FACULTAD DE MEDICINA
UNIVERSIDAD DE
CANTABRIA

GRADO DE MEDICINA

TRABAJO DE FIN DE GRADO

Portal thrombosis in cirrhosis: role of thrombophilic disorders.

Trombosis portal en la cirrosis: papel de los trastornos trombofílicos.

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Santander, junio 2020

ÍNDICE

ABSTRACT

Introduction: In patients with liver cirrhosis, the contribution of inherited and acquired prothrombotic disorders in the development of non-malignant PVT is inconclusive. The purpose of this study was to examine the prevalence of inherited and acquired thrombophilia in cirrhotic non-malignant PVT at our center. As secondary aims we explored the influence these disorders on the clinical presentation of PVT and response to anticoagulation.

Methods: we conducted a retrospective review regarding the presence of inherited and acquired thrombophilia in this setting from January 2012 to November 2019. Tests included gene mutational analysis for Factor V Leiden, prothrombin G20210A, JAK2 exon 12 – 15, Calreticulin (performed only if JAK2 mutation was negative) in addition to activated protein C resistance, antithrombin III, protein C and S levels, and antiphospholipid antibodies. Clinical, epidemiological, laboratory, and radiological data were collected. Patients were followed until death, liver transplantation, or end of the study (June 2020).

Results: we included 77 patients with liver cirrhosis and non-malignant PVT in whom a thrombophilic study had been performed. Except for the screening of JAK2 V617 and calreticulin mutations which were only investigated in 20 patients, the remaining thrombophilic tests were available in the whole cohort. Four patients (5.2%) had a thrombophilic disorder: antiphospholipid syndrome in 2 patients, prothrombin gene mutation in 1 and factor V Leiden mutation in another patient. This latter patient was also diagnosed of polycythemia vera after detecting a JAK2 V617F mutation. Complete thrombosis of the main portal vein and rethrombosis after stopping anticoagulation were more frequent in patients with thrombophilia, but the rates of recanalization under anticoagulant therapy were similar among groups.

Conclusions: the low prevalence of acquired and inherited thrombophilia found in patients with cirrhosis and PVT support testing for these disorders on an individual basis and avoiding universal screening to reduce costs and unwarranted testing.

Abstract: 300 words. Key words: Liver cirrhosis, Portal vein thrombosis, Thrombophilia

RESUMEN

Introducción: En los pacientes con cirrosis hepática, la contribución de los trastornos protrombóticos hereditarios y adquiridos en el desarrollo de la TVP no maligna no es concluyente. El propósito de este estudio fue examinar la prevalencia de la trombofilia hereditaria y adquirida en la TVP cirrótica no maligna en nuestro centro. Como objetivos secundarios exploramos la influencia de estos trastornos en la presentación clínica de la TVP y la respuesta a la anticoagulación.

Métodos: realizamos una revisión retrospectiva sobre la presencia de trombofilia hereditaria y adquirida en este entorno desde enero de 2012 hasta noviembre de 2019. Las pruebas incluyeron análisis de mutación genética para el Factor V Leiden, protrombina G20210A, JAK2 exón 12 - 15, Calreticulina (realizado sólo si la mutación JAK2 fue negativa) además de resistencia a la proteína C activada, niveles de antitrombina III, proteína C y S, y anticuerpos antifosfolípidos. Se reunieron datos clínicos, epidemiológicos, de laboratorio y radiológicos. Se hizo un seguimiento de los pacientes hasta la muerte, el trasplante de hígado o el final del estudio (junio de 2020).

Resultados: incluimos 77 pacientes con cirrosis hepática y PVT no maligna en los que se había realizado un estudio trombofílico. A excepción del análisis de JAK2 V617 y las mutaciones de calreticulina, que sólo se investigaron en 20 pacientes, las pruebas trombofílicas restantes estaban disponibles en toda la cohorte. Cuatro pacientes (5,2%) tenían un trastorno trombofílico: síndrome antifosfolípido en 2 pacientes, mutación del gen de la protrombina en 1 y mutación del factor V Leiden en otro paciente. A este último paciente también se le diagnosticó policitemia vera tras detectar una mutación JAK2 V617F. La trombosis completa de la vena porta principal y la retrombosis después de detener la anticoagulación fue más frecuente en los pacientes con trombofilia, pero las tasas de recanalización bajo la terapia anticoagulante fueron similares entre los grupos.

Conclusiones: la baja prevalencia de trombofilia adquirida y hereditaria encontrada en pacientes con cirrosis y PVT apoya la realización de pruebas para estos trastornos de forma individual y evitar la detección universal para reducir los costos y las pruebas injustificadas.

Resumen: 347 palabras. Palabras clave: Cirrosis hepática, Trombosis de la vena porta, Trombofilia.

INTRODUCTION

Non-malignant portal vein thrombosis (PVT) is defined as a thrombus that develops within the portal vein trunk and intrahepatic portal branches, which may also involve the splenic (SV) or superior mesenteric veins (SMV). In the absence of recanalization, the portal venous lumen is obliterated and portoportal collaterals develop resulting in portal cavernoma. The latter transformation is generally used to define the chronic stage of PVT (**Figure 1**) [1]. It constitutes the most common thrombotic event in patients with cirrhosis, with increased rates in the setting of advanced liver disease. The reported prevalence of PVT varies with different diagnostic methods and target populations, ranging between approximately 10%-25% in patients with decompensated cirrhosis and 1%-5% in those with compensated cirrhosis [2]. Despite being a well-known complication of liver cirrhosis, the contribution of PVT to hepatic decompensation and overall mortality is still a matter of debate [1,3-5]. Discrepancies among studies regarding patient selection criteria (compensated vs decompensated), degree and extent of thrombosis (occlusive vs nonocclusive), treatment strategies (anticoagulation vs no anticoagulation), sample size and time of follow-up have led to conflicting data [6]. There is consequently no consensus on its optimal management and no definitive recommendations have been reported in clinical guidelines or consensus conferences [1,4,5,7,8].

The mechanisms involved in the development of PVT in patients with cirrhosis are also not yet fully understood. Of the three pathophysiologic factors predisposing to thromboembolism described in the triad of Virchow (slow blood flow, endothelial damage and hypercoagulability), portal flow seems to be the most influential in the setting of cirrhosis [4]. The efficacy of transjugular intrahepatic portosystemic shunt (TIPS) in restoring PVT patency by presumably increasing portal flow [1] and the identification of a reduced portal flow as a major risk factor for PVT development support this notion [9,10]. Other potential mechanisms involved include a state of hypercoagulability in more advanced disease, bacterial translocation and inflammation, and vascular injury to the portal venous system secondary to several procedures (e.g. splenectomy) [3].

Inherited and acquired prothrombotic disorders may also play a role, although current data are conflicting. The limited number of studies available are mostly case-control studies with small sample sizes. Their study design, target population (diverse ethnicities and geographical locations), diagnostic criteria for PVT, and assessment of thrombophilic conditions vary widely, and contribute to the inconsistent results (Table 1) [11-33]. Moreover, none of these studies have properly evaluated whether the presence of thrombophilia impact the progression rate or response to treatment. Among the different thrombophilic genetic defects, Factor V Leiden (FVL) and prothrombin G20210A (PTHR) mutations have been the most frequently studied. Three meta-analysis concluded that they increased the risk of PVT in patients with cirrhosis [34-36], although in one of them this association was not shown for PTHR [35] and all of them are biased by the quality of the studies included. Inherited protein C, protein S or antithrombin III are difficult to

detect due to co-existent liver synthetic dysfunction [4]. Their levels, however, do not seem to be associated with PVT development [37]. The methylene tetrahydrofolate reductase (MTHFR) C677T and plasminogen activator inhibitor (PAI)– type 1 4G-4G mutations have also been described as independent predictors of PVT [18], although these polymorphisms have not been conclusively associated with increased thrombotic risk [38]. The role of acquired prothrombotic disorders has been less evaluated in patients with liver cirrhosis and PVT. In contrast to non-cirrhotic PVT, the association between myeloproliferative disorders and antiphospholipid syndrome is so far inconclusive [3]. Due to the conflicting data, current guidelines make no strong recommendation regarding testing for these conditions in either a screening capacity before PVT diagnosis or confirmatory once thrombosis has developed [1,4,7,8].

AIMS

The purpose of this study was to examine the prevalence of inherited and acquired thrombophilia in cirrhotic non-malignant PVT at our center. As secondary aims we explored the influence of these disorders on the clinical presentation of PVT and response to anticoagulation.

MATERIAL AND METHODS

Patients

The Marques de Valdecilla University Hospital (Santander, Cantabria, Spain) is an urban, academic tertiary care center. Since 2012 we began to test for thrombophilia in patients with cirrhosis who developed a non-malignant PVT. In this report, we conducted a retrospective review regarding the presence of inherited and acquired thrombophilia in this setting from January 2012 to November 2019. The identification of PVT cases was performed using three approaches: 1) Database from the Gastrointestinal and Hepatology Service; 2) Individual review of all thrombophilic studies performed during the study period by the Department of Hematology; 3) Hospital discharge records.

Cirrhosis was confirmed on the basis of clinical, laboratory, and imaging studies or liver biopsy, and PVT was diagnosed as part of biannual screening for hepatocellular carcinoma (HCC) or during hospitalization for decompensated cirrhosis. Patients without thrombophilic study or with malignant PVT (i.e. presence of vascularization of the thrombus at contrast imaging, mass-forming features of PVT and/or evidence of disruption of vessel walls) were excluded. The presence of a cavernomatous transformation of the portal vein was not considered an exclusion criterion.

Definitions

PVT was defined as the absence of flow in part of or in the entire lumen of any site among portal vein trunk, portal vein branches, superior mesenteric vein (SMV) or splenic vein (SV) caused by the presence of solid material within the vein, as documented by an imaging technique (Doppler ultrasound [US], computed tomography [CT], or magnetic resonance imaging [MRI]). **Thrombosis** was considered complete when the blood flow was absent, or the thrombus involved more than 90% of the vessel diameter. Otherwise, it was defined as partial. Evolution of thrombosis was classified as previously reported by Delgado et al [39]. **Recanalization** was considered complete when the portal vein trunk, portal vein branches, SMV, and SV were all completely patent. Recanalization was considered partial when some parts of the thrombus persisted but there was at least a 50% reduction in the thickness or length of the thrombus, or when complete patency was achieved in the portal vein trunk and in at least one of the following segments if previously thrombosed: main intrahepatic branches, SV or SMV. Lack of recanalization according to the definition above was considered to be a non-response to treatment. **Thrombosis progression** was considered to occur when thrombus thickness increased>50% or when the thrombosis extended to previously unaffected segments of the spleno-porto-mesenteric axis.

Anticoagulation therapy

The decision to start and type of anticoagulation treatment was at the discretion of the

physician taking care of the patient and was begun after initiation of appropriate primary or secondary prophylaxis of variceal bleeding. In general, full-dose low-molecular-weight heparin (LMWH) was started and switched after 4-6 weeks to vitamin k antagonists to maintain INR between 2 and 3. Patients with significantly prolonged INR in the setting of advanced liver cirrhosis were maintained with LMWH. Among patients receiving LMWH, factor Xa assay was not performed to verify the efficacy of anticoagulation.

Follow up

The date of first abdominal imaging study detecting PVT was considered as time zero for computing follow-up. Clinical, epidemiological, laboratory, and radiological data were collected at PVT diagnosis. Patients were followed until death, liver transplantation (LT), or end of the study (June 2020). Imaging follow-up was not performed according to a strict protocol, but at the discretion of the attending physicians. In general, it consisted of abdominal US and CT/MRI within 6 months of start of anticoagulation and then abdominal Doppler US every 6 months. The most recent follow-up imaging studies were used to evaluate PVT recanalization if performed at least 4 weeks after PVT diagnosis. All data was extracted from the electronic medical record.

Thrombophilic study

Test for thrombophilia were delayed until at least four weeks after PVT diagnosis, at which time LMWH were switched to vitamin K antagonists. Tests included gene mutational analysis for Factor V Leiden, prothrombin G20210A, JAK2 exon 12 – 15, Calreticulin (performed only if JAK2 mutation was negative) in addition to activated protein C resistance, antithrombin III, protein C and S levels, and antiphospholipid antibodies. The latter included anticardiolipin (aCL), antibeta2 glycoprotein (aB2GPI), and lupus anticoagulant (LA). The hypercoagulable panel was interpreted by Hematology, and the presence of liver cirrhosis was taken into consideration in all patients.

Blood samples were collected in vacutainer tubes containing NaCitrate 3.2% in 1/9 proportion. After centrifugation (2500 rpm), 1 ml aliquots were stored at -30ºC and used within 30 days. Protein C and antithrombin III were determined using automated chromogenic assay for quantitative determination on IL Coagulation Systems (HemosIL Werfen®). Free Protein S level was determined using an automated latex ligand immunoassay on IL Coagulation Systems (HemosIL Werfen®). Activated Protein C resistance was determined with coagulometric test based on TTPa parameter (HemosIL Werfen®). Normal values were established according to 100 control patients of the same age range and gender and were as follows: antithrombin, 85-140%; protein C, 85-140%; protein S, 70-120%. LA was determined using diluted Russell´s viper venom test and silica Cotting time (HemosIL Werfen®). Serum IgG and IgM aCL and aB2GPI levels were measured by ELISA following manufacturer's instructions (Orgentec Diagnostika, Mainz, Germany) and expressed in GPL or MPL units or U/ml, respectively. Titers were considered to be positive when they were above the 99th percentile, thus corresponding

to values above 20 GPL, MPL or U/ml (medium: 20-30 or high: >30 titers). If positive, they were repeated at least 12 weeks later in order to confirm their positivity.

For genetic determinations, DNA was extracted from peripheral blood leukocytes according to standard protocols. Detection of JAK2 V617F, Prothrombin G20210A, and FVL G1691A mutation was performed using LightCycler® 2.0 Real-Time PCR System (Roche Diagnostics, Mannheim, Germany). DNA extracted from HEL cells served as a positive control for the JAK2 V617F mutation. To assess the allelic burden of the JAK2 V617F mutation in carriers, melting curves with dilution series using DNA from HEL cells were obtained and compared to the patient's melting curve. Minimum allelic burden reliably detectable was 5 %.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee for Clinical Research of Cantabria. A waiver of informed consent was provided since the study was considered a retrospective review.

Statistical analysis

Continuous variables were assessed by Kolmogorov-Smirnov test for normality and expressed as mean ± standard deviation (SD) or median and interquartile range. Categorical variables were expressed as counts and percentages. Comparisons between groups was performed using Student´s T test or Mann-Whitney U test for continuous variables and $\chi 2$ or Fisher´s exact test for categorical variables as applicable. Follow-up was calculated from the time of PVT diagnosis to the date of the last imaging study available before death, LT, or 1 June 2020. Statistical analysis was performed with IBM SPSS Statistics v22.0 for Mac (IBM Corp., Armonk, NY, United States).

RESULTS

Prevalence of thrombophilia

During the study period, 166 cases of PVT were evaluated, of which 89 were excluded (Figure 2). The final cohort included 77 patients with liver cirrhosis and non-malignant PVT in whom a thrombophilic study had been performed. Except for the screening of JAK2 V617 and calreticulin mutations which were only investigated in 20 patients, the remaining thrombophilic tests were available in the whole cohort.

Four patients (5.2%) had a thrombophilic disorder: antiphospholipid syndrome in 2 patients, prothrombin gene mutation in 1 and factor V Leiden mutation in another patient. This latter patient was also diagnosed of polycythemia vera after detecting a JAK2 V617F mutation. The remaining patients tested negative for JAK2 and calreticulin mutations. A detailed description of these four patients is provided in Table 2.

Characteristics of patients with and without thrombophilia

The clinical and epidemiological profile of patients with and without thrombophilia was similar (Table 3). Most patients had an alcoholic liver disease, were decompensated before PVT diagnosis and were on non-selective betablocker treatment in the setting of primary or secondary prophylaxis of variceal bleeding. Three patients, all in the non-thrombophilic group, had suffered a previous arterial or venous thrombotic event (myocardial infarction in 1 patient, deep vein thrombosis in another, and pulmonary embolism in the remaining patient).

Extension and clinical characteristics of thrombosis at diagnosis

Diagnosis of PVT was made by CT or MRI in the majority of patients. The portal vein or its branches were the only thrombosed vessels in 50 patients (64.9%). In 2 patients (2.6%) the thrombosis extended to the SV, in 17 (22.1%) to the SMV, and in 4 patients (5.2%) it involved the entire splenoportomesenteric venous axis. Three patients (3.9%) had isolated thrombosis of the SMV and one (1.3%) of the SV. Portal cavernoma was established in nine patients (11.7%). In most cases, thrombosis was partial, regardless of its location. In patients with thrombophilia, however, complete thrombosis of the main portal vein and its right vein was more frequent in comparison to patients without thrombophilia (Table 4). Four patients, all in the non-thrombophilic group, had a local predisposing local factor. In all them PVT developed several weeks after radiofrequency ablation of HCC.

Thirty-three patients (42.9%) showed new symptoms overlapping with the diagnosis of PVT. The most frequent decompensation event was variceal bleeding followed by hepatic encephalopathy. PVT only led to the development of mesenteric ischemia in one patient (1.5%). No differences in clinical presentation or analytical parameters were observed between patients with and without thrombophilia (Table 4).

Anticoagulation and Outcome of Thrombosis

Five patients were excluded from this analysis. Four of them were participating in a randomized control trial to evaluate the effect of rivaroxaban in patients with advanced liver disease with PVT (Tromboxabab; EudraCT Number 2016-003240-37) and the other patient died soon after PVT diagnosis. In the remaining 72 patients, anticoagulation was frequently started (76.6%), while the placement of a TIPS was rare (5.2%) and always indicated by complications of cirrhosis, and not by progression of PVT (Table 5).

Therapy was maintained with LMWH in 12 patients, with vitamin K antagonists in 46, and with apixaban in one patient. Median delay from PVT diagnosis to the beginning of anticoagulation treatment was 9 days (interquartile range, 0–42 days) and its median duration was 12.6 months (interquartile range, 6.2–27.0). Compared with untreated patients, those who received anticoagulation or TIPS more frequently achieved partial or total resolution of PVT (66.1% vs. 23.1%; p = 0.011). After ceasing anticoagulation, rethrombosis developed in ten patients (32.3%), with a trend for this event to occur more frequently in patients with thrombophilia (100% vs 27.6%; p=0.097). No other difference regarding treatment and outcome was observed between patients with and without thrombophilia (Table 5).

DISCUSSION

In patients with liver cirrhosis, the contribution of inherited and acquired prothrombotic disorders in the development of non-malignant PVT is inconclusive. The limited available data is hampered by the heterogeneity and small sample size of the studies. The present report constitutes one of the largest series in this topic and, contrary to most published studies, includes a thorough thrombophilia workup. The interpretation of the hypercoagulable panel by Hematology is another strength of the present work as many previous studies do no to provide information in this regard. Our results show a very low prevalence of inherited and acquired thrombophilia in patients with cirrhotic non-malignant PVT and question the utility of universal screening in this setting.

The prevalence of thrombophilia in our cohort was similar to prevalence of these disorders in the general population [38] and is also in agreement with other previous reports that did not find an association between the presence of inherited or acquired thrombophilia and the risk of PVT in patients with liver cirrhosis [11,16,21,22,24,27,28,30,33,39]. Of interest, although limited by the low number of patients with thrombophilia, complete thrombosis of the main portal vein and rethrombosis after stopping anticoagulation were more frequent in these patients. In contrast, the rates of recanalization under anticoagulant therapy were similar among groups and in keeping with those reported to date [40]. Definite conclusions about the prevalence of prothrombotic disorders and the usefulness of their screening in this setting can neither be drawn from the findings of our study nor from the previously reported data due to the relatively small sample size. However, the available data together with associated healthcare costs support reserving these thrombophilia tests for patients with family histories of prothrombotic defects, patients with multiple sites of thrombosis, recurrent thrombosis, or when treatment decisions (i.e., anticoagulation duration) may be affected.

The main limitations of our study are related to its retrospective and unicenter design. The relatively small sample size and the absence of a control group of patients with cirrhosis and without PVT should also be acknowledged. However, the overall interpretation of our results would probably not change given the low prevalence of thrombophilic disorders found in our cohort. Finally, JAK2 and calreticulin mutations were not performed in all patients as these tests were later included in the thrombophilia workup.

CONCLUSIONS

We found a very low prevalence of acquired and inherited thrombophilia in patients with cirrhosis and PVT. Our results support testing for these disorders on an individual basis and avoiding universal screening to reduce costs and unwarranted testing. Future prospective studies integrating evaluation of liver disease stage, local and genetic factors are needed to identify individualized criteria to perform these tests and to evaluate their impact on the progression rate or response to treatment.

ACKNOWLEDGEMENTS

First of all, I would like to thank the tutors of this End of Degree Project, Dr. Emilio Fábrega and Dr. Ignacio Fortea. Thank you for this introduction to the world of research. I hope it will accompany me in the future. Thanks for all the support and advice received throughout this strange year; especially to you Iñaki, every time I had doubts you always tried to solve them in the shortest time possible.

Secondly, I have to thank Inés, resident of the Digestive Service of the HUMV, for the great support and help in carrying out this work, especially in the development of the database; without your help it would have been impossible for me to make the deadlines. In addition, I must thank many other residents from various services of the hospital who spent afternoons in the meeting room and helped us with our doubts or simply gave us their support and advice. Thank you all very much.

Thank you also to you Paloma, my colleague in the career and work.There are many afternoons shared in the hospital working and supporting us; thank you very much.

Finally, I would like to mention several friends who have accompanied me throughout the career. All of you have always tried to help me or at least listened to my problems or concerns. Thank you very much to Carmen, Valeria, Aida, Marta, Jorge, Alberto, Nacho, Juan and especially to you, Javi. I hope that this stage will be the first of a life together. In addition, I have to thank my parents and my sister enormously for all the effort they make every day so that I can be here and for all the hours of phone calls to help me in times of need.

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FIGURES

Figure 1. Types of portal vein thrombosis according to the age of the thrombus. Taken from Intagliata *et al* [3]

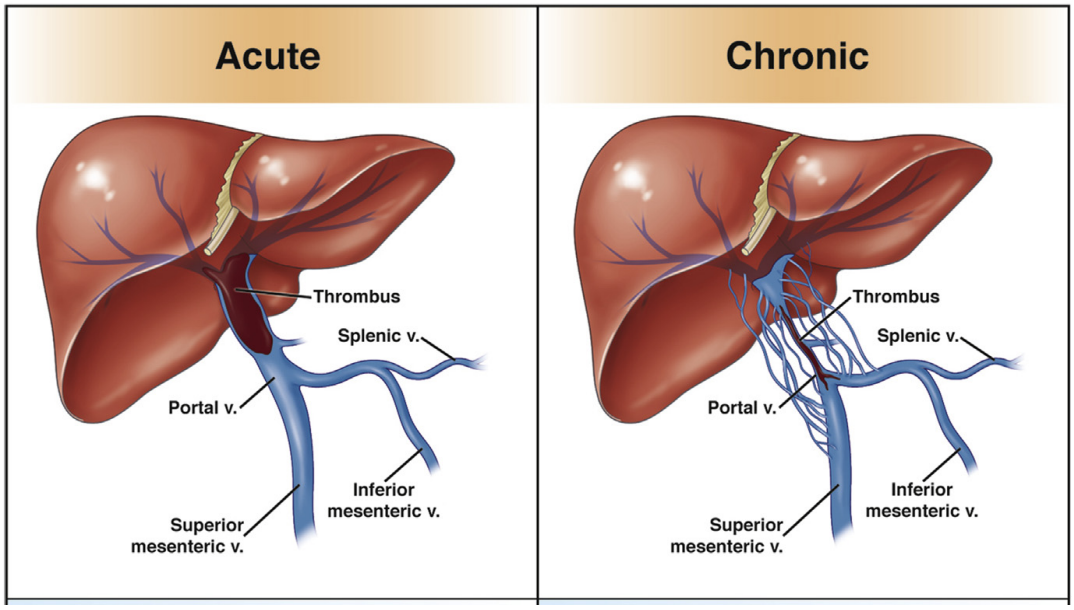
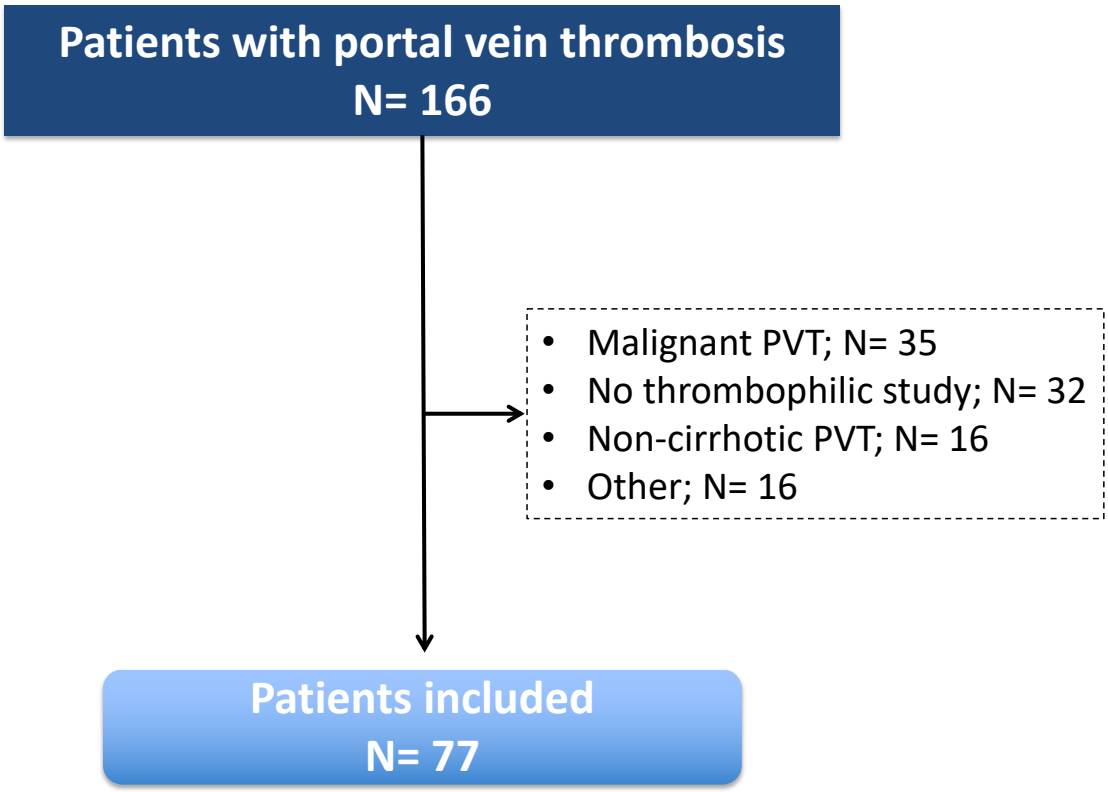


Figura 2. Flowchart of patients



Abreviations: PVT: Portal vein thrombosis.

TABLES

Table 1. Large studies evaluating the prevalence of acquired and inherited thrombophilia in non-malignant portal vein thrombosis in patients with liver cirrosis.

Author and year	N**	Study period and type	Population	PTHR	FVL	APS	JAK2	MTHFR	PAI	Comments
Mahmoud *et al*; 1997	32	NS Retrospective	UK	-	1/32 (3.1%)	-	-	-	-	Authors concluded FVL was not a major contributor of PVT. Not all 32 patients had liver cirrhosis.
Amitrano *et al*; 2000	23	1998-1999 Case-control	Italy	8/23 (34.8%)	3/13 (13%)	0/23 (0%)	-	10/23 (43.5%)	-	PTHR and MTHFR were strongly associated with PVT.
Amitrano *et al*; 2004	79	1998-2002 Case-control	Italy	15/70 (21.4%)	8/70 (11.4%)	0/70 (0%)	-	15/70 (21.4%)	-	ACA IgG and ACA IgM at low levels in PVT. PTHR increased more than fivefold the risk of PVT.
Mangia *et al*; 2005	43	1997-1999 Case-control	Italy	2/43 (4.7%)	1/43 (2.3%)	-	-	9/43 (20.9%)	-	PTHR, FVL and MTHFR were evenly distributed among patients with and without PVT. Authors concluded they were not causative of PVT
Amitrano *et al*; 2006	78	1998-2002 Case-control	Italy	17/78 (21.4%)	-	-	-	-	-	PTHR was associated with PVT, and factor II levels were higher in patients with PTHR and PVT
Pasta *et al*; 2006	78	2000-2005 Case-control	Italy	-	-	-	-	19/78 (24.4%)	-	MTHFR was associated with PVT development.
Colaizzo *et al*; 2008	91	NS Retrospective	Italy	-	-	-	5/91 (5.5%)	-	-	Intestinal infarction and previous thrombosis were more frequent in patients harboring JAK2. Authors suggested to search for JAK2 in the setting of severe PVT, previous thrombosis and no thrombopenia
Gabr *et al*; 2010	21	NS Case-control	Egypt	-	-	-	-	7/21 (33%)	-	Authors concluded that MTHFR was associated with an increased risk of PVT.
Amitrano *et al;* 2011	50	NS Case-control	Italy	-	-	0/50 (0%)	-	-	-	Antiphospholipid antibodies played no role in PVT associated with liver cirrhosis

Author and year	N**	Study period and type	Population	PTHR	FVL	APS	JAK2	MTHFR	PAI	Comments
Ayala *et al;* 2012	50	2001-2006 Case-control	Spain	1/49 (2%)	1/49 (2%)	-	0/50 (0%)	7/48 (14.6%)	-	No association was observed between pre-transplant PVT and presence of genetic thrombophilia
Delgado *et al*; 2012	43	2003-2010 Retrospective	Spain	3/43 (7%)	1/43 (2.3%)	1/43 (2.3%)	-	-	-	Multicenter study. Thrombophilia in 16% of patients and it was not associated with response to anticoagulation. Deficiency of protein S, C and antithrombin in 2, 1, and 1 patient, respectively.
Qi *et al*; 2012	71	2009-2011 Prospective	China	-	-	-	1/71 (1.4%)	-	-	Prevalence very close to that of a Chinese hospital population of patients without PVT.
Senzolo *et al*; 2012	56	2007-2008 Prospective	UK, Italy	4/56 (7%)	2/56 (3.6%)	0/56 (0%)	-	-	-	Bicenter study. One patient had combined thrombophilia (FVL + PTHR).
Werner *et al*; 2013	69	2005-2011 Retrospective	USA	0/22 (0%)	0/22 (0%)	0/22 (0%)	-	-	-	One patient had antithrombin deficiency.
Karakose *et al*; 2015	38	2005-2009 Prospective	Turkey	4/38 (10.5%)	5/38 (13.1%)	-	1/38 (2.6%)	5/38 (13.2%)	-	Unicenter study.
Nery *et al*; 2015	67	2000-2006 RCT	France	NS	NS	-	-	-	-	Multicenter RCT. PTHR and FVL were studied in 283 patients, 67 of whom developed PVT. Their presence was not associated with PVT
Saugel *et al*; 2015	21	2009-2011 Case-control	Germany	0/21 (0%)	1/21 (4.8%)	-	2/21 (9.5%)	-	-	There was a trend for higher frequency of JAK2 mutation in cirrhotic patients with PVT than those without PVT.
Lancelloti *et al*; 2016	24	2013 Case-control	Italy	1/24 (4.2%)	0/24 (0%)	NS	-	-	-	PTHR and FVL were infrequent and not associated with PVT development
Pasta *et al*; 2016	350	2000-2014 Prospective	Italy	18/350 (5%)	29/350 (8%)	-	-	88/350 (25%)	111/350 (31%)	Individual patient data from 3 prospective studies. At least one thrombophilic genetic factor was present in 54% of patients. MTHFR and PAI were associated with PVT.
Ventura *et al*; 2016	38	2009-2013 Case-control	Italy	11/38 (10.5%)	4/38 (10.5%)	2/38 (5.2%)	-	13/38 (34.2)	-	PTHR and hyperhomocysteinemia were associated with PVT development
Artaza *et al*; 2018	32	2009-2015 Retrospective	Spain	0/24 (0%)	2/24 (8.3%)		1/24 (4.2%)	-	-	Thrombophilia in 4 patients (16%). Elevated homocysteine in 1/24 (4.2%). No association between thrombophilia and evolution of PVT

Author and year	N**	Study period and type	Population	PTHR	FVL	APS	JAK2	MTHFR	PAI	Comments
Senzolo *et al*; 2018	149	2008-2012 Prospective	International	7/64 (10.9%)	7/71 (9.9%)	-	1/32 (3.1%)	-	-	Centers from Europe, Canada and Korea. Thrombophilia testing in less than 50% of the patients. Authors did not search for an association between PVT and thrombophilia.
Cagin *et al*; 2019	98	2009-2015 Case-control	Turkey	15/98 (15.3%)	12/98 (12.2%)	-	-	16/98 (16.3%)	-	FVL mutation was the only type of thrombophilia associated with PVT. Reduced levels of protein C, S and AT-III: 74.4%, 72.4% and 64.2%.
Tremblay *et al*, 2020	73	2000-2019 Retrospective	USA	4/63 (6.3%)	4/65 (6.1%)	2/66 (3%)	1/45 (2.2%)	1/27 (3.7%)	20/34 (58.8%)	Thrombophilia testing was not complete in most patients and infrequently led to change in management. No patient had PNH, protein C, S or AT-III deficiency or MPL and CALR mutations

* The minimum number of patients with portal vein thrombosis to consider a study as large was 20.

** Denotes the number of patients that developed portal vein thrombosis within each study, not to the total cohort in each of them.

*** Percentages are calculated based on the number of patients tested for each type of thrombophilia, not the total cohort.

Abbreviations: ACA: anti-cardiolipin antibodies; APS: antiphospholipid syndrome; AT-III: antithrombin III; FVL: factor V Leiden; JAK2: Janus Kinase 2 mutation; MTHFR: methylenetetrahydrofolate reductase TT677 genotype; PAI-1: plasminogen activator inhibitor type 1; PNH: paroxysmal nocturnal hemoglobinuria; PTHR: Prothrombin G20210A mutation; PVT: portal vein thrombosis; RCT: randomized control trial; UK: United Kingdom.

Table 2. Clinical, imaging, endoscopic and laboratory features of patients with thrombophilia

Variable *	Case 1	Case 2	Case 3	Case 4
Type of thrombophilia	APS	APS	PV + FVL (heterozygous)	PTHR (heterozygous)
Age (years)	51	77	72	69
Gender	Female	Male	Male	Male
Race	Caucasian	Caucasian	Caucasian	Caucasian
Comorbidity	Diabetes	Diabetes	Diabetes	Diabetes
Etiology of liver disease	Hepatitis C	Alcohol	Alcohol	Alcohol
Child-Pugh	B (7 points)	B (7 points)	B (7 points)	A (6 points)
MELD (points)	11	9	12	11
Previous variceal bleeding	Yes	No	No	Yes
EV without bleeding		High risk	High risk	
Non-selective betablockers	Yes	Yes	No	Yes
Previous ascites	Yes	Yes	No	Yes
Previous SBP	No	No	No	No
Previous HE	Episodic	No	No	Episodic
Previous decompensation	Yes	Yes	No	Yes
HCC (No/BCLC stage)	No	No	No	A
Previous thrombotic events	No	No	No	No
Imaging for PVT diagnosis	CT	US	US	CT
Localization and extension	Main PV / Complete	Main PV / Partial	PV and branches / Complete	Right hepatic vein / Complete
Portal cavernoma	Yes	No	No	No
Local predisposing factor	No	No	No	No
Decompensation at diagnosis	Ascites	EV bleeding and ascites	Ascites	No
Other symptoms	No	No	No	No
Analytical parameters at diagnosis				
Leucocytes (x103 µL)	3.4	5.1	2.3	5.0
Platelets (x103 µL)	60	140	65	162
Hemoglobin (gr/dL)	9.8	11.6	11	13.9

Variable *	**Case 1**	**Case 2**	**Case 3**	**Case 4**
Creatinine (mg/dL)	0.96	0.97	0.88	0.85
Sodium (mEq/L)	138	134	138	137
ALT (U/L)	56	44	62	26
AP (U/L)	119	235	47	123
Bilirubin (mg/dL)	0.9	1.2	2.1	1.4
Albumin (gr/dL)	2.9	3.2	4.2	3.8
INR	1.45	1.14	1.34	1.27
Treatment	Acenocoumarol	Acenocoumarol	LMWH	No
PVT evolution	Progression	Partial resolution	Total resolution	Stability
Rethrombosis		Yes	Yes	
Exitus/LT	LT	Death	Death	LT
Time of follow-up (months)	21.3	16.9	85.0	24.0

* Quantitative variables were expressed as median and interquartile range and qualitative variables as absolute value (proportion).
Abbreviations: ALT: alanine aminotransferase; AP: Alkaline phosphatase, APS: antiphospholipid syndrome; BCLC: Barcelona Clinic Liver Cancer; CT: computed tomography; EV: esophageal varices; HCC: hepatocellular carcinoma; INR: international normalized ratio; LMWH: low-molecular-weight heparin; LT: liver transplantation; MELD: Model for End-Stage Disease; PV: polycythemia vera; PVT: portal vein thrombosis; TIPS: Transjugular intrahepatic portosystemic shunt, US: ultrasound.

Table 3. Clinical and epidemiological profile of patients in the whole cohort and in patients with and without thrombophilia

Variable *	Population (N= 77)	Non-thrombophilia (N=73)	Thrombophilia (N=4)	p
Age (years)	61.9 (55.0-67.6)	61.7 (55.0-67)	70.6 (55.5-76.0)	0.160
Gender (male)	67 (87)	64 (87.7)	3 (75.0)	0.434
Race (Caucasian)	76 (98.7)	72 (98.6)	4 (100)	1
Diabetes Mellitus	24 (31.2)	20 (27.4)	4 (100)	0.008
Dyslipemia	12 (15.6)	12 (16.4)	0 (0)	1
Arterial hypertension	22 (28.6)	22 (30.1)	0 (0)	0.320
Chronic kidney injury	5 (6.5)	5 (6.8)	0 (0)	0.961
HIV	4 (5.2)	4 (5.5)	0 (0)	1
Etiology of liver disease				0.979
Alcohol	49 (63.6)	46 (63.0)	3 (75)	
Hepatitis C	8 (10.4)	7 (9.6)	1 (25)	
Alcohol + hepatitis C	9 (11.7)	9 (12.3)	0 (0)	
Other	11 (14.3)	11 (15.1)	0 (0)	
Child-Pugh (points)	7 (6-9)	7 (6-9)	7 (6-7)	0.279
Child A/B/C (%)	35 / 50 / 15	36 / 49 / 15	1 / 3 / 0	0.530
MELD (points)	12 (10-14)	13 (10-14)	11 (10-12)	0.283
Previous TIPS	4 (5.2)	4 (5.5)	0 (0)	1
Liver allograft cirrhosis	3 (3.9)	3 (4.1)	0 (0)	1
Esophageal varices (Low/High risk)	14 (32) / 22 (50)	14 (33.3) / 20 (47.6)	0 (0) / 2 (50)	0.351
Previous variceal bleeding	33 (42.9)	31 (42.5)	2 (50)	1
Non-selective betablockers	51 (66.2)	48 (65.8)	3 (75)	1
Previous ascites (No/Yes/Refractory) (%)	27 / 65/ 8	28 /64 / 8	25 / 75 / 0	0.818
Previous SBP	6 (7.8)	6 (8.2)	0 (0)	1
Previous HE (No/Episodic/Recurrent) (%)	75 / 24 / 1	77 / 22 / 1	2 / 2 / 0	0.429
Any previous decompensation	62 (80.5)	59 (80.8)	3 (75)	1
HCC (No/BCLC stage A /B) (%)	87 / 12 / 1	88 / 11 / 1	3 / 1 / 0	0.682

Variable *	Population (N= 77)	Non-thrombophilia (N=73)	Thrombophilia (N=4)	p
Previous abortions	0 (0)	0 (0)	0 (0)	
Previous arterial/venous thrombotic events	3 (3.9)	3 (4.1)	0 (0)	1

* Quantitative variables were expressed as median and interquartile range and qualitative variables as absolute value (proportion).

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; HCC: hepatocellular carcinoma; HE: hepatic encephalopathy; HIV: human immunodeficiency virus; MELD: Model for End-Stage Disease; SBP: spontaneous bacterial peritonitis; TIPS: Transjugular intrahepatic portosystemic shunt

Table 4. Extension and clinical characteristics of portal vein thrombosis at diagnosis in the whole cohort and in patients with and without thrombophilia

Variable *	Population (N= 77)	Non-thrombophilia (N=73)	Thrombophilia (N=4)	p
CT or MRI for PVT diagnosis	67 (87.0)	65 (89)	2 (50)	0.080
Localization and extension				
Right PV (Partial/total) (%)	27 (35.1) / 8 (10.4)	27 (37.0) / 6 (8.2)	0 (0) / 2 (50)	**0.020**
Left PV (Partial/total) (%)	18 (23.4) / 5 (6.5)	17 (23.3) / 5 (6.8)	1 (25) / 0 (0)	0.864
Main PV (Partial/total) (%)	49 (63.6) / 8 (10.4)	48 (65.8) / 6 (8.2)	1 (25) / 2 (50)	**0.025**
SV (Partial/total) (%)	5 (6.5) / 2 (2.6)	5 (6.8) / 2 (2.7)	0 (0) / 0 (0)	0.810
SM vein (Partial/total) (%)	21 (27.3) / 3 (3.9)	21 (28.8) / 3 (4.1)	0 (0) / 0 (0)	0.385
Portal cavernoma	9 (11.7)	8 (11)	1 (25)	0.398
Local predisposing factor	4 (5.2)	4 (5.4)	0 (0)	1
Symptoms at diagnosis	33 (42.9)	32 (43.8)	1 (25)	0.631
Acute mesenteric ischemia	1 (1.3)	1 (1.4)	0 (0)	1
Abdominal pain	7 (9.1)	7 (9.6)	0 (0)	1
Fever	2 (2.6)	2 (2.7)	0 (0)	1
Variceal bleeding	14 (18.2)	13 (17.8)	1 (25)	0.560
Ascites (total/de novo)	38 (49.4) / 5 (6.5)			0.358
SBP	6 (7.8)	6 (8.2)	0 (0)	1
HE	10 (13.0)	10 (13.7)	0 (0)	1
Analytical parameters at diagnosis				
Leucocytes (x103 µL)	5.0 (3.3-6.0)	5.0 (3.3-6.1)	4.2 (2.6-5.1)	0.376
Platelets (x103 µL)	79 (62-110)	79 (62-108)	103 (61-157)	0.455
Hemoglobin (gr/dL)	12.8 (10.4-14.4)	12.8 (10.4-14.4)	11.3 (10.1-13.3)	0.532
Creatinine (mg/dL)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.9 (0.8-1)	0.826
Sodium (mEq/L)	139 (137-141)	139 (137-141)	137 (135-138)	0.455
ALT (U/L)	34 (23-46)	34 (22-44)	50 (31-61)	0.747
Alkaline phosphatase (U/L)	114 (78-154)	110 (78-154)	121 (65-207)	0.931
Bilirubin	1.6 (1.1-2.5)	1.6 (1.1-2.7)	1.3 (1.0-1.9)	0.398
Albumin (gr/dL)	3.4 (3.0-3.8)	3.4 (3.0-3.8)	3.5 (3.0-4.1)	0.678
INR	1.34 (1.23-1.52)	1.34 (1.23-1.53)	1.31 (1.17-1.42)	0.376

* Quantitative variables were expressed as median and interquartile range and qualitative variables as absolute value (proportion).

Abbreviations: ALT: alanine aminotransferase; CT: computed tomography; INR: international normalized ratio; MRI: magnetic resonance imaging; PVT: portal vein thrombosis; SM: superior mesenteric vein; SV, splenic vein.

Table 5. Treatment and outcome of portal vein thrombosis in the whole cohort and in patients with and without thrombophilia

Variable *	Population (N= 77)	Non-thrombophilia (N=73)	Thrombophilia (N=4)	p
Anticoagulation	59 (76.6)	56 (80)	3 (75)	1
Acenocoumarol	46 (78.0)	44 (78.6)	2 (66.7)	0.832
LMWH	12 (20.3)	11 (19.6)	1 (33.3)	
Apixaban	1 (1.7)	1 (1.8)	0 (0)	
Duration (months)	12.6 (6.2-27.0)	12.1 (6.0-25.3)	22.2 (8.1-157.2)	0.476
TIPS	4 (5.2)	4 (5.5)	0 (0)	1
PVT evolution				0.744
Stability	22 (30.5)	21 (30.9)	1 (25)	
Progression	8 (11.1)	7 (10.3)	1 (25)	
Partial resolution	12 (16.6)	11 (16.2)	1 (25)	
Total resolution	30 (41.7)	29 (42.6)	1 (25)	
Rethrombosis after ceasing anticoagulation	10 (32.3)	8 (27.6)	2 (100)	0.097
Exitus	37 (48.1)	35 (47.9)	2 (50)	180
Liver transplantation	17 (22.1)	15 (20.5)	2 (50)	0.210
Time of follow-up (months)	27.0 (10.9-55.5)	27.5 (10.8-55.5)	22.7 (18.0-69.7)	0.995

* Quantitative variables were expressed as median and interquartile range and qualitative variables as absolute value (proportion).

Abbreviations: LMWH: low-molecular-weight heparin; PVT: portal vein thrombosis; TIPS: Transjugular intrahepatic portosystemic shunt