxis, probability of bleeding was 9%, 20% and 32% at 1, 3 and 5 years respectively. Nine (5%) patients died after a median 51 (8–280) months, only one due to variceal bleeding.

Conclusions: The course of varices in chronic non-cirrhotic nontumoral PVT appears to be similar to that in cirrhosis. Using the same therapeutic approach as for cirrhosis is associated with a low risk of bleeding and death.

Keywords: Portal cavernoma, variceal development, variceal growth, portal hypertensive bleeding, mortality.

4.1. Introduction

Chronic non-cirrhotic nontumoral portal vein thrombosis (PVT) is a rare vascular disorder of the liver with variceal bleeding being its main manifestation (1) (2). Indeed, several retrospective cohort studies have shown a high prevalence of esophageal varices at the time of chronic PVT diagnosis (3) (4). Due to the low incidence and prevalence of PVT, specific studies aimed at determining adequate strategies for endoscopic screening and management of varices are scarce and small sized. Consequently, the 2015 Baveno VI Consensus suggested to apply in patients with PVT the same recommendations validated for patients with cirrhosis and portal hypertension, i.e. to perform a baseline endoscopy at diagnosis of PVT and subsequent endoscopies at 2 or 3 year intervals in patients with no esophageal varices or small esophageal varices at baseline; to use beta-blockers or endoscopic band ligation as a primary prophylaxis; and to use drug plus endoscopic band ligation to treat variceal bleeding and prevent re-bleeding (5). However, whether this is also an effective and safe strategy in patients with PVT remains to be determined.

The aim of our study was to assess the course of varices in a large cohort of patients with chronic PVT with complete obstruction of either the portal vein trunk and/ or both branches by determining the prevalence of esophageal and gastric varices at initial endoscopy; the incidence of varices and predictive factors for its development in those without varices at initial endoscopy; the probability of, and predictive factors for the growth of small to large esophageal varices; and the incidence, outcome, and predictive factors of gastroesophageal variceal bleeding, rebleeding and death.

4.2. Methods

4.2.1. Study design

Patients with PVT prospectively registered in 2 referral centres for vascular disorders of the liver (from July 1984 at Hospital Clinic in Barcelona and from March 1983 at Hôpital Beaujon, Clichy, Paris) were eligible for the study. All patients had given written informed consent to use their clinical data for research purposes. The guidelines of good clinical practice enumerated in the Declaration of Helsinki of 1964 and the revision in Edinburgh in 2000 were followed and the ethical committees of the 2 participating hospitals approved the study protocol.

Clinical records of these patients, with special attention to reports of upper endoscopies, were reviewed and data retrospectively collected in a predesigned case report form. Patients with liver disease, spontaneous or anticoagulation-induced recanalization, or partial thrombosis of the portal or splenic veins, or isolated complete thrombosis of the splenic or superior mesenteric vein with patent portal vein were excluded from the analysis (Figure 4.1). Liver disease was reasonably discarded by means of: 1) Clinical history; 2) ruling out etiological factors for liver disease; 3) Imaging studies and 4) liver biopsy in doubtful cases. Time of inclusion into the study was considered the date of the first upper gastrointestinal endoscopy in patients with an imaging study showing PVT causing portal hypertension due to complete obstruction of the portal trunk and/or both branches of the portal vein.

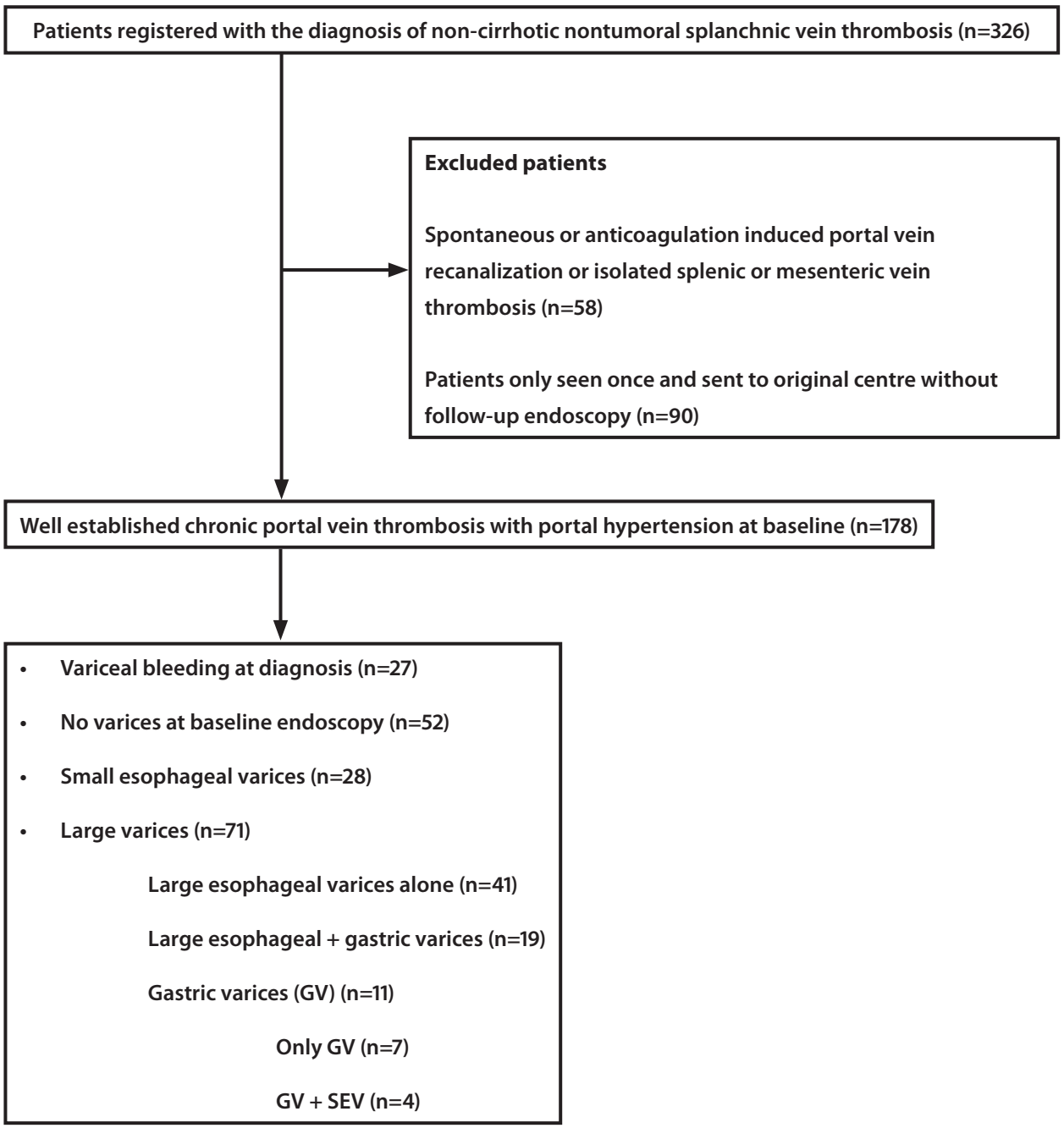

Figure 4.1 Flowchart of patients included in the study.

Dates of first screening endoscopy and of subsequent endoscopies were recorded. Follow-up data were collected up to February 2014 or death. End-points evaluated during follow-up included: a) in patients without varices: the development of esophageal and/or gastric varices during follow-up; b) in those with small esophageal varices: growth to large esophageal varices; c) and in patients with large esophageal varices, the incidence of portal hypertension related bleeding. Additionally, the outcome of portal hypertensive related bleeding and death were also recorded.

Due to the retrospective nature of the study, time between follow-up endoscopies was not homogeneous. The median interval between follow-up endoscopies was calculated by dividing the time period between initial screening endoscopy and the latest surveillance endoscopy in relation

to the studied outcome (appearance, growth of varices or bleeding from varices, respectively) by the total number of endoscopies performed during this period of time. This interval was defined as the Time/Endoscopy (TE) index.

4.2.2. Definitions

PVT was considered acute when patients presented with abdominal pain or intestinal ischemia in absence of clinical, endoscopic or imaging evidence of portal hypertension. Such patients were considered to have developed stable chronic portal vein thrombosis, and therefore being eligible for the study, if there was no recanalization of the portal vein but development of a portal cavernoma, confirmed at imaging investigations performed at least 6 months after the acute PVT episode. Patients with chronic PVT at diagnosis were those presenting with portal cavernoma with clinical, ultra-sonographic or endoscopic signs of portal hypertension.

Esophageal varices were defined as large (LEV) or small (SEV) if ≥5mm or <5mm respectively (6). The gastric varices (GV) were defined according to the classification by Sarin et al (7). Bleeding related to portal hypertension (variceal bleeding and portal hypertensive gastropathy) was defined according to Baveno VI criteria (8).

In most patients an exhaustive etiological study of an underlying prothrombotic disorder was performed as previously described (3) (9) (10).

4.2.3. Statistical analysis

Quantitative data were expressed as means ± standard deviation, or median with range with statistical analysis performed using the Student's t test or Mann Whitney test when appropriate. Qualitative data were expressed as frequencies and percentages and analysed using Pearson's chi-squared test or Fischer's exact test when appropriate. Backward logistic regression was used to determine independent predictors (Odds Ratio OR with 95% CI) of presence of varices at baseline. Independent predictors for variceal appearance, growth and bleeding events were estimated as Hazard Ratio (HR) with 95% CI, using Cox regression analysis and extended Cox regression analysis for time varying covariates. Age was adjusted to the outcome analysed. The risk of varices appearance, growth of varices and occurrence of variceal bleeding during follow-up was described with the cumulative incidence function taking into account death as competing risk. This provides more accurate estimations of varices appearance, growth of varices and occurrence of variceal bleeding rates than censoring patients at the time of death in a Kaplan-Meier analysis (11). Competing risk analysis was performed with the R package cmprsk, with the aid of the CumIncidence function developed by Scrucca et al. (12). Variables with p-value <0.1 in the univariate analysis were considered for the multivariate analyses. The maximum number of variables included in the multivariate analysis was 1 per 5-10 outcomes. A p-value <0.05 was considered to be statistically significant. Data analysis was performed with SPSS version 20 (Chicago, IL, USA) and R (www.r-project.org).

4.3. Results

A total of 326 patients with PVT were prospectively registered in the 2 referral centers with the diagnosis of splanchnic vein thrombosis. One hundred and forty seven patients were excluded: 90 had no follow-up endoscopy data after first visit since they were referred back to the primary center, 42 had spontaneous or anticoagulation induced total recanalization of the PVT, 11 had partial thrombosis of the splanchnic vessels not causing portal hypertension, and 5 had isolated complete thrombosis of the splenic or superior mesenteric vein. Finally, 178 patients were included in the study (Figure 4.1). Baseline characteristics and etiological factors are shown in table 4.1. An inherited prothrombotic factor and at least one acquired systemic prothrombotic factor was detected in 29% and 48% of evaluated patients, respectively (Table 4.1). Median (range) follow-up was 49 (1–598) months.

Table 4.1 Baseline demographic, clinical and imaging features of patients included in the study (n = 178)

	N, Mean	%, SD
Male gender	96	54%
Age, years	41	±16
Hematocrit, %	38	±7
Platelet count, x10^9	283	±269
Platelet count <100 x10^9	21	14%
Platelet count <150 x10^9	45	29%
Prothrombin time, %	76	±22
ALT, U/L	43	±38
AST, U/L	34	±23
Alkaline phosphatase, U/L	194	±204
GGT, U/L	95	±128
Albumin, g/L	40	±6
Known acute PVT at diagnosis	37	21%
Inherited * prothrombotic factor (evaluated in 158 patients)	42	27%
Acquired † prothrombotic factor (evaluated in 168 patients)	81	50%
Myeloproliferative disease (evaluated in 165 patients)	64	39%
Any inherited or acquired prothrombotic factor (evaluated in 158 patients)	94	59%
Two or more prothrombotic factors (evaluated in 158 patients)	30	19%
PVT without either SV or SMV thrombosis	63	35%
PVT plus SV thrombosis without SMV thrombosis	23	13%
PVT plus SMV thrombosis without SV thrombosis	25	14%
PVT plus SV and SMV thrombosis	67	38%
Ascites at baseline (evaluated 174 patients)	37	21%
Splenomegaly (evaluated in 156 patients)	111	71%
Splenectomy	15	9%
Anticoagulation	84	51%

* Prothrombin gene mutation, Factor V Leiden mutation, Protein C and S deficiency, Anti thrombin III deficiency.

† Myeloproliferative disorders, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria and excluding local factors, oral contraceptives and pregnancy.

N – number of patients; SD – Standard deviation; PVT – Portal vein thrombosis; SV – Splenic vein; SMV – Superior mesenteric vein

Variceal bleeding was the first manifestation of PVT in 27 patients (15%) (EV in 26 and GV in 1). In the remaining 151 patients, no varices were present in 52 (34%), SEV (all without red signs) in 28 (19%) and

LEV in 60 patients (40%) (in 19 of them with associated GV). In 11 (7%) additional patients, there were large GV (in 4 associated with SEV) (Supplementary figure 4.1). In summary, 71 patients had LEV and/or GV susceptible of primary prophylaxis (47% of patients not presenting with variceal hemorrhage). Among them, red signs were not mentioned in 12 patients and were present in 20 of the remaining 60 patients (33%). Ascites was present in 37/174 (21%) patients, but was usually mild, only detectable at imaging studies in 25. During the follow-up 17 additional patients developed ascites.

At the time of inclusion in the study, 84 patients were receiving anticoagulation and 43 additional patients received anticoagulation subsequently during follow-up. The reasons for anticoagulation were prothrombotic conditions in 83 patients (Myeloproliferative disorders 57, genetic or other acquired thrombophilic factors in 26), re-thrombotic events without an identified thrombophilic factor in 11 and 33 patients presenting with severe acute PVT episode. During follow-up anticoagulation was stopped in 22 patients, in 6 of them due to complications attributed to it. Anticoagulation was re-started later on due to new thrombotic events in 6 patients.

In patients without variceal bleeding at diagnosis, presence of ascites and of splenomegaly was the only independent predictor for the presence of varices of any size at baseline endoscopy (Table 4.2) and (Figure 4.2). They were also independent predictors of presence of large gastroesophageal varices requiring primary prophylaxis. To exclude the potential confounding factor of the presence of splenomegaly in patients with a myeloproliferative neoplasm, the analysis was repeated excluding these patients. Ascites and splenomegaly still were the only independent predictors of presence of varices at baseline endoscopy. However, EV were present in 11% of patients without either ascites or splenomegaly.

Table 4.2 Factors associated with presence of any varices at baseline endoscopy excluding patients with variceal bleeding at diagnosis (n=151).

	Univariate analysis	**Multivariate analysis**		
	O.R. 95 % C.I.	**p value**	**O.R. 95% C.I.**	**p value**
Hematocrit, %	0.94 [0.89 to 0.99]	0.027		
Platelet count, x10^9	1 [1 to 1]	0.108		
Platelet count <150 x10^9	1.87 [0.84 to 4.19]	0.127		
Prothrombin time, %	0.98 [0.97 to 1]	0.078		
ALT, U/L	1.01 [1 to 1.02]	0.204		
Albumin, g/L	0.93 [0.87 to 0.99]	0.021		
Known acute PVT at diagnosis	2.98 [1.41 to 6.32]	0.004		
Inherited * prothrombotic factor (evaluated in 104 patients)	1.08 [0.5 to 2.35]	0.846		
Acquired † prothrombotic factor (evaluated in 138 patients)	1.18 [0.59 to 2.35]	0.633		
PVT without either SV or SMV thrombosis	0.93 [0.48 to 1.83]	0.837		
PVT plus SV and SMV thrombosis	0.76 [0.39 to 1.47]	0.410		
Ascites at baseline	3.34 [1.22 to 9.14]	0.019	4.05 [1.26 to 13.03]	0.019
Splenomegaly (evaluated in 132 patients)	4.35 [2.04 to 9.3]	<0.001	3.91 [1.77 to 8.66]	0.001

* Prothrombin gene mutation, Factor V Leiden mutation, Protein C and S deficiency, Anti thrombin III deficiency.

† Myeloproliferative disorders, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria and excluding local factors, oral contraceptives and pregnancy.

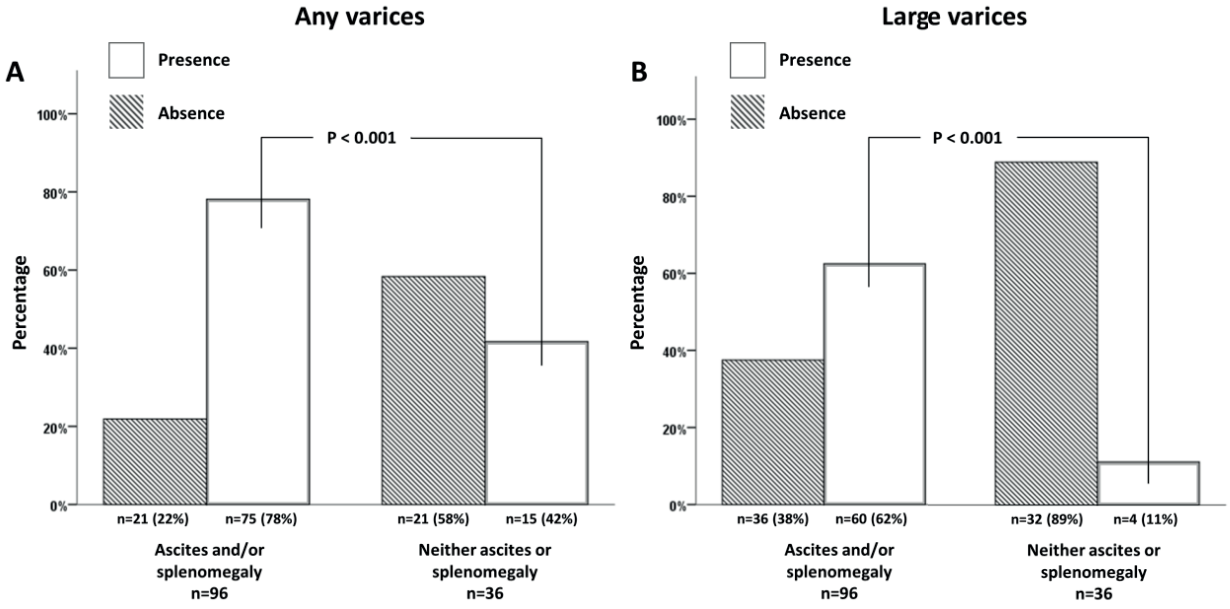

Figure 4.2 Ascites and splenomegaly predict presence of varices at initial endoscopy.

4.3.1. Development of varices in patients without varices at initial endoscopy

Forty out of the 52 (77%) patients without esophageal or gastric varices at initial endoscopy had at least one surveillance endoscopy. Surveillance endoscopy was not performed in the remaining 14 patients due to a follow-up < 2 years in 9 patients and for unknown reason in 5. The median elapsed time for development of varices was 37.5 months (range 7 – 166), the median TE index was 17.6 months (range 4 – 94) and the median number of follow-up endoscopies performed 2 (range 1–9).

Varices developed in 10 (25%) patients (SEV in 5, LEV in 4 and IGV1 alone in 1), with an actuarial probability of 2%, 22% and 22% at 1, 3 and 5-years respectively (Figure 4.3a). At univariate Cox regression analysis, including the use of anticoagulation, only splenomegaly had a trend to be associated with a higher risk of variceal formation (Supplementary table 4.1). Due to the retrospective nature of the study the potential impact of rethrombosis on the splanchnic area could not be evaluated.

4.3.2. Esophageal variceal growth

Thirty three patients had SEV (in 28 at initial endoscopy and in 5 additional patients during follow-up endoscopies). In 24 of them (73%), at least one follow-up endoscopy was performed. Follow-up endoscopy was not performed due to follow-up time less than 2 years in 5 patients and for unknown reason in 4. Median elapsed time was 27 months (range 9 – 218), the TE index was 11 months (range 5–83) and the median number of endoscopies performed 2 (range 1–19).

Growth from SEV to LEV occurred in 10/24 (42%) patients, 4 of whom also developed GV (GOV2 in 2, GOV1 in 1, IGV1 in1). Additionally, 2 patients maintained SEV but developed large GV (Supplementary figure 4.1). Actuarial probability of variceal growth (esophageal or gastric) was 13%, 40% and 54% at 1, 3 and 5-years respectively (Figure 4.3b). At univariate Cox regression analysis there were no significant factors associated with variceal growth, including anticoagulant therapy and coexisting myeloprolif-

erative disorders. Interestingly, in 3 patients (12.5%) SEVs disappeared during follow-up. Only 1 of them was on anticoagulation. Variceal disappearance was confirmed during a follow-up at 25, 114 and 125 months during which 3, 5 and 3 follow-up endoscopies were performed respectively.

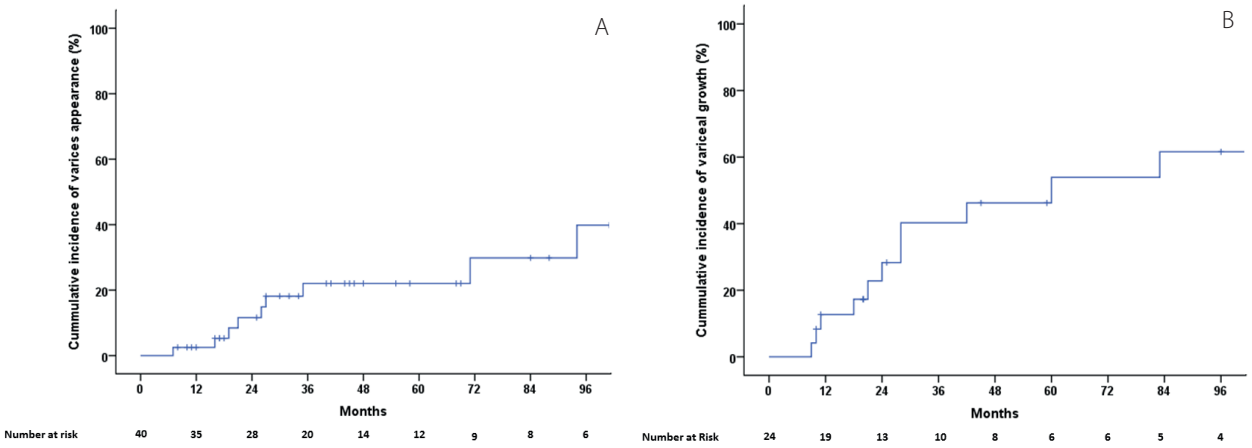

Figure 4.3 (A) Actuarial probability of development of varices. (B) Actuarial probability of growth of SEVs.

4.3.3. Preventing first variceal bleeding

4.3.3.1 Patients with large esophageal varices

LEVs were identified in 74 patients. Twenty-three patients also had concomitant GV (GOV2: n=13, GOV1: n=8 and IGV1: n=2). In 60/74, LEVs were found at the baseline endoscopy and in the remaining 14 patients they appeared during follow-up after a median of 27.5 months (range 9–94) months. In 3 of them LEV were identified during a variceal bleeding episode at 28, 60 and 94 months after the previous endoscopy which showed small esophageal varices in 2 and no varices in 1 patient, respectively. Therefore, 71 patients were candidates for primary prophylaxis. Four patients were not treated for unknown reasons (3 of them (75%) - developed portal hypertensive bleeding episodes). Sixty-seven patients received primary prophylaxis: 59 only with non-selective beta-blockers (NSBB), 5 with NSBB + endoscopic band ligation (EBL) and 3 only with EBL because of contraindications/side effects of NSBB. Median dose of NSBB was 100 mg (range 10–240 mg). Twenty one of the 67 patients (31%) had a portal hypertensive hemorrhage. The actuarial probability of bleeding was 9%, 20% and 32% at 1, 3 and 5 years respectively (Figure 4.4a). Bleeding rates were similar among patients receiving only NSBB (19/59: 32%) or EBL (alone or with NSBB) 2/8: 25%. One patient bled during the first prophylactic EBL session. Sources of bleeding were EV in 16, GV in 2, portal hypertensive gastropathy in 2 and ectopic varices in 1. Univariate Cox regression analysis, including treatment with anticoagulants and coexisting myeloproliferative disorders, did not identify any predictive factor for first bleeding in this population (Supplementary table 4.2).

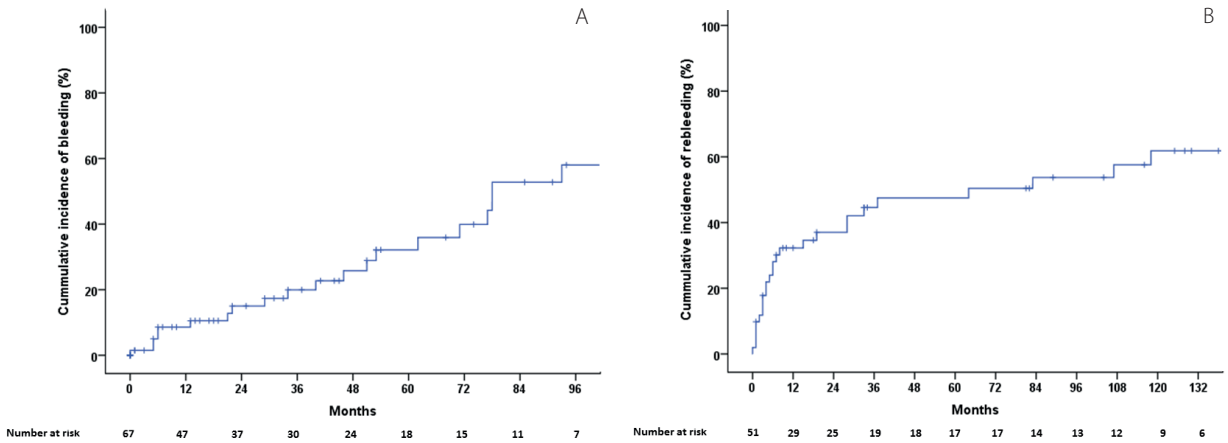

Figure 4.4 (A) Actuarial probability of portal hypertension-related bleeding in patients on primary prophylaxis. (B) Actuarial probability of rebleeding after a portal hypertensive bleeding.

4.3.3.2 Gastric varices

Fourteen patients had GV; IGV1 in 6 patients, IGV2 (gastric corpus) in 4 and GOV2 in 4. Six patients had concomitant SEV and 8 without esophageal varices. In 1 patient GOV2 were diagnosed at variceal bleeding. In 4 patients GV were small and primary prophylaxis was not initiated. Thus, only 9 of these patients received primary prophylaxis with NSBB. None of these patients bled during a median follow-up of 46 (6–248) months. As previously mentioned, 23 additional patients had GV in association to LEV and were submitted to primary prophylaxis, 2 bled from GV.

4.3.4. Acute bleeding episodes

4.3.4.1 First bleeding episode

At least one portal hypertensive bleeding episode occurred in 57 patients (at diagnosis in 28 patients and in 29 additional patients during follow-up). Source of bleeding was EV in 48 patients, GV in 4, ectopic varices in 1 and portal hypertensive gastropathy or enteropathy/colopathy in 4. Clinical data of the gastrointestinal bleeding episode are summarized in Table 4.3. Twenty-one (37%) patients were on primary prophylaxis and 15 (26%) were receiving anticoagulants (Coumadin in 11, LMWH in 4) at the time of upper gastrointestinal bleeding. 75% of patients received blood with a median of 4 packed blood cell units (range 1–40). Hemostatic endoscopic therapy was the mainstay of treatment (Table 4.3). Failure to control bleeding or early re-bleeding occurred in 9 (17%) patients. Six of them underwent emergency surgery as rescue therapy (derivative in 5 and non-derivative in 1). Despite surgery, 3 patients had further re-bleeding finally controlled by adding NSBB. There was no mortality related to this first gastrointestinal bleeding episode despite 15 patients were receiving anticoagulation when they bled.

Table 4.3 Clinical features of first portal hypertensive bleeding episode (N = 57).

	N, Mean	%, SD
Male gender	34	60%
Age, years	42	19
Bleeding under primary prophylaxis	21	37%
Bleeding under anticoagulation	15	26%
Percentage of patients requiring blood transfusion		75%
Number of packed RBC units	4	7
Treatment used (% of patients)		
Only vasoactive drugs		30%
EBL and vasoactive drugs		23%
EIS and vasoactive drugs		26%
Cyanoacrylate injection and vasoactive drugs		2%
Not mentioned		19%
Failure to control bleeding episode		16%
Rescue surgical shunt		11%
Mortality		0

SD – Standard deviation; EBL – Endoscopic band ligation; EIS – Endoscopic injection sclerotherapy.

4.3.4.2 Secondary prophylaxis and rebleeding

Of the 51 patients surviving the first bleeding episode without need of rescue surgery, 30 began endoscopic therapy (EBL or EIS) alone or with concomitant NSBB, 16 were treated only with NSBB, 4 did not receive secondary prophylaxis for unknown reasons and one had elective shunt surgery. The median dose of propranolol was 80mg (range 10–360mg). Twenty-four (47%) patients rebled on secondary prophylaxis. Actuarial probabilities of rebleeding on secondary prophylaxis at 1, 3 and 5-years were 32%, 45% and 47% (Fig 4b) without significant differences between patients in whom bleeding was the first manifestation of PVT (n=24) and those in whom the first bleeding developed during follow-up (n=27). Sources of rebleeding were EV in 17, GV in 2, post EBL ulcers in 3, ectopic varices in 1 patient, portal hypertensive colopathy and enteropathy in 1 patient each and unknown origin in 1 patient. Blood transfusions were given in 73% of patients with a median of 4 packed blood cell units (range 1–21). Failure to control rebleeding episode occurred in 4 patients with rescue surgery required to control the bleeding episode in 3 patients. Ten additional patients were submitted to elective surgery (6 non derivative and 4 derivative) to prevent further re-bleeding. Only one patient, refusing rescue surgery, died as a consequence of variceal re-bleeding. Univariate Cox regression analysis did not identify any clinical or imaging factor predicting rebleeding in this population. Again, neither anticoagulant therapy nor myeloproliferative disorders were associated with higher rebleeding rate (Supplementary table 4.3).

4.3.5. Survival

During follow-up, 9 (5%) patients died. One, 3 and 5 year actuarial probabilities of survival were 99%, 98% and 96%, respectively (Figure 4.5). Four patients died due to multi-organ failure, 2 due to multiple extra-splanchnic thrombotic events, 1 to extra-hepatic malignancy, 1 from a malabsorptive syndrome of unknown origin and 1 because of variceal rebleeding. Age, altered liver enzymes, and

presence of ascites at baseline were significantly associated with mortality at univariate Cox regression analysis. Due to the low number of events no multivariate analysis was performed.

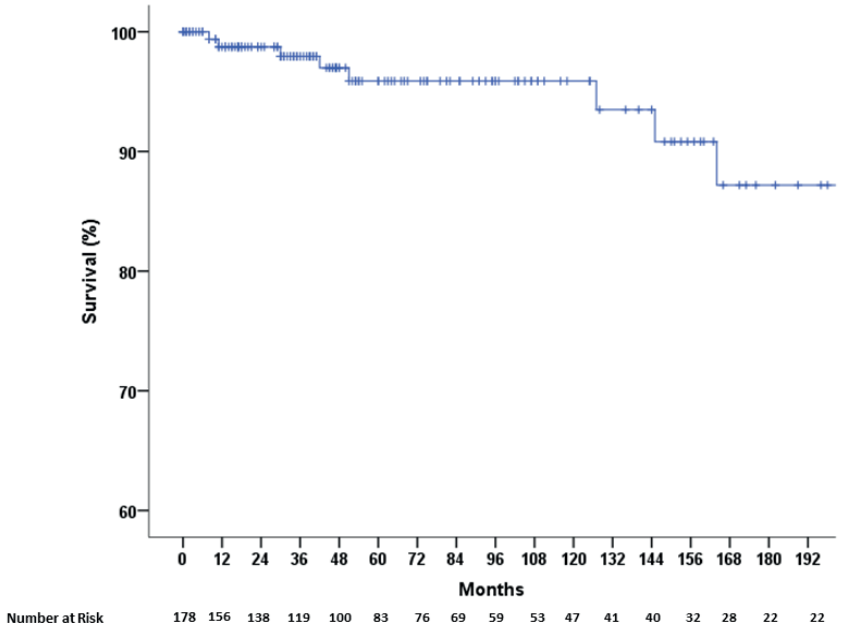

Figure 4.5 Survival probability in patients with chronic portal vein thrombosis.

4.4. Discussion

The current study includes a large cohort of consecutive patients with chronic PVT followed in 2 referral centers for patients with portal hypertension and vascular liver disorders. The strengths of the study derive from i) endoscopic follow-up performed according to a relatively standardized schedule in patients without varices or with small esophageal varices; ii) primary and secondary prophylaxis of variceal bleeding applied in a relatively uniform manner in almost all patients with adequate indication; iii) an etiologic work-up of pro-thrombotic factors in most of patients and anticoagulant therapy given according to a uniform management protocol (10).

Variceal bleeding was the first manifestation of PVT in 27 patients (15%), similar to what was reported in other previous studies in patients without cirrhosis or malignancy (3) (13).

It is important to note that the number of patients in whom variceal bleeding was the first manifestation of PVT markedly decreased with time. Indeed, only 7 of the 120 (6%) patients diagnosed of PVT after 2001 had variceal bleeding as the presenting symptom of chronic PVT. This likely reflects the fact that currently PVT is diagnosed earlier in its course by highly sensitive and now widely available imaging studies in patients with no or few clinical manifestations.

Seventy one percent of our patients had esophageal varices at the first upper endoscopy. This percentage was 55% (98/178) if bleeding varices or those at high risk of bleeding were only considered. Considering only the 151 patients without variceal bleeding at diagnosis of PVT, 34% of them did not have varices, 19% had SEV and 47% LEV requiring primary prophylaxis (40% esophageal and 7% gastric varices). The percentage of varices found in our cohort of patients at baseline endoscopy is similar to

that found at screening endoscopy in previous studies in patients with cirrhosis (14) (15) (16). However, in these studies the proportion of small and large varices differed ((14), (16) or was not specified ((15). Therefore a comparison with the prevalence of small and large varices detected in our study cannot be performed.

Ascites and splenomegaly were found to be independent predictors of the presence of gastro-esophageal varices at baseline endoscopy. Gastro-esophageal varices were present in over 85% of patients with ascites and in 74% of those with splenomegaly. However, among patients without ascites or splenomegaly still 42% had gastroesophageal varices, although only 11% had large gastro-esophageal varices requiring primary prophylaxis. Thus, although the risk of having large varices is low in patients without ascites or splenomegaly, the absence of splenomegaly and/or ascites cannot be safely used as a criterion to rule out the presence of high-risk varices. This finding supports the recent the Baveno VI meeting recommendations that it is mandatory to perform screening endoscopy in all patients at diagnosis of chronic PVT (5).

Actuarial probability of development of varices in patients without varices at initial endoscopy was of 2% at 1 year and 22% at 3 and 5-years respectively. Our data differ from the study by Amitrano et al, (13) where no development of varices was observed during the follow-up in 20 patients with portal and/or splenic vein thrombosis. We have no clear explanation for this discrepancy; however, the larger number of patients included in our study and the longer follow-up of our patients may explain the difference. Our findings support the current empirical recommendation that patients with PVT without varices need to be submitted to follow-up screening endoscopies. Indeed, the observed incidence of esophageal varices in our study is almost identical to that found in the prospective timolol study (17) and only slightly lower than the 5%, 17% and 28% at 1, 2 and 3 years respectively reported in patients with cirrhosis by Merli et al. (18). Although ours was not a prospective study, in our cohort of patients the median interval time between baseline and follow-up endoscopies was 17.6 months, lower than the 2-3 years interval recommended to assess variceal development in patients with compensated cirrhosis (5).

There are scarce data on the probability of variceal growth in patients with PVT. Amitrano et al. reported variceal growth of SEV during follow-up in 3 out of 8 patients with PVT (13). In the current study, the actuarial probability of growth of SEV requiring primary prophylaxis was 13%, 40% and 54% at 1, 3 and 5 years respectively. This rate was similar to that reported by Merli et al. (19) in which majority of patients with cirrhosis belonged to Child-Pugh classes A and B (41% at 3 years and 51% at 5 years). The median interval time between baseline endoscopy showing SEV and the one detecting variceal growth divided by the total number of endoscopies performed during this period of time was 11 months, which is close to the 12 – 18 months recommended for evaluating the potential for growth of small varices in patients with cirrhosis (5). Interestingly, in 3 (11%) patients, SEV disappeared during follow-up. Thus, our results strongly suggest that patients with PVT and SEV should undergo follow-up endoscopies to identify variceal growth/regression.

In our study, 3 patients bled during follow-up before identifying LEV, and therefore without receiving primary prophylaxis. All of them had the initial endoscopy showing no or small varices over 2 years before. This finding further supports the need to perform endoscopies at the 1-2 year interval recommended for patients with cirrhosis (6).

Once varices become large, the actuarial probability of bleeding despite primary prophylaxis was 9%, 20% and 32% at 1, 3 and 5 years respectively. A figure that is comparable to bleeding rates in patients with cirrhosis and large varices on primary prophylaxis (20) (22), (22) (23) (24) and clearly lower than the observed incidence of bleeding in the 4 patients of our cohort that did not receive prophylaxis (3 of 4). Thus, although the number of patients without prophylaxis was very low, our data suggests that the recommendation for primary prophylaxis of variceal bleeding in cirrhosis is valid for patients with chronic PVT. It is important to remark that no robust data on the spontaneous bleeding risk in patients with chronic PVT and large varices exists. Rate of first bleeding was similar in patients receiving only NSBB or EBL (+/-NSBB). However, because most patients received NSBB, our study cannot provide strong information regarding comparison of efficacy between both methods in primary prophylaxis.

It is important to remark that our study was unable to identify any relationship between the use of anticoagulation and the course of esophageal varices. Thus, there were no significant differences in variceal development, growth or bleeding in patients receiving or not anticoagulation.

Overall, at least one portal hypertensive bleeding episode occurred in 57 (32%) patients. Although transfusion of blood products was required in 75% patients and rescue shunt surgery due to failure to control bleeding in 6/57 (11%) patients, there were no deaths related to the first bleeding episode, which is in accordance with previous data (3) (11) (25) (26) on the extremely low mortality of variceal bleeding in patients with PVT. This low mortality occurred despite 26% of patients bleeding while under anticoagulation treatment, confirming previous observations in an independent population (26) (27) that anticoagulation did not have a major impact in the outcome of variceal bleeding in patients with PVT. A similar observation has been reported in patients with cirrhosis (28).

In our cohort of patients with previous variceal bleeding, despite the use of secondary prophylaxis, the actuarial probability of re-bleeding at 1, 3 and 5 years was 32%, 45% and 47% respectively, a rebleeding rate similar to that reported in the literature for variceal rebleeding during secondary prophylaxis in patients with cirrhosis (29) (30) (31) (32). Rebleeding rates in our study were lower than those reported in a large study by Spaander et al. (26) but within the range of the rebleeding rate reported in an smaller study by the same group where patients were submitted to secondary prophylaxis with EBL (33) and in the study by Orr et al. (34). By contrast, our rebleeding rates were slightly higher than those reported by Sarin et al. although they included patients with both PVT and non-cirrhotic portal hypertension (25). Any how, the observed rebleeding rate clearly shows that there is still a room for improvement.

Although gastrointestinal bleed at diagnosis of PVT (13), anticoagulant therapy (26) extension of thrombosis to the splenic vein, presence of gastric fundal varices (33) and thrombosis of the superior mesenteric vein (35) have all been described as predictive factors associated with re-bleeding episodes during follow-up, we could not confirm these findings in our study. Finally, in our cohort of patients with PVT the mortality was very low only occurring in 9 patients (5%) with an actuarial probability of survival of 99% and 96% at 1 and 5 years respectively, confirming the good prognosis of these patients (13) (26) (34) (36). In our study, by univariate Cox regression analysis, age, altered liver enzymes and ascites were significantly associated with mortality, as previously observed by Janssen et al. (35) (26) and Orr et al. (34).

In this study, selection bias was minimized by including all patients with non-cirrhotic nontumoral PVT registered and followed at the two centers. The long study period of over 20 years could be associated with a change in the management of patients seen early in the study, compared to those diagnosed more recently with the latter patients being more likely to receive anticoagulation with consequently greater possibility of portal vein recanalization (37). However, this potential bias was reduced by only including patients with well-developed chronic portal vein thrombosis with portal hypertension. Finally, and despite that the presence of an underlying liver disease was plausibly discarded, we cannot completely exclude that, in any case a minority, of patients an unrecognized liver disease may have been missed.

In conclusion, the study confirms that gastroesophageal varices are a frequent finding in patients with chronic PVT. They are especially frequent in patients with ascites, even only detected at imaging studies, or with splenomegaly. Varices at high risk of bleeding are infrequent, but not rare in the absence of these two factors. Most progression, indicated by development of varices in patients without varices at diagnosis, and variceal growth in patients with small varices, takes place early in the course of portal vein thrombosis. The risk appears to be similar to that of patients with cirrhosis and therefore calls for a similar schedule of follow-up endoscopies, In short, every 2-3 years in patients without varices and every 1-2 years in those with small varices.

The risk of first variceal bleeding on primary prophylaxis and of rebleeding are also similar to those observed in cirrhosis provided a similar therapeutic approach based on NSBB and endoscopic therapy is used. Anticoagulation does not seem to be associated with higher risk of bleeding and rebleeding. Mortality of bleeding in patients with PVT is very low, and mostly related to conditions not directly related with PVT.

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Supplementary Data

Supplementary table 4.1 Factors associated with appearance of varices during follow-up.

	HR [95% CI]	p-value
Male gender	2.67 [0.66 to 10.77]	0.169
Age	0.96 [0.91 to 1.02]	0.161
Platelet count, x10^9	1 [1 to 1]	0.375
Platelets <100	0.04 [0.00 to 20138]	0.638
Platelets <150	0.71 [0.08 to 6.11]	0.756
Prothrombin time, %	1 [0.96 to 1.03]	0.928
ALT, U/L	1.02 [0.99 to 1.05]	0.285
AST, U/L	1.02 [0.99 to 1.05]	0.257
Alkaline phosphatase, U/L	1 [0.99 to 1]	0.400
GGT, U/L	1 [0.99 to 1.01]	0.941
Albumin, g/L	1.01 [0.87 to 1.17]	0.907
Known acute PVT at diagnosis	0.5 [0.1 to 2.4]	0.383
Inherited prothrombotic factor	1.78 [0.42 to 7.56]	0.437
Acquired prothrombotic factor	2.58 [0.64 to 10.32]	0.181
Myeloproliferative disorders	1.32 [0.35 to 4.91]	0.683
Any inherited or acquired prothrombotic factor	1.85 [0.46 to 7.44]	0.384
Two or more prothrombotic factors	3.43 [0.82 to 14.46]	0.093
PVT without either SV or SMV thrombosis	0.51 [0.11 to 2.46]	0.401
PVT plus SV thrombosis without SMV thrombosis	1 [0 to 8046.01]	1.000
PVT plus SMV thrombosis without SV thrombosis	1.5 [0.31 to 7.25]	0.614
PVT plus SV and SMV thrombosis	0.88 [0.24 to 3.29]	0.851
Ascites at baseline endoscopy	0.04 [0 to 419.74]	0.499
Splenomegaly	6.61 [0.8 to 54.95]	0.080
Anticoagulation as time dependent variable	2.11 [0.43 to 10.42]	0.360

*Prothrombin gene mutation, Factor V Leiden mutation, Protein C and S deficiency, Anti thrombin III deficiency,
†Myeloproliferative disorders, antiphospholipid syndrome
HR, Hazard ratio; CI, Confidence Interval; PVT, Portal vein thrombosis; SV, Splenic vein; SMV, Superior mesenteric vein

Supplementary table 4.2 Factors associated with portal hypertensive bleeding while on primary prophylaxis

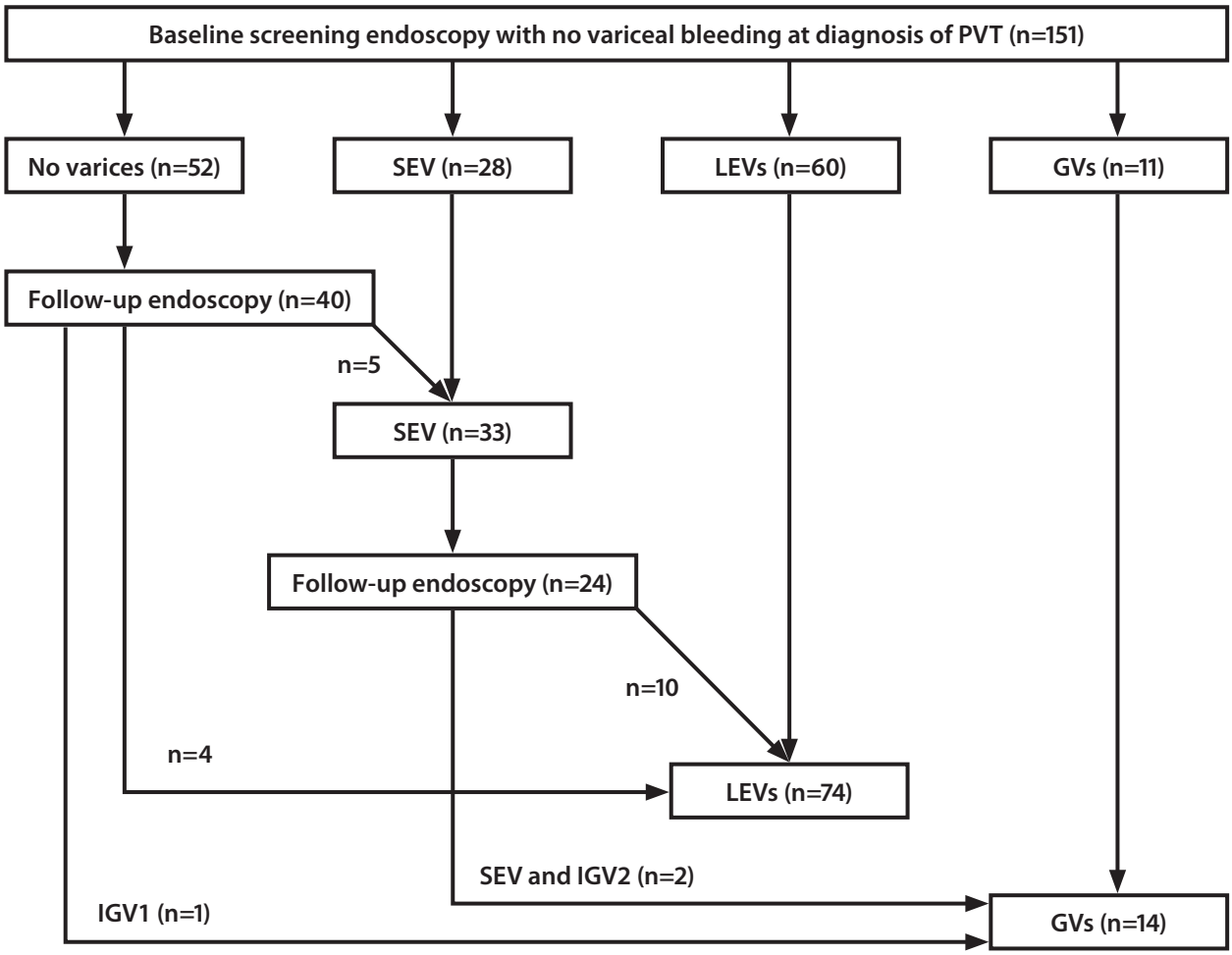
	HR [95% CI]	p-value
Age, years	1 [0.97 to 1.04]	0.831
Age of thrombus (when known acute PVT at diagnosis)	1.1 [0.9 to 1.34]	0.356
Male gender	1.71 [0.69 to 4.24]	0.249
Known acute PVT at diagnosis	0.55 [0.13 to 2.4]	0.426
Inherited prothrombotic factor*	1.17 [0.41 to 3.38]	0.768
Acquired prothrombotic factor†	1.24 [0.49 to 3.13]	0.653
Any inherited or acquired prothrombotic factor	1.33 [0.5 to 3.5]	0.566
Myeloproliferative disorder	1.83 [0.70 to 4.83]	0.220
Two or more prothrombotic factors	1.11 [0.37 to 3.35]	0.856
Anticoagulation	1.23 [0.47 to 3.26]	0.676
Anticoagulation as a time dependent variable	1.09 [0.44 to 2.69]	0.850

*Prothrombin gene mutation, Factor V Leiden mutation, Protein C and S deficiency, Anti thrombin III deficiency
†Myeloproliferative disorders, antiphospholipid syndrome
HR, Hazard ratio; CI, Confidence Interval; PVT, Portal vein thrombosis

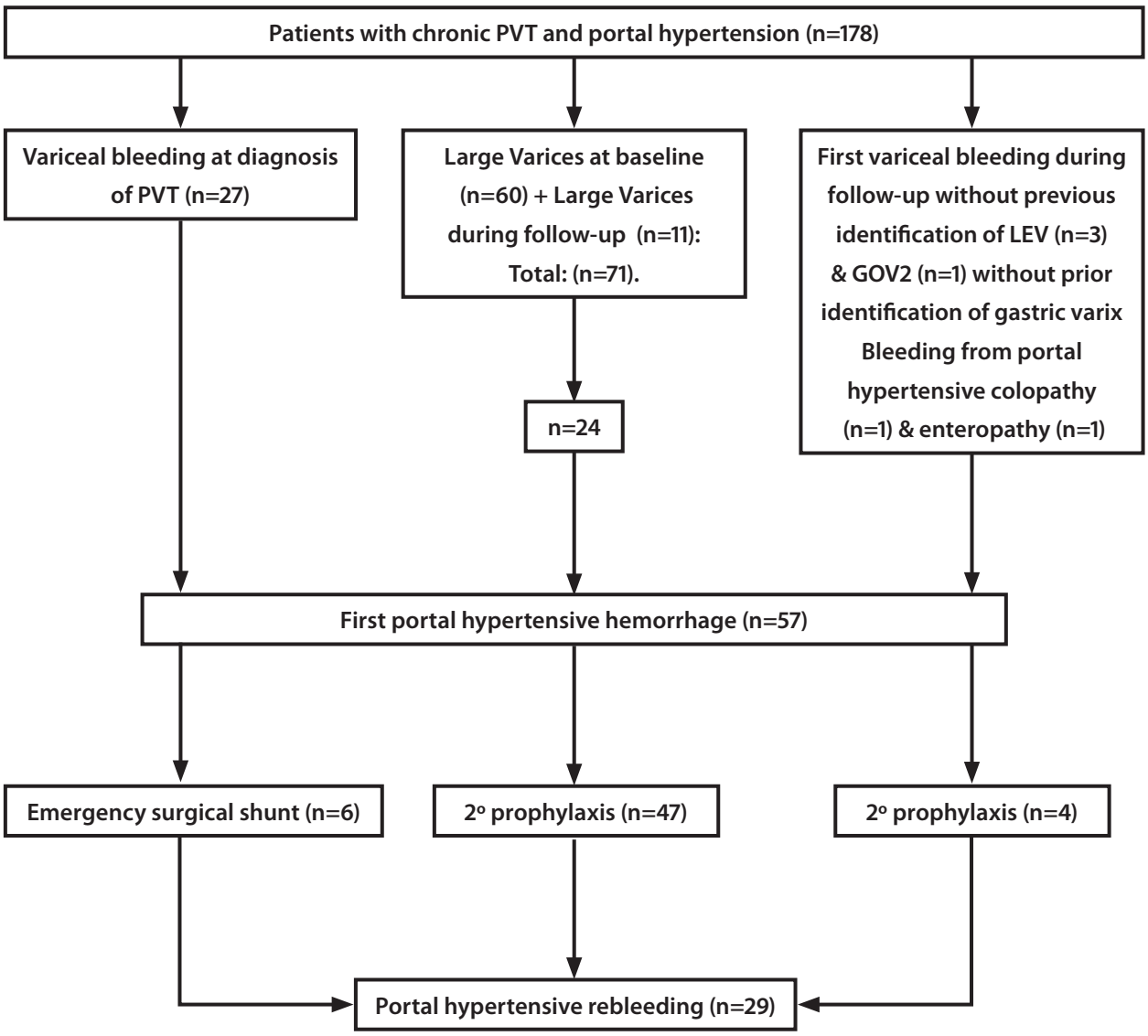
Supplementary table 4.3 Factors associated with portal hypertensive rebleeding.

	HR [95% CI]	p-value
Age, years	0.99 [0.97 to 1.02]	0.595
Age of thrombus (when known acute PVT at diagnosis)	0.56 [0.16 to 1.96]	0.366
Male gender	1.69 [0.71 to 4.02]	0.236
Known acute PVT at diagnosis	0.05 [0 to 5717.69]	0.610
Inherited prothrombotic factor	0.43 [0.13 to 1.44]	0.171
Acquired prothrombotic factor	0.66 [0.29 to 1.5]	0.320
Any inherited or acquired prothrombotic factor	0.56 [0.24 to 1.27]	0.165
Myeloproliferative disorder	0.61 [0.26 to 1.43]	0.253
Two or more prothrombotic factors	0.39 [0.09 to 1.65]	0.198
Splenomegaly	21.72 [0 to 296098.75]	0.526
Anticoagulation	0.59 [0.25 to 1.41]	0.235
Secondary prophylaxis of variceal bleeding	1.08 [0.26 to 4.59]	0.914

*Prothrombin gene mutation, Factor V Leiden mutation, Protein C and S deficiency, Anti thrombin III deficiency
†Myeloproliferative disorders, antiphospholipid syndrome
HR, Hazard ratio; CI, Confidence Interval; PVT, Portal vein thrombosis



Supplementary figure 4.1 Flow chart illustrating development of varices in PVT.



Supplementary figure 4.2 Flow chart illustrating the portal hypertensive bleeding and rebleeding episodes

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CHAPTER 5 ANTICOAGULATION IN CIRRHOSIS AND PORTAL VEIN THROMBOSIS IS SAFE AND IMPROVES PROGNOSIS IN ADVANCED CIRRHOSIS

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Abstract

Background: The role of portal vein thrombosis (PVT) in the natural history of cirrhosis is controversial.

Aims: We analyzed safety and effect of anticoagulation therapy (AT) on PVT recanalization and orthotopic liver transplant (OLT) free survival.

Methods: 80 consecutive patients from a prospective registry of cirrhosis and nontumoral PVT at a tertiary centre were analyzed. AT effect on PVT recanalization and OLT free survival was determined by time-dependent Cox regression analysis.

Results: Average MELD score was 15±7. Portal hypertension related complications at PVT diagnosis were present in 65 (81.3%) patients. Isolated portal vein trunk/branch thrombosis was present in 53 (66.3%) patients. AT was started in 37 patients. AT was stopped in 17 (45.9%) patients, in 4 (10.8%) due to bleeding events. No variceal bleeding occurred while on AT. Anticoagulation was restarted in 6/17 (35.2%) patients due to rethrombosis. In 67 patients with adequate follow-up imaging, AT significantly increased PVT compared with patients who did not receive anticoagulation (51.4% (18/35) vs 6/32 (18.8%), p=0.005). OLT free survival after a median follow-up of 25 (1–146) months was 32 (40%). Although there was no significant effect of AT on overall OLT free survival, OLT free survival was higher among patients with MELD ≥15 receiving AT compared to those who did not (p=0.011). Baseline MELD at PVT detection independently predicted PVT recanalization (HR 1.11, 95%CI1.01–1.21,p=0.027) and mortality/liver transplantation (HR 1.12, 95% CI1.05–1.19, p<0.001).

Conclusions: Although AT did not improve overall OLT free survival, it was associated with higher survival in advanced cirrhosis. Anticoagulation increased PVT recanalization and should be maintained after PVT recanalization to avoid rethrombosis.

Keywords: Portal vein thrombosis; cirrhosis; anticoagulation; rethrombosis; orthotopic liver transplantation; prognosis

5.1. Introduction

In cirrhosis, non tumoral portal vein thrombosis (PVT) prevalence varies between 0.6 and 26% (1) (2) (3). The accuracy of abdominal Doppler ultrasound (US) for detecting PVT varies between 26 and 87%; this is due to three reasons: false negative reports since majority of patients who develop PVT have partial thrombosis at diagnosis, identification of portal collaterals as the portal vein and also because of de novo PVT after US in patients awaiting orthotopic liver transplantation (OLT) (2) (4) (5). In a prospective study in patients with cirrhosis awaiting liver transplantation, abdominal Doppler US detected PVT in 8.4% patients at baseline and de novo PVT was detected in an additional 7.4% patients at the time of liver transplantation (6).

The impact of the cirrhosis severity on development of PVT is well established but the impact of PVT on survival is controversial due to different patient selection criteria in published studies (3) (7). In a large prospective study in patients with cirrhosis, the development of PVT did not independently predict worsening of liver disease (3). However, the study did not include Child-Pugh C patients and PVT was partial in most patients and as such its conclusions may not be applicable to patients with advanced cirrhosis or those who develop occlusive PVT.

The efficacy and safety of anticoagulation in patients with cirrhosis and PVT is controversial. A prospective study evaluating prophylactic anticoagulation with low molecular weight heparin (LMWH) in advanced cirrhosis (Child-Pugh scores 7-10) decreased the incidence of PVT, decompensations of cirrhosis and mortality compared to controls (8). Complete recanalization of PVT in patients with cirrhosis receiving anticoagulation was associated with lower incidence of portal hypertension related events and higher OLT free survival (9). A meta-analysis in patients with cirrhosis concluded that PVT recanalization rates were significantly higher (71% vs 42%) receiving anticoagulation and there was no significant difference in major and minor bleeding in patients with cirrhosis who did and did not receive anticoagulants (10). However, there are several limitations to this meta-analysis, including small sample size, a mixture of different types of studies and the absence of an evaluation of the effect of anticoagulation on OLT free survival. Recently, in a large retrospective study, anticoagulation in patients with nontumoral PVT independently predicted better prognosis (11). However, in this study, there were only 13% patients belonging to Child-Pugh C and patients with less advanced cirrhosis (Child-Pugh A) were significantly more likely to be given anticoagulation compared to Child-Pugh C patients which makes it difficult to generalize the effect of anticoagulation to patients with more advanced cirrhosis.

In this study, we retrospectively analyzed the safety and effect of anticoagulation on nontumoral PVT recanalization and OLT free survival in a prospectively collected cohort of patients, majority of whom with advanced cirrhosis and nontumoral PVT who did or did not receive anticoagulant therapy (AT).

5.2. Methods

Initially, 95 patients diagnosed with cirrhosis and PVT identified between 1st January 2002 and 31st December 2017 and registered in a prospective clinical registry were evaluated and data from 80 consecutive patients with clinical, imaging and laboratory or biopsy proven features of cirrhosis with nontumoral PVT were analyzed retrospectively. Reasons for exclusion of 15 patients are given in Figure 5.1. Patients were diagnosed with PVT during abdominal US with/without Doppler as part of semestral screening for hepatocellular carcinoma (HCC) or during hospitalization for decompensated cirrhosis. Date of diagnosis of PVT was considered as time zero for computing follow-up. In patients with equivocal diagnosis, contrast enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) were used to determine presence and extent of PVT and to rule out HCC.

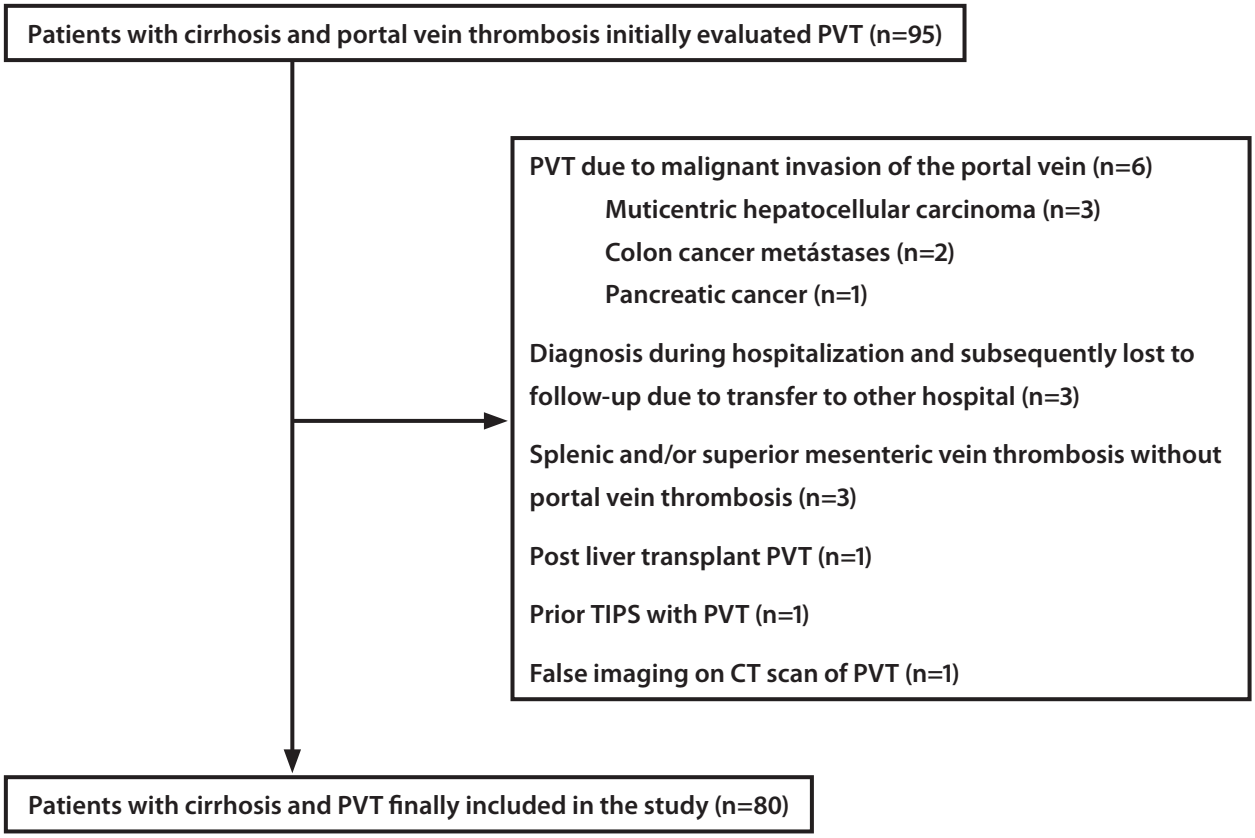

Figure 5.1 Flow chart of patients included in the study.

PVT was defined as thrombosis involving one of more of the segments of the splanchnic circulation: Portal vein (Trunk and/or left and/or right branches), splenic vein and superior mesenteric vein. A totally occlusive thrombus in a segment of the splanchnic circulation was defined by the absence of blood flow at Doppler evaluation or the lack of contrast enhancement during venous portal phase of CT or MRI scan. Presence of any blood flow detected within the thrombosed segment defined partial venous thrombosis. However, before 1st January 2014, the description of totally occluding and partially occluding portal vein thrombosis was not consistent and therefore in the study, we were able to assess the extent of the thrombosed segments of the splanchnic circulation detected in imaging studies in all patients but not the degree of luminal occlusion in all patients. PVT was considered malignant in the presence of venous expansive thrombus, neovascularity or direct invasion of the portal vein (12).

5.2.1. Study cohort

Inclusion criteria: Patients with clinical, laboratory and imaging studies compatible with cirrhosis with PVT without HCC.

Exclusion criteria: HCC at diagnosis of PVT, systemic or non-HCC neoplasms at study inclusion, TIPS placed prior to diagnosis of PVT.

5.2.2. PVT and anticoagulant therapy

The decision to start and type of AT (warfarin or LMWH), was at the discretion of the physician taking care of the patient and reasons for not starting AT were noted. In patients started on warfarin, target INR was between 2 and 3. Warfarin was preferentially given in patients with less advanced cirrhosis (Child-Pugh A, B 7-8) while LMWH was given in patients with more advanced cirrhosis (Child-Pugh B 9 and C). Among patients receiving LMWH, factor Xa assay was not performed to verify the efficacy of anticoagulation as this is not part of routine clinical surveillance laboratory tests at our centre. Among patients with chronic PVT, AT was started if a new thrombotic event or underlying acquired or genetic thrombophilic etiology was detected. All patients with PVT managed with anticoagulation had platelet counts more than 40 x 10^9/L.

5.2.3. Follow-up and clinical end-points

PVT recanalization was defined as a composite end point including a regression in the extent of the thrombus in one or more segments of the splanchnic circulation and/or complete or partial recanalization in those patients with total/partial thrombosis of a vascular segment compared to baseline imaging. The most recent follow-up imaging studies were used to evaluate PVT recanalization if performed at least 4 weeks after the baseline imaging study in which PVT was diagnosed. Imaging follow-up was performed with abdominal USG preferably with Doppler and CT/MRI within 6 months of start of anticoagulant therapy and then abdominal Doppler US every 6 months. Bleeding events, the site of bleeding and relation to anticoagulation were considered. Patients were followed-up till 10th January 2018, death or OLT. Cause of death and principal motive for OLT was registered. Individual formal consent was not required, and institutional ethics committee approval was obtained and the study was conducted according to the 1964 Declaration of Helsinki, later amendments or comparable ethics standards.

5.2.4. Statistical analysis

Continuous variables were expressed as mean±standard deviation or median (Range) as applicable and quantitative variables as percentages. Continuous variables were analyzed for normality distribution by the Kolmogorov-Smirnov test and groups of continuous variables were compared by unpaired Student's t-test or Mann-Whitney test as appropriate. Chi-square or Fishers's exact test as appropriate were used for categorical data. Kaplan-Meier (KM) curves were used to compare OLT free survival in patients with and without AT and in Child-Pugh and MELD subclasses respectively and also in those with and without any PVT recanalization (Log-rank and Breslow tests). Cox-regression

Table 5.1 Baseline features of the entire study cohort and of patients who did and did not start anticoagulation.

		Study cohort (n=80)		No anticoagulation (n=43)		Anticoagulation started (n=37)		
		Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	p value
Age (years)		60	9	60	10	59	8	0.468
Male gender		53	66.3%	25	58.1%	28	75.7%	
Etiology of cirrhosis	Alcohol	45	56.3%	25	58.1%	20	54.1%	0.829
	Viral	11	13.8%	6	14.0%	5	13.5%	
	Alcohol + viral	10	12.5%	4	9.3%	6	16.2%	
	Others	14	17.5%	8	18.6%	6	16.2%	
Child-Pugh score		8	2	9	2	8	2	0.522
Child-Pugh class	A	21	26.3%	9	20.9%	12	32.4%	0.356
	B	34	42.5%	18	41.9%	16	43.2%	
	C	25	31.3%	16	37.2%	9	24.3%	
MELD score		15	7	16	7	14	6	0.495
PHT complications at diagnosis of PVT		65	81.3%	37	86.0%	28	75.7%	0.236
	Variceal bleed	30	38.0%	22	51.2%	8	22.2%	0.008
	Ascites	62	77.0%	33	76.7%	29	78.4%	0,861
	Hepatic encephalopathy	9	11.2%	5	11.6%	4	10.8%	1
	Jaundice	15	18.8%	9	20.9%	6	16.2%	0.590
Abdominal pain		17	24.3%	6	17.6%	11	30.6%	0.256
Fever		9	13.2%	4	12.1%	5	14.3%	0.591
Portal cavernoma at diagnosis of PVT		10	12.5%	9	20.9%	1	2.7%	0.01
Portal vein trunk and/or branch thrombosis alone		53	66.3%	30	69.8%	23	62.2%	0.473
PV + SV + SMV thrombosis		6	7.5%	3	7.0%	3	8.1%	0.790
PV + SV thrombosis		5	6.3%	4	9.3%	1	2.7%	0.392
PV + SMV thrombosis		16	20.0%	6	14.0%	10	27.0%	0.148
Banding of varices prior to diagnosis of PVT		29	37.7%	11	27.5%	18	48.6%	0.116
Esophageal varices (n =77)		69	90.8%	36	92.3%	33	89.2%	0.708
Size of esopphageal varices	Small	25	36.2%	14	38.9%	11	33.3%	0.802
	Large	44	63.8%	22	61.1%	22	66.7%	
Gastric varices (n=77)		20	26.3%	11	28.2%	9	24.3%	0.701
Type of gastric varices	GOV1	7	38.9%	3	27.3%	4	44.4%	0.655
	GOV2	3	16.7%	1	9.0%	2	22.2%	
	IGV1	7	38.9%	4	36.4%	3	33.3%	
	GOV1 and IGV1	1	5.6%	1	9.0%	0	0.0%	
	Not mentioned	2	10.0%	2	18.2%	0	0.0%	
Severity of portal hypertensive gastropathy	Mild	49	70.0%	22	61.1%	27	79.4%	1
	Severe	16	22.9%	10	27.8%	6	17.6%	
Hb (g/dL)		10.6	2.2	10.2	2.0	11.0	2.4	0.223
Platelets (x 10^9/L)		108.8	80.2	106.9	92.1	111.0	65.1	0.751
INR		1.4	0.3	1.4	.3	1.4	.2	0.730
Ureia (mg/dL)		52	36	60	31	44	39	<0.001
Creatinine (mg/dL)		1.0	0.62	1.0	.5	1.0	.7	0.558
AST (U/L)		51	47	52	57	50	35	0.913
ALT (U/L)		40	29	40	33	39	24	0.327
Alkaline phosphatase (U/L)		143	151	149	183	138	108	0.104
Total serum bilirubin (mg/dL)		3.1	4.3	3.6	5.1	2.5	3.1	0.730
Total serum proteins (g/dL)		6.4	1.0	6.3	1.1	6.5	.9	0.813
Serum albumin (g/dL)		3.1	1.8	3.0	2.0	3.2	1.8	0.504

PHT – Portal hypertension, PVT – portal vein thrombosis, vein thrombosis; PV – Portal vein; SV – Splenic vein; SMV – Superior mesenteric vein thrombosis.

model for multivariate analysis was used. The effect of AT on OLT free survival was determined by time-dependent Cox regression with intention to treat analysis. A p value <0.05 was considered to be statistically significant. Data analysis was performed with the SPSS 21 statistical package (IBP SPSS statistics for Windows. version 21; IBM Corp; USA).

5.3. Results

The demographic, clinical and laboratory features of the patients included in the study are highlighted in table 5.1. The average MELD score was 15 ± 7 and average Child-Pugh score 8 ± 2 with two thirds of the patients having advanced cirrhosis ((Child-Pugh B (n=34) (42.5%) and Child Pugh C (n=25) (31.3%)). Imaging studies showed evidence of portal cavernoma in 10 (12.5%) patients. Portal vein trunk and/or branch thrombosis without concomitant splenic or superior mesenteric vein thrombosis was detected in 53 (66.3%) patients.

Esophageal varices were present in 69 (90.8%) and gastric varices in 20 (26.3%) prior to PVT diagnosis. Esophageal variceal banding for prophylaxis of variceal bleeding had been performed prior to PVT detection in 29 (37.7%) patients. In addition, 20 (25%) patients were already on beta blockers. One or more concomitant portal hypertension related complications at the time of PVT diagnosis were present in 65 (81.3%) patients with ascites in 62 (77.5%) and variceal bleeding in 30 (38%) being most common.

5.3.1. Anticoagulant therapy

AT was started in 37 patients (warfarin in 22, LMWH in 15) within the following time frames after PVT detection: within 1 month (n=14); 1 – 3 months (n=13); 3 – 6 months (n=3); 7 – 12 months (n=3) and >12 months (n=4). During follow-up, three patients who were started on LMWH were switched to warfarin and one patient on warfarin was switched to LMWH.

There were no differences in etiology of cirrhosis, severity of liver disease (Child-Pugh and MELD scores) and platelet counts in patients who did or did not receive anticoagulation. Prior history of variceal bleeding and portal cavernoma were significantly more common in patients who did not receive anticoagulation.

Esophageal varices were present in 33 (89.2%) of these 37 patients and gastric varices in 9 (24.3%) patients. Primary or secondary prophylaxis for variceal bleeding was done with endoscopic banding in 14, beta blockers in 4 or endoscopic banding + beta blockers in 12 patients prior to starting anticoagulation. No prophylaxis of variceal bleeding was performed in 7 patients for the following reasons: absence of varices in 2, small esophageal varices in 2, gastroesophageal varix (GOV2) not considered large enough to warrant bleeding prophylaxis in 1 and for unknown reason in 2 patients with large esophageal varices.

Anticoagulation was not started in 43 patients for the following reasons: severe thrombocytopenia in 11, risk of fall in 2, ongoing portal hypertension related bleeding at diagnosis of PVT in 1 and patient's refusal in 1. In 28 patients, anticoagulation was not started due to decision of the clinician taking care of the patient probably due to coagulation changes and cirrhosis decompensations at the time of PVT detection.

AT was stopped during follow-up in 17 (45.9%) patients (Supplementary table 5.1); in 6 (16.2%), due to complete recanalization of PVT. In 4 (10.8%) patients, anticoagulation was stopped due to non variceal bleeding or worsening anemia and in 3 (8.1%) patients due to aggravation of preexistent thrombocytopenia to platelet counts <40 x 10^9/L. There were no variceal bleeding episodes documented in the patients while on anticoagulation. Only one patient had to stop anticoagulation due to worsening anemia probably related to occult small intestinal bleeding related to portal hypertension.

AT was restarted in 6/17 (35.3%) patients following new thrombotic events in the splanchnic circulation. The median duration of anticoagulation was 10 (1 – 59) months.

5.3.2. Anticoagulant therapy and OLT free survival

After a median follow-up of 25.5 (1 – 146) months, 38 patients died and 10 patients underwent OLT. The OLT free survival was 32 (40%). The main reasons for mortality and OLT are shown in Supplementary table 5.2. There were 4 deaths due to variceal bleeding (3 from esophageal variceal bleeding and 1 from uncontrollable jejunal variceal bleeding) and none of these patients were on anticoagulation.

OLT free survival rates at 1, 3 and 5 years were 67%, 54% and 34% respectively (Figure 5.2). We did not find significant differences in the overall OLT free survival at 5 years in patients with and without AT (Log Rank p=0.169) (Figure 5.3) with survival rates at 1, 3 and 5 years of 81%, 64% and 35% in patients on AT versus 56%, 45% and 33% in those not recieving anticoagulation. However, the OLT free survival in the first 48 months was significantly higher (Breslow p=0.023) in patients on AT (Figure 5.3).

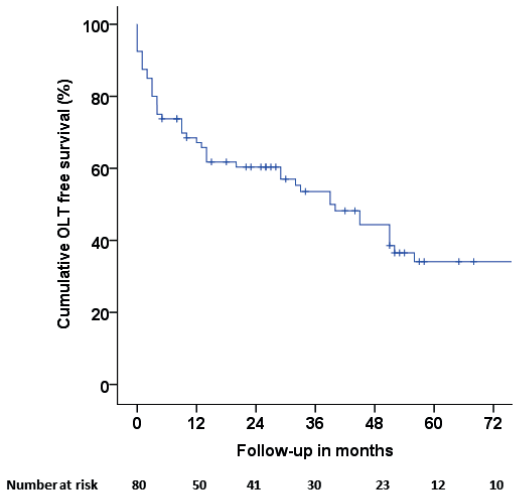

Figure 5.2 Kaplan-Meier survival analysis of the study sample (n=80).

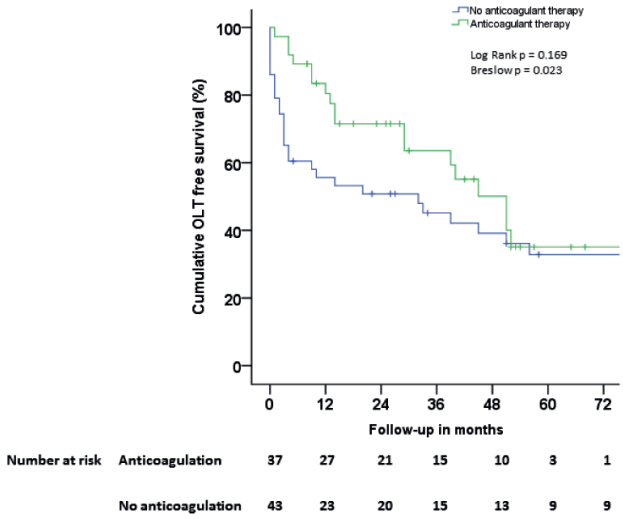

Figure 5.3 Kaplan-Meier analysis evaluating association of anticoagulation and OLT free survival.

Factors associated with death and or liver transplantation by Cox regression analysis were higher Child-Pugh (p <0.001) and MELD score (p <0.001), ascites (p=0.006) and hepatic encephalopathy (p <0.002) (Table 5.2 and supplementary table 5.4). The increase in OLT free survival in patients receiving AT by time dependent Cox regression analysis was not statistically significant even after correcting for variceal bleeding at diagnosis of PVT. On multivariate analysis, only baseline MELD score at PVT detection independently predicted mortality or liver transplantation (HR 1.12, 95% CI 1.05–1.19, p<0.001). (Table 5.3).

Table 5.2 Univariate analysis of factors associated with death and or liver transplantation in patients with cirrhosis and PVT.

		95% CI		
	HR	**Lower**	**Upper**	**p value**
Age (years)	1.002	.970	1.036	0.883
Male gender	.888	.485	1.628	0.701
Etiology of cirrhosis (Alcohol/Non-alcohol)	.963	.512	1.811	0.907
Child-Pugh score	1.371	1.216	1.545	<0.001
MELD score	1.142	1.090	1.196	<0.001
PHT complications at diagnosis of PVT	1.886	.798	4.457	0.148
Variceal bleeding at diagnosis of PVT	.981	.542	1.773	0.948
Moderate to large volume ascitis at diagnosis of PVT	3.396	1.426	8.090	0.006
Hepatic encephalopathy at diagnosis of PVT	1.969	1.278	3.033	0.002
Jaundice at diagnosis of PVT	1.734	.854	3.519	0.127
Esophageal varices	27.002	.192	3802.766	0.192
Gastric varices	1.314	.540	3.201	0.547
Portal vein trunk and or branch thrombosis alone	1.102	.596	2.038	0.756
PV + SV + SMV thrombosis	.824	.566	1.201	0.315
PV + SV thrombosis	.564	.296	1.075	0.082
PV + SMV thrombosis	.743	.501	1.101	0.138
Hb (g/dL)	.941	.825	1.073	0.363
Platelet count (x10^9/L)	1.000	1.000	1.000	0.102
INR	8.364	2.875	24.333	<0.001
Ureia (mg/dL)	1.008	1.002	1.014	0.008
Creatinine (mg/dL)	1.502	1.093	2.064	0.012
Total serum bilirubin (mg/dL)	1.082	1.024	1.144	0.005
Total serum proteins (g/dL)	.709	.521	.966	0.029
Serum albumin (g/dL)	.525	.330	.837	0.007
Anticoagulation (Time dependent)	1.219	.636	2.339	0.551

HR – Hazard Ratio; CI – Confidence interval; PHT – Portal hypertension; PVT – portal vein thrombosis, vein thrombosis; PV – Portal vein; SV – Splenic vein; SMV – Superior mesenteric vein thrombosis.

Table 5.3 Multivariate analysis of factors associated with death and/or liver transplantation.

		95% CI		
	HR	**Lower**	**Upper**	**p value**
Baseline MELD score at diagnosis of PVT	1.121	1.052	1.195	<0.001
≥ Grade 2 hepatic encephalopathy at diagnosis of PVT	1.083	.653	1.796	0.758
Moderate to large volume ascitis at diagnosis of PVT	1.388	.519	3.712	0.514
Variceal bleeding at diagnosis of PVT	1.062	.523	2.158	0.867
Serum albumin (g/dL)	.902	.530	1.533	0.702
Anticoagulant therapy	.601	.309	1.170	0.134

HR – Hazard Ratio; CI – Confidence interval; PVT – Portal vein thrombosis.

As expected, the OLT free survival rates were significantly different (p<0.001) in the Child-Pugh classes with OLT free survival rates at 1, 3 and 5 years of 95%, 95% and 72% in Child-Pugh class A, 79%, 57% and 27% in Child-Pugh class B and 27%, 12% and 12% in Child-Pugh class C patients respectively (Supplementary figure 5.1). The association between severity of liver disease and OLT free survival was also evident with significantly higher OLT free survival in patients with MELD score <15 who had 1, 3 and 5 year survival rates of 91%, 78% and 48% compared to 31%, 16% and 12% in patients with MELD score ≥15, respectively (p<0.001) (Supplementary figure 5.2).

The potential effect of AT on OLT free survival was also analyzed according to the severity of liver disease at the time of detection of PVT. Among Child-Pugh class A patients, those on AT had OLT free 1, 3 and 5 year survival rates of 92%, 92% and 47% compared to 83%, 83% and 83% (p=0.072) in those without AT, respectively, suggesting a potentially deleterious effect of anticoagulation in these patients with compensated cirrhosis (Figure 5.4).

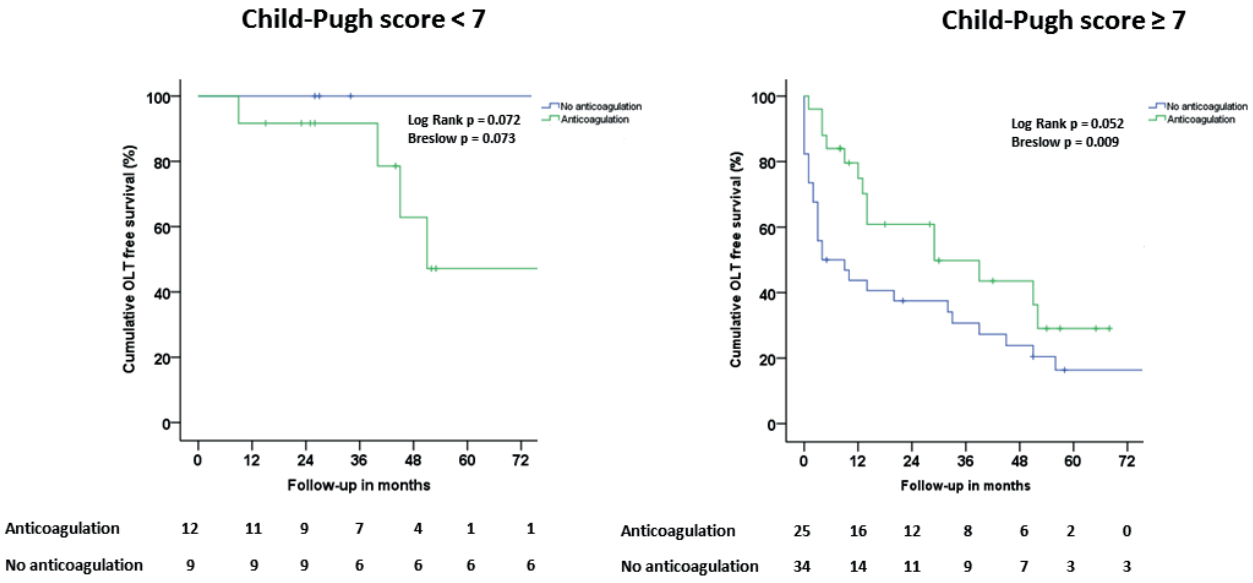

Figure 5.4 Evaluating effect of anticoagulation on OLT free survival in Child-Pugh class A and Child-Pugh class B + C patients.

In Child-Pugh B and C patients, those receiving anticoagulation had significantly better OLT free survival rates at 1, 3 and 5 years of 75%, 50% and 29% compared to 44%, 31% and 16% in patients not given anticoagulation (p=0.052) (Figure 5.4) suggesting a benefical effect of AT in patients with decompensated cirrhosis. When evaluating the effect of AT on OLT free survival according to MELD scores at diagnosis of PVT, no significant difference in cumulative survival was noted in patients with MELD scores <15 who did or did not receive AT. However, OLT free survival was significantly higher in patients with baseline MELD scores ≥15 at diagnosis of PVT who received AT compared to those who did not (p=0.011) (Figure 5.5).

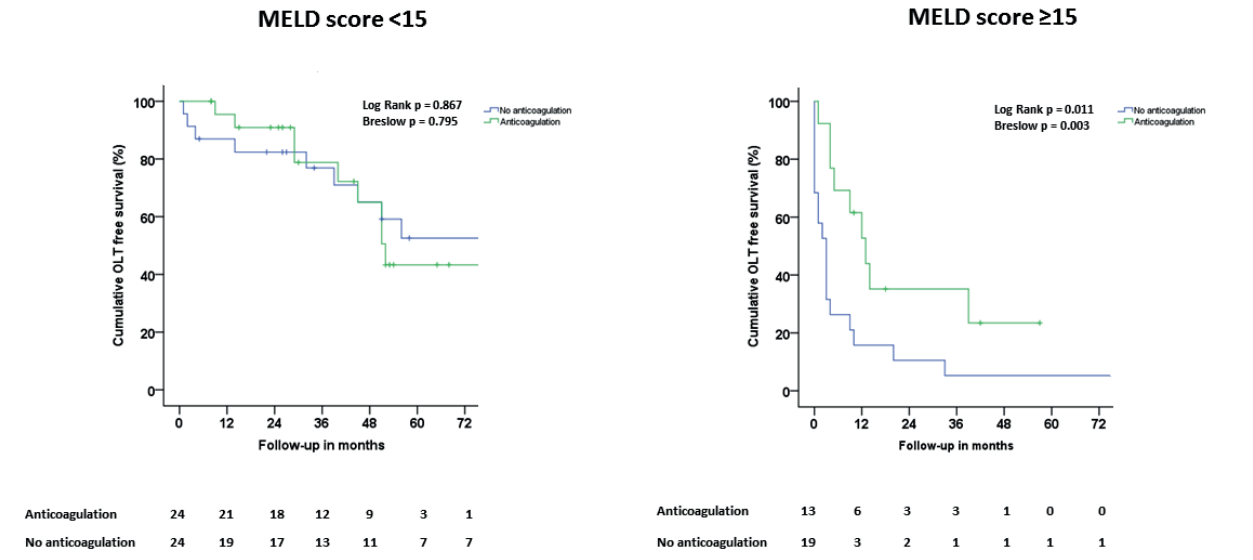

Figure 5.5 Evaluating effect of anticoagulation on OLT free survival in patients with MELD score <15 and ≥15.

5.3.3. Anticoagulant therapy and PVT recanalization

There was no adequate imaging test to evaluate PVT recanalization in 13 (16.3%) patients during follow-up. (Supplementary table 5.3). Out of the 67 patients with PVT ((anticoagulant therapy (n=35) and no anticoagulant therapy (n=32)) with at least one follow-up imaging study, any recanalization (partial or total recanalization of PVT or reduction of thrombosis extent in at least one segment of the splanchnic circulation compared to baseline imaging studies) was documented in 24 (35.8%) patients. Overall, the median time to evaluation of any recanalization of PVT was 22 (1 – 132) months, with the median time to final imaging study being 14.5 (1 – 101) months in patients with any recanalization of PVT and 29 (1 – 132) months in patients who did not have any recanalization of PVT.

Spontaneous recanalization of PVT occurred in 6/32 (18.8%) patients who did not receive AT which was significantly lower than the recanalization rates of 18/35 (51.4%) in patients who received AT (p=0.005). There were no differences in recanalization rates according to type of AT (LMWH vs varfarine) (Supplementary table 5.5). On univariate Cox regression analysis, baseline MELD score (HR 1.12, 95% CI 1.04–1.21, p=0.004), hepatic encephalopathy (HR 3.10, 95% CI 1.34–7.20, p=0.008), variceal bleeding (HR 0.28, 95% CI 0.10–0.75, p=0.012) and AT (HR 4.23, 95% CI 1.73–10.32, p=0.002) were found to be significantly associated with any recanalization of PVT (Table 5.4). On multivariate analysis, only baseline MELD score at diagnosis of PVT independently predicted any recanalization of PVT (Table 5.5). Cumulative OLT free survival was not significantly different in patients with and without any degree of PVT recanalization (p=0.768) (Figure 5.6).

Table 5.4 Factors associated with any PVT recanalization during follow-up.

		95% CI		
	HR	**Lower**	**Upper**	**p value**
Age (years)	1.032	.982	1.085	0.216
Male gender	.929	.383	2.251	0.87
Etiology of cirrhosis (Alcohol/non-alcohol)	.901	.368	2.210	0.82
Child-Pugh Score	1.210	1.008	1.453	0.041
MELD score	1.120	1.038	1.209	0.004
PHT related complications at diagnosis of PVT	.687	.281	1.678	0.41
Variceal bleeding at diagnosis of PVT	.276	.101	.754	0.012
Moderate/large volume ascitis at diagnosis of PVT	1.796	.703	4.591	0.221
≥ Grade 2 hepatic encephalopathy	3.104	1.337	7.205	0.008
Jaundice at diagnosis of PVT	2.167	.801	5.866	0.128
Esophageal varices	27.883	.051	15360.607	0.301
Gastric varices	1.313	.397	4.349	0.655
PVT trunk and or branch thrombosis alone	.556	.249	1.245	0.154
PV + SV + SMV thrombosis	1.138	.721	1.797	0.578
PV + SV thrombosis	.929	.503	1.718	0.815
PV + SMV thrombosis	1.127	.697	1.824	0.626
Hb (g/dL)	1.141	.950	1.370	0.158
Platelet count (x10^9/L)	1	1	1	0.313
INR	10.313	1.794	59.275	0.009
Ureia (mg/dL)	1.003	.990	1.017	0.636
Creatinine (mg/dL)	1.760	1.040	2.979	0.035
Total serum bilirubin (mg/dL)	1.107	1.017	1.204	0.018
Total serum proteins (g/dL)	1.361	.805	2.302	0.25
Serum albumin (g/dL)	.857	.436	1.682	0.653
Anticoagulation (Time dependent)	4.228	1.733	10.316	0.002

HR – Hazard Ratio; CI – Confidence interval; PHT – Portal hypertension; PVT – Portal vein thrombosis; PV – Portal vein. SV – Splenic vein; S
MV – Superior mesenteric vein thrombosis.

Table 5.5 Multivariate analysis of factors associated with any PVT recanalization.

		95% CI		
	HR	Lower	Upper	p value
Baseline MELD score at diagnosis of PVT	1.105	1.012	1.207	0.027
Variceal bleed at diagnosis of PVT	0.444	.142	1.387	0.163
Moderate/large volue ascitis at diagnosis of PVT	.988	.320	3.050	0.984
≥ Grade 2 hepatic encephalopathy	1.420	.551	3.655	0.468
Anticoagulant therapy	2.203	.720	6.737	0.166

HR – Hazard Ratio, CI – Confidence interval; PVT – Portal vein thrombosis.

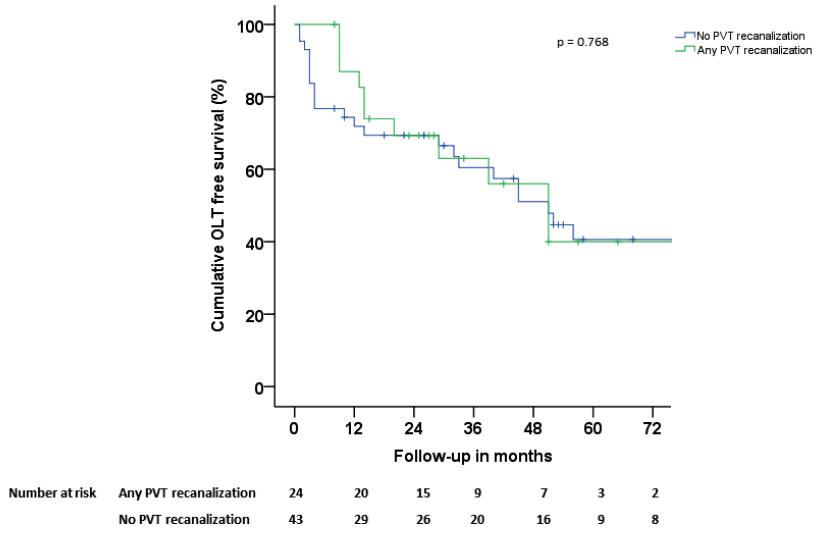

Figure 5.6 Kapan-Meier analysis evaluating any recanalization of the PVT and OLT free survival.

5.4. Discussion

In this retrospective analysis of a prospective clinical registry of nontumoral PVT in cirrhosis, majority of patients had advanced cirrhosis and portal hypertension related complications at diagnosis of PVT. Patients with variceal bleeding at PVT detection were significantly less likely to start AT. Anticoagulation significantly increased PVT recanalization rates and there was no difference in recanalization rates among patients given LMWH or warfarin. We could not determine beneficial effect of PVT recanalization or anticoagulation on the overall OLT free survival which however improved survival in patients with advanced cirrhosis (Child-Pugh classes B and C and MELD scores ≥15). MELD score at diagnosis of PVT independently predicted PVT recanalization and OLT free survival.

The decision for anticoagulation in cirrhosis requires consideration of the bleeding risk due to portal hypertension and advanced cirrhosis and the potential benefit of recanalization of a thrombosed vessel (13). Patients with cirrhosis are at higher risk of bleeding as well as of developing thrombotic vascular events (9) (14). PVT in patients with cirrhosis, specially when occlusive and extensive at the time of OLT, is associated with longer operative times, higher blood transfusion requirements and re-interventions as well as higher early post liver transplant mortality but does not seem to influence waiting list mortality (2) (5) (15) (16) (17). Anticoagulation has been recommended in patients with cirrhosis and PVT unrelated to HCC who are listed for liver transplantation (18) (19).

Two thirds of the patients in this study belonged to Child-Pugh B and C classes at PVT detection. This association between PVT and advanced cirrhosis has been reported in previous studies (3) (20). Additionally, in line with previous reports (21), at the time of PVT diagnosis, more than two thirds of patients in our study had esophageal varices and one fourth had gastric varices as well as one or more complications of portal hypertension highlighting the need for adequate prophylaxis of variceal bleeding prior to starting anticoagulation. In our study, patients presenting with variceal bleeding at detection of PVT were significantly less likely to start AT. Such a limitation to AT prescription in patients with previous PHT related bleeding has also been shown in the study by Ageno et al (22). Anticoagulation was ultimately started only in 37 (46.3%) patients probably due to the fear of the clinicians of bleeding complications in this group of patients with advanced cirrhosis and coagulation changes at the time of PVT detection.

The safety of anticoagulation in patients with cirrhosis is often debated. There were no variceal bleeding episodes in patients on AT. Bleeding due to anticoagulation occurred in 4 (10.8%) patients, with only one patient developing worsening anemia due to occult gastrointestinal bleeding probably due to underlying portal hypertension. Actually, bleeding in patients with portal hypertension on anticoagulation has not been found to be associated with increased need for rescue therapy including TIPS, 5 day rebleeding rate, duration of hospitalization and 6 week mortality (23). Additionally, in a large multicentre prospective study evaluating anticoagulation in PVT, although bleeding risk was higher in patients with cirrhosis, anticoagulation duration was independently associated with lower risk of major bleeding and thrombotic vascular events (13). In the meta-analysis by Qi et al, the pooled incidence of bleeding related to anticoagulation in patients with cirrhosis and PVT was 3.3% and that of major bleeding events was 1.4% (24). A study analyzing anticoagulation in patients with cirrhosis detected a higher risk of major and minor UGIB in patients with PVT compared to patients with venous thromboembolism (29% vs 19%; p=0.024) but there was no significant difference in major bleeding episodes (p=0.376) (9). Lofreddo et al reported similar incidences of major and minor bleeding in patients with cirrhosis with and without anticoagulation of 11% with a significantly lower incidence of variceal bleeding in patients on anticoagulation compared to those not on anticoagulation (10). Until recently, there were no cases of death related to major bleeding events while patients were on anticoagulation (13) (21). Kwon et al, have reported two cases of fatal bleeding in patients with cirrhosis with PVT related to duodenal variceal bleed and intracranial hemorrhage while on anticoagulation. Both patients belonged to Child-Pugh class B and had prior history of variceal bleeding (25), highlighting the need for careful and individualized decisions for anticoagulation in patients with cirrhosis diagnosed with PVT.

The 3 patients in our study who died due to complications related to variceal bleeding did not receive AT. Anticoagulation was stopped due to worsening thrombocytopenia (platelet count <40 x 10^9 cel/L) in 3 and bleeding related to anticoagulation in 4 patients. These results validate the view that anticoagulation in patients with cirrhosis and clinically significant portal hypertension is as safe as in patients without portal hypertension if adequate primary or secondary prophylaxis of variceal bleeding is performed prior to starting AT (9) (10) (20) (21) (26).

Classically, LMWH and varfarin or acenocumarol have been used for AT. Data from cohort studies suggest that direct acting oral anticoagulants are safe and effective in patients with cirrhosis and PVT (27). None of the patients in our study cohort received direct acting anticoagulants. Their utility and

adequate dosage adjustment specially in patients with advanced cirrhosis and PVT should be analyzed in large multicentre studies as this may improve patient compliance and may also have a more predictable anticoagulant effect. PVT recanalization was significantly higher in patients who recieved AT compared to those without AT (18/35 (51.4% vs 6/32 (18.8%), p=0.005). This is in the lower range of the published data with recanalization rates of PVT in patients with cirrhosis on anticoagulation ranging between 33–75% (6) (9) (10) (11) (16) (24) (26) (28). We did not find differences in recanalization rates according to the type of anticoagulant used. Although, on univariate Cox regression analysis, anticoagulant therapy, baseline MELD scores and hepatic encephalopathy were factors associated with higher recanalization rates, on multivariate analysis, only baseline MELD score at PVT detection independently predicted higher PVT recanalization rates. To our knowledge, this is the first study suggesting that the beneficial effect of anticoagulation on PVT recanalization is higher in patients with more advanced cirrhosis.

The rethrombosis rate in patients who stopped anticoagulation was 35.3% (6/17) which is similar to that in the studies by Pettinari et al and Delgado et al (11) (21), and higher than the rethrombosis rates of 21% and 27% previously reported (16) (29). All of these data, reinforce the concept of a permanent acquired prothrombotic state in the portal venous system of patients with cirrhosis which may justify maintaining anticoagulation indefinitely in patients with cirrhosis and PVT in the absence of contraindications especially in patients listed for OLT to avoid extension of thrombosis (16) (20) (21) (29).

There is controversy regarding the effect of PVT on prognosis in patients with cirrhosis, with a large prospective study suggesting no effect of PVT on OLT free survival or aggravation of liver disease (3). Among patients with cirrhosis and candidates for liver transplantation, some studies suggest no influence of PVT on post transplant survival (30) (31) while other studies have shown higher early (90 day) post transplant mortality and graft failure (17) and 1 year post transplant mortality (5) (6) (15) (20). In our study, although AT did not influence overall OLT free survival, the OLT free survival was significantly higher in the first 4 years of anticoagulation compared to that in patients not receiving anticoagulation. A similar beneficial effect of AT on OLT and event free survival in patients with cirrhosis and PVT was noted in the first two years of anticoagulation in a recent study (9). In our study, AT was associated with higher OLT free survival in patients with advanced cirrhosis (Child-Pugh B and C and MELD scores ≥15) but not in those patients with compensated or less advanced cirrhosis (Child-Pugh A and MELD <15). These results suggest that the beneficial effect of AT in patients with cirrhosis and PVT is significantly higher in patients with decompensated cirrhosis compared to those with compensated cirrhosis as has been alluded to in the recent study by Pettinari et al wherein OLT free survival was significantly higher in Child-Pugh B class B patients receiving anticoagulation with a trend for better survival in Child-Pugh C patients compared to patients who did not receive anticoagulation (11). This may be due to more pronounced portal hemodynamic changes and imbalances in procoagulant factors in patients with advanced cirrhosis secondary to endothelial dysfunction and bacterial translocation (9) (20) (32). The beneficial effect of AT in these patients may go beyond the macroscopic PVT recanalization and may be related to a decrease in thrombotic events within the hepatic microvasculature related to inflammation and deposition of fibrin and fibrinogen as has been shown in murine models (33) (34) and in explanted livers in patients with cirrhosis (35) (36).

The exact significance of PVT recanalization on OLT free survival is unclear, especially because most of the patients who develop PVT have partial thrombosis at detection. The number of liver related events was lower in patients with at least partial recanalization of PVT while on anticoagulation but this did not achieve statistical significance (21). La Mura et al found that OLT free survival was significantly higher in patients with complete recanalization compared to those with partial or no recanalization of PVT (9). We did not find any influence of PVT recanalization on the OLT free survival as has also been recently reported (11).

Our study has some limitations: The retrospective and non randomized nature of the study and the absence of a specific protocol to guide decisions for AT use before 2010 does not exclude potential confouding factors including inherent selection bias. The decision to start anticoagulation by the treating physician was however individualized to the patient based on the patients` clinical condition, platelet count and comorbidities at detection of PVT and the potential benefits from anticoagulation and risk of bleeding. Additionally, baseline and follow-up cross-sectional imaging studies including CT scan and MRI to determine extent of PVT was not performed systematically in all patients and the degree of PVT luminal obstruction at baseline was not uniformly reported and therefore the extent of PVT may have been underestimated due to sub-optimal evaluation of splenic and superior mesenteric veins. However, CT scan requires contrast injection with consequent risk of nephrotoxicity and ionizing radiation which was why abdominal Doppler US was primarily used in this cohort of patients majority of whom with advanced cirrhosis at baseline and follow-up. Despite these limitations, the study is unique as majority of patients had advanced cirrhosis at the time of detection of PVT and the safety and effect of AT on a robust outcome namely OLT free survival was evaluated. In addition, the incidence of rethrombosis was also determined among patiens who stopped anticoagulation.

In conclusion, in patients with cirrhosis and PVT, although anticoagulation did not influence overall OLT free survival, it was associated with a significantly higher OLT free survival in the first four years of anticoagulant therapy. Higher OLT free survival related to anticoagulation was noted only in patients with advanced or decompensated cirrhosis. Anticoagulant therapy significantly improved PVT recanalization and should be maintained after PVT recanalization to avoid rethrombosis. Baseline MELD score at PVT detection independently predicted of PVT recanalization and OLT free survival. Large prospective trials evaluating the role of anticoagulation in early survival benefit in patients with advanced or decompensated cirrhosis are urgently required to confirm the findings of this study.

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Supplementary Data

Supplementary table 5.1 Reasons for stopping and restarting anticoagulation

	Number
Stopped anticoagulation	**17**
End of therapeutic period	6
Severe thrombocytopenia	3
Poor compliance	2
Severe epistaxis	1
Abdominal wall hematoma	1
Hematoma at site of injection	1
Worsening anemia	1
Dental treatment	1
Lung cancer and severe hemoptises	1
Restarted anticoagulation for rethrombosis	**6**

Supplementary table 5.2 Reasons for mortality and liver transplantation

Cause of mortality	
Septic complications	17
End stage liver disease	7
Not specified	4
Esophageal variceal bleeding	3
Small bowel ischemia	2
Hepatocelular carcinoma	1
Uncontrollable jejunal variceal bleeding	1
Pulmonary neoplasia	1
Incarcerated inguinal hernia	1
Cerebal abcess	1
Liver transplantation	**10**
Portal hypertension related complications	8
Hepatocellular carcinoma within Milan criteria	2

Supplementary table 5.3 Resons for no follow-up imaging to evaluate PVT recanalization

Reasons for no follow-up imaging evaluation of recanalization	**Number (n=13)**
Died at same hospitalization where PVT was diagnosed	7
Unknown reason	3
Not enough follow-up (<4 weeks) after PVT and died	2
Unreliable patient who missed scheduled follow-up imaging	1

PVT – Portal vein thrombosis

Supplementary table 5.4 Factors at baseline associated with death and/or liver transplantation during follow-up.

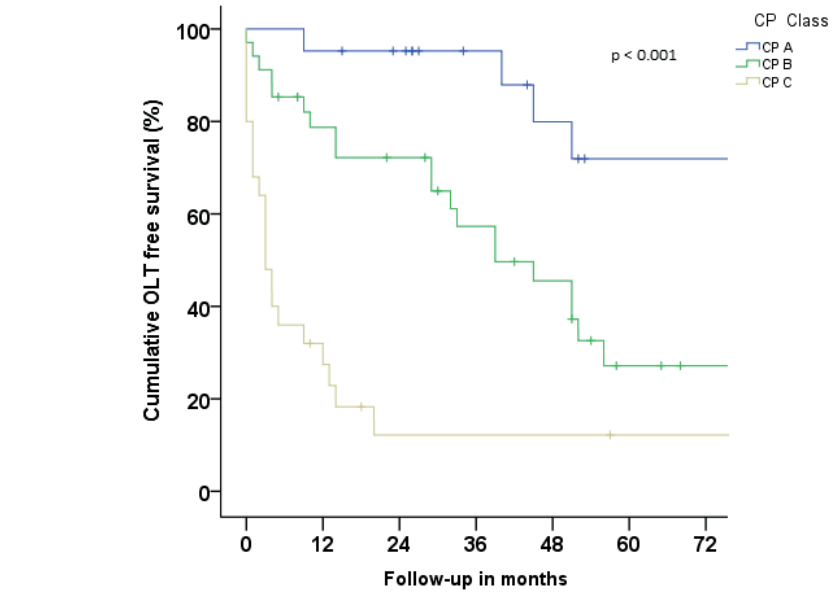
		Death or liver transplantation				
		No (n=32)		Yes (n=48)		
		Mean/N	SD/%	Mean/N	SD/%	p value
Age (years)		61	48	59	33	0.891
Male gender		22	68.8%	31	64.6%	0.699
Etiology of cirrhosis	Alcohol	20	62.5%	25	52.1%	0.23
	Viral	5	15.6%	6	12.5%	
	Alcohol + viral	1	3.1%	9	18.8%	
	Others	6	18.8%	8	16.7%	
Child-Pugh score		7	5	9	5	0.003
Child-Pugh class	A	14	43.8%	7	14.6%	0.002
	B	14	43.8%	20	41.7%	
	C	4	12.5%	21	43.8%	
MELD score		12	7	17	7	<0.001
PHT complications at diagnosis of PVT		23	71.9%	42	87.5%	0.079
Variceal bleed at diagnosis of PVT		8	25.8%	22	45.8%	0.073
Moderate to large volume ascites at diagnosis of PVT		21	65.6%	41	85.4%	0.038
≥ Grade 2 hepatic encephalopathy at diagnosis of PVT		2	6.2%	7	14.6%	0.303
Jaundice at diagnosis of PVT		5	15.6%	10	20.8%	0.559
Abdominal pain		6	20.0%	11	27.5%	0.502
Fever		2	7.1%	7	17.5%	0.308
Portal cavernoma at diagnosis of PVT		6	18.8%	4	8.3%	0.187
PV trunk and/or branch thrombosis alone		20	62.5%	33	68.8%	0.562
PV + SV + SMV thrombosis		1	3.1%	5	10.4%	0.128
PV + SV thrombosis		3	9.4%	2	4.2%	0.055
PV + SMV thrombosis		8	25.0%	8	16.7%	0.138
Banding of varices prior to diagnosis of PVT		10	31.3%	19	42.2%	0.398
Esophageal varices		28	90.3%	41	91.1%	1
	Small	10	35.7%	15	36.6%	0.941
	Large	18	64.3%	26	63.4%	
Gastric varices		5	16.1%	15	33.3%	0.094
	GOV1	1	25.0%	6	42.9%	0.238
	GOV2	1	25.0%	2	14.3%	
	IGV1	1	25.0%	6	42.9%	
	GOV1 and IGV1	1	25.0%	0	0.0%	
Portal hypertensive gastropathy	Mild	18	69.2%	31	70.5%	0.255
	Severe	6	23.1%	10	22.7%	
Hb (g/dL)		11.1	2.4	10.2	2.1	0.334
Platelets (x 10^9/L)		127	103	96	58	0.154
INR		1.3	.2	1.4	.3	0.131
Ureia (mg/dL)		39	22	61	41	0.007
Creatinine (mg/dL)		.9	.2	1.1	.8	0.385
AST (U/L)		44	30	56	56	0.077
ALT (U/L)		35	17	43	34	0.823
Alkaline phosphatase (U/L)		129	117	153	170	0.478
Total serum bilirubin (mg/dL)		2.1	2.9	3.8	5.0	0.004
Total serum proteins (g/dL)		6.7	.9	6.2	1.0	0.091
Serum albumin		3.3	.6	3.0	.7	0.116
Anticoagulation started		19	51.40%	18	48.60%	0.055

PHT – Portal hypertension; PVT – Portal vein thrombosis; PV – Portal vein; SV – Splenic vein; SMV – Superior mesenteric vein.

Supplementary table 5.5 Comparing features at baseline in patients with and without PVT recanalization.

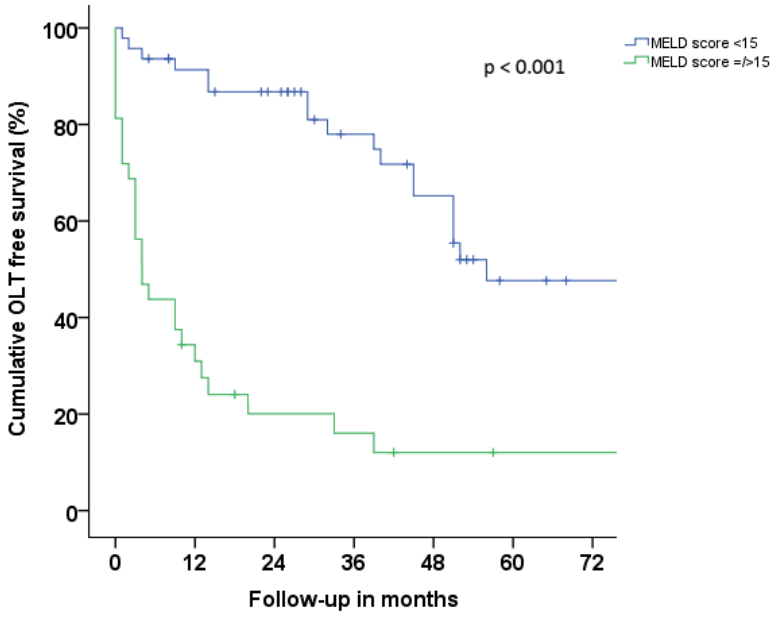
		No recanalization (n=43)		Any recanalization (n=24)		
		Mean/N	**SD/%**	**Mean/N**	**SD/%**	**p value**
Age (years)		59	9	60	10	0.9
Male gender		29	67.4%	17	70.8%	0.774
Etiology of cirrhosis	Alcohol	24	55.8%	13	54.2%	0.753
	Viral	7	16.3%	2	8.3%	
	Alcohol + viral	5	11.6%	4	16.7%	
	Others	7	16.3%	5	20.8%	
Child-Pugh score		8	2	8	2	0.836
Child-Pugh class	A	12	27.9%	9	37.5%	0.619
	B	18	41.9%	10	41.7%	
	C	13	30.2%	5	20.8%	
MELD score		14	6	14	6	0.798
PHT complications at diagnosis of PVT		35	81.4%	17	70.8%	0.32
Variceal bleeding at diagnosis of PVT		18	41.9%	5	21.7%	0.102
Moderate/large volume ascites at diagnosis of PVT		32	74.4%	18	75.0%	0.958
Hepatic encephalopathy at diagnosis of PVT		4	9.3%	2	8.3%	0.894
Jaundice at diagnosis of PVT		7	16.3%	5	20.8%	0.743
Abdominal pain		9	23.7%	5	21.7%	0.716
Fever		4	11.1%	4	17.4%	0.586
Portal cavernoma at diagnosis of PVT		8	18.6%	0	0.0%	0.043
PV trunk and/or branch thrombosis alone		31	72.1%	12	50.0%	0.071
PV + SV + SMV thrombosis		2	4.7%	3	12.5%	0.498
PV + SV thrombosis		4	9.3%	1	4.2%	0.745
PV + SMV thrombosis		6	14.0%	8	33.3%	0.173
Banding of varices prior to diagnosis of PVT		16	38.1%	9	37.5%	0.743
Esophageal varices		35	85.4%	24	100.0%	0.077
	Small	10	28.6%	11	45.8%	0.174
	Large	25	71.4%	13	54.2%	
Gastric varices		8	19.5%	5	20.8%	1
	GOV1	3	42.9%	3	60.0%	0.433
	GOV2	1	14.3%	0	0.0%	
	IGV1	3	42.9%	1	20.0%	
	GOV1 and IGV1	0	0.0%	1	20.0%	
Portal hypertensive gastropathy	Mild	23	62.2%	19	82.6%	0.402
	Severe	10	27.0%	4	17.4%	
Hb (g/dL)		10.8	2.0	11.1	2.6	0.143
Platelets (x10^9/L)		111571	89889	105500	61655	0.798
INR		1.3	.2	1.4	.3	0.798
Ureia (mg/dL)		49	27	47	47	0.197
Creatinine (mg/dL)		1.0	.4	1.0	.9	0.443
AST (U/L)		43	24	51	39	0.897
ALT (U/L)		36	24	41	24	0.443
Alkaline phosphatase (U/L)		127	96	139	134	0.668
Total serum bilirubin (mg/dL)		2.5	3.1	3.4	5.0	0.798
Total serum protein (g/dL)		6.4	.9	6.8	.9	0.627
Serum albumin (g/dL)		3.1	.6	3.3	.6	0.871
Anticoagulation started		6	18.80%	18	51.40%	0.005
Type of anticoagulant	Warfarin	10	47.60%	11	52.40%	1
	LMWH	7	50%	7	50%	
Total duration of anticoagulant therapy		21	18	20	1	0.866
Duration of follow-up in months		43	41	36	8	0.501

PHT – Portal hypertension; PVT – Portal vein thrombosis; PV – Portal vein; SV – Splenic vein; SMV – Superior mesenteric vein; LMWH – Low molecular weight heparin.



Number at risk								
	CP A	21	20	18	13	10	7	7
	CP B	34	24	21	15	11	4	2

Supplementary figure 5.1 Kaplan-Meier survival analysis acorrding to Child-Pugh class



Number at risk								
	MELD < 15	48	40	35	25	20	10	8
	MELD ≥ 15	32	9	5	4	2	1	1

Supplementary figure 5.2 Kaplan-Meier survival analysis according to MELD scores <15 and ≥15

CHAPTER 6 DISCUSSION AND CONCLUSIONS

Changes in coagulation in cirrhosis are now better understood and the prothrombotic tendency in cirrhosis is well recognized which makes the concept of prophylactic anticoagulation as a therapeutic intervention in advanced cirrhosis to prevent development of PVT and progression of cirrhosis increasingly attractive as has been already been done in a prospective study (1).

In the first manuscript "Incidence and clinical significance of development of portal vein thrombosis in cirrhosis: a prospective study", we have, in this large prospective observational study involving a majority of patients with compensated cirrhosis with clinically significant portal hypertension, shown that, the cumulative incidence of nontumoral PVT was 3.7% at 1 year and 7.6% at 3 years. The reported prevalence of PVT in patients with cirrhosis especially those with advanced or decompensated cirrhosis varies widely between 0.6 and 26% (2) (3). The findings of our study are very similar to the cumulative incidence of PVT of 4.6% and 8.2% at 1 and 3 years determined in the largest prospective study which included patients with cirrhosis belonging to Child-Pugh classes A and B (4). The incidence of PVT in patients with decompensated cirrhosis (Child-Pugh B and C) awaiting liver transplantation is probably higher as has been suggested in the study by Francoz et al (5). Despite our efforts at consecutive patient recruitment across the spectrum of severity of cirrhosis, 184 (76.3%) patients in the study cohort belonged to Child-Pugh class A in whom the risk of development of PVT is probably lower compared to patients belonging to Child-Pugh classes B and C, which explains the lower than expected incidence of PVT in the study.

Portal vein flow velocity below 15 cm/second on abdominal Doppler ultrasound is an independent predictor of development of PVT in cirrhosis (6). However, despite clinical recommendations, there is considerable inter observer and inter equipment variation in measurement of portal vein flow velocity (7), which was also observed during the course of the study. Therefore, we did not consider the portal vein flow velocity in the study. Prolonged prothrombin time reflecting advanced cirrhosis, presence of large esophageal varices and NSBB have been found to be independent predictors of development of PVT irrespective of effects on heart rate or portal vein blood flow velocity (4) (8). In our study, MELD score and clinical features suggestive of clinically significant portal hypertension namely, prior decompensation of cirrhosis, presence of esophageal and / or gastric varices, requirement of NSBB, diuretics and thrombocytopenia, were found to be associated with development of nontumoral PVT in patients with cirrhosis. On multivariate analysis, only prior decompensation of cirrhosis and thrombocytopenia independently predicted nontumoral PVT development, reflecting the pathophysiological role of portal hypertension. These results however have to be considered with some caution as the number of patients who developed nontumoral PVT was low (n = 15). Unlike in the study by Nery et al, presence of esophageal varices did not independently predict development of PVT (4). Although, 139/221 (62.9%) patients in our study had esophageal and / or gastric varices at study inclusion, 63 (26.1%) were on NSBB and 59 (27.2%) had undergone banding for prophylaxis of variceal bleeding which makes it difficult to interpret the clinical significance of presence of varices as a predictive factor for development of PVT.

Nontumoral PVT although associated with, was not an independent predictor of new decompensations of cirrhosis. Male gender, MELD score, ascites at baseline as well lower hemoglobin and thrombocytopenia at study inclusion were found to be independent predictors of decompensation of cirrhosis. Ascites and thrombocytopenia are clinical surrogate markers of clinically significant portal hypertension (HVPG > 10mmHg) which along with MELD score independently predicts decompensation of cirrhosis (9) (10). Male gender, prolonged prothrombin time and increased serum bilirubin levels have been previously identified as predictors of decompensation of cirrhosis (11) (12). We did not find a link between low hemoglobin levels and higher risk of cirrhosis decompensations though hypothetically, this may reflect the effect of hypersplenism due to underlying portal hypertension.

Male gender, MELD score, active alcohol intake and low serum hemoglobin values were found to be independent predictors of lower OLT free survival as has been previously reported (13) (14) (15). We could not find a link between development of nontumoral PVT and lower OLT free survival. This was probably due to the low incidence of PVT and also the fact that 86.7% (13/15) patients who developed PVT had partial thrombosis as has also been previously reported (4). Partial thrombosis of the portal vein probably does not significantly affect blood inflow to the liver trough the portal vein which may explain its lack of influence on cirrhosis decompensations and mortality. Development of PVT in cirrhosis is most probably due to underlying portal hypertension with consequent sluggish blood flow in the portal vein, and its development, does not seem to influence portal pressure or flow due to prior development of extensive portosystemic collaterals (16). The results of our study therefore confirm that the risk of development of PVT is relatively low in patients with compensated cirrhosis and that majority of patients who develop PVT have partial thrombosis which does not affect OLT free survival.

In our study two thirds of patients had weight excess and obesity and half of the patients had one or more cardiovascular comorbidities reflecting the growing prevalence and need to understand the clinical significance of obesity and metabolic syndrome in patients with cirrhosis. Berzigotti et al, in a prospective study in patients with compensated cirrhosis have shown that the BMI was an independent predictor of decompensation of cirrhosis (17) suggesting that weight reduction may be a useful therapeutic option in overweight and obese patients. More recently, a study by Stine et al, suggested that patients with high risk non-alcohol steatohepatitis (NASH) related cirrhosis (Age > 60 years, BMI > 30kg/m2, hypertension and diabetes mellitus) had a significantly higher risk of developing PVT prior to liver transplantation compared to patients with low risk NASH and non-NASH cirrhosis (18). However, we did not find an association between obesity and cardiovascular comorbidities and the development of PVT, cirrhosis decompensations or mortality which was probably due to the relatively short follow-up period of 29 (1 – 58) months which was half of that in the study by Berzigotti et al. This reinforces the need for large multicenter studies with prolonged follow-up to evaluate and clarify the role of BMI and cardiovascular comorbidities in the natural history of cirrhosis.

The second manuscript entitled "Natural history and management of esophagogastric varices in chronic noncirrhotic, nontumoral portal vein thrombosis" involved a large cohort of consecutive patients with chronic PVT followed in two referral centers for patients with portal hypertension and vascular liver disorders. The study confirms that esophagogastric varices are a frequent finding in pa-

tients with chronic PVT. Variceal bleeding was the initial presentation in 27 (15%) patients and the initial endoscopy showed small esophageal varices (SEVs) in 28 (19%), large esophageal varices (LEVs) in 60 (40%), and gastric varices without LEVs in 11 (7%). Turnes et al, showed that anticoagulation achieves recanalization in acute PVT in up to 40% patients. Esophageal and/or gastric varices were detected in 55% of patients after a median of 7 months following diagnosis of acute PVT with varices appearing as soon as 1 month after detection of acute PVT (19). We found that varices were especially frequent in patients with concomitant ascites, even when detected only at imaging studies or in those patients with splenomegaly which indirectly reflects underlying clinically significant portal hypertension. Varices at high risk of bleeding were found to be infrequent in the absence of these two factors.

Most progression, indicated by development of varices in patients without varices at diagnosis and variceal growth in patients with small varices, took place early in the course of PVT. The risk appears to be similar to that of patients with cirrhosis and therefore calls for a similar schedule of follow-up endoscopies, every 2 – 3 years in patients without varices at baseline and every 1 – 2 years in those with small varices. These findings validate the empirical suggestion of endoscopic screening in patients with chronic NCNTPVT without varices at baseline and follow-up endoscopies in patients with SEVs suggested in the Baveno VI recommendations (20).

We found that the risks of first variceal bleeding on primary prophylaxis and of rebleeding are also similar to those observed in cirrhosis provided a similar therapeutic approach based on NSBB and endoscopic therapy is used (21) (22) (23) (24) (25) (26). Interestingly, AT did not seem to be associated with higher risk of bleeding and rebleeding.

Mortality related to digestive tract bleeding in patients with PVT was found to be very low and mostly related to comorbid conditions and not directly related to PVT as has been previously reported (27) (28) (29).

The strengths of this study derive from (1) endoscopic follow-up performed according to a relatively standardized schedule in patients without varices or with SEVs, (2) primary and secondary prophylaxis of variceal bleeding applied in a relatively uniform manner in almost all patients with adequate indication, and (3) an etiologic workup of prothrombotic factors in most patients and anticoagulant therapy given according to a uniform management protocol.

In the third manuscript, "Anticoagulation in cirrhosis and portal vein thrombosis is safe and improves prognosis in advanced cirrhosis", we have shown in this retrospective analysis of a large prospective cohort of patients with cirrhosis and nontumoral PVT that, majority of patients had advanced cirrhosis and portal hypertension related complications at the time of detection of nontumoral PVT. Patients with variceal bleeding at the time of PVT detection were significantly less likely to be given anticoagulation. This reflects physician concerns regarding risk of bleeding due to anticoagulation in patients presenting with variceal bleeding at diagnosis of PVT as has been shown by Ageno et al where up to 1 in 4 patients with cirrhosis and splanchnic vein thrombosis did not receive anticoagulation (30).

We confirmed that anticoagulant therapy after adequate primary or secondary prophylaxis of variceal bleeding was safe with no documented variceal bleeding events while on anticoagulation. Bleeding related to anticoagulation occurred in 4/37 (10.8%) with only one patient developing wors-

ening anemia related to occult gastrointestinal bleeding due to underlying portal hypertension. There are several studies suggesting that patients with cirrhosis given adequate prophylaxis of variceal bleeding have significantly lower risk of variceal bleeding on anticoagulant therapy (31). In a large retrospective study involving 182 patients with cirrhosis and PVT, there were no significant differences in bleeding rates in patients who did and did not receive anticoagulation (32). This has also been reported by La Mura et al, who suggest that the risk of bleeding in patients with cirrhosis is related to underlying portal hypertension and not anticoagulation, provided that patients receive adequate prophylaxis of variceal bleeding (33).

We found that anticoagulation was significantly associated with higher PVT recanalization rates but there was no beneficial effect of PVT recanalization or anticoagulation on the OLT free survival on the entire study cohort. We did not find differences in the recanalization rates in patients receiving LMWH or warfarin. Pettinari et al have recently shown that anticoagulation significantly improved PVT recanalization rates in patients with cirrhosis and was an independent predictor of higher OLT free survival (32). However, in this study only 24/182 (13.2%) patients belonged to Child-Pugh class C, with patients belonging to Child-Pugh class A being significantly more likely to be given anticoagulation compared to Child-Pugh class C (Only 5 patients received anticoagulation). Interestingly, the effect of PVT recanalization on OLT free survival was not mentioned in this study (32). La Mura et al, have shown that total recanalization of PVT was significantly associated with lower risk of decompensations of cirrhosis and higher OLT free survival (33).

In our study, subgroup analysis, showed a significant beneficial effect of AT on overall OLT free survival in the first 4 years of anticoagulation as well as on overall survival only in patients with advanced cirrhosis (Child-Pugh B and C or MELD score ≥15). This finding is interesting as it seems that a subgroup of patients with advanced cirrhosis who have more imbalances in anticoagulant and procoagulant factors and consequent microthrombotic events in liver sinusoids thought to be responsible for progression of cirrhosis, may benefit more from anticoagulant therapy. Pettinari et al, have also noted that patients belonging to Child-Pugh B and C who received anticoagulation had longer survival compared to those who did not (32).

MELD score was found to be an independent predictor of PVT recanalization and OLT free survival. We did not find previous reports of MELD score as an independent predictive factor of PVT. MELD reflects degree of hepatocellular dysfunction and therefore more advanced cirrhosis and is a good predictive factor of prognosis in cirrhosis (14).

Anticoagulation had to be restarted in one third of patients, after stopping it, due to rethrombotic events in the portal vein. These findings are similar to those reported by Delgado et al (34) and more recently in the study by Pettinari et al (32). Therefore anticoagulation should be maintained after PVT recanalization to avoid rethrombosis which probably occurs due to persisting portal hypertension and sluggish blood flow in the portal vein.

6.1. Future plans for translational investigation

6.1.1. Coagulation changes, markers of microthrombotic events and progression of cirrhosis

Blood and serum samples of all patients included in the prospective study on incidence and clinical significance of nontumoral PVT in cirrhosis were collected at baseline and in some patients during follow-up and have been stored in the biobank. We plan to study the role of inflammation and coagulation changes on development of Nontumoral PVT, cirrhosis decompensations and long term OLT free survival in these patients.

The identification of imbalances between procoagulant and anticoagulant factors and their link with serum levels of inflammatory cytokines may help detect patients at higher risk of developing microscopic and macroscopic thrombosis. Novel markers such as microparticles (MP) also called extracellular vesicles and cytokeratin 18 may identify subgroups of patients at higher risk of decompensations of cirrhosis and lower OLT free survival.

Research in rat models suggests that portal myofibroblasts activate endothelial cells trough vascular endothelial growth factor laden MPs driving scar progression from portal tracts into hepatic parenchyma (35). Tissue factor (TF) a highly procoagulant protein is usually not present in the blood under physiological conditions but its levels are increased 17 to 38 fold in patients with cirrhosis and acute liver injury in the form of TF-MPs (36). Serum levels of M65EpiDeath, a marker of overall epithelial cell death based on cytokeratin 18 has been found to be an indicator of severity of cirrhosis and an independent factor predicting survival (37). Therefore, the potential utility of these markers in prediction of risk of development of PVT, cirrhosis decompensations and OLT free survival will also be explored in the patients included in the study.

Due to the high prevalence of weight excess and obesity in patients with chronic liver disease and cirrhosis, their potential role as a thrombogenic agent as well as the influence of cardiovascular comorbidities on long term outcome of patients with cirrhosis needs clarification. We will be following-up these patients to understand the role of obesity and cardiovascular risk factors in the development of cirrhosis decompensations and OLT free survival.

6.1.2. Non-invasive markers of high risk varices in chronic noncirrhotic nontumoral portal vein thrombosis (NCNTPVT) and optimization of secondary prophylaxis of variceal bleeding

Accurate non-invasive techniques to screen patients with chronic NCNTPVT for varices at higher risk of bleeding are required. Current technology such as 2D-Shear Wave elastography evaluation of spleen stiffness does not accurately predict grade of esophageal varices and higher risk of bleeding (40).

The detection of patients at higher risk of rebleeding and optimization of endoscopic techniques in combination with medical treatment including beta blockers require improvement in order to optimize the management of these patients following an episode of variceal bleeding. We also plan to evaluate the role of transient elastography evaluation of the spleen stiffness alone or in combination with liver stiffness as well as clinical and laboratory data, to detect recurrence of varices after esophageal variceal eradication by band ligation for primary or secondary prophylaxis of variceal bleeding.

6.1.3. Anticoagulation and markers of inflammation

The potential role of anticoagulation in improving prognosis beyond macroscopic recanalization of PVT needs clarification. The identification of changes in the levels of inflammatory cytokines and procoagulant and anticoagulant factors in patients who receive or do not receive anticoagulation may clarify the role of prophylactic anticoagulation especially in patients with advanced cirrhosis. Prophylactic anticoagulation in patients with advanced cirrhosis has been shown to be associated with a decrease in markers of inflammation and bacterial translocation in the study by Villa E et al (1).

The application of liver volumetric evaluation by contrast enhanced CT scan alone or in combination with markers of liver function such as indocyanine green elimination at baseline and during follow-up may help improve the accuracy of estimation of prognosis as has been shown in alcoholic hepatitis (38) (39).

Blood samples of some patients have been obtained at study inclusion before development of PVT, at the time of detection of PVT and during follow-up, both in patients who did and not receive anticoagulation. We plan to evaluate the link between markers of inflammation and bacterial translocation in these patients and the development of PVT as well as the influence of anticoagulant therapy on their levels and their potential utility in predicting prognosis.

6.2. Conclusion

The studies performed in this thesis allow us to make the following conclusions:

Among patients with cirrhosis and without PVT at baseline, MELD score and clinical features suggestive of clinically significant portal hypertension were associated with development of PVT highlighting the pathophysiologic role of severity of portal hypertension. PVT was associated with but was not an independent predictor of decompensation of cirrhosis or lower OLT free survival.

The course of varices in chronic noncirrhotic, nontumoral PVT appears to be similar to that in cirrhosis; using the same therapeutic approach as for cirrhosis is associated with a low risk of bleeding and death.

Finally, in patients with cirrhosis and nontumoral PVT, although anticoagulation did not improve overall OLT free survival, it was associated with higher survival in patients with advanced cirrhosis. Anticoagulation in the patients, majority of whom with advanced cirrhosis, significantly increased PVT recanalization and should be maintained after PVT recanalization to avoid rethrombosis.

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