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Summary of PhD Thesis

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UNIVERSITY "CAROL DAVILA"- BUCHAREST
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PORTAL VEIN THROMBOSIS IN THE CIRRHOTIC PATIENT: INCIDENCE, MANAGEMENT, RISK FACTORS AND CLINICAL OUTCOME

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Abbreviation

AC – Anticoagulant

ACLF – acute on chronic liver failure

DOACs – direct oral anticoagulants

EV – esophageal varices

IVC - Inferior vena cava

LC - Liver cirrhosis

LMWH – low molecular weight heparin

MELD – Model for End Stage Liver Disease

NO – nitric oxide

NSBB – non selective beta blockers

PV - Portal Vein

PVT - Portal vein thrombosis

RMST - restricted mean survival time

rTPA - recombinant tissue plasminogen activator

SHV - Suprahepatic vein

TIPS - Transjugular intrahepatic portosystemic shunt

VBL – variceal band ligation

VKAs – vitamin K antagonists

vWF – von Willenbrand factor

Introduction

Portal vein thrombosis (PVT) is a common condition in patients with liver cirrhosis (LC), in most cases asymptomatic and incidentally diagnosed . It involves the formation of a thrombus in the intra or extrahepatic portion of the portal vein with the possibility of extension to the level of the superior mesenteric vein. Obstruction of the vascular lumen can be partial (non-obstructive PVT) or complete (obstructive PVT). It is frequently associated with liver cirrhosis due to vascular stasis. The lack of symptoms in PVT is due to the insidious formation and chronicity, acute PVT cases being much rare.

Worldwide, the incidence and prevalence of PVT in the cirrhotic patient shows an important variation depending on the degree of liver function impairment quantified by the Child Pugh score.

The present study aimed to perform an evaluation of patients diagnosed with PVT in the records of a tertiary gastroenterology center including incidence data, risk factors, treatment and prognosis.

The scientific objectives to be solved within the research were: the collection of accurate and complete data in patients with liver cirrhosis and portal vein thrombosis, the analysis of epidemiological, clinical-biological and imaging characteristics.

The aim was to identify risk factors that could help to implement measures to prevent the occurrence of PVT, to analys of comparative survival in patients with and without PVT. Related to PVT management, response to anticoagulant treatment, survival, and bleeding complications associated with anticoagulants (AC) were monitored.

I. GENERAL PART

1. Portal vein anatomy

The portal vein (PV) is about 6-8cm long, originating from the confluence with the mesenteric and splenic veins, anteriorly from the inferior vena cava (IVC) and posteriorly from the pancreatic head. It is a valveless vein and provides 75% of the liver's blood supply, the remaining 25% being provided by the hepatic artery (HA). VP brings blood from the entire digestive tract (except the lower part of the rectum), from the spleen, pancreas, gall bladder. At the level of the hepatic hilum, the VP divides into right and left branches distributed to the right and left lobes of the liver, then into segmental and subsegmental branches that branch until the sinusoids are formed. These in turn open into the central vein inside the hepatic lobule from where the blood is taken by the suprahepatic veins (SHV) which open into the inferior vena cava (IVC)[1]

2. Epidemiology of Portal Vein Thrombosis

2.1 Global data

Portal vein thrombosis (PVT) is a frequent complication associated with liver cirrhosis whose impact can influence the course of the disease, increasing the risk of liver decompensation, variceal bleeding and decreasing survival, including in patients undergoing a liver transplant. PVT may increase progressively with advancing age, degree of liver damage, and procoagulant status.

Liver cirrhosis is the most important risk factor in the development of PVT, the risk being about 7 times higher in the cirrhotic patient compared to the general population. The reported incidence in patients with cirrhosis varies by Pugh-Child score. Thus, a cumulative incidence at 1 and 5 years of 4.6% and 10.7% respectively was reported for Child A. for Child B[2–4] . At the same time, the prevalence in those with compensated cirrhosis is around 1% and increases up to 25% in liver transplant candidates.[5,6] These data highlight the increased risk of PVT with the progression of liver disease.

3. The natural history of Portal Vein Thrombosis

The natural course of PVT involves progression, regression or stabilization of the thrombus, and data in the literature are variable as to what the overall trend is. It is generally accepted that the degree of occlusion (complete vs. partial) as well as the severity of cirrhosis dictate the natural course of PVT.[7] Cases of complete occlusion are rare, thus an incidence of complete VP occlusion at 12 and 24 months of 9% and 14% respectively was noted.[8]

Studies of patients on the waiting list for liver transplantation have generally shown a lower rate of thrombus resolution. [7,9] and factors associated with PVT regression were low MELD score at diagnosis or improvement during follow-up.[10] Location of the thrombus in the right or left branch was associated with a lower rate of progression compared to location at the level of the trunk.[11] Absence of large collaterals greater than 9 mm around the VP is a predictive factor for PVT regression [12].

Given the high rate of post-regression recurrence, the importance of long-term follow-up of patients even after thrombus resolution emerges

4. Clinical presentation and Impact of Portal Vein Thrombosis in the natural history of the cirrhotic patient

4.1 Clinical presentation

It varies according to acute vs. chronic presentation, the degree of occlusion (partial vs.), the nature of the thrombus (malignant vs. non-malignant), and the stage of liver cirrhosis. Since most cases are chronic forms, in which PVT sets in insidiously, the patient often remains asymptomatic and the diagnosis is discovered incidentally. Acute forms can also go unnoticed without generating symptoms. When they appear, the symptoms are non-specific, most commonly abdominal pain, dyspeptic syndrome, but they can evolve to abdominal distension with hemorrhagic diarrhea when the thrombus extends to the mesenteric vessels generating intestinal ischemia.[13,14]

Patients with liver cirrhosis who develop PVT may present as a decompensation of cirrhosis with the development of ascites, the establishment of resistance to diuretics and refractory ascites, or the development of spontaneous bacterial peritonitis. Recently, a new concept has been proposed that indicates the evaluation of the presence of PVT as a precipitating factor in the exacerbation of chronic liver failure (ACLF). Thus, 3 such associations between PVT and ACLF were proposed. Acute PVT leads to hepatic ischemic lesions which can precipitate the appearance of ACLF, on the other hand ACLF implies a proinflammatory status that can favor PVT. [15,16]

4.2 Impact of PVT on the natural history of cirrhosis

Whether or not thrombus extension dictates the progression of liver cirrhosis is still a matter of debate. The development of thrombus in the vein, especially in cases where it is complete, causes an increase in resistance in the portal bed, resulting in an increase in portal hypertension, which can increase the risk of variceal bleeding or the occurrence of refractory ascites. In patients with porto-systemic collaterals and low or absent portal hepatopetal flow, the development of PVT may be have no cosequence.[17]

Arguments in favor of the negative effect of PVT on the evolution of cirrhosis arise mainly from studies that correlated the response to AC therapy with a better prognosis. Thus, effective AC therapy was correlated with a decrease in variceal bleeding and a decrease in the risk of liver decompensation.[18–21]

The increase in mortality and morbidity after liver transplantation, already proven in numerous studies, has a multifactorial cause, being related to a more complex surgical procedure, increased transfusion requirements, complications such as primary nonfunction, hepatic artery thrombosis, postoperative pancreatitis or sepsis.[22]

5. Risk factors

The pathophysiology of portal vein thrombosis (PVT) respects Virchow's triad, being multifactorial in which vascular stasis, endothelial injury and hypercoagulability are the main predisposing changes.

Alteration of coagulation is one of the components associated with the risk of PVT. Thrombocytopenia and platelet dysfunction is counteracted by overexpression of von Willebrand factor (vWF). Decreased production of procoagulant factors (factors V, VII, and X) that would result in prolonged prothrombin time is counteracted by decreased production of anticoagulant factors proteins such as C and S. Hypoproduction of protein C (anticoagulant factor) and increased factor VIII (procoagulant) leads to a tendency towards coagulability. These changes associated with venous stasis and endothelial injury favor thrombosis.[23,24]

Endothelial injury plays an important role in the pathogenesis of PVT and appears to be primarily related to the alteration of nitric oxide (NO) bioavailability by decreasing the activity of the NO synthase enzyme. Hyperproduction of ON leads to splanchnic congestion, vascular tension and consequent endothelial injury. Endothelial dysfunction markers such as von Wilebrand factor, p-selectin,

Endoscopic band ligation of esophageal varices (EV) as a risk factor in the development of PVT is a controversial topic and difficult to accept by the medical community. It is proven that EV can have a negative impact on portal hemodynamics, but the idea that it also induces endothelial injury favoring the development of PVT is unclear and insufficient studied.

Vascular stasis occurs due to the presence of fibrosis and the destruction of sinusoids at the hepatic level, through the phenomenon of theft of porto-systemic shunts and the use of non-selective beta blockers (NSBB). There is evidence to support that a reduction in portal vein velocity below 15cm/s is associated with a 10-20 times greater risk of developing PVT.[3]

6. Management of Portal Vein Thrombosis

6.1 Anticoagulation (AC)

The main goal of anticoagulant therapy recanalization and to prevent the extension of the thrombus, which can have a negative impact in patients who will undergo liver transplantation.

Once initiated, anticoagulation must be maintained until the complete resolution of the thrombus or for at least 6 months, and in those with complete recanalization but waiting for a liver transplant, long-term anticoagulation should be considered. [25–28].

Currently available treatment options for PVT include vitamin K antagonists (VKAs), low molecular weight heparin (LMWH), as well as direct-acting oral anticoagulants (DOACs). As a rule, initiation of anticoagulation with LMWH is preferred. However, each of these agents have advantages and disadvantages[29]

6.2 Trombolisis

Thrombolysis in PVT can be performed either locally or by a systemic approach. Therapeutic agents used for thrombolysis include streptokinase, urokinase, or recombinant tissue plasminogen activator (rTPA).

However, it may be the risk of complication of not recommended in the presentation of the peace with LC and acute PVT. (18)

6.3 Mechanical recanalisation

Options include mechanical thrombectomy and balloon angioplasty of the PV, which may also be combined with local thrombolysis. Small studies have reported 100% success rate in combinations of mechanical recanalization and pharmacologic thrombolysis, without bleeding complications. [30,31]

Balloon angioplasty through the transjugular approach is preferred as it has a lower risk of reaction.[32]

6.4 Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS involves creating a low-resistance pathway for blood flow from an intrahepatic portion between the VP and a suprahepatic vein by placing a stent. VP recanalization via TIPS has been used in liver transplant candidates and chronic PVT, thus facilitating the surgical technique of VP anastomosis during liver transplantation.[33]

II. PERSONAL CONTRIBUTION

7. The working hypotesis and general objectives

The working hypotesis

The present study aimed to perform an analysis of patients diagnosed with liver cirrhosis and portal vein thrombosis for a more detailed understanding and characterization of this population.

General objectives

- Highlighting an incidence of PVT in a tertiary hepatology and liver transplant center
- Analysis of the effectiveness and safety of anticoagulant therapy in patients with PVT
- Identification of risk factors associated with PVT
- The impact of PVT on the evolution of CH

8. General methodology

8.1 Inclusion criteria

We performed an observational, retrospective and prospective study on a total number of 375 patients diagnosed with liver cirrhosis and selected from the database of the Hepatology Department of the Fundeni Clinical Institute between January 2017 and February 2020.

Eligibility criteria:

- Age over 18 years
- Patients diagnosed with liver cirrhosis and portal vein thrombosis
- Patients diagnosed with liver cirrhosis without portal vein thrombosis (control group)
- Admission to the clinic during the study period, for investigations or therapeutic maneuvers related to the diagnosis of liver cirrhosis with or without thrombosis.
- Signing the informed consent

Exclusion criteria:

- The presence of hepatocarcinoma
- The presence of other untreated neoplasms

8.2 Data synthesis

The collected data were entered into the Microsoft Excel 2010 database and IBM SPSS version 20 statistical processing was used.

A classical descriptive statistical analysis of the variables was performed, the continuous variables the central tendency was estimated using the mean and the median and the tendency to variability was estimated using the standard deviation (SD), the minimum, the maximum and the range. Multivariate analysis was performed by linear regression for continuous variables and logistic regression for categorical ones, and P values less than 0.05 were considered statistically significant.

Survival analysis - RMST ("restricted mean survival time" - mean survival for survival studies in which there are still surviving patients), median survival were determined.

9. Study 1- Epidemiological data and clinical-biological picture

9.1 Introduction

To date, in our country no registry includes patients with liver cirrhosis and associated complications, so the date of incidence or prevalence related to the presence of PVT is not available.

The aim of our study was to introduce a large number of cirrhotic patients with and without PVT to allow correlations to be made in terms of epidemiological, clinico-biological and imaging characteristics.

9.2 Pacients and Methods

We performed an epidemiological, observational, retrospective and prospective study on a group of 145 patients diagnosed with PVT and a control group of 230 patients without PVT. In total, 375 patients diagnosed with CH were admitted to the Fundeni Clinical Institute between January 2017 and February 2020. Patients with a previous diagnosis and those newly diagnosed with chronic PVT were identified, excluding those with tumor thrombosis or associated HCC .

New diagnosis was considered in those incidentally diagnosed with PVT during the periodic medical evaluation performed at study entry. Clinical and laboratory data at the time of diagnosis were collected retrospectively and included liver function tests (AST, ALT, GGT, alkaline phosphatase, total and direct bilirubin), platelet count, INR, creatinine, tests for infection chronic HBV and HCV.

Data analyse

Data were analyzed using IBM SPSS version 20 statistics.

9.3 Results and discussions

During the study, during the period of follow-up and inclusion of patients in the database, 16 cases of de novo PVT were identified. Thus, the cumulative incidence of PVT calculated at 3 years in cirrhotic patients included in the study was 4.26%.

The present study gathered a number of 145 patients diagnosed with PVT and 230 patients without PVT who formed the control group. No significant difference was noted between the groups in terms of age, M:F ratio, MELD and Child-Pugh scores, the 2 groups being homogeneous in terms of the liver disease stage.

In the group with PVT there was an average age of 55 years, respectively 54 years in the group without PVT and the M: F distribution was 1.05:1 in the group with PVT and 1.12:1 in the group without PVT.

The majority of patients were diagnosed with liver cirrhosis Child B (56.3% in the group without PVT and 60% in the group with PVT) with an average of 7.26 points in the group without PVT, respectively 7.14 points in the group with PVT. The mean MELD score was 12.46: 13.24 in the group with PVT and 11.74 in the group without PVT.

In the PVT group, there was a predominance of partial thromboses (113 patients, 77.93%) noted predominantly in the the portal vein trunk (80 patients, 55.17%) followed by the confluent (62 patients 42.7%). Only a small percentage presented the extension of the thrombosis at the mesenteric vein (n=38, 26.2%)

In the group with PVT a predominance of hepatic encephalopathy was observed: 22.6% versus 8.07%, refractory ascites: 30.7% versus 19.2% and spontaneous bacterial peritonitis (SBP) 15.17% versus 13.4%. The differences were statistically significant for refractory ascites and hepatic encephalopathy but not for SBP.

In the present study variables such as spleen diameter, portal vein diameter, portal vein velocity were also monitored. There were statistically significant differences between the two groups regarding the degree of splenomegaly and the velocity in PV (mean splenic diameter of 17 vs. 14 cm, p=0.001; vel med =9.7 vs. 14.9 cm/sec, p=0.002).

10. Study 2 - Risk factors and predictors in PVT

10.1 Introduction

There is evidence to support that a reduction in portal vein velocity below 15cm/s is associated with a 10-20 times greater risk of developing PVT.

The role of PV velocity in the occurrence of PVT is also linked in other studies.[3,34,35] NSBB therapy is a controversial topic but studies have not yet prouved a causal relationship with regard to PVT risk. [36]

Variceal band ligation (VBL) may have a negative impact on portal hemodynamics, but the idea that it promotes endothelial injury favoring the development of PVT is unclear and insufficiently studied.[37–39]

The aim of this study was to determine potential risk factors associated with PVT. The main objective was to analyse if there is a relationship between the development of PVT and VBL. Secondary objectives were to establish a corelation between PV velocity, BBNS as well as protein C and S deficiency and the risk of PVT.

10.2 Pacients and methods

A total of 375 patients diagnosed with cirrhosis with or without PVT were enrolled in the study at the Fundeni Clinical Institute between January 2017 and February 2020. .

Inclusion criteria were the presence of cirrhosis with or without PVT, 18 years or older and exclusion criteria included hepatocellular carcinoma or absence of preprocedural imaging evaluation in those who underwent endoscopic esophageal band ligation (VBL). Demographic and clinical characteristics included age, sex, etiology of cirrhosis, model for end liver disease (MELD) score, Child score, varices grade, beta-blocker therapy, history of variceal ligation, and type of endoscopic esophageal variceal ligation (prophylactic/). therapeutic).

In the same time, values of the velocity in PV and the level of proteins C and S were collected.

Therapeutic and follow-up protocol

The study was a retrospective and prospective case-control. All patients underwent prophylaxis of hemorrhagic events: endoscopic screening was used and, depending on the presence and severity of esophageal varices, the interventional method (band ligation-VBL) or/and the pharmacological method (NSBB) was used.

Variceal ligation was recommended in case of large varices, signs of gravity with red spots (as primary prophylaxis) or in case of recent history or acute variceal bleeding (as secondary prophylaxis).

A multi-band ligator was used and 4-6 elastic bands were used during each session. All patients received propranolol in decreasing doses to achieve a heart rate between 55-60/min. They were followed up every 3-4 weeks, undergoing an endoscopy and repeating the VBL session until the varicose veins were eradicated.

Portal vein patency was assessed using abdominal Doppler ultrasound at six-month intervals or at each follow-up visit during the VBL program.

The mean follow-up period was considered in the study until the last contact (death, liver transplant, last follow-up visit).

Statistical analysis

Data were analyzed using IBM SPSS statistics version 20. Multivariate analysis was performed by linear regression for continuous variables and logistic regression for categorical variable. P values less than 0.05 were considered statistically significant.

10.3 Results - VBL is a risk factor in the development of PVT

Of the 375 patients, 129 had a previous diagnosis of PVT and 246 were without PVT. From the total number of patients, those with a history of variceal ligation were identified. Thus, it was identified that 88 (23.46%) patients performed at least one VBL session and of the 287 (76.53%) patients who did not perform VBL, 68 (18.13%) only had beta blockers for the primary prophylaxis of hemorrhagic events.(Table.1)

Tabel Nr.1 - Patients characteristics in the two groups.

	Non VBL n=287	VBL n= 88	P
Etiology			
HBV (+- VHD)	98(34.1%)	37(42.1%)	
VHC	90(31.4%)	23(26.1%)	0.13
Ethanol	84(29.3%)	23(26.1%)	
Criptogenic	9(3.1%)	3(3.4%)	
Autoimun	6(2.1%)	2(2.3%)	
MELD score			
9-14	53.65 (%)	23.66(%)	
15-19	64.22 (%)	52.98(%)	0.93
>20	11.38(%)	5.69(%)	
Child Score			
A	38.21 (%)	91 (%)	
B	47.10(%)	86 (%)	0.12
C	6.61(%)	5(%)	
Refractory ascites	34 (%)	30 (%)	0.01

Of those with VBL, 20 (22.7%) underwent VBL as secondary prophylaxis, 68 (77.27%) underwent primary prophylaxis. Thus, 215 VBL procedures were performed with an average number of sessions of 2 (range 1-10).

Monitoring of study patients

Median follow-up was 92.55 months (range 22-230). The PVT group included a number of 111 patients (29.6%) of whom 67% (n=63) had at least one VBL session, prior to the diagnosis of PVT: 38% (n=42) of patients diagnosed with PVT had performed primary and 19% secondary prophylaxis (n=21).

A logistic regression was performed to assess whether VBL (primary and secondary prophylaxis) are risk factors for the development of PVT. The model was significant (p = 0.005, OR -1.4, CI 1.1-18,324), resulting in an approximately 1.4-fold increase in PVT risk after VBL

Tabel Nr. 2 - Logistic regression endoscopic ligature and risk of PVT

	Odds ratio		95% C.I. inim	axim
The degree of eophagus varices	.217	.335	0518	.251
Endoscopic ligature	1.407	**.005**	.1	8.324
Primary prophylaxis	1.486	**.028**	.60	.851
Secondary Prophylaxis	.592	**.017**	.555	.75
The number of VE taping sessions	.83	.608	.791	.493

10.4 Results -Velocity in portal vein and risk of PVT.

In the study population, the portal vein velocity determined on ultrasounds performed before the diagnosis of PVT was identified for the subgroup of patients diagnosed with PVT, and in the subgroup of patients without PVT, the velocity in the PV at study entry was noted.

Using linear regression, the correlation between portal vein velocity and the risk of thrombosis was analyzed. It has been shown that the decrease in the velocity in PV is strongly correlated with PVT, the lower the velocity, the higher the risk of developing PVT.

Using the ROC curve, a cut-off value of 12cm/sec was determined and analyzing by logistic regression whether this value can be used as a predictive factor for the occurrence of portal vein thrombosis, it was obtained that the velocity in the portal vein <12cm/sec increases the risk of PVT by about 18 times (OR=18.06, p=0.0001)(Fig.1).

The sensitivity and specificity for PV velocity of this cut-off was 82% and 78%, the test being statistically significant (p=0.001)

Tabel Nr. 3 - Linear regression PV velocity and risk of PVT.

		Odds ratio	P	95% C.I.	
				minim	maxim
	Velocity in PV <12cm/sec	18.6	0.0001	10.423	3.804

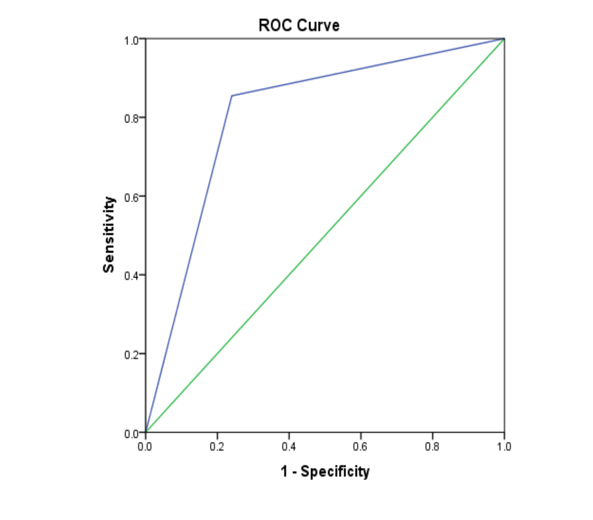

Fig.1 - ROC curve and PV velocity

10.5 Results - Proteins C, S and risk of PVT

The level of proteins C and S could be determined in a smaller number of patients. Using linear regression, no correlation was found between PVT and the low level of PC and PS (OR=-0.008, p=0.251); (OR=-0.006, p=0.427)

Using ROC curves to establish the specificity and sensitivity of proteins S and C in predicting PVT risk, AUC =0.663 for PS and AUC 0.672 for PC were obtained, the models being statistically insignificant (p=0.054 ; p=0.042).

10.6 Results BBNS therapy and risk of PVT

Looking at NSBB therapy, 68 patients were identified who had only beta-blocker therapy with no history of VBL. It was observed whether beta-blocker therapy correlates with the decrease in PV velocity, respectively with the risk of PVT. There was a correlation between NSBB therapy and the risk of PVT (OR 0.0511, p=0.018, %CI 0.933-

0.914. However, no correlation was found between NSBB administration and portal vein velocity. (OR 0.137, p=0.533)

10.7 Discussion

The present study proved a negative influence of VBL by increasing the risk of developing PVT. However, the data in our study were mostly collected retrospectively and prospective, randomized studies are needed to establish a correct risk stratification of a post VBL PVT.

At the same time, the velocity in PV<12cm/sec proved its predictive value in the development of PVT, something also proven in other studies.

Establishing a high-risk profile could place patients eligible for liver transplantation and at risk of PVT into a group to benefit from prophylactic anticoagulant therapy.

11. Study 3 - Evaluation of the effectiveness and safety of anticoagulant therapy in patients with Portal Vein Thrombosis

11.1 Introduction

Evidence for the use of anticoagulant therapy (AC) in PVT is growing and a considerable percentage of patients with PVT are managed with AC with either low molecular weight heparin (LMWH) or vitamin K antagonists (VKAs).[21,40,41] The primary objective of this study was to evaluate the safety profile and effectiveness of AC therapy in PVT in patients with liver cirrhosis on the waiting list in a tertiary hepatology center. The main outcomes were thrombus regression and occurrence of bleeding events.

11.2 Pacients and methods

We conducted a case control, observational, retrospective and prospective study within the Fundeni Clinical Institute between January 2017 and February 2020.

A total of 140 LC patients divided into two groups were enrolled: a group of 73 patients who received anticoagulant therapy and a group of 67 patients without anticoagulant treatment.

Inclusion criteria were age 18 years or older, end-stage liver disease, presence of PVT, patients eligible for liver transplantation. Exclusion criteria included hepatocellular carcinoma, Budd Chiari syndrome, or patients ineligible for liver transplantation

Therapeutic and follow-up protocol.

All patients underwent prophylaxis for hemorrhagic events. A protocol for the use and monitoring of AC therapy was carried out: in the first week, a loading dose of 200 U/kg of enoxaparin was administered to all patients; subsequently, AC with enoxaparin (n = 40) or VKA (n = 33) was used. During the study period, both groups were followed up periodically.

Thrombosis evolution (regression, progression, or stable PVT) was assessed by CT scan every 3 months. Events leading to discontinuation of AC therapy were bleeding with secondary anemia, liver transplantation, and patient death. Median follow-up was 32 months (range: 3-109).

Statistical analysis.

The data were analyzed. P values less than 0.05 were considered statistically significant11.3

11.3 Results

PVT regression was reported in 54 patients (38.6%) in the AC group and in 9 patients (6.4%) in the untreated group. The difference in the evolution of PVT in the two groups was analyzed by binary logistic regression. It was observed that in the group of anticoagulated patients the PVT regression rate was significantly higher (OR = 2.77, p = 0.007, 95% CI: 2.104-122), the anticoagulated patient being twice as likely to present or thrombus regression. This effect was observed after approximately 6 months of AC therapy.

Bleeding events were more common in the AC therapy group, 16 cases of which 3 were mild (2 epistaxis, one oral bleed) and 13 variceal bleeds requiring hospitalization. The untreated group had only five cases of variceal bleeding. Of all patients with variceal bleeding, 5 occurred after VBL in the AC group and 2 in the untreated group.

Simple univariate binary logistic regression was performed to assess whether MELD score, platelets, and anticoagulation were predictors of bleeding events(Table.4) Only one variable proved to be a significant predictor for hemorrhagic complications:

platelets less than 50x103 / mm3 increase the risk of hemorrhagic events in these patients 2 times (OR = -2.163; CI 95%: 0.035-0.385, p = 0.002).

Tabel Nr. 4 – Predictors of bleeding events

	OR	**95%CI**	**p**
Thrombocites < *$50x10^3/mm^3$*	**2.163**	**0.035-0.385**	**0.002**
MELD	0.510	0.131-1.599	0.320
Anticoagulation	0.780	0.863-10.733	0.222

11.4 Discussions

Portal vein thrombosis is a frequent complication in the cirrhotic patient, the causal relationship regarding worsening of liver disease is still debated.

In our study, using AC had a positive effect on the evolution of PVT - more than half of the AC group experienced thrombosis regression (55.6%).

The AC protocol of our study consists of a loading dose and a maintenance dose: LMWH in the loading phase followed by LMWH or AVK. Data from the literature support the continuation of AC therapy even after thrombus regression until the time of transplantation with a high risk of recurrence. [42–44].

Although more than 50% of patients treated with AC experienced PVT regression, a significant percentage of them (21.9%) experienced a bleeding event (more than 60% of those undergoing hospitalization and discontinuation of AC therapy). In our study, the main risk factor for bleeding events was the platelet level. This study demonstrates the efficiency and effectiveness of anticoagulant therapy in the patient with LC and PVT.

12. Study 4 - Clinical impact and survival in Portal Vein Thrombosis

12.1 Introduction

Studies in the literature correlate the occurrence of portal vein thrombosis in cirrhotic patients with the increased risk of liver decompensation, however, recent studies have demonstrated that the occurrence of PVT is associated with a more advanced form of LC since diagnosis without necessarily influencing the progression of the disease. [45]. Data on long-term survival of patients with PVT are unclear.

The evidence regarding post-liver transplant survival in the patient with PVT is much clearer, with studies showing that mortality at 30 days and at one year post-transplant is higher than in the non-PVT population.[46,47]

12.2 Pacients and methods

The present study was retrospective and prospective, observational, non-randomized, on a sample of 211 patients diagnosed with LC with or without associated PVT. Group A consisted of 144 patients in whom PVT was identified, while group B consisted of 67 patients in whom PVT was not identified. The presence of LC was diagnosed using one or more of the following elements suggestive of portal hypertension including: cirrhotic appearance of the liver with splenomegaly on imaging, thrombocytopenia (platelets <110000/mm3), evidence of esophageal varices on endoscopic examination, presence of encephalopathy hepatic. All patients with LC underwent a complete imaging examination to rule out hepatocelular carcinoma.

Clinical and laboratory data were collected retrospectively and prospectively 6 months after study entry for all patients and included transaminases, bilirubin, creatinine, platelet count, INR, HBV and HCV serology..

Statistical analysis

Survival analysis - RMST ("restricted mean survival time" - mean survival for survival studies in which there are still surviving patients), median survival were determined**.**

Study objectives

The main objectives of the study were OS: (overall survival) and OR (odds ratio), which express the risk of a certain variable for the occurrence of portal vein thrombosis.

12.3 Results

The survival analysis was done on the whole sample, and separately on the group of patients with PVT. Mortality in the study was 20%. There were 43 deaths, 19 in women and 24 in men.

Overall survival in patients with PVT is 29.86%. During the follow-up period, there were 43 deaths from a number of 144 patients diagnosed with PVT.

Tabel Nr. 5 - Global survival

Strata	N Deaths (%)	RMST	Median Survival (95% CI)
Lot Intreg	43 / 211 (20.37)	185.00	191.00 (180.00 la N/A)

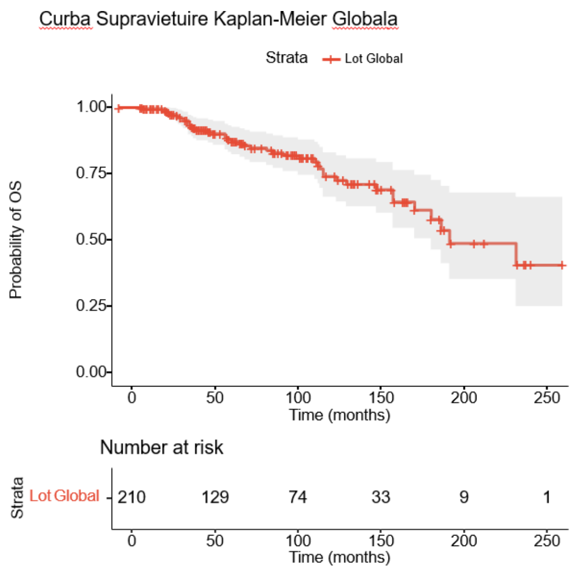

Figure.3 - Global Survival

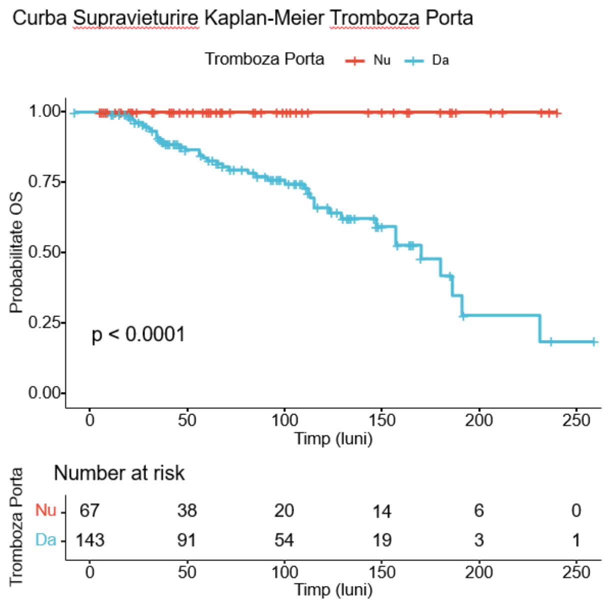

Figure. 4 - Presence of PVT and survival rate

Upper gastrointestinal bleeding did not appear to influence overall survival although the percentage of deaths among these patients was higher, 27.84% versus 27.09%. At the same time, patients in Child A class at 6 months had the most favorable prognosis, while patients in Child C class at 6 months had the worst prognosis, the differences being significant (p=0.035).

Hepatic encephalopaty and refractory ascites were significantly more frequent in the group of patients with PVT (22% vs 7.82%, p=0.001 and 30.7% vs 19.2%, p=0.011) and attracted a worse prognosis, the differences between the survival curves being statistically significant (p=0.011, p=0.0014).

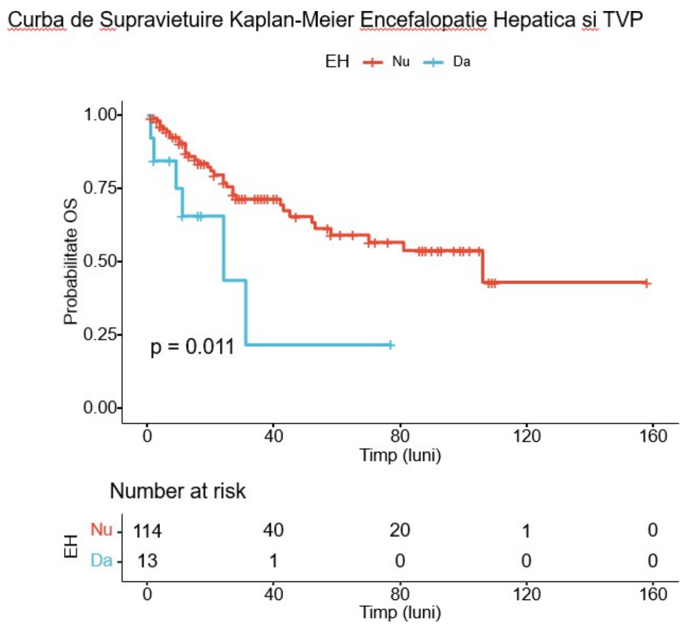

Figure.5 - HE and survival rate

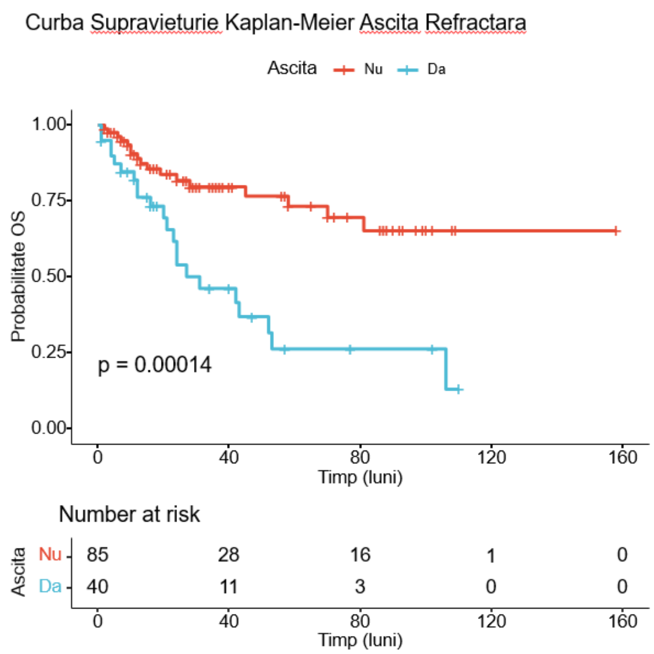

Figure.6 – Refractory ascites and survival rate in PVT

Anticoagulant treatment determines a positive influence on survival, being statistically significant (p=0.015)

Regarding liver transplantation, statistically significant differences were obtained regarding the influence of liver transplantation on survival, although survival was better in the group of transplanted patients.

12.4 Discussion

In our study, the overall mortality was 20% with no difference related to sex or the etiology of the underlying disease but with statistically significant differences related to the presence of PVT. Our study demonstrated that the presence of PVT in the cirrhotic patient had a significant impact leading to increased mortality (p=0.0001).

In the present study, the presence of PVT was correlated with a higher rate of refractory ascites, respectively of hepatic encephalopathy (p=0.011; p=0.0001) and these complications were associated with reduced survival (p=0.011, 0.0014).

In our study, survival was clearly superior in anticoagulated patients (p=0.015) and in the case of transplanted patients survival was superior but without statistical significance (p=0.098).

13. Personal Contributions

- • Determination of the incidence of PVT in a group of patients from a tertiary center for digestive diseases and liver transplant
- • Studying the effectiveness and safety profile of AC therapy in PVT
- • Identification of predictors in the development of PVT
- • Evaluation of the impact of PVT on the evolution of the liver disease and on survival

Future research directions may be:

- • Expanding the current database by continually adding new studies and periodically tracking those that include them.
- • Building a register with the participation of all university centers in Romania which will be the basis for carrying out further studies in an attempt to identify other prognostic factors that will not guide the therapeutic approach of each individual patient in the future.
- • Carrying out studies on a large number of patients to correctly define the risk of developing PVT and the impact on the evolution of liver disease.

BIBLIOGRAPHY

1. Corness JA, McHugh K, Roebuck DJ, Taylor AM (2006) The portal vein in children: radiological review of congenital anomalies and acquired abnormalities. Pediatr Radiol 36:87–96.

2. Ogren M, Bergqvist D, Bjorck M, et al. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23796 consecutive autopsies. World J Gastroenterol. 2006;12:2115–2119.

3. Stine JG, Wang J, Shah PM, Argo CK, Intagliata N, Uflacker A, et al.. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: A matched case-control study. Liver Int. (2018) 38:94–101. doi.

4. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, Plessier A, Roulot D, Chaffaut C, Bourcier V, Trinchet JC, Valla DC; Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015 Feb;61(2):660-7. doi: 10.1002/hep.27546. Epub 2015 Jan 5. PMID: 25284616.

5. Ponziani FR, Zocco MA, Garcovich M, D'Aversa F, Roccarina D, Gasbarrini A. What we should know about portal vein thrombosis in cirrhotic patients: a changing perspective. World J Gastroenterol. 2012;18:5014–5020.

6. Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F; faculty of the 7th International Coagulation in Liver Disease. Concepts and Controversies in Haemostasis and Thrombosis Associated with Liver Disease: Proceedings of the 7th International Coagulation in Liver Disease Conference. Thromb Haemost. 2018;118:1491-1506. Faccia M, Ainora ME, Ponziani FR, Riccardi L, Garcovich M, Gasbarrini A, Pompili M, Zocco MA. Portal vein thrombosis in cirrhosis: Why a well-known complication is still matter of debate. World J Gastroenterol 2019; 25(31): 4437-4451 [PMID: 31496623 DOI: 10.3748/wjg.v25.i31.4437].

7. Francoz C, Valla D, Durand F. Portal vein thrombosis, cirrhosis, and liver transplantation. J Hepatol. 2012 Jul;57(1):203-12. doi: 10.1016/j.jhep.2011.12.034. Epub 2012 Mar 21. PMID: 22446690.

8. Luca A, Caruso S, Milazzo M, Marrone G, Mamone G, Crinò F, Maruzzelli L, Miraglia R, Floridia G, Vizzini G. Natural course of extrahepatic nonmalignant partial portal vein thrombosis in patients with cirrhosis. Radiology. 2012 Oct;265(1):124-32. doi: 10.1148/radiol.12112236. Epub 2012 Aug 13. PMID: 22891357.

9. Hidaka H, Kokubu S, Sato T, et al. Antithrombin III for PV thrombosis in patients with liver disease: a randomized, double-blind, controlled trial. Hepatol Res. 2018;48:107–e116.

10. Xu S, Guo X, Xu Xet al. Natural history and predictors associated withthe evolution of portal venous system thrombosis in liver cirrhosis.Eur.J. Gastroenterol. Hepatol.2021;33: e423–30.

11. Naymagon L, Tremblay D, Zubizarreta N, Moshier E, Mascarenhas J,Schiano T. Safety, efficacy, and long-term outcomes of anticoagulationin cirrhotic portal vein thrombosis.Dig. Dis. Sci.2021;66:

12. Yokoyama S, Ishizu Y, Honda Tet al. Absence of large portal collateralvessels is associated with spontaneous improvement of cirrhotic portalvein thrombosis.Hepatol. Res.2022;52: 199–209.

13. Senzolo, M.; Garcia-Tsao, G.; García-Pagán, J.C. Current knowledge and management of portal vein thrombosis in cirrhosis. J. Hepatol. 2021, 75, 442–453.

14. Valeriani, E.; Riva, N.; Di Nisio, M.; Ageno, W. Splanchnic Vein Thrombosis: Current Perspectives. Vasc. Health Risk. Manag. 2019, 15, 449–461.

15. Shukla A, Jain A. Association of acute-on-chronic liver failure with vascular liver diseases. Hepatol Int. 2019;13:399–402.

16. Sarin SK, Choudhury A, Sharma MK, et al. APASL ACLF Research Consortium (AARC) for APASL ACLF working Party. Acute-onchronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int. 2019 Jul;13:353–390.

17. Maruyama H, Okugawa H, Takahashi M, Yokosuka O. De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. Am J Gastroenterol. 2013;108:568–574.

18. De Santis A., Moscatelli R., Catalano C., et al. Systemic thrombolysis of portal vein thrombosis in cirrhotic patients: a pilot study. Dig Liver Dis. 2010;42:451–455.

19. Senzolo M. Riva N. Dentali F. Sartori M.T. Ageno W. Portal vein thrombosis in decompensated cirrhosis: rationale for treatment. Clin Transl Gastroenterol. 2019; 10e00026.

20. La Mura V, Braham S, Tosetti G, Branchi F, Bitto N, Moia M, Fracanzani AL, Colombo M, Tripodi A, Primignani M. Harmful and Beneficial Effects of Anticoagulants in Patients With Cirrhosis and Portal Vein Thrombosis. Clin Gastroenterol Hepatol. 2018 Jul;16(7):1146-1152.e4. doi: 10.1016/j.cgh.2017.10.016. Epub 2017 Oct 21. PMID: 29066371.

21. Delgado MG, Seijo S, Yepes I, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol 2012;10:776-783. doi:10.1016/j.cgh.2012.01.012.

22. Kaiser Raja, Mathew Jacob, Sonal Asthana Department of Hepatology, Hepatobiliary Surgery & Multiorgan Transplantation, Global Integrated Liver Care Program, BGS Global Hospitals, Bangalore, India.

23. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365:147-156.

24. Tripodi A, Primignani M, Lemma L, Chantarangkul V, Mannucci PM. Evidence that low protein C contributes to the procoagulant imbalance in cirrhosis. J Hepatol. 2013;59:265–270.

25. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American association for the study of liver diseases. Hepatology. 2021;73:366–413.

26. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol. 2016 Jan;64(1):179–202.

27. Simonetto, Douglas A. MD1; Singal, Ashwani K. MD, MS, FACG2; Garcia-Tsao, Guadalupe MD, FACG3; Caldwell, Stephen H. MD4; Ahn, Joseph MD, MS, MBA, FACG5; Kamath, Patrick S. MD1. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation.

The American Journal of Gastroenterology 115(1):p 18-40, January 2020. | DOI: 10.14309/ajg.0000000000000486.

28. de Franchis R., VI Faculty Baveno. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–752.

29. Shukla A., Jain A., Kahalekar V., et al. Mutations in CYP2C9 and/or VKORC1 haplotype are associated with higher bleeding complications in patients with Budd-Chiari syndrome on warfarin. Hepatol Int. 2019.

30. Rossi C., Zambruni A., Ansaloni F., et al. Combined mechanical and pharmacologic thrombolysis for portal vein thrombosis in liver-graft recipients and in candidates for liver transplantation. Transplantation. 2004;78:938–940.

31. Blum U., Haag K., Rossle M., et al. Noncavernomatous portal vein thrombosis in hepatic cirrhosis: treatment with transjugular intrahepatic portosystemic shunt and local thrombolysis. Radiology. 1995;195:153–157.

32. Aytekin C., Boyvat F., Kurt A., Yologlu Z., Coskun M. Catheter-directed thrombolysis with transjugular access in portal vein thrombosis secondary to pancreatitis. Eur J Radiol. 2001;39:80–82.

33. Salem R., Vouche M., Baker T., et al. Pretransplant PV recanalization-transjugular intrahepatic portosystemic shunt in patients with complete obliterative portal vein thrombosis. Transplantation. 2015 Nov;99:2347–2355.

34. Turon F, Driever EG, Baiges A, Cerda E, García-Criado Á, Gilabert R, et al. Predicting portal thrombosis in cirrhosis: A prospective study of clinical, ultrasonographic and hemostatic factors. J Hepatol. (2021) 75:1367–76. doi: 10.1016.

35. Abdel-Razik A, Mousa N, Elhelaly R, Tawfik A. De-novo portal vein thrombosis in liver cirrhosis: risk factors and correlation with the model for end-stage liver disease scoring system. Eur J Gastroenterol Hepatol. (2015) 27:585–92. doi:

36. Violi F, Corazza GR, Caldwell SH, Perticone F, Gatta A, Angelico M, Farcomeni A, Masotti M, Napoleone L, Vestri A, Raparelli V, Basili S; PRO-LIVER Collaborators. Portal vein thrombosis relevance on liver cirrhosis: Italian Venous Thrombotic Events Registry. Intern Emerg Med. 2016;11:1059-1066. Faccia M, Ainora ME, Ponziani FR, Riccardi L, Garcovich M, Gasbarrini A, Pompili M, Zocco MA. Portal vein thrombosis in cirrhosis: Why a well-known complication is still matter of debate. World J Gastroenterol 2019; 25(31): 4437-4451 [PMID: 31496623 DOI: 10.3748/wjg.v25.i31.4437].

37. Xu YT, Wei JJ, Ye XJ, Zeng DW, Lin S, Fan H, Wang CD, Zhuang ZH. (Effect of band ligation or combined with tissue adhesive in the treatment of gastroesophageal varices and portal vein blood flow situational changes). Zhonghua Gan Zang Bing Za Zhi. 2021 May 20;29(5):468- 471. Chinese. doi: 10.3760/cma.j.cn501113-20190109- 00001. PMID: 34107586.

38. Florescu, Mădălina, Iacob, Speranţa, Gheorghe, Cristian and Gheorghe, Liana. "The Predictive Role of Variceal Band Ligation in the Development of Portal Vein Thrombosis in Cirrhotic Patients" Internal Medicine, vol.19, no.2, 2022, pp.7-15. https://doi.org/10.2478/inmed-2022-0204.

39. Avgerinos A, Armonis A, Stefanidis G, Mathou N, Vlachogiannakos J, Kougioumtzian A, Triantos C, Papaxoinis C, Manolakopoulos S, Panani A, Raptis SA. Sustained rise of portal pressure after sclerotherapy, but not band ligation, in acute variceal bleeding in cirrhosis. Hepatology. 2004 Jun;39(6):1623-30.doi: 10.1002/ hep.20236. PMID: 15185303.

40. Qi X, De Stefano V, Li H, Dai J, Guo X, Fan D. Anticoagulation for the treatment of portal vein thrombosis in liver cirrhosis: A systematic review and meta-analysis of observational studies. Eur J Intern Med 2015;26:23-29. doi:10.1016/j.ejim.2014.12.002.

41. Sasso R., Rockey D.C. Anticoagulation therapy in patients with liver cirrhosis is associated with an increased risk of variceal hemorrhage. Am J Med. 2019;132:758–766.

42. Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, Romano L, Balzano A. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. J Clin Gastroenterol. 2010;44:448-451. Faccia M, Ainora ME, Ponziani FR, Riccardi L, Garcovich M, Gasbarrini A, Pompili M, Zocco MA. Portal vein thrombosis in cirrhosis: Why a well-known complication is still matter of debate. World J Gastroenterol 2019; 25(31): 4437-4451 [PMID: 31496623 DOI: 10.3748/wjg.v25.i31.4437].

43. Chen H, Turon F, Hernández-Gea V, Fuster J, Garcia-Criado A, Barrufet M, Darnell A, Fondevila C, Garcia-Valdecasas JC, Garcia-Pagán JC. Nontumoral portal vein thrombosis in patients awaiting liver transplantation. Liver Transpl. 2016;22:352-365. Faccia M, Ainora ME, Ponziani FR, Riccardi L, Garcovich M, Gasbarrini A, Pompili M, Zocco MA. Portal vein thrombosis in cirrhosis: Why a well-known complication is still matter of debate. World J Gastroenterol 2019; 25(31): 4437-4451 [PMID: 31496623 DOI: 10.3748/wjg.v25.i31.4437].

44. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol. 2016 Jan;64(1):179-202. doi: 10.1016/j.jhep.2015.07.040. Epub 2015 Oct 26. PMID: 26516032.

45. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, Plessier A, Roulot D, Chaffaut C, Bourcier V, Trinchet JC, Valla DC; Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015 Feb;61(2):660-7. doi: 10.1002/hep.27546. Epub 2015 Jan 5. PMID: 25284616.

46. Ghabril M, Agarwal S, Lacerda M, Chalasani N, Kwo P, Tector AJ. Portal Vein Thrombosis Is a RiskFactor for Poor Early Outcomes After Liver Transplantation: Analysis of Risk Factors and Outcomes forPortal Vein Thrombosis in Waitlisted Patients. Transplantation 2016; 100: 126-133 [PMID: (17) (PDF) Tailored classification of portal vein thrombosis for liver transplantation: Focus on strategies for portal vein inflow reconstruction. Available from: https://www.researchgate.net/publication/341991590_Tailored_classification_of_portal_vein_thrombosis_for_liver_transplantation_Focus_on_strategies_for_portal_vein_inflow_reconstruction [accessed Jul 10 2024].

47. Kotsifa, E.; Kykalos, S.; Machairas, N.; Nikiteas, N.; Sotiropoulos, G.C. Management of portal vein thrombosis in cirrhotic patients enlisted for liver transplantation: From diagnosis to treatment (Review). Biomed. Rep. 2021, 15, 94.