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Natural history and clinical impact of non-neoplastic portal vein thrombosis in cirrhotics with hepatocellular carcinoma

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) increases the risk of non-neoplastic portal vein thrombosis (PVT) in cirrhosis. However, data on its natural history and prognostic role in HCC patients are lacking.

Materials and methods: Cirrhotic HCC patients undergoing laparoscopic ablation were consecutively enrolled and followed-up to 36 months. HCC and PVT characteristics and evolution were reviewed. PVT evolution was categorized according to changes in occlusion (cut-off 20%) and extension to other segments and classified as 'complete/progressive' or 'partial/ameliorated'. Variables associated with the presence of PVT and evolution patterns were analyzed, as well as their impact on survival.

Results: Seven-hundreds-fifty patients were included, 88 with PVT. On multivariate analysis, the presence of PVT at HCC diagnosis was associated with pre-treatment total tumor volume (TTV) (p<.001) and clinically-significant portal hypertension (p=.005). During follow-up, 46 de novo PVT occurred, 27/46 (58.7%) in presence of viable tumor. Among 115 PVT diagnosed in presence of HCC, 83 had available radiological follow-up, and 22 were anticoagulated. The 'complete/progressive' evolution pattern was associated with occlusive PVT at diagnosis and absence of anticoagulation in all PVT, whereas to Child-C score and non-response to HCC treatment in untreated patients. Overall survival was lower in the presence of PVT, specifically for 'complete/progressive' PVT (p<0.001). A higher competing risk of death emerged for 'complete/progressive' PVT, both for HCC-related (p<0.001) and non-HCC-related (p<0.001) death.

Conclusions: Non-neoplastic PVT in HCC is characterized by a higher risk of progression, correlated with the HCC activity, when not treated. Complete/progressive PVT is an independent factor associated with mortality, both HCC and non-HCC related.

BACKGROUND AND RATIONALE

Solid and hematological malignancies are often associated with a pro-thrombotic paraneoplastic syndrome and the occurrence of venous thromboembolic events (VTE). Cancer-associated VTE has been associated with worse survival, increased morbidity, need for hospitalization and potential delay or discontinuation of cancer therapy [1]. Therefore, thromboprophylaxis is currently recommended during hospitalization and in the post-operative setting for cancer patients, as is the timely initiation of anticoagulant treatment at the onset of thrombosis [2]. In contrast, in cirrhotic patients with hepatocellular carcinoma (HCC), the potential impact of deep vein thrombosis, and in particular portal vein thrombosis (PVT), has often been overlooked and no treatment guidelines are currently available.

Non-neoplastic PVT is the most common thrombotic complication in patients with cirrhosis, with an overall annual incidence of 3.7% - 24.4%, reaching a prevalence of up to 26% in liver transplant candidates [3-7]. Although its pathophysiology has yet to be fully understood, multiple risk factors have been identified. Endogenous and exogenous, congenital and acquired, local and systemic conditions may interact synergistically, increasing the risk of PVT in cirrhosis. Previous studies have found that the presence of HCC appears to be associated with a higher risk of PVT compared to cirrhosis alone, probably due to pro-thrombotic disturbances promoted by the tumor itself [8-10].

Still, the impact of PVT on the prognosis of patients with cirrhosis and HCC remains controversial. Previous historical cohorts have shown that the presence of PVT was independently associated with increased mortality in patients with untreated HCC [11, 12], whereas data on the impact of PVT in patients undergoing cancer treatment are lacking. Indeed, patients with HCC have often been excluded from more recent cohorts studying the natural history and clinical impact of PVT in cirrhosis [4, 13-23].

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SPECIFIC AIMS

- To perform a revision of the available literature on local and systemic thrombotic complications in cirrhotic patients with hepatocellular carcinoma.

- To evaluate the prevalence, evolution according to anticoagulant treatment and impact on survival of non-neoplastic PVT in a monocentric cohort of patients with cirrhosis and newly diagnosed HCC evaluated by laparoscopic microwave ablation.

- To compare platelet aggregation, a marker of platelet function, in patients with cirrhosis with vs. without HCC.

Local and systemic thrombotic complications in cirrhotic patients with hepatocellular carcinoma – a review of the literature

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Under review. **HEPATOMA RESEARCH**

Conflict of interest disclosure: none

This article will be published in a Special Issue: **"Challenges in the Management of Hepatocellular Carcinoma in Cirrhotics with Clinically Significant Portal Hypertension"**
Guest Editors: Sarah Shalaby, Marco Senzolo

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This Special Issue will contain other 4 reviews entitled:

1. Sarah Shalaby; Patrizia Burra; Marco Senzolo. Hepatic venous pressure gradient in hepatic resection for hepatocellular carcinoma. Hepatoma Res.OAE Publishing Inc., 11/2023. DOI: 10.20517/2394-5079.2023.88

2. Edoardo Poli, Eleonora De Martin. Progression of liver disease and associated risk of hepatocellular carcinoma. Under Review.

3. Jacopo Lanari, Marina Polacco, Umberto Cillo. Role of temporary portosystemic surgical shunt before liver resection. Under Review.

4. Marco Grasso, Sarah Shalaby, Chiara di Renzo, Patrizia Burra, Marco Senzolo, Alberto Zanetto. Limits of systemic treatments for HCC in decompensated patients

ABSTRACT

Venous thromboembolic events (VTE) represent a significant and common complication in patients with hepatocellular carcinoma (HCC) in the context of cirrhosis. While some patient-related risk factors for VTE are shared with the non-cirrhotic population, the presence of HCC amplifies the risk, potentially due to the pro-thrombotic paraneoplastic alterations associated with the tumor. This review aims to examine the current evidence regarding hemostatic disorders observed specifically in cirrhotic patients with HCC and comprehensively examine VTE events in this specific population, with a specific emphasis on portal vein thrombosis (PVT). PVT is the most common thrombotic complication in this population and can have significant implications for the eligibility and success of treatment modalities such as liver transplant or surgical interventions. Identifying risk factors associated with PVT occurrence in these patients is essential to guide preventive measures and enhance patient outcomes. This review aims to provide a clear background for further research and investigations into effective prophylaxis and treatment strategies for VTE in cirrhotic patients with HCC by comprehensively revising the current evidence on these topics.

Deep vein thrombosis and hemostatic disorders in oncologic patients

Approximately 10-15% of oncologic patients will develop a venous thromboembolic event (VTE) during the course of the disease [1], yet the incidence varies significantly from 0.1% to 60%, in relation to different combinations of general and cancer-specific risk factors.

Even though most VTE events occur within the first 3 to 6 months after cancer diagnosis [2] it is not uncommon for VTE to be diagnosed in conjunction with cancer. Indeed, idiopathic VTE should be considered as a possible indirect sign of an underlying malignancy, which should be always investigated.

Despite previous studies suggesting a low VTE-related mortality rate, a recent meta-analysis revealed a rate of 1.9 fatal recurrent cancer-associated VTE cases per 100 patient-years. Additionally, it highlighted a higher case-fatality rate for recurrent VTE (15%) compared to bleeding events (9%) [2]. In addition, thromboembolic events are considered an adverse prognostic factor in oncologic patients [3, 4]. Thus, thromboprophylaxis is frequently recommended in this setting. The utilization of the Korana risk score, which takes into account factors such as cancer site, platelet count, hemoglobin levels, the use of erythropoiesis-stimulating agents, leukocyte count, and body mass index, has been proposed as a means to identify patients who might derive advantages from primary VTE prevention [5]. Currently, the American Society of Clinical Oncology (ASCO) [6] advises the use of pharmacological prophylaxis for the following categories of patients: those with an active malignancy and acute medical illness or limited mobility during hospitalization, as well as individuals with locally advanced or metastatic cancer who are undergoing systemic anti-cancer therapy and have an intermediate-to-high risk of VTE (identified by Khorana score ≥2).

Indeed, malignancies are often associated with a pro-thrombotic paraneoplastic syndrome that can manifest clinically with overt thrombotic events, chronic disseminated intravascular coagulation, or asymptomatic and detected only through coagulation tests. The tumor type usually represents the primary determinant of the type and degree of coagulative alterations that can be encountered, as some tumors may display a more proinflammatory or secretory phenotype (tissue factor, growth

factors, pro/anti-angiogenic factors, pro-coagulant microvesicles, proinflammatory cytokines, etc), whereas other tumors may cause a greater degree of endothelial dysfunction or mechanically causing blood stasis through extrinsic vascular compression [7]. The degree of impairment of the hemocoagulative system seems also to grow together with the progression of the malignancy, increasing to a greater extent in the metastatic stage of the disease [8]. Nevertheless, early stages of various malignancies often reveal subtle hemostatic changes, such as slightly elevated levels of plasmatic coagulation markers (including prothrombin fragment 1+2 [F1+2], fibrinopeptide A [FPA], thrombin–antithrombin complex [TAT], and D-dimer), acquired protein C resistance, and an increased presence of circulating microvesicles (MV) originating from both tumor and blood cells [7, 9]. The ability of cancer cells to stimulate neoangiogenesis plays also a fundamental role in driving tumor growth and aggressiveness [10]. Indeed, during the metastatic stage, various elements of the hemostatic system, such as thrombin, tissue factor (TF) and activated factor VII (FVIIa), factor Xa (FXa), fibrinogen, and vascular cells, have been observed to contribute, as evidenced by experiments conducted in both in vitro and in vivo tumor models [7]. Risk factors for cancer-associated venous thromboembolism are summarized in Table 1 [9-15].

Table 1. Risk factors for cancer associated venous thromboembolism.

Patient-related	Cancer-related	Treatment-related
Female sex	Site of cancer: high risk in brain, pancreas, kidney, stomach, lung, bladder, gynecologic, and hematologic malignancies	Prolonged hospitalization
Ethnicity: lower risk in Asians, higher in African-Americans	Stage of cancer	Surgery: open surgery > minimally invasive surgery
Old age	Histological type: adenocarcinoma lung cancer > squamous cell carcinoma	Chemotherapy and hormonal therapy
Obesity	Hypersecretory type: unregulated secretion of proinflammatory cytokines	Antiangiogenic therapy
	Thrombocytosis and increased platelet activation	Erythropoiesis stimulating agents
	Increased soluble tissue factor expression by tumor cells	Blood transfusions
		Central venous line

Hemostatic disorders in cirrhotic patients with HCC

Patients with cirrhosis frequently have complex alterations in their hemostatic system. However, hemocoagulative alterations detected with standard coagulation tests, thrombocytopenia, and hemorrhagic complications related to portal hypertension have challenged the management and prophylaxis of VTE in cirrhotic patients with malignancies. Indeed, although routine diagnostic tests suggest a bleeding tendency, it is now accepted that these tests do not reflect hemostatic competence in this population. Blood coagulation in such patients is rebalanced, owing to the parallel reduction of pro-coagulant (low fibrinogen; factors II, V, VII, IX, X, XI; low platelets count; low plasmin inhibitor) and anticoagulant factors (low antithrombin; protein C and S; low level of heparin cofactor II; low plasminogen) with the contribution of high levels of von Willebrand factor and factor VIII

[16]. The observed bleeding tendency in cirrhotic patients cannot solely be attributed to reduced coagulation capabilities but should also be attributed to other mechanisms influenced by underlying conditions that increase the risk of hemorrhage. These conditions include hemodynamic changes resulting from portal hypertension, endothelial dysfunction, bacterial infections, and renal failure. Furthermore, the relative deficiency of key factors in the coagulation system renders the balance delicate in these patients, and it may shift towards either hemorrhage or thrombosis based on the prevailing risk factors at any given moment [17]. Among factors shifting this balance towards the pro-thrombotic site the presence of hepatocellular carcinoma (HCC) has also been included [18]. As a matter of facts, an increasing body of evidence indicates that HCC occurring in the context of cirrhosis is linked to pro-thrombotic changes, which may collaboratively enhance hypercoagulability and the risk of thrombosis, such as: higher levels of platelet adhesive glycoprotein Von Willebrand factor, increased thrombin generation due to rebalanced pro and anticoagulant factors, reduced activation of fibrinolysis, higher levels of pro-thrombotic circulating MV, including those bearing tissue factor (TF), increased level of circulating fibrinogen, production of thrombopoietin by HCC cells and thrombocytosis, increased platelet activation and platelet aggregation [18] and increased markers of neutrophil extracellular traps (NETs) [19]. Specifically, numerous studies have documented elevated levels of plasmatic fibrinogen in patients with HCC, especially those with extensive tumor burden [20, 21], which could be a result of systemic inflammation [22] or direct synthesis by tumor cells [23]. A recent study delved into changes in blood clotting and clot breakdown mechanisms in patients with HCC. The findings revealed that HCC was linked to a substantial rise in thrombin generation, indicating heightened clot-forming ability and decreased activation of fibrinolysis [24]. In individuals with cirrhosis and HCC, there seems to be an elevated presence of pro-thrombotic macrovesicles, including those originating from the endothelium, platelets, and leukocytes, especially those carrying tissue factor (TF), in comparison to cirrhotic patients without HCC and healthy individuals [25].

The prevalence of thrombocytosis (conventionally defined as a platelet count > 450 x 10^9/L), has been estimated to range between 3–9% in patients with HCC and cirrhosis [26], which would collocate this malignancy among those with low prevalence of thrombocytosis [27]. However, the actual prevalence of thrombocytosis might be underestimated in these patients, due to the underlying masking effect of portal hypertension [28–30]. Thus, the threshold for the definition of thrombocytosis should probably be redefined for these patients. Nevertheless, in patients with HCC a platelet count >450 x 10^9/L has been associated with larger tumor volume, increased vascular invasion, extra-hepatic metastases, high serum α-fetoprotein and worse overall survival [31]. The excess production of thrombopoietin by tumor cells could potentially contribute to the relatively elevated platelet count observed in these individuals [32]. Indeed, it has been shown that platelet count and serum thrombopoietin levels decreased after a surgical resection of the tumor or trans-arterial chemoembolization, and re-elevated when the tumor recurred [33], concomitantly with a new increase of levels of α-fetoprotein. Moreover, recent studies have demonstrated that platelet count may be a predictor of survival in HCC patients, and the degree of platelet activation might correlate with poor outcomes [27]. This effect appears to be unrelated to the stage of cirrhosis or the extent of thrombocytopenia [34]. Similarly, the study revealed a substantial elevation in Von Willebrand factor levels associated with the presence of HCC [35]. Still, further studies will need to clarify hemostatic balance in these patients according to tumor burden and severity of liver disease.

Venous thromboembolism in patients with HCC

Numerous studies have indicated that individuals with cirrhosis and HCC face an elevated risk of developing VTE. These studies have also explored potential risk factors associated with this heightened risk (Supplementary Table 1) [36–42].

Supplementary Table 1. Risk Factors associated with VTE occurrence in cirrhotic patients with HCC

Studies considering patients with and without HCC				
Author, Year	**Type of study (time of inclusion)**	**Patients (n)**	**VTE**	**Risk Factors associated with VTE occurrence**
Lesamana, 2010 [36]	Case control study (2004 - 2007)	87 cirrhotics (+ HCC); 169 cirrhotics (–HCC)	HCC (+) prevalence 4.6% vs HCC (-) prevalence 4.7%	Diabetes mellitus (OR 3.88; p 0.031) HCC not a risk factor for VTE (OR 0.176; p 0.099)
Yassine, 2022 [37]	Retrospective cohort study (2015 -2020)	157'400 with cirrhosis (7% with overall liver cancer) and 9'832'890 without cirrhosis		Cirrhosis (OR 0.921, p < 0.001) Liver cancer (OR 1.47, p<0.001) Hypoalbuminemia (OR 3.83, p<0.001) Diabetes Mellitus (OR 1.31, p<0.001) BMI > 30 (OR 1.62, p<0.001) Non Caucasians (OR 1.22, p<0.001)
Faccia 2022 [38]	Retrospective study (1982 – 2017)	7'445 hospitalized cirrhotic patient (1524 + HCC) 1524 cirrhotics (+ HCC); 5921 cirrhotics (– HCC)	HCC (+) prevalence 1.7%, HCC (-) prevalence 1.2%	HCC (OR 1.98 p=0.002) Hepatic Encephalopathy (OR 3.21 p<0.0001) Extra-hepatic tumors (OR 2.48 p=0.0007) Infection (OR 3.01 p=0.0001) Cardiac/respiratory insufficiency (OR 2.40 p=0.003) AMI/Stroke (OR 7.86 p=0.003)
Studies considering only patients with HCC				
Connolly, 2008 [39]	Retrospective (1998-2004)	194 with cirrhosis (CHILD A/B/C 60/87/46) + HCC	Incidence of 6.7%	Concomitant presence of PVT (11.5% vs 4.4 %, p 0.04)

Wang, 2018 [40]	Retrospective (2000- 2015)	270 with HCC (229 with cirrhosis CHILD A/B/C 97/89/43)	2- years cumulative incidence 5.93% 75% of VTE occurring within 3 months of diagnosis of HCC	>3 hepatic lesions vs single lesion (OR = 3.6, p 0.048); Multi-organ extra-hepatic metastasis (OR = 12; p 0.028)
Al-Taee, 2019 [41]	Retrospective study (2008 – 2013)	54'275 with HCC	2.8% prevalence	age ≥ 65 (OR 1.23; p=0.0004) African ethnicity (OR 1.20, p=0.002) Metastatic disease (OR 2.11, p<0.0001) Higher Elixhauser comorbidity index* (OR = 1.26, p<0.0001) Longer hospital stay (OR 2.05, p<0.0001)
Chen, 2021 [42]	Retrospective study (2016 – 2020)	355 consecutive patients with HCC who underwent laparoscopic hepatectomy	Incidence of 18.6%	Age>60 (OR 3.03, p=0.008) Sex F vs M (OR 13.96, p<0.001) BMI>25 (OR 4.22, p=0.005) Comorbidities (OR 9.03, p<0.001)

*Elixhauser comorbidity index: method of categorizing comorbidities of patients based on ICD)

Venous thromboembolic event (VTE), hepatocellular carcinoma (HCC), odds ratio (OR), body mass index (BMI), Portal vein thrombosis (PVT).

Despite the considerable heterogeneity among the cohorts described in various studies and differences in inclusion criteria, the commonly detected risk factors can be summarized as presented in Table 2 [36, 42].

Table 2. Risk Factors associated with VTE occurrence in cirrhotic patients with HCC

	Risk Factors	OR	Author
Cancer related	HCC extra hepatic metastasis	12; 2.11	Wang 2018; Al-Taee 2019 [40], [41]
	HCC	3.6; 1.98; 0.176	Wang 2018; Faccia 2022; Lesamana 2010 [36], [38], [40]
	Extra-hepatic tumors	2.48	Faccia 2022 [38]
	Liver cancer (not specified)	1.47	Abou Yassine 2022 [37]
Liver disease related	Hypoalbuminemia	3.83	Abou Yassine 2022 [37]
	Hepatic encephalopathy	3.21	Faccia 2022 [38]
	Portal vein thrombosis	NA	Conolly 2008 [39]
Patient related – medical history	Extra-hepatic comorbidities	9.03; 1.26	Chen 2021; Al-Taee 2019 [41], [42]
	Acute Miocardial Infarction/Stroke	7.86	Faccia 2022 [38]
	Diabetes mellitus	3.88; 1.31	Lesamana 2010; Abou Yassine 2022 [36], [37]
	Infection	3.01	Faccia 2022 [38]
	Cardiac/Respiratory Insufficiency	2.4	Faccia 2022 [38]
	Long hospitalization	2.05	Al-Taee 2019 [41]
Patient related - demographics	Sex (F vs M)	13.96	Chen 2021 [42]
	BMI (> 25-30)	4.22; 1.62	Chen 2021; Abou Yassine 2022 [37], [42]
	Age (> 60-65)	3.03; 1.23	Chen 2021; Al-Taee 2019 [41], [42]
	Non Caucasians	1.22	Yassine 2022 [37]
	Black vs White	1.20	Al-Taee 2019 [41]

Venous thromboembolic event (VTE), hepatocellular carcinoma (HCC), body mass index (BMI).

Portal vein thrombosis in patients with HCC

Among cirrhotic patients, portal vein thrombosis (PVT) stands out as the most frequent thrombotic complication, occurring within one year at rates varying from 7% to 26% [43, 44]. Distinguishing between malignant and non-malignant PVT is of utmost importance, as the presence of macrovascular invasion by the tumor not only impacts a patient's prognosis but also serves as an exclusion criterion for potentially curative treatments [45, 46].

It was first reported in the early 1990s by Nonami et al. [47] that the presence of HCC represented an added risk factor for the development of PVT. In their autopsy-based investigation, it was found that 34.8% of individuals with HCC developed PVT, in contrast to only 11.4% of those without HCC (p < 0.001). Notably, patients with HCC exhibited a higher occurrence of both intra-hepatic and extra-hepatic thrombosis, including both partial and complete forms, compared to individuals without HCC. In the study of Davidson et al. [48] the authors found out that patients with HCC who underwent liver transplantation (LT) experienced a notably greater occurrence of PVT compared to those without liver malignancies (6 out of 22 vs. 10 out of 110, p < 0.05). This was confirmed in the study of Ravaioli et. al [49] which discovered that the prevalence of PVT was notably higher among recipients with HCC, reaching 40.8%, compared to recipients without HCC, where it was 30.7% (p = 0.05). Moreover, in the study of Zanetto et al. [20] the authors conducted a comparison between patients with and without HCC who were matched based on the severity of their underlying liver disease. They observed that within one year, the occurrence of PVT was over twice as high among individuals with cancer when compared to cirrhotic patients without cancer (24.4% vs. 11.4%; p = 0.05). The factors that increase the risk of PVT in patients with HCC are outlined in Supplementary Table 2 and in Table 3 [20, 38, 47-51].

Supplementary Table 2. Risk Factors associated with PVT occurrence in cirrhotic patients with HCC

Author, Years	Type of study	Patients with Liver Disease (n)	PVT	Risk Factor
Nonami,1992 [47]	Retrospective study (1989 - 1990)	849 patients who underwent LT, (87 HCC and cirrhosis, 47 HCC without cirrhosis) 401 cirrhosis	HCC (+) incidence 34.8% vs HCC without cirrhosis incidence 8.5 %, Post necrotic cirrhosis incidence 15.7 %	Encephalopathy p<0.02 Ascites p<0.005 Gastrointestinal bleeding <0.001 Previous splenectomy<0.01
Davidson,1994 [48]	Prospective study (1988-1992)	132 patients who underwent LT (12 cryptogenetic cirrhosis, 22 cirrhosis and HCC, 5 autoimmune hepatitis)	Cirrhosis + HCC incidence (6/22 27.3%) vs Cirrhosis incidence (10/110 9.1%)	Autoimmune chronic active hepatitis χ2:13.3 p<0.001 Cryptogenetic cirrhosisχ2: 7.2 p< 0.01 HCC χ2:5.7 p<0.05
Ravaioli,2011 [49]	Retrospective study (1998-2008)	889 patients LT candidates (282 with HCC)	HCC(+) incidence 37/282 13%	HCC significantly associated with PVT risk at multivariate analysis (HR: 1.81; p< 0.05)
Zanetto, 2017 [20]	Prospective study (2012-2013) follow-up 1 year	41 patients with cirrhosis and HCC (CHILD A/B/C 20/12/9) 35 patients with non HCC cirrhosis (CHILD A/B/C 9/17/9)	HCC(+) incidence 10/41 24.4% vs HCC(-) incidence 4/35 11.4%	HCC(+) HR:10.34, p=0.03 Thromboelastogram: Maximum Clot Firmness (MCF* > 25 mm) HR:6, p=0.001
Cagin, 2016 [50]	Retrospective study (2009-2014)	461 patients with cirrhosis: HCC+ 69 (15%), HCC- 392 (85%)	HCC(+) prevalence (13/69 18.8%), HCC(-) (32/392 8.2%)	HCC significantly associated with PVT p<0.001
Serag, 2020 [51]	Prosepective study (follow-up 1 year)	44 patients with cirrhosis + HCC (CHILD	HCC(+) incidence (10/44 22.7%);	Differences between PVT (+) and PVT (-) in all cirrhotics with and without HCC:

		A/B/C 12/20/12) 47 patients with cirrhosis (CHILD A/B/C 14/18/14)	HCC(-) incidence (6/47 12.7%)	In cirrhotics with HCC Annexin A5/PS + MP ratio p<0.001 PS + MPs p<0.001 Portal flow velocity p<0.001 **
Faccia 2022 [38]	Retrospective study (1982 – 2017)	7445 hospitalized cirrhotic patient (HCC+ 1524)	HCC(+) prevalence (162/1524 10.6%); HCC (-) prevalence (220/5921 3.7%)	(multivariate logistic regression analyses) Endoscopic signs of portal hypertension OR 1.33 p=0.02 Hepatic Hencephalophaty OR13.98 p<0.0001 HCC OR 4.59 p<0.0001 Diabetes OR 1.68 p=0.0001 Abdominal surgery/invasive procedure OR 2.03 p<0.0001
Senzolo 2023 [44]	Retrospective study	750 cirrhotic HCC patiens	88/750 PVT at diagnosis	(multivariate analyses the occurrence of PVT at HCC diagnosis) Pre-treatment total tumor volume (p < 0.001) Clinically significant portal hypertension (p= 0.005)

* Maximum Clot Firmness (MCF) is the maximum amplitude in millimeters reached in the thromboelastogram. MCF >25 mm was associated with a 5-fold increased PVT risk [RR: 4.8 (2–11.3); p = 0.0001] ** Cut off HCC (+): Annexin A5/MP ratio < 0,0277; PS + MPs > 38.7 nm/L, Portal flow velocity < 15 cm/sec. Cut off HCC (-): Annexin A5/MP ratio < 0,0028; PS + MPs > 35.3 nm/L, Portal flow velocity < 15 cm/sec

Portal vein thrombosis (PVT), liver transplant (LT), Maximum Clot Firmness (MCF). hepatocellular carcinoma (HCC), hazard ratio (HR).

Table 3. Risk factor for PVT in cirrhotic patients with HCC

Group	Risk factor	OR/HR	Author
Cancer related	HCC features	HR: 10.34; HR: 1.81; NA; OR: 4.59	Zanetto 2017; Ravaioli 2011; Cagin 2016; Faccia 2022 [20], [38], [49], [50]
	Liver cancer	NA	Davidson 1994 [48]

	Chronic active hepatitis	NA	Davidson 1994 [48]
Liver disease related	Encephalopathy	OR: 13.98; NA	Faccia 2022; Nonami 1992; [38], [47]
	Clinically significant portal hypertension	OR: 1.33	Faccia 2022 [38]
	Ascites	NA	Nonami 1992 [47]
	Gastrointestinal bleeding	NA	Nonami 1992 [47]
Abnormal tests	Thromboelastography (MCF>25mm)	HR: 6	Zanetto 2017 [20]
	Annexin A5/PS ratio (<00277264) PS+MPs (>38.7 nmol/L)	NA	Serag 2020 [51]
	Portal flow velocity (<15cm/sec)	NA	Serag 2020 [51]
Patient related	Abdominal surgery/invasive procedure	OR: 2.03	Faccia 2022 [38]
	Diabetes	OR: 1.68	Faccia 2022 [38]
	Splenectomy	NA	Nonami 1994 [47]

Hepatocellular carcinoma (HCC), Hazard ratio (HR), Not Available (NA), odds ratio (OR), Maximum Clot Firmness (MCF).

Interestingly, a very recently published study described the natural history of PVT in HCC patients, demonstrating that HCC features represent an independent risk factor for the occurrence and progression of non-neoplastic PVT in cirrhotic patients, and the presence of occlusive or progressive PVT seems to be an independent factor associated with mortality [44].

Anticoagulant treatment in patients with HCC

The perceived risk of bleeding in cirrhosis and the need for invasive treatments for HCC led to underuse of thromboprophylaxis and undertreatment of thrombotic complications in the past. However, patients with cirrhosis are not naturally anticoagulated [24] and anticoagulant drug showed potential benefits in advanced liver disease going beyond treatment of thrombosis which may include the reduction of liver fibrosis, portal hypertension, and improvement in survival. [52].

Indeed, the use of anticoagulation has firmly established itself as a cornerstone in the management of thrombotic conditions in individuals with cirrhosis. Data consistently showed that anticoagulation is more effective in resolving thrombosis than no treatment for VTE and PVT, with rates of bleeding complications comparable to general population [53]. As a result, expert consensus has undergone a notable change, and current practice guidelines now endorse the use of anticoagulation in both cirrhotic patients with atrial fibrillation and those with venous thromboembolism (VTE) [54, 55]. Still, experts emphasize the necessity for additional research, including randomized controlled trials, to ascertain the true effects of anticoagulants in this particular population. Furthermore, they suggest exploring the potential applications of anticoagulants beyond VTE (and their indications besides VTE) and atrial fibrillation [53]. Indeed, the presence of HCC should be taken into account in these future studies, as a risk factor for occurrence and recurrence of VTE.

On the other hand, if the treatment of VTE in acute phase is quite well established, more difficult is to decide what to do when the acute phase of unprovoked VTE has passed: specifically whether and for how long to extend the treatment to prevent a second recurrence. Data from the RIETE registry highlight that patients with VTE and cirrhosis compared to non-cirrhotic patients with VTE have a higher one-year cumulative incidence of both major or clinically relevant bleeding (HR: 2.86; 95% CI: 1.91–4.27; p< 0.006) and of recurrent VTE (HR: 2.08; 95% CI: 0.996–4.36; p< 0.042) [56]. A systematic review by Hoolwerf et al. on direct oral anticoagulants (DOACs) treatment in cirrhosis highlights a VTE recurrence rate of 8% in patients treated with DOACs compared to 13% in VKAs/LMWH patients with any VTE recurrence in both groups, while the major bleeding risk ranged

from 4% to 15% in patients with DOACs and from 7% to 28% in VKAs/LMWH ones [57]. In a single center case series Child-Pugh B patients with unprovoked VTE were treated with apixaban reduced dose (25mg bid, 18 subjects) or dabigatran (110mg bid, 14 patients) after two to six months of full anticoagulation with LMWH. During a median follow-up of 50 months the VTE recurrence rate was 2.2%/year and major bleeding was 1.5%/year [58]. Even though these data are promising, the extension of anticoagulant in cirrhotic patients with unprovoked VTE and type of drug to be preferred is still a challenging decision: an individual approach on a case-by-case basis may be still recommended until more solid evidence will be available.

Among patients diagnosed with cirrhosis and portal vein thrombosis (PVT), the utilization of anticoagulant therapy has been associated to several potential extra-hepatic benefits, including an increased rate of vessel recanalization, a reduced likelihood of experiencing recurrent splanchnic vein thrombosis, and improved overall survival when compared to patients who did not receive anticoagulation [59, 60]. Current clinical guidelines [61, 62] suggest to consider anticoagulation therapy for individuals with cirrhosis and PVT who potential candidates for transplantation, and in those in whom PVT occupies over half of the vessel's lumen or extends to the confluence of the splenic and superior mesenteric veins.

In a recent study [44] the authors analyzed for the first time the evolution of non-neoplastic PVT in cirrhotic patients with HCC. Among 83 patients with PVT diagnosed in presence of HCC 22 were anticoagulated for a median time of 10 months (IQR: 8-18), whether the others were not [44]. No patients discontinued anticoagulation because of complications. At the end of follow-up, PVT was defined as globally improved in 50%, progressed in 9.1% and remained stable in 40.9% patients vs 6.6%, 62.3% and 31.4% of untreated patients, respectively. Thus, in this cohort it would appear that such treatment is effective in ameliorating/preventing progression of PVT. However, the sample is too small to draw any conclusions. Only one small study previously evaluated 51 patients diagnosed with HCC and PVT, 12 treated with anticoagulation and 39 were untreated. In this study anticoagulation was not associated with a difference in PVT progression. However, in this study PVT

were mainly chronic and anticoagulation was discontinued for 3 patients because of complications [60]. Thus, future studies need to further investigate the efficacy and safety of anticoagulation in patients with acute PVT and HCC.

CONCLUSIONS

VTE is a frequently encountered complication in cancer patients, and cirrhotic patients with HCC or other malignancies are not exempt from this risk. While many patient-related risk factors are shared with the non-cirrhotic population, the presence of HCC seems to magnify the risk in various scenarios. This could be attributed to pro-thrombotic paraneoplastic alterations associated with HCC activity, which may synergistically contribute to a state of hypercoagulability and thrombosis. Notably, tumor activity appears to play a significant role in the development and progression of PVT, alongside the severity of the underlying liver disease. Additionally, the presence of PVT may impact patient survival, underscoring the importance of prophylaxis and early treatment initiation. Nevertheless, it is essential not to overlook the consideration of other potentially modifiable risk factors unrelated to the tumor or cirrhosis, particularly when the hepatic tumor is effectively controlled with treatment. Additional research is required to evaluate both the effectiveness and safety of anticoagulation treatment in individuals who have acute portal vein thrombosis along with hepatocellular carcinoma.

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Role of non-neoplastic portal vein thrombosis in the natural history of patients with cirrhosis and first diagnosis of hepatocellular carcinoma

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ABSTRACT:

Background & Aims: Hepatocellular carcinoma (HCC) can increase the risk of non-neoplastic portal vein thrombosis (PVT) in cirrhosis. However, natural history of PVT and its prognostic role in HCC patients are unknown.

Approach & Results: Consecutive cirrhotic HCC patients undergoing laparoscopic ablation were retrospectively evaluated and followed-up to 36 months. HCC and PVT characteristics and evolution were reviewed. PVT was categorized according to lumen occupancy ($\leq 50\%$, $>50\%<100\%$ and $=100\%$) and extension to other veins. Evolution of thrombosis was considered at 1 year from diagnosis. Variables associated with presence of PVT and evolution patterns were analyzed, as well as their impact on survival. Seven-hundreds-fifty patients were included, 88 with PVT. On multivariate analysis, the occurrence of PVT at HCC diagnosis was associated with pre-treatment total tumor volume ($p<0.001$) and clinically significant portal hypertension ($p=0.005$). During follow-up, 46 de novo PVT occurred, 27/46 (58.7%) in presence of viable tumor. Among 115 PVT diagnosed in presence of HCC, 83 had available radiological follow-up, and 22 were anticoagulated. The 'complete/progressive' evolution pattern was associated with non-response to HCC treatment in non-anticoagulated patients. The presence of PVT was independently associated with lower overall survival, particularly when progressive or occlusive ($p<0.001$). A higher competing risk of death emerged for 'complete and progressive' PVT, both for HCC-related ($p<0.001$) and non-HCC-related ($p=0.002$) death.

Conclusions: HCC represents an independent risk factor for the occurrence and progression of PVT in cirrhosis. Since progressive and occlusive PVT seems to be an independent factor associated with mortality, screening and prompt treatment of this complication should be considered.

INTRODUCTION

Non-malignant portal vein thrombosis (PVT) is the most common thrombotic complication in patients with cirrhosis, with an overall annual incidence of 3.7%-24.4%,(1) reaching a prevalence of up to 26% in liver transplant candidates.(2-6) Although its pathophysiology has yet to be fully understood, multiple risk factors have been identified. Endogenous and exogenous, congenital and acquired, and local and systemic conditions may interact synergistically, increasing the risk of PVT in cirrhosis. Among these factors, it has been suggested that the presence of hepatocellular carcinoma (HCC) may be associated with a higher risk of PVT than cirrhosis alone, which could be due to pro-thrombotic perturbations which seem to be promoted by HCC.(7-9) Still, the impact of PVT on the prognosis of patients with cirrhosis and HCC remains controversial. Previous historical cohorts have shown that the presence of PVT was independently associated with increased mortality in patients with untreated HCC,(10, 11) whereas data on the impact of PVT in patients undergoing cancer treatment are lacking. Indeed, patients with HCC have often been excluded from more recent cohorts studying the natural history and clinical impact of PVT in cirrhosis and, when included, have not been analyzed separately.(3, 12-22)

In this study, we aimed to evaluate the prevalence, evolution according to anticoagulant treatment, and impact on survival of non-neoplastic PVT in a cohort of patients with cirrhosis and first diagnosis of HCC undergoing treatment with laparoscopic microwave ablation.

PATIENTS AND METHODS

Patients

All consecutive patients with cirrhosis and a new diagnosis of HCC who were candidates for laparoscopic microwave ablation (MWA) as first treatment at the Hepatobiliary Surgery and Liver Transplantation Unit of the Padova University Hospital from January 2015 to December 2018, were retrospectively evaluated for the study. We decided to enroll this kind of patients for two reasons: a) to have a cohort of patients with HCC homogeneously treated; b) because laparoscopic ablation is the more frequent treatment procedure performed for HCC patients (i.e. more than 200 procedures each year) at Padova University. According to our center protocol, also decompensated patients were treated with MWA as bridge/downstaging to liver transplantation.(23)

Diagnosis of cirrhosis and HCC were based on EASL Guidelines.(24, 25) Exclusion criteria were: a) use of anticoagulant or antiplatelet agents in the two weeks prior to laparoscopic microwave ablation; b) neoplastic PVT; c) non-HCC malignancy; d) recurrence of previous PVT or chronic PVT (diagnosed >6 months prior to HCC), e) isolated thrombosis of the superior mesenteric vein and/or splenic vein; f) previous creation of a transjugular intrahepatic portosystemic shunt (TIPS). Thus, only non-neoplastic PVT were considered, which will be referred as PVT in the manuscript. Splanchnic vessel patency, HCC characteristics and demographic, clinical and laboratory data were collected from medical records at inclusion. The presence of clinically significant portal hypertension (CSPH) was defined as the presence of one or more of these conditions: presence of abdominal portosystemic collaterals visualized by upper endoscopy or imaging studies, previous portal-hypertensive hemorrhage, platelet count <100×10^9/L associated with splenomegaly (longitudinal spleen diameter >12 cm).(26) This study was approved by the Ethical Committee of Padova University Hospital (Prot. AOP/0564) and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients follow-up

All patients were followed up until liver transplantation, death, TIPS creation, or a maximum of 36 months, whichever came first, actively searching for de novo PVT occurrence. Causes of death were derived from medical records, latest imaging and, when available, autoptic histology and classified as HCC-related (liver-related death in which there was evidence of progression or recurrence of the neoplastic disease) or HCC-unrelated based on the last radiological staging and clinical charts. All patients underwent radiological follow-up every 3 months per protocol.

PVT diagnosis

The percentage of vessel occlusion in each splanchnic venous segment [main portal vein (MPV), intrahepatic portal branches (IHB), superior mesenteric vein (SMV), and splenic vein (SV)] was assessed on the portal venous phase of contrast-enhanced images performed for HCC diagnosis. For visualization of the lumen of each venous segment analyzed on actual orthogonal images of the short axis, an initial coronal image was obtained to visualize the long axis of the vessel. A perpendicular plane was drawn on these images and, with a multiplanar reconstruction, the transverse image of the vessel was obtained. Quantification of the occlusion of the vessel was performed by identifying the most occluded part of the single vessel and analyzing both transverse and longitudinal sections. To quantify the lesions in the transverse section, we used the percentage of the area, not the diameter, since calculations based on diameter measurements are inaccurate in eccentric thrombi. The percent of area reduction was then calculated from the vessel's total area and the residual lumen's area according to the following formula: % area reduction = (1- [B area/A area]) x 100 (Supplementary Figure 1).

Supplementary Figure 1. Quantification of the occlusion of the vessel was performed. The percent of area reduction was calculated from the vessel's total area and the residual lumen's area (B) according to the following formula: % area reduction = (1- [B area/A area]) x 100.

Stenosis   Area total vessel   Area patent lumen

% area reduction = (1 − [B area/A area]) x 100
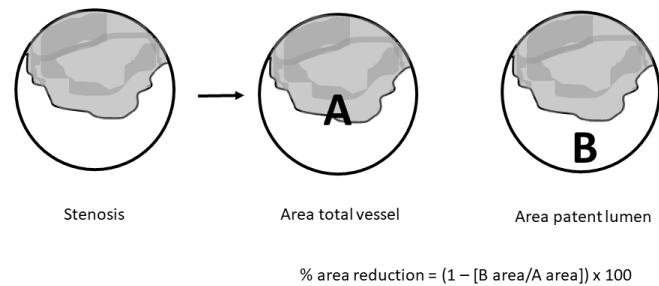
According to the latest expert consensus,(27) PVT was defined as partial or complete, when thrombotic material occupied < or =100% of the vessel lumen, respectively. Partial PVT were further divided into two subclasses according to the % of lumen occupied by the thrombus (≤50%, >50%). Comparison with previous radiological images was performed in order to determine the time of onset of thrombosis. Two radiologists with specific expertise in cirrhosis and HCC and blinded to the report and patient outcome reviewed all images. Agreement between the two radiologists per patient and portal vein segment were calculated. Finally, Kappa statistics were also obtained. Report of radiologist one was used for final analysis.

Suspicion and diagnosis of neoplastic thrombosis was made according to the following radiological criteria: proximity of the neoplastic lesion to the vessel, continuity of the thrombosis with the HCC nodules, thrombus expanding the vessel lumen >23 mm in diameter, thrombosis with wash-in in the arterial phase.(28)

Every de novo PVT occurring during follow-up was characterized using the same methods as baseline PVT. PVT occurring within 30 days of locoregional treatment for HCC and involving IHB close to the treated area, were classified as 'iatrogenic' and not considered a de novo PVT.(29) Neoplastic PVT occurring during follow-up were not considered as de novo PVT, but as HCC progression.

Evaluation of PVT evolution

In all patients with viable tumors at the time of PVT diagnosis (baseline or de novo) and with radiological follow-up >3 months after PVT diagnosis, the evolution of thrombus and HCC was assessed over a 12-month period or until transplantation, TIPS, death, or loss to follow-up, whichever occurred first (Supplementary Figure 2).

Supplementary Figure 2. Follow-up scheme of different type of patients during the study.
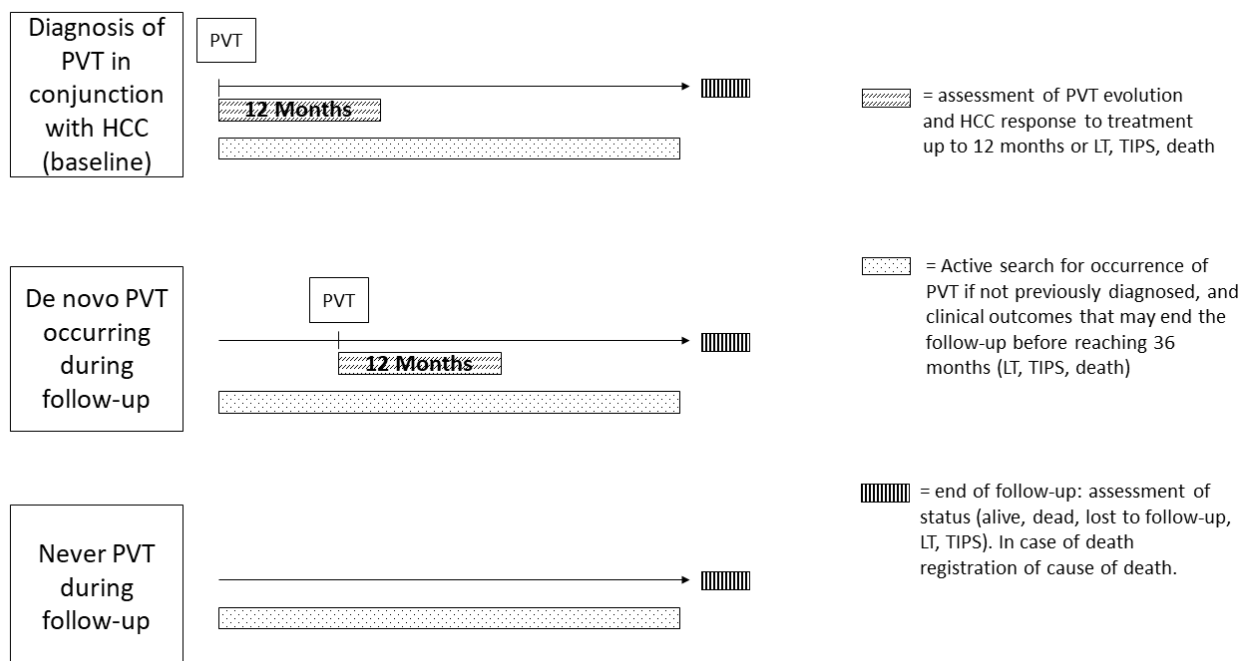
The evolution of thrombosis was classified in each segment, at the time intervals of 3, 6, and 12 months, as:

a) Progressive: changes of class from ≤50% to >50%, from >50% to 100% or from ≤50% to 100% of vessel occlusion;

b) Stable: no change in class of degree of occlusion (≤50%, >50% and =100%);

c) Ameliorated: regression from 100% to <100%, and from >50% to ≤50% of vessel occlusion;

At the end of the follow-up, the evolution pattern of PVT in all segments was summarized as:

a) Complete/progressive: (i) partial PVT that changes class from ≤50% to >50%, from >50% to 100% or from ≤50% to 100% of vessel occlusion, (ii) complete PVT (100%) at diagnosis remaining complete (100%), (iii) any type of extension of PVT to other splanchnic segments/vessels during follow-up.

b) Partial/ameliorated: (i) partial PVT (<100%) that improves or remains stable, (ii) complete PVT (100%) that improves during follow-up.

The decision to treat PVT with anticoagulation was based on the physician's choice.

HCC characterization

Morphological features of HCC were assessed on contrast-enhanced imaging at diagnosis: the number of nodules, maximum nodular diameter, presence of vascular invasion, and total tumor volume (TTV).(30) In patients with PVT, the concomitant evolution of HCC was assessed (Supplementary Figure 2), classifying the response to treatment (complete, partial, or progressing) according to EASL criteria.(24) Moreover, only intrahepatic nodules > 1cm with a wash in/wash out pattern were considered as active HCC.

Statistical analysis

Continuous variables, expressed as the median and interquartile range (IQR), were compared with Student's t-test. Categorical variables, expressed as absolute numbers and percentages, were compared with Fisher's exact test and the chi-square test. Agreement between the two radiologists per patient and portal vein segment were calculated. Kappa statistics were also calculated. We performed five main analyses (Figure 1).

Figure 1. Flow chart of the study, showing the patients considered for each analysis performed in the study. Analysis 1: factors associated with the presence of PVT at the diagnosis of HCC; Analysis 2: factors associated with the pattern of evolution of PVT; Analysis 3: survival analysis according to the presence of PVT; Analysis 4: survival analysis according to the pattern of evolution of PVT; Analysis 5: survival analysis according degree of vessel occlusion at end of follow-up.
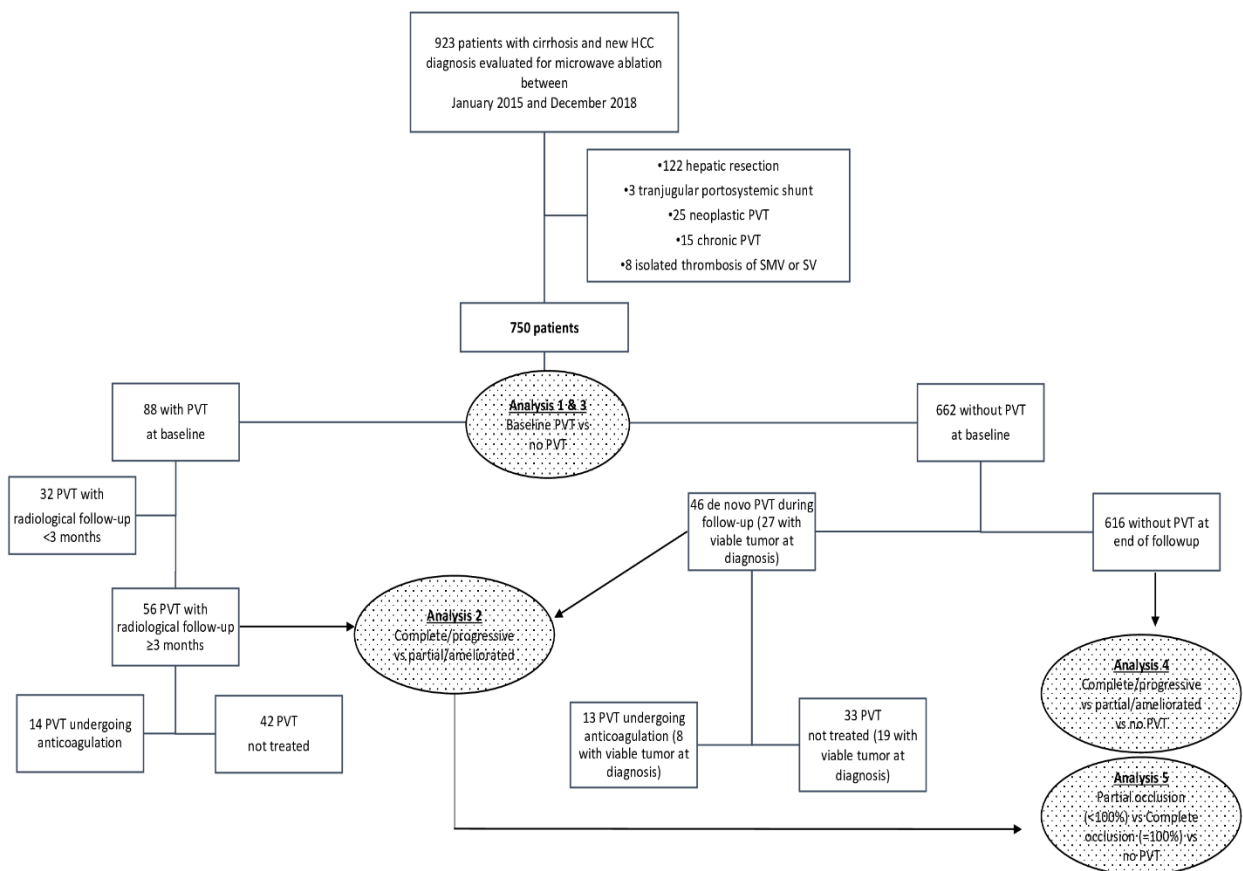
First, a multivariate nominal logistic regression model was used to identify variables significantly associated with the risk of PVT co-occurrence at HCC diagnosis. Results were expressed as odds ratios (OR) and 95% confidence intervals (95%CI). Relevant variables with p<0.1 when comparing the groups of patients with and without PVT were included in the multivariate model (analysis 1). Similarly, variables associated with the pattern of PVT evolution (competitive/progressive vs. partial/ameliorated), were identified. Results were expressed as beta coefficients and standard error (analysis 2). Sub-analyses were performed according to the time at which PVT occurred (baseline or de novo) and anticoagulant treatment.

Finally, survival analyses were performed. The impact of the presence of PVT on survival was analyzed first (analysis 3), followed by the impact of the evolution pattern (analysis 4) and of the degree of occupancy at end of follow-up (analysis 5). For the latter analysis partial PVT (occupancy of the lumen <100%) were compared to those with complete occlusion of the vessel (occupancy of the lumen =100%) and with patients without PVT. Survival curves were calculated using the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate Cox survival models were also calculated. The proportional hazards hypothesis was tested on the basis of Schoenfeld residuals. In the multivariate Cox model, variables with p<0.1 were included in the univariate analysis.

Since previous literature indicates that the prognosis of HCC patients is influenced not only by cancer-related death but also by liver failure and extra-hepatic causes of death, weighted competing-risk analyses were performed using the methodology provided by Fine &Gray. Missing data of study covariates always involved less than 10% of patients and were estimated using the Maximum Likelihood Estimation method.

Survival analysis results were expressed as hazard ratios (HR) and 95%CI. P<0.05 was considered statistically significant for multivariate analyses. Statistical analysis was conducted using the statistical packages SPSS version 22.0 (SPSS Inc, Chicago, Illinois, USA), JMP® Pro 16.2.0 (2020-2021 SAS Institute Inc.) and STATA/SE 17.0 (1985-2021 StataCorp LLC).

RESULTS

Prevalence of PVT at HCC diagnosis

Among the 923 patients who were candidates for microwave treatment, 173 were excluded (Figure 1). Seven hundred and fifty patients were finally included, 88 of whom had PVT at baseline (11.3%). The majority of PVT was partial (80.7%) and 43.2% extended to other splanchnic vessels (Table 1). No cavernomatous transformation was found at diagnosis.

Table 1. Characteristic of portal vein thrombosis at baseline

	Partial ≤50%	Partial >50%	Complete	Total
Portal vein trunk only	13	7	4	24
Portal vein trunk and intrahepatic branches	4	4	3	11
Portal vein trunk and Superior Mesenteric Vein	12	5	2	19
Portal vein trunk, intrahepatic branches and Superior Mesenteric Vein	2	4	3	9
Portal vein trunk, Superior Mesenteric Vein and Splenic Vein	4	0	0	4
Portal vein trunk, intrahepatic branches, Superior Mesenteric Vein and Splenic Vein	3	1	1	5
Portal vein trunk, intrahepatic branches and Splenic Vein	0	1	0	1
Intrahepatic branches only	7	4	4	15
Total	45	26	17	**88**

Patients with PVT had worse liver function, higher prevalence of CSPH, and more advanced HCC than patients without thrombosis. On multivariate analysis, the variables associated with the presence of PVT were pre-treatment TTV (OR 1.1; 95%CI 1.05-1.15; p<0.001) and the presence of CPSH (OR 2.9; 95% CI 1.37-6.59; p=<0.005) (Table 2).

Table 2. Baseline characteristic of patients with HCC undergoing undergoing laparoscopic microwave ablation, with and without PVT at baseline

	PVT N = 88	No PVT N = 662	Univariate p value	Multivariate	
				Odds Ratio (95% Confidence Interval)	p value
Age, years - median (IQR)	64 (59-69)	67 (59-73)	0.220		
BMI - median (IQR) BMI < 25 - number (%) 25 ≤ BMI < 30 - number (%) BMI ≥ 30 - number (%)	26.3 (23-28.7) 29 (32.9) 41 (46.6) 18 (20.5)	25.8 (23.7-28.8) 232 (35.0) 335 (50.7) 95 (14.3)	0.878		
Gender Female - number of patients (%)	12 (13.6)	100 (15.1)	0.126		
Etiology of liver disease – number of patients (%) HCV HBV Alcol Criptogenic NASH	44 (50) 12 (13.6) 23 (26.1) 5 (5.7) 9 (10.2)	314 (47.5) 112 (16.9) 190 (28.7) 41 (6.2) 62 (9.4)	0.660 0.433 0.610 0.848 0.799		
Child-Pugh score – number (%) A/B/C	45/38/5 (51.1/43.2/5.7)	490/159/13 (74/24/2)	**<0.001**		
MELD - median (IQR)	11 (8-14)	6 (6-6)	**<0.001**	0.99 (0.98-1.03)	0.950
ECOG > 1 – number of patients (%)	6 (6.8)	102 (15.4)	0.323		
ALBI score (≤ -2.60 / -2.60 < ALBI score ≤ -1.39 / > -1.39 – number (%)	12/61/15 (13.7/69.3/17)	84/508/70 (12.9/76.7/10.6)	0.105		
Clinically significant portal hypertension - number of patients (%)	78 (88.6)	352 (53.2)	**<0.001**	2.90 (1.37-6.59)	**0.005**

Varices (no/low risk/high risk) - number of patients (%)	46/26/16 (52.2/29.5/18.1)	455/132/75 (68.7/19.9/11.3)	**0.022**		
Previous bleeding related to portal hypertension - number of patients (%)	21 (23.8)	59 (8.9)	**<0.001**		
Ascites (minimal/moderate/severe) - number of patients (%)	23/17/0 (26.1/19.3/0)	108/33/9 (16.3/5/1.4)	**<0.001**		
Encepalopathy - number of patients (%)	15 (17)	53 (8)	**0.013**		
Splenomegaly - number of patients (%)	68 (77.3)	319 (48.2)	**<0.001**		
Platelets, $\times 10^9$/L - median (IQR)	92 (57-130)	102 (74-155)	**<0.001**		
INR - median (IQR)	1.2 (1.1-1.4)	1.2 (1.1-1.3)	**0.002**		
Creatinin, mg/dl - median (IQR)	0.8 (0.7-1)	0.9 (0.7-1)	0.276		
Sodium, mEq/L - median (IQR)	138 (137-141)	138 (136-140)	0.110		
Bilirubin, mg/dl - median (IQR)	1.3 (0.9-1.9)	1.1 (0.7-1.7)	**0.001**		
Albumin, g/L - median (IQR)	38 (34-42)	36 (33-40)	0.387		
HCC characteristics - median (IQR) Pre-treatment TTV (mm^3) Nodules number (number) Maximum diameter (mm) AFP (ng/mL)	16,018 (5,621-44,385) 2 (1-2) 31 (23-50) 16.3 (5.9-275.3)	9,205 (4,190-22,877) 1 (1-2) 23 (18-30) 5.9 (3.3-18.2)	**0.002** **0.033** **0.008** **0.058**	1.10 (1.05-1.15) 1.05 (0.9-1.1)	**<0.001** 0.147

Diabete mellitus - number of patients (%)	24 (27.3)	215 (32.5)	0.325		
Arterial hypertension - number of patients (%)	28 (31.8)	286 (43.2)	**0.042**		

Legend: PVT= portal vein thrombosis; IQR = interquartile range; BMI = body mass index; HCV = hepatitis C virus: HBV = hepatitis B virus; NASH = non-alcoholic steatohepatitis; MELD = Model for End Stage Liver Disease; INR = international normalized ratio; TTV = total tumor volume; AFP = alpha fetoprotein

De novo PVT

No patients underwent TIPS during follow-up or started anticoagulation for indications other than PVT. During a median follow-up of 21 months (IQR 8-36), among the 662 patients without PVT at baseline, 53 developed a de novo PVT. Of these patients, 7 were considered 'iatrogenic', which all resolved spontaneously within 6 months of the locoregional treatment and none presented neoplastic thrombosis later on in the follow-up. Thus, 46 de novo PVT occurred within a median time of 13.6 months (IQR: 4.6-21.5) from baseline, 27/46 (58.7%) in the presence of a viable tumor at diagnosis [median TTV 17734 mm^3 (IQR: 2874-63713)]. Most de novo PVT were partial (76.1%), and 41.3% extended to other splanchnic vessels.

There was an overall agreement of thrombosis classification of 92%, 88% for intrahepatic branches and 94% for the main portal vein trunk between the two radiologists that reviewed the images. Kappa corresponding kappa statistics were 0.82 (95% CI = 0,75-0.86) per patient; 0.85 (95% CI = 0,83-0.90); per MPV trunk; 0.80 (95% CI = 0,72-0.83) for IHB.

Evolution of PVT

Among the 134 patients with PVT (88 at baseline and 46 de novo), 32 were excluded from the evaluation of the evolution due to lack of radiological follow-up (death in 19 patients and liver transplantation in 2 patients within 3 months since baseline, inability to review follow-up images in 11 patients). Thus, the evolution of PVT was analyzed in 102 patients (Table 3); of these, 27-(26.5%)

were treated with anticoagulant therapy, and 75 (73.5%) were not. PVT were followed up to 12 months for a median of 9 months (IQR: 6-12), with a median number of 4 images per patient (IQR: 2-4).

Table 3. Characteristic of portal vein thrombosis with evolution analysis (baseline and de novo)

	Partial ≤50%	Partial >50%	Complete	Total
Portal vein trunk only	12	4	3	19
Portal vein trunk and intrahepatic branches	4	6	5	15
Portal vein trunk and Superior Mesenteric Vein	10	2	4	16
Portal vein trunk, intrahepatic branches and Superior Mesenteric Vein	3	10	7	20
Portal vein trunk, Superior Mesenteric Vein and Splenic Vein	1	1	0	2
Portal vein trunk, intrahepatic branches, Superior Mesenteric Vein and Splenic Vein	2	0	1	3
Portal vein trunk, intrahepatic branches and Splenic Vein	0	2	0	2
Intrahepatic branches only	10	14	1	25
Total	42	39	21	102

Evolution of PVT in patients treated with anticoagulants

Among the 27 anticoagulated patients, no patients discontinued anticoagulation because of complications. At the end of follow-up, PVT was defined as globally improved in 15 (55.6%), progressed in 2 (7.4%) and remained stable in 10 (37%) patients. The evolution per individual segment is shown in Supplementary Table 1.

Supplementary Table 1. Evolution of thrombosis, per single segments, in anticoagulated and untreated patients

	Intrahepatic brances				Portal vein trunk				Superior mesenteric vein				Splenic vein			
	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%
ANTICOAGULATED (N = 27)																
PROGRESSIVE	2	0	0	14.3	2	0	0	8.7	1	0	0	7.7	0	0	0	0
STABLE	1	3	3	50	4	4	4	52.2	3	0	2	38.5	1	0	0	100
AMELIORATED	2	2	1	35.7	6	2	1	39.1	5	2	0	53.8	0	0	0	0
UNTREATED (N = 75)																
PROGRESSIVE	11	17	0	54.9	16	9	0	46.3	10	4	0	50	3	0	0	50
STABLE	4	5	5	27.5	9	5	8	40.7	5	1	5	39.3	0	1	1	33.3
AMELIORATED	5	4	0	17.6	5	1	1	13	2	1	0	10.7	1	0	0	16.7

Among the 22 anticoagulated patients with viable HCC at PVT diagnosis (i.e. excluding the 5 patients in complete response at the time of diagnosis of de novo PVT), 17/22 (77.3%) were treated with low molecular weight heparin, 2/22 (9.1%) with fondaparinux, and 3/22 (13.6%) with vitamin k antagonist, for a median time of 10 months (IQR: 8-18), all at anticoagulant dosage. At the end of follow-up, PVT was defined as globally improved in 10 (45.5%), progressed in 2 (9%) and remained stable in 10 (45.5%) patients. The evolution per individual segment is shown in Supplementary Table 2.

Supplementary Table 2. Evolution of thrombosis diagnosed in presence of active HCC, per single segments, in anticoagulated and untreated patients

	Intrahepatic brances				Portal vein trunk				Superior mesenteric vein				Splenic vein			
	ANTICOAGULATED (N = 22)															
	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%
PROGRESSIVE	2	0	0	15.4	2	0	0	11.2	1	0	0	9.0	1	0	0	100
STABLE	1	2	3	46.1	2	3	3	44.4	2	2	1	45.5	0	0	0	1
AMELIORATED	2	2	1	38.5	5	2	1	44.4	5	0	0	45.5	0	0	0	1
	UNTREATED (N = 61)															
	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%	PARTIAL ≤ 50%	PARTIAL > 50%	COMPLETE	%
PROGRESSIVE	9	14	0	56.1	13	6	2	51.2	7	3	1	50	1	0	0	25
STABLE	4	5	3	29.3	9	4	5	43.9	5	1	3	40.9	0	1	1	50
AMELIORATED	4	2	0	14.6	2	0	0	4.9	2	0	0	9.1	1	0	0	25

Natural history of PVT in untreated patients

Among the 75 patients not treated with anticoagulation, PVT progressed overall in 47 (62.7%), improved in 5 (6.7%), and remained stable in 23 (30.6%) patients. The evolution of thrombosis in individual segments is shown in Supplementary Table 1. Overall, no variable was found to be associated with the pattern of evolution (Supplementary Table 3).

Supplementary Table 3. Univariate and multivariate analysis of factors associated with PVT evolution-pattern in all patients

	COMPLETE/ PROGRESSIVE N = 48	PARCIAL /AMELIORATED N = 27	Univariate p value	Multivariate β coefficient (standard error)	p value
Age, years - median (IQR)	66 (61-73)	67 (62-70)	0.782		
BMI - median (IQR) BMI < 25 - number (%) 25 ≤ BMI < 30 - number (%) BMI ≥ 30 - number (%)	26 (25-30) 15 (31.3) 23 (47.9) 10 (20.8)	25 (24-27) 10 (37.0) 12 (44.6) 5 (18.5)	0.250		
Gender Female - number of patients (%)	10 (20.8)	2 (7.4)	0.128		
Etiology of liver disease – number of patients (%) HCV HBV Alcol Criptogenic NASH	22 (45.8) 8 (16.7) 12 (25.0) 2 (4.2) 3 (6.3)	11 (40.7) 3 (11.1) 11 (40.7) 2 (7.4) 2 (7.4)	0.670 0.514 0.156 0.549 0.847		
Child-Pugh score – number of patients (%) A B C	23 (48.9) 23 (48.9) 1 (2.1)	18 (66.7) 6 (22.2) 3 (11.1)	**0.036**	**Ref.** 1.177 (0.963) -1.955 (1.712)	0.221 0.253
MELD - median (IQR)	11 (6-13)	10 (6-15)	0.668		
ECOG > 1 – number of patients (%)	6 (12.5)	6 (22.1)	0.270		
ALBI score (≤ -2.60 / -2.60 < ALBI score ≤ -1.39 / > -1.39 – number (%)	7/33/8 (14.6/68.8/35.4)	2/22/3 (7.4/81.5/11.1)	0.111		
Clinically significant portal hypertension – number of patients (%)	38 (79.2)	22 (81.5)	0.810		

Varices (no/low risk/high risk) - number of patients (%)	23/13/12 (47.9/27.1/25)	14/7/6 (51.9/25.9/22.2)	0.603		
Previous bleeding related to portal hypertension - number of patients (%)	14 (29.2)	5 (18.5)	0.309		
Ascites (minimal/moderate/severe) - number of patients (%)	18/7/1 (37.5/14.6/2.1)	4/3/0 (15.4/11.5/0)	0.128		
Encephalopathy - number of patients (%)	7 (14.6)	2 (7.4)	0.359		
Splenomegaly - number of patients (%)	36 (75)	20 (74.1)	0.929		
Platelets, × 10^9/L - median (IQR)	74 (60-96)	85 (54-130)	0.657		
INR - median (IQR)	1.3 (1.2-1.3)	1.2 (1.1-1.4)	0.490		
Creatinin, mg/dl - median (IQR)	0.8 (0.7-1)	0.8 (0.6-1)	0.389		
Sodium, mEq/L - median (IQR)	137 (135-140)	139 (136-140)	0.198		
Bilirubin, mg/dl - median (IQR)	1.5 (1-2.2)	1.2 (0.9-1.7)	0.480		
Albumin, g/L - median (IQR)	34 (30-40)	36 (31-40)	0.989		
HCC characteristics - median (IQR) TTV (mm^3) Nodules number (number) Maximum diameter (mm) AFP (ng/mL)	9,689 (1,520-34,425)	10,671 (2,291-59,389)	0.670 0.977		

	1 (1-2)	1 (1-2)	0.606		
	24.5 (14-35.8)	25 (10-45)	0.102		
	18.8 (4.2-187.3)	8.4 (2.3-72.4)			
Diabete mellitus - number of patients (%)	15 (31.3)	11 (40.7)	0.407		
Arterial hypertension - number of patients (%)	16 (33.3)	7 (25.9)	0.504		
PVT extension at diagnosis – number of patients (%) Main portal trunk Intrahepatic portal branches Superior mesenteric vein Splenic vein Number of thrombosed segments -(1/2/3/4)	36 (75) 32 (66.7) 21 (43.8) 4 (8.3) 19/14/14/1 (39.6/29.2/29.2/2)	18 (66.7) 19 (70.4) 7 (25.9) 2 (7.4) 14/8/4/1 (51.9/29.6/14.8/3.7)	0.440 0.741 0.126 0.887 0.523		
Degree of vessel occlusion at diagnosis – number of patients (%) Main portal trunk (complete) Intrahepatic portal branches (complete) Superior mesenteric vein (complete) Splenic vein (complete) Overall (complete)	9 (18.8) 5 (10.4) 5 (10.4) 1 (2.1) 13 (27.1)	1 (3.7) 0 (0) 0 (0) 0 (0) 0 (0)	0. 139 0.174 0.241 0.687 **0.009**		0.998
				13.805 (5,874)	

Among the subgroup of 61 patients not treated with anticoagulation and with viable HCC at PVT

diagnosis (i.e. excluding the 14 patients in complete response at the time of diagnosis of de novo

PVT), PVT progressed overall in 34 (55.7%), improved in 6 (9.8%), and remained stable in 21 (34.5%) patients. The overall rate of thrombosis progression was significantly higher than in patients treated with anticoagulation (p<0.001). The evolution of thrombosis in individual segments is shown in Supplementary Table 2, showing progression rates in separate segments of 56.1%, 51.2%, 50%, and 25% in IHB, MPV, SMV, and SV, respectively. Similarly, stability rates were 29.3%, 43.9%, 40.9%, and 50%, and amelioration rates of 14.6%, 4.9%, 9.1%, and 25%, respectively. In these patients the lack of complete response to HCC treatment was independently associated with the 'complete/progressive' evolution pattern (Table 4).

Table 4. Univariate and multivariate analysis of factors associated with PVT evolution-pattern in patients not treated with anticoagulation and with active HCC at PVT diagnosis

	COMPLETE/ PROGRESSIVE N = 39	PARCIAL /AMELIORATED N = 22	Univariate p value	Multivariate	
				β coefficient (standard error)	p value
Age, years - median (IQR)	65 (59-72)	56 (63-70)	0.604		
BMI - median (IQR) BMI < 25 - number (%) 25 ≤ BMI < 30 - number (%) BMI ≥ 30 - number (%)	26 (23-30) 11 (35.9) 20 (51.3) 8 (20.5)	26 (24-27) 8 (36.3) 11 (50.0 3 (13.6)	0.533		
Gender Female - number of patients (%)	8 (20.5)	2 (9.1)	0.247		
Etiology of liver disease – number of patients (%) HCV HBV Alcol Criptogenic NASH	17 (43.6) 8 (20.5) 10 (25.6) 1 (2.6) 3 (7.7)	9 (40.9) 2 (9.1) 7 (31.8) 2 (9.1) 2 (9.1)	0.839 0.247 0.605 0.258 0.848		

Child-Pugh score – number of patients (%) A B C	19 (48.7) 19 (48.7) 1 (2.6)	14 (63.6) 5 (22.7) 3 (13.6)	**0.060**	**Ref.** - 1.199 (0.744) 1.246 (1.297)	0.107 0.337
MELD - median (IQR)	11 (6-13)	10 (6-15)	0.668		
ECOG > 1 – number of patients (%)	6 (15.4)	3 (13.6)	0.853		
ALBI score (≤ -2.60 / -2.60 < ALBI score ≤ -1.39 / > -1.39 – number (%)	6/26/7 (15.4/66.7/17.9)	2/17/3 (9.1/77.3/13.6)	0.864		
Clinically significant portal hypertension – number of patients (%)	31 (79.5)	19 (86.4)	0.502		
Varices (no/low risk/high risk) - number of patients (%)	18/10/11 (46.2/25.6/28.2)	12/6/4 (54.5/27.3/18.2)	0.721		
Previous bleeding related to portal hypertension - number of patients (%)	11 (28.2)	4 (18.2)	0.383		
Ascites (minimal/moderate/severe) - number of patients (%)	14/7/0 (35.9/17.9/0)	3/3/0 (13.6/13.6/0)	0.358		
Encephalopathy - number of patients (%)	6 (15.4)	2 (9.1)	0.484		
Splenomegaly - number of patients (%)	29 (74.4)	17 (77.3)	0.800		
Platelets, × 10^9/L - median (IQR)	73 (56-92)	77 (52-134)	0.810		
INR - median (IQR)	1.3 (1.2-1.4)	1.2 (1.1-1.4)	0.475		

Creatinin, mg/dl - median (IQR)	0.8 (0.7-1)	0.8 (0.7-0.9)	0.636		
Sodium, mEq/L - median (IQR)	137 (134-140)	139 (136-140)	0.287		
Bilirubin, mg/dl - median (IQR)	1.7 (1-2.3)	1.2 (1-1.8)	0.371		
Albumin, g/L - median (IQR)	34 (30-40)	37 (31-42)	0.724		
HCC response to treatment – number of patients (%)	6 (15.4)	11 (50)	**0.004**	-1.849 (0.722)	**0.010**
HCC characteristics - median (IQR) TTV (mm^3) Nodules number (number) Maximum diameter (mm) AFP (ng/mL)	14,141 (3,056-65,469) 2 (1-2) 28 (19-41) 37 (4.4-327.8)	29,855 (4,401-72,932) 1 (1-2) 30 (18-51) 6.3 (2.3-71.6)	0.578 0.883 0.523 **0.069**		
Diabete mellitus - number of patients (%)	14 (35.9)	10 (45.5)	0.463		
Arterial hypertension - number of patients (%)	12 (30.8)	7 (31.8)	0.932		
PVT extension at diagnosis – number of patients (%) Main portal trunk Intrahepatic portal branches Superior mesenteric vein Splenic vein Number of thrombosed segments -(1/2/3/4)	27 (69.2) 25 (64.1) 16 (41) 2 (5.1) 19/10/9/1 (48.7/25.6/23.1/2.6)	14 (63.6) 16 (72.7) 6 (27.3) 2 (9.1) 11/7/3/1 (50/31.8/13.6/1.6)	0.655 0.491 0.283 0.548 0.801		

Degree of vessel occlusion at diagnosis – number of patients (%)					
Main portal trunk (complete)	7 (17.9)	1 (4.5)	0.321		
Intrahepatic portal branches (complete)	3 (7.7)	0 (0)	0.303		
Superior mesenteric vein (complete)	4 (10.3)	0 (0)	**0.095**		
Splenic vein (complete)	1 (2.6)	0 (0)	0.368		
Overall (complete)	9 (23.4)	0 (0)	**0.046**		0.999
				21.370 (12,322)	

Survival analysis

During a median follow-up of 21 months (IQR 8-36), 300 patients (40%) died, 101 (13.5%) underwent liver transplantation and 60 (8%) were lost to follow-up. Of the patients who died, 123 died from HCC progression [43 with PVT (24 at baseline and 19 de novo)], while the other 177 died from non-HCC-related causes [68 with PVT (51 at baseline, 17 de novo)]. Among the latter, 96.3% of patients died from liver failure or complications of portal hypertension.

The presence of PVT was an independent predictor of mortality [HR 1.62-62, 95%C.I. 1.14-2.31, p=0.008], together with Child-Pugh class B/C vs A [HR 1.77, 95%C.I. 1.32-2.37, p<0.001], ALBI score [HR 1.55, 95%C.I. 1.01-2.37, p=0.045], AFP [HR 1.2, 95%C.I. 1.10-1.40, p=0.<001], maximum nodule diameter [HR 1.16, 95%C.I. 1.10-1.23, p<0.001] and number of HCC nodules at PVT diagnosis [HR 1.124, 95%C.I. 1.03-1.21, p=0.004] (Supplementary Table 4).

Supplementary Table 4. Univariate and multivariate analysis of factors associated with survival according to presence of PVT.

	Univariate		Multivariate	
	Hazard Ratio (95% Confidence Interval)	**p value**	**Hazard Ratio (95% Confidence Interval)**	**p value**
PVT	2.38 (1.85-3.05)	**<0.001**	1.62 (1.14-2.31)	**0.008**
Age > 70 years	1.12 (0.89-1.41)	0.309		
Gender	0.97 (0.74-1.28)	0.862		
BMI > 25	0.88 (0.70-1.11)	0.286		
Diabetes mellitus	1.13 (0.90-1.41)	0.297		
Arterial hypertension	1.04 (0384-1.30)	0.696		
Etiology of liver disease HCV HBV Alcol Criptogenic NASH	 1.16 (0.84-1.60) 1.07 (0.81-1.41) 1.11 (0.77-1.60) 0.877 (0.54-1.43)	 0.357 0.624 0.577 0.600		
MELD > 10	1.20 (1.10-1.31)	**<0.001**		
Child A **Child B/C**	2.52 (2.01-3.15)	**<0.001**	1.77 (1.32-2.37)	**<0.001**
ALBI score ≤ -2.60 **-2.60 < ALBI score ≤ -1.39** **ALBI score > -1.39**	 1.59 (1.07-2.37) 2.95 (1.83-4.76)	 **0.022** **<0.001**	 1.55 (1.01-2.37) 1.60 (0.91-2.80)	 **0.045** 0.101
Clinically significant portal hypertension	1.65 (1.32-2.06)	**<0.001**	1.22 (0.95-1.57)	0.119
Performance status	1.26 (0.95-1.69)	0.103		
Maximum diameter	1.19 (1.14-1.24)	**<0.001**	1.16 (1.10-1.23)	**<0.001**

|				
Total tumor volume	1.08 (1.06-1.10)	**<0.001**		
Nodules number	1.25 (1.16-1.34)	**<0.001**	1.12 (1.03-1.21)	**0.004**
Alfafetoprotein	1.45 (1.30-1.63)	**<0.001**	1.24 (1.10-1.40)	**<0.001**

The 6- and 12-month probabilities of survival were 78% and 65% for patients with PVT and 92% and 81% respectively in those who did not develop PVT during follow-up (Figure 2).

Figure 2. Kaplan-Meier estimates of survival probabilities according to presence of PVT (A), and according to presence of PVT and its evolution-pattern (B). PVT = portal vein thrombosis; P/A = partial/ameliorated evolution pattern; C/P= complete/progressive
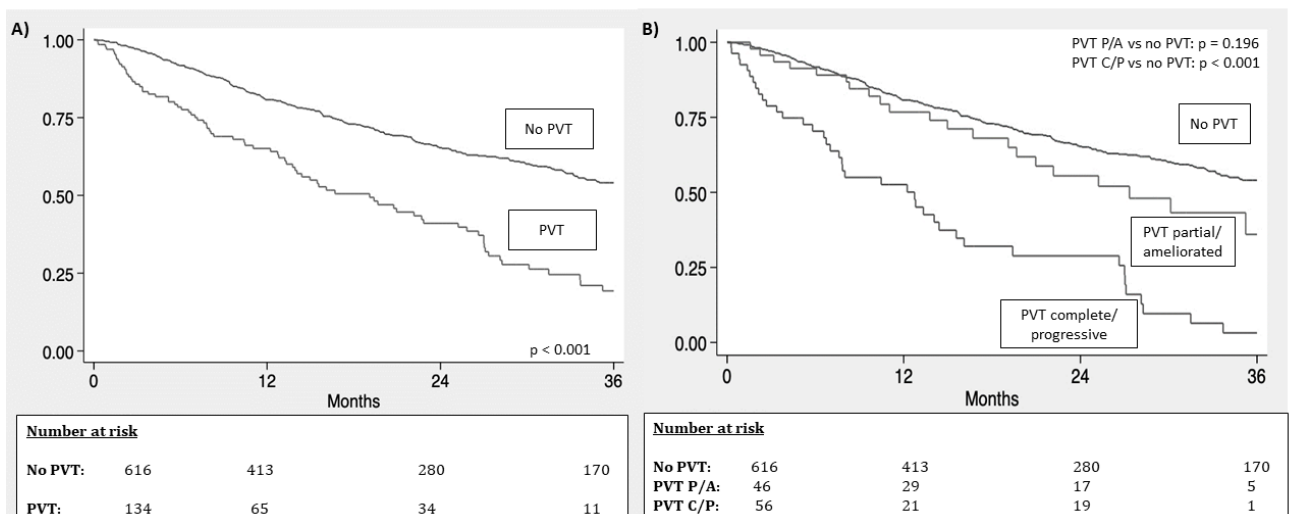
A significantly higher competing risk of death emerged for the presence of PVT, both for HCC-related and non-HCC-related deaths (Supplementary Figure 3, Supplementary Tables 5 and 6).

Supplementary Figure 3. Cumulative HCC (A) and non-HCC (B) related mortality by PVT presence, and cumulative HCC (A) and non-HCC (B) related mortality by PVT evolution-pattern. PVT = portal vein thrombosis; P/A = partial/ameliorated evolution pattern; C/P= complete/progressive
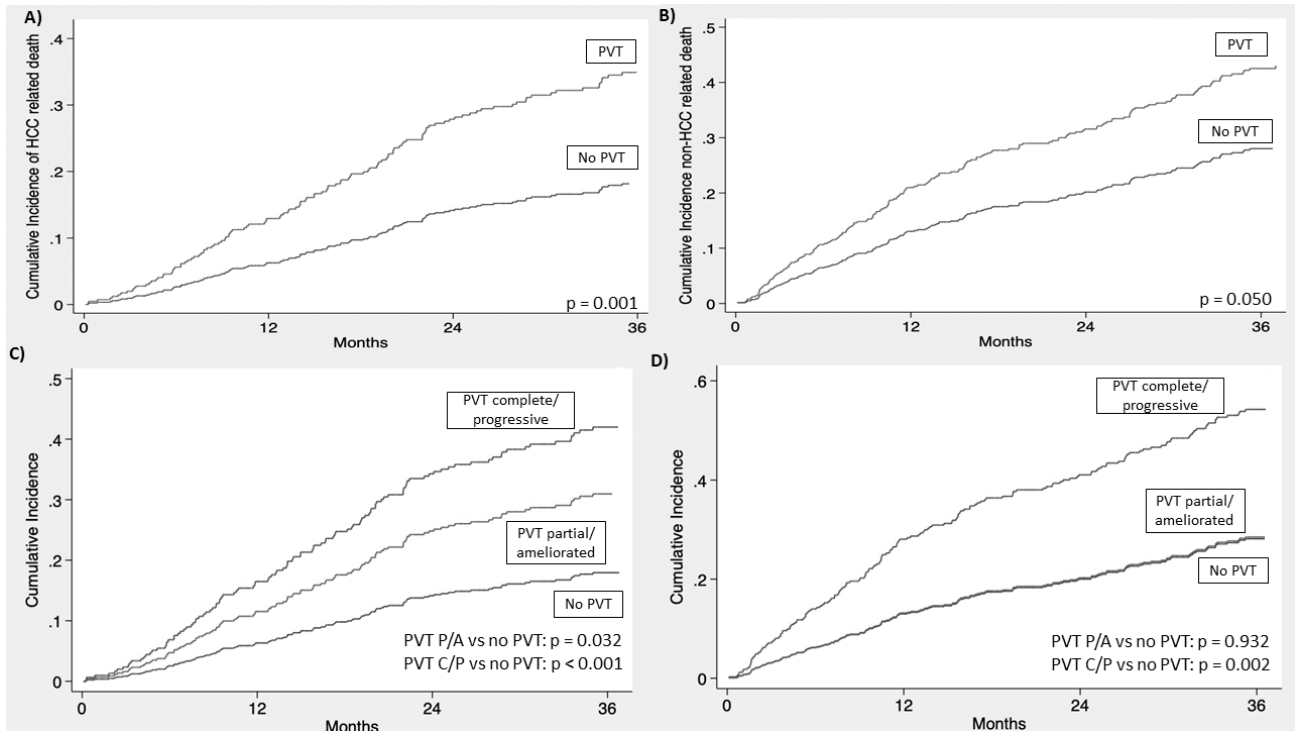
Supplementary Table 5. Univariate and multivariate competing risk analysis according to presence of PVT in HCC related mortality.

	Univariate		Multivariate	
	Hazard Ratio (95% Confidence Interval)	**p value**	**Hazard Ratio (95% Confidence Interval)**	**p value**
PVT	2.14 (1.47-3.13)	**<0.001**	2.04 (1.36-3.07)	**0.001**
Age > 70 years	0.39 (0.12-0.123)	**<0.001**	0.05 (0.01-0.15)	**<0.001**
Gender	0.53 (0.31-0.90)	**0.018**	0.76 (0.43-1.34)	0.338
BMI > 25	1.13 (0.78-1.65)	0.502		
Diabetes mellitus	1.04 (0.74-1.48)	0.813		

Arterial hypertension	0.95 (0.68-1.33)	0.770		
Etiology of liver disease HCV HBV Alcol Criptogenic NASH	1.54 (0.98-2.42) 0.73 (0.45-1.17) 1.12 (0.65-1.94) 0.69 (0.30-1.60)	0.058 0.185 0.676 0.386		
MELD > 10	1.27 (1.12-1.45)	**<0.001**	1.07 (0.92-1.26)	0.389
Child A **Child B/C**	1.38 (0.96-1.99)	**0.080**		
ALBI score ≤ -2.60 **-2.60 < ALBI score ≤ -1.39** **ALBI score > -1.39**	0.98 (0.59-1.64) 0.89 (0.43-1.87)	0.944 0.763		
Clinically significant portal hypertension	1.34 (0.96-1.89)	**0.090**	0.96 (0.67-1.38)	0.820
Performance status	0.42 (0.22-0.78)	**0.007**	0.43 (0.21-0.88)	**0.021**
Maximum diameter (mm)	1.11 (1.04-1.18)	**0.001**	1.02 (0.95-1.10)	0.584
Total tumor volume	1.06 (1.03-1.08)	**<0.001**		
Nodules number	1.25 (1.13-1.38)	**<0.001**	1.15 (1.01-1.30)	**0.033**
Alfafetoprotein	1.48 (1.26-1.75)	**<0.001**	1.40 (1.16-1.69)	**<0.001**

Supplementary Table 6. Univariate and multivariate competing risk analysis according to presence of PVT in non-HCC related mortality.

	Univariate		Multivariate	
	Hazard Ratio (95% Confidence Interval)	**p value**	**Hazard Ratio (95% Confidence Interval)**	**p value**
PVT	1.68 (1.21-2.35)	**0.002**	1.59 (0.99-2.55)	**0.050**
Age > 70 years	3.41 (2.57-4.53)	**<0.001**	4.43 (3.24-6.06)	**<0.001**
Gender	1.48 (1.08-2.03)	**0.014**	1.17 (0.84-1.64)	0.357
BMI > 25	0.76 (0.56-1.01)	**0.059**		
Diabetes mellitus	1.20 (0.90-1.60)	0.215		
Arterial hypertension	1.09 (0.83-1.45)	0.53		
Etiology of liver disease HCV HBV Alcol Criptogenic NASH	0.77 (0.48-1.24) 1.34 (0.95-1.88) 0.99 (0.62-1.58) 1.01 (0.56-1.80)	0.290 **0.095** 0.954 0.986		
MELD > 10	1.04 (0.916-1.18)	0.544		
Child A **Child B/C**	2.38 (1.79-3.18)	**<0.001**	1.77 (1.24-2.54)	**0.002**
ALBI score ≤ -2.60 **-2.60 < ALBI score ≤ -1.39** **ALBI score > -1.39**	2.15 (1.16-4.00) 4.62 (2.31-9.26)	**0.015** **<0.001**	2.44 (1.28-4.62) 3.72 (1.68-8.25)	**0.045** **<0.001**
Clinically significant portal hypertension	1.54 (1.16-2.07)	**0.003**	1.48 (1.07-2.04)	**0.017**
Performance status	2.03 (1.47-2.81)	**<0.001**	1.71 (1.19-2.46)	**0.004**

Maximum diameter	1.16 (1.08-1.25)	**<0.001**	1.77 (1.08-1.28)	**<0.001**
Total tumor volume	1.05 (1.02-1.08)	**<0.001**		
Nodules number	1.08 (0.97-1.20)	0.138		
Alfafetoprotein	1.16 (0.99-1.35)	**0.059**	1.03 (0.93-1.15)	0.580

When considering the evolution of PVT, the pattern 'complete/progressive' remained an independent predictor of mortality [HR 3.40, 95%C.I. 2.39-4.83, p<0.001], together with Child-Pugh class B/C vs A [HR 1.60, 95%C.I. 1.19-2.15, p=0.002], ALBI score [HR 1.60, 95%C.I. 1.05-2.45, p=0.029], AFP [HR 1.25, 95%C.I. 1.11-1.41, p<0.001], maximum nodule diameter [HR 1.164, 95%C.I. 1.10-1.22, p<0.001] and number of HCC nodules at PVT diagnosis [HR 1.50, 95%C.I. 1.06-1.24, p<0.001] (Figure 2, Supplementary Table 7).

Supplementary Table 7. Univariate and multivariate analysis of factors associated with survival according to presence of PVT and its evolution-pattern.

	Univariate		Multivariate	
	Hazard Ratio (95% Confidence Interval)	**p value**	**Hazard Ratio (95% Confidence Interval)**	**p value**
No PVT **PVT partial/ameliorated** **PVT complete/progressive**	1.50 (0.98-2.31) 4.19 (2.99-5.87)	**0.062** **<0.001**	1.33 (0.86-2.06) 3.40 (2.39-4.83)	0.196 **<0.001**
Age > 70 years	1.18 (0.94-1.48)	.0162		
Gender	0.96 (0.75-1.32)	0.976		
BMI > 25	0.89 (0.71-1.35)	0.359		
Diabetes mellitus	1.15 (0.91-1.45)	0.232		
Arterial hypertension	1.06 (0.85-1.33)	0.603		
Etiology of liver disease HCV HBV	 1.15 (0.82-1.60)	 0.411		

Alcol	1.07 (0.81-1.41)	0.642		
Criptogenic	1.07 (0.73-1.56)	0.722		
NASH	0.87 (0.53-1.41)	0.567		
MELD > 10	1.18 (1.07-1.30)	**0.001**		
Child A **Child B/C**	2.49 (1.97-3.13)	**<0.001**	1.60 (1.19-2.15)	**0.002**
ALBI score ≤ -2.60 **-2.60 < ALBI score ≤ -1.39** **ALBI score > -1.39**	1.45 (1.32-2.41) 2.86 (1.99-4.01)	**0.042** **0.030**	1.60 (1.05-2.45) 1.74 (1.00-30.4)	**0.029** **0.050**
Clinically significant portal hypertension	1.63 (1.30-2.04)	**<0.001**	1.17 (0.92-1.52)	0.203
Performance status	1.28 (0.95-1.71)	0.106		
Maximum diameter	1.19 (1.13-1.24)	**<0.001**	1.16 (1.10-1.22)	**<0.001**
Total tumor volume	1.08 (1.06-1.10)	**<0.001**		
Nodules number	1.24 (1.15-1.34)	**<0.001**	1.50 (1.06-1.24)	**<0.001**
Alfafetoprotein	1.41 (1.26-1.59)	**<0.001**	1.25 (1.11-1.41)	**<0.001**

Furthermore, a significantly higher competing risk of death was found only for 'complete/progressive' PVT for non-HCC-related death, compared to patients who never developed PVT. At the same time, it was substantially higher for both evolution-patterns of PVT for HCC-related death (Supplementary Figure 3, Supplementary Tables 8 and 9).

Supplementary Table 8. Univariate and multivariate competing risk analysis according to presence of PVT and its evolution-pattern in HCC related mortality.

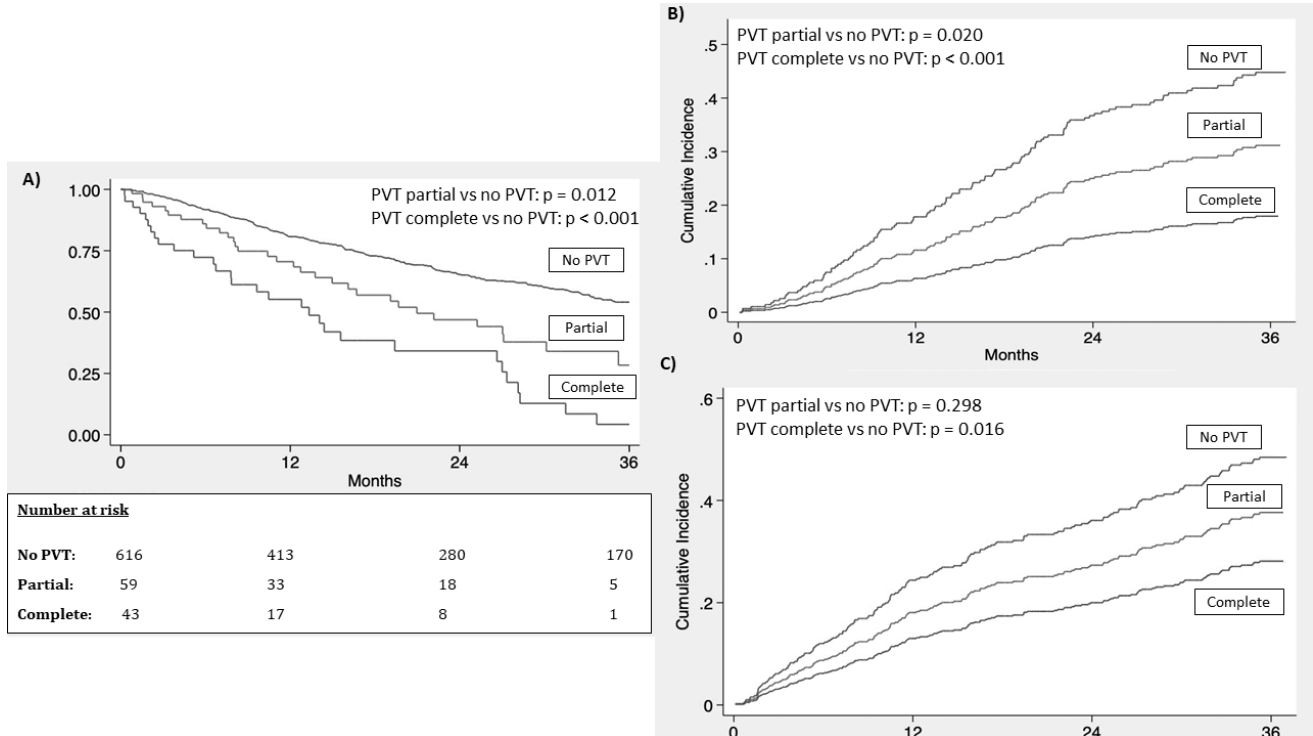|	Univariate		Multivariate	
	Hazard Ratio (95% Confidence Interval)	**p value**	**Hazard Ratio (95% Confidence Interval)**	**p value**
No PVT **PVT partial/ameliorated** **PVT complete/progressive**	1.87 (1.03-3.40) 2.75 (1.63-4.64)	**0.039** **<0.001**	1.88 (1.06-3.36) 3.18 (1.72-5.89)	**0.032** **<0.001**
Age > 70 years	0.40 (0.01-0.13)	**<0.001**	0.44 (0.01-0.14)	**<0.001**
Gender	0.52 (0.30-0.90)	**0.019**	0.83 (0.46-1.50)	0.535
BMI > 25	1.11 (0.75-1.63)	0.597		
Diabetes mellitus	1.05 (0.73-1.50)	0.799		
Arterial hypertension	0.99 (0.71-1.41)	0.999		
Etiology of liver disease HCV HBV Alcol Criptogenic NASH	1.48 (0.93-2.36) 0.75 (0.47-1.21) 1.02 (0.57-1.81) 0.69 (0.30-1.60)	**0.098** 0.244 0.951 0.389		
MELD > 10	1.27 (1.12-1.45)	**<0.001**	1.09 (0.92-1.30)	0.324
Child A **Child B/C**	1.39 (0.96-2.02)	**0.084**		
ALBI score ≤ -2.60 **-2.60 < ALBI score ≤ -1.39** **ALBI score > -1.39**	0.99 (0.60-1.65) 0.90 (0.44-1.88)	0.945 0.763		
Clinically significant portal hypertension	1.67 (0.94-1.94)	**0.079**	0.95 (0.65-1.39)	0.791
Performance status	0.46 (0.24-0.87)	**0.017**	0.64 (0.33-1.24)	0.184
Maximum diameter	1.12 (1.05-1.20)	**0.001**	1.04 (0.96-1.13)	0.338
Total tumor volume	1.06 (1.03-1.09)	**<0.001**		
Nodules number	1.24 (1.12-1.37)	**<0.001**	1.04 (0.99-1.32)	0.067
Alfafetoprotein	1.51 (1.27-1.80)	**<0.001**	1.40 (1.16-1.69)	**<0.001**

Supplementary Table 9. Univariate and multivariate competing risk analysis according to presence of PVT and its evolution-pattern in non-HCC related mortality.

	Univariate		Multivariate	
	Hazard Ratio (95% Confidence Interval)	**p value**	**Hazard Ratio (95% Confidence Interval)**	**p value**
No PVT **PVT partial/ameliorated** **PVT complete/progressive**	1.01 (0.56-1.83) 2.37 (1.50-3.73)	0.962 <0.001	1.02 (0.55-1.91) 2.09 (1.30-3.36)	**0.932** **0.002**
Age > 70 years	3.78 (2.81-5.07)	**<0.001**	4.52 (3.30-6.20)	**0.005**
Gender	1.50 (1.09-2.06)	**0.013**	1.16 (0.84-1.60)	0.375
BMI > 25	0.79 (0.58-1.07)	0.124		
Diabetes mellitus	1.22 (0.90-1.64)	0.198		
Arterial hypertension	1.08 (0.81-1.44)	0.609		
Etiology of liver disease HCV HBV Alcol Criptogenic NASH	0.80 (0.49-1.30) 1.30 (0.91-1.85) 1.09 (0.68-1.74) 1.03 (0.58-187)	0.367 0.152 0.728 0.905		
MELD > 10	1.03 (0.91-1.17)	0.631		
Child A **Child B/C**	2.38 (1.77-3.20)	**<0.001**	1.63 (1.12-2.36)	**0.010**
ALBI score ≤ -2.60 **-2.60 < ALBI score ≤ -1.39** **ALBI score > -1.39**	2.00 (1.15-3.98) 4.53 (2.29-8.99)	**0.004** **<0.001**	2.47 (1.31-4.63) 4.08 (1.87-8.91)	**0.005** **<0.001**
Clinically significant portal hypertension	1.50 (1.12-2.02)	**0.007**	1.49 (1.08-2.04)	**0.014**
Performance status	2.01 (1.43-2.81)	**<0.001**	1.73 (1.20-2.49)	**0.003**
Maximum diameter	1.15 (1.06-1.25)	**<0.001**	1.18 (1.08-1.28)	**<0.001**
Total tumor volume	1.05 (1.02-1.08)	**0.001**		

Nodules number	1.10 (0.99-1.22)	**0.092**	1.05 (0.94-1.16)	0.385
Alfafetoprotein	1.11 (0.95-1.30)	0.191		

Considering the degree of occlusion of the vessel at end of follow-up, the presence of PVT (both partial and complete) were independent predictors of mortality [partial PVT HR 1.62, 95%C.I. 1.11-2.35, p=0.012, complete PVT HR 3.41, 95%C.I. 2.31-5.04, p<0.001], together with Child-Pugh class B/C vs A, ALBI score and HCC burden (Supplementary Figure 4, Supplementary Table 10).

Supplementary Figure 4. Kaplan-Meier estimates of survival probabilities according to presence of PVT and its degree of vessel occlusion at end of follow-up. Cumulative HCC (B) and non-HCC (C) related mortality by PVT presence, and its degree of lumen occupancy at end of follow-up. PVT = portal vein thrombosis; Partial refers to thrombosis occupying <100% of the lumen; Complete refers to thrombosis occupying 100% of the lumen

Supplementary Table 10. Univariate and multivariate analysis of factors associated with survival according to presence of PVT and its degree of lumen occupancy at end of follow-up.

	Univariate		Multivariate	
	Hazard Ratio (95% Confidence Interval)	**p value**	**Hazard Ratio (95% Confidence Interval)**	**p value**
No PVT **PVT partial (<100%)** **PVT complete (=100%)**	1.85 (1.36-2.81) 3.74 (2.56-5.46)	**<0.001** **<0.001**	1.62 (1.11-2.35) 3.41 (2.31-5.04)	**0.012** **<0.001**
Age > 70 years	1.18 (0.94-1.48)	.0162		
Gender	0.96 (0.75-1.32)	0.976		
BMI > 25	0.89 (0.71-1.35)	0.359		
Diabetes mellitus	1.15 (0.91-1.45)	0.232		
Arterial hypertension	1.06 (0.85-1.33)	0.603		
Etiology of liver disease HCV HBV Alcol Criptogenic NASH	1.15 (0.82-1.60) 1.07 (0.81-1.41) 1.07 (0.73-1.56) 0.87 (0.53-1.41)	0.411 0.642 0.722 0.567		
MELD > 10	1.18 (1.07-1.30)	**0.001**		
Child A **Child B/C**	2.49 (1.97-3.13)	**<0.001**	1.66 (1.24-2.23)	**0.001**
ALBI score ≤ -2.60 **-2.60 < ALBI score ≤ -1.39** **ALBI score > -1.39**	1.45 (1.32-2.41) 2.86 (1.99-4.01)	**0.042** **0.030**	1.57 (1.03-2.40) 1.76 (1.01-3.08)	**0.038** **0.046**
Clinically significant portal hypertension	1.63 (1.30-2.04)	**<0.001**	1.17 (0.91-1.50)	0.226
Performance status	1.28 (0.95-1.71)	0.106		
Maximum diameter	1.19 (1.13-1.24)	**<0.001**	1.16 (1.10-1.22)	**<0.001**
Total tumor volume	1.08 (1.06-1.10)	**<0.001**		
Nodules number	1.24 (1.15-1.34)	**<0.001**	1.48 (1.06-1.24)	**0.001**
Alfafetoprotein	1.41 (1.26-1.59)	**<0.001**	1.26 (1.12-1.42)	**<0.001**

Furthermore, a significantly higher competing risk of death was found for both partial and complete PVT for HCC-related death and only for complete PVT for non-HCC-related death, compared to patients who never developed PVT (Supplementary Figure 4, Supplementary Tables 11 and 12).

Supplementary Table 11. Univariate and multivariate competing risk analysis according to presence of PVT and its degree of lumen occupancy at end of follow-up in HCC related mortality.

	Univariate		Multivariate	
	Hazard Ratio (95% Confidence Interval)	**p value**	**Hazard Ratio (95% Confidence Interval)**	**p value**
No PVT **PVT partial (<100%)** **PVT complete (=100%)**	1.89 (1.09-3.27) 3.00 (1.72-5.24)	**0.024** **<0.001**	1.93 (1.11-3.37) 3.54 (1.83-6.87)	**0.020** **<0.001**
Age > 70 years	0.40 (0.01-0.13)	**<0.001**	0.44 (0.01-0.14)	**<0.001**
Gender	0.52 (0.30-0.90)	**0.019**	0.85 (0.47-1.53)	0.590
BMI > 25	1.11 (0.75-1.63)	0.597		
Diabetes mellitus	1.05 (0.73-1.50)	0.799		
Arterial hypertension	0.99 (0.71-1.41)	0.999		
Etiology of liver disease HCV HBV Alcol Criptogenic NASH	1.48 (0.93-2.36) 0.75 (0.47-1.21) 1.02 (0.57-1.81) 0.69 (0.30-1.60)	**0.098** 0.244 0.951 0.389		
MELD > 10	1.27 (1.12-1.45)	**<0.001**	1.09 (0.92-1.29)	0.345
Child A **Child B/C**	1.39 (0.96-2.02)	**0.084**		
ALBI score ≤ -2.60 **-2.60 < ALBI score ≤ -1.39** **ALBI score > -1.39**	0.97 (0.58-1.63) 0.88 (0.42-1.86)	0.930 0.783		
Clinically significant portal hypertension	1.67 (0.94-1.94)	**0.079**	0.95 (0.64-1.39)	0.782

Performance status	0.46 (0.24-0.87)	**0.017**	0.64 (0.33-1.25)	0.191
Maximum diameter	1.12 (1.05-1.20)	**0.001**	1.04 (0.96-1.13)	0.352
Total tumor volume	1.06 (1.03-1.09)	**<0.001**		
Nodules number	1.24 (1.12-1.37)	**<0.001**	1.15 (0.99-1.32)	0.057
Alfafetoprotein	1.51 (1.27-1.80)	**<0.001**	1.41 (1.16-1.70)	**<0.001**

Supplementary Table 12. Univariate and multivariate competing risk analysis according to presence of PVT

and its degree of lumen occupancy at end of follow-up in non-HCC related mortality.

	Univariate	p value	Multivariate	p value
	Hazard Ratio (95% Confidence Interval)	**p value**	**Hazard Ratio (95% Confidence Interval)**	**p value**
No PVT **PVT partial (<100%)** **PVT complete (=100%)**	1.43 (0.88-2.32) 2.01 (1.18-3.40)	0.146 **0.010**	1.31 (0.79-2.16) 2.00 (1.14-3.52)	0.298 **0.016**
Age > 70 years	3.78 (2.81-5.07)	**<0.001**	4.55 (3.32-6.24)	**<0.001**
Gender	1.50 (1.09-2.06)	**0.013**	1.14 (0.82-1.59)	0.434
BMI > 25	0.79 (0.58-1.07)	0.124		
Diabetes mellitus	1.22 (0.90-1.64)	0.198		
Arterial hypertension	1.08 (0.81-1.44)	0.609		
Etiology of liver disease HCV HBV Alcol Criptogenic NASH	0.80 (0.49-1.30) 1.30 (0.91-1.85) 1.09 (0.68-1.74) 1.03 (0.58-187)	0.367 0.152 0.728 0.905		
MELD > 10	1.03 (0.91-1.17)	0.631		
Child A **Child B/C**	2.38 (1.77-3.20)	**<0.001**	1.69 (1.17-2.44)	**0.005**
ALBI score ≤ -2.60 **-2.60 < ALBI score ≤ -1.39** **ALBI score > -1.39**	2.15 (1.19-4.00) 4.04 (2.09-8.58)	**0.003** **<0.001**	2.48 (1.31-4.68) 3.96 (1.79-8.77)	**0.005** **<0.001**

Clinically significant portal hypertension	1.50 (1.12-2.02)	**0.007**	1.49 (1.09-2.05)	**0.013**
Performance status	2.01 (1.43-2.81)	**<0.001**	1.74 (1.21-2.51)	**0.003**
Maximum diameter	1.15 (1.06-1.25)	**<0.001**	1.18 (1.08-1.28)	**<0.001**
Total tumor volume	1.05 (1.02-1.08)	**0.001**		
Nodules number	1.10 (0.99-1.22)	**0.092**	1.04 (0.94-1.16)	0.462
Alfafetoprotein	1.11 (0.95-1.30)	0.191		

DISCUSSION

This is the first study to specifically investigate the natural history of non tumoral PVT in a large cohort of patients with cirrhosis and HCC, demonstrating a different natural history and impact on prognosis of portal vein thrombosis compared to cirrhotic population without malignancy, possibly related to the biological activity of the tumor.

Solid and hematological malignancies are often associated with a paraneoplastic prothrombotic syndrome. Cancer-associated VTE is also associated with worsened survival, morbidity, need for hospitalization and potential delay or discontinuation of cancer therapy.(31) Thus, thromboprophylaxis has long been recommended during hospitalization and in the post-surgical setting for cancer patients.(32). On the contrary in cancer and in particular HCC, splanchnic vein thrombosis have been often overlooked.

Increasing data on HCC demonstrate that this tumor seem to represent a specific risk factor for VTE independent of severity of liver disease, with a prevalence in hospitalized patients ranging from 1-7%.(31, 33) However, the perceived risk of bleeding in cirrhosis and the need for invasive treatments for HCC led to underuse of thromboprophylaxis and undertreatment of thrombotic complications. Of all thrombotic events, PVT is the most frequent, with a reported incidence at 1 year after diagnosis of HCC up to 25%.(7, 9) Indeed, retrospective studies have shown that the prevalence of PVT is significantly higher in patients who are candidates for liver transplant when they present with HCC (13-41%) than without it (9-31%),(5, 28, 34, 35) which is also the case in cirrhotic patients admitted to intensive care units.(36, 37) In spite of the relatively low initial tumor burden in this cohort, we identified a significant prevalence of PVT co-diagnosed with HCC (11.3%). Interestingly, even within this cohort, TTV was independently associated with the occurrence of PVT at baseline, besides the presence of CSPH. Although the main pathophysiological mechanisms leading to the formation of PVT may be shared with those of cirrhosis,(20, 38) the presence of HCC-driven coagulopathy could shift towards the prothrombotic side also in the plasma component of Virchow's triad.(8, 31)

especially in patients with multinodular HCC and TTV>5cm^3.(9) Thus, HCC volume could be the determinant of the severity of these alterations and favor the appearance of PVT.

During the follow-up, we identified a rate of de novo PVT of 7%. Although this appears to be a low incidence compared to previous cohorts,(5, 28, 34, 35) our population is likely to show the lowest rates compared to the entire HCC population due to baseline characteristics (71% Child A and low baseline tumoral burden).

In cirrhotic patients without HCC several studies have reported that in most cases, partial PVT resolves spontaneously or remains stable, with rates up to 42% and 70%, respectively.(4, 39, 40) On the contrary in the present cohort the progression rate in untreated patients was much higher (62.7%), compared to pooled rates in patients without HCC (29-33%).(40, 41) Also the spontaneous recanalization rate was minimal (6.7%), compared to patients without HCC (22-42%),(40, 41). The only factors influencing the pattern of PVT progression was HCC response to treatment, suggesting that tumour persistence may hinder thrombosis regression regardless of PVT characteristics at diagnosis, thus leaving little room for monitoring in the absence of therapy.

In the small group of patients that have been treated with anticoagulation in our cohort, it would appear that such treatment is effective in ameliorating/preventing progression of PVT. However, the sample is too small to draw any conclusions. Future studies need to further investigate the efficacy and safety of anticoagulation in patients with acute PVT and HCC.

In our cohort, the presence of PVT and its evolution (i.e. 'complete/progressive' pattern) also impacted the prognosis of patients, independently from tumor progression, reinforcing the rationale for prevention and treatment. In fact, a significant impact on mortality risk was seen for both HCC-related and unrelated deaths. Interestingly, when considering the degree of vessel occupancy at the end of follow-up, the presence of residual thrombus (independently from the grade) influenced the outcome. The latter result, if confirmed by future studies, could justify complete recanalization as a therapeutic goal.

The clinical impact of PVT on the natural history of cirrhosis is still debated. A multicenter study found no association between PVT and risk of decompensating events or mortality in patients with Child-Pugh A and B cirrhosis.(16) However, the high rate of spontaneous recanalization in this study may explain the lack of association with decompensation and survival, in addition to the fact that different patterns of PVT evolution were not considered in the analysis. Furthermore, Luca et al. found no significant differences in 2-year liver failure rates and 2-year survival according to the evolution of PVT, but higher incidence of decompensations.(4) However, causes of death were not reported, stable partial PVT was grouped with progressive PVT for the analysis of clinical outcomes and complete PVT was excluded from the analysis. Senzolo et al. found that PVT that does not reach recanalization after anticoagulant therapy increases mortality in patients with Child-Pugh B/C cirrhosis.(42) Thus, it has been hypothesized that PVT may mainly affect the prognosis only of cirrhotic patients with poor liver function.

However, the presence of PVT, particularly when 'complete/progressive', may limit the blood supply to the liver and alter splanchnic hemodynamics.(39, 43-50) Furthermore, the presence of complete PVT may discourage hepatic resections and is considered a contraindication to transarterial chemoembolization, limiting access to curative treatment/ bridge to transplantation for HCC, thus impacting also on HCC related-deaths.

This study has some limitations. First, it is a retrospective study, which did not allow us to accurately identify the timing of relevant clinical events related to liver disease decompensation to assess their correlation with the occurrence of PVT and its evolution or to assess the role of medical treatments in the occurrence of PVT. Furthermore, this is a highly selected cohort (newly diagnosed HCC candidate to microwave ablation at our center) and it was impossible to assess when the presence of PVT limited the sequentiality of HCC treatments. Thus, these results would need prospective internal and external validation to be confirmed. However, our cohort is somewhat unique as it includes a consequent, homogeneous HCC population with a high prevalence of untreated and well-characterized PVT, allowing the description of the natural history of PVT in HCC patients.

CONCLUSIONS

In conclusion, the results of this study supports the hypothesis that HCC volume is associated with the risk of PVT occurrence in patients with newly diagnosed HCC and that, if confirmed by future studies, it may therefore be worth considering the initiation of thromboprophylaxis in patients with large HCC at diagnosis. Thresholds for initiating such treatment remain to be determined in future studies including all stages of HCC. Furthermore, in patients with HCC, the evolution of PVT seems to be characterized by a much higher risk of progression than in cirrhotic patients without HCC, which seem to be conditioned by the evolution of the tumor itself in the absence of anticoagulant treatment. These results, together with the impact on survival of complete/progressive thrombosis found in this study, suggest that all patients with HCC and PVT should be promptly treated, with the aim of preventing progression of partial thrombosis and recanalizing complete thrombosis. Considering the remarkable progress made in the treatment of HCC, continuously loosening the criteria for curative treatments even in the decompensated stages of cirrhosis, and the ongoing quest for individualization of treatment, these results underline even more the importance of taking into account the presence and evolution of PVT in future studies aimed at re-evaluating the treatment algorithms of this neoplasm, beside the recommendations for prophylaxis/treatment of PVT in these patients.

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