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Management of Portal vein Thrombosis in Cirrhosis

Babu Lal Meena, MD, DM[1] Shiv Kumar Sarin, MD, DM, DSc (Hony.)[1]

[1] Department of Hepatology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi, India

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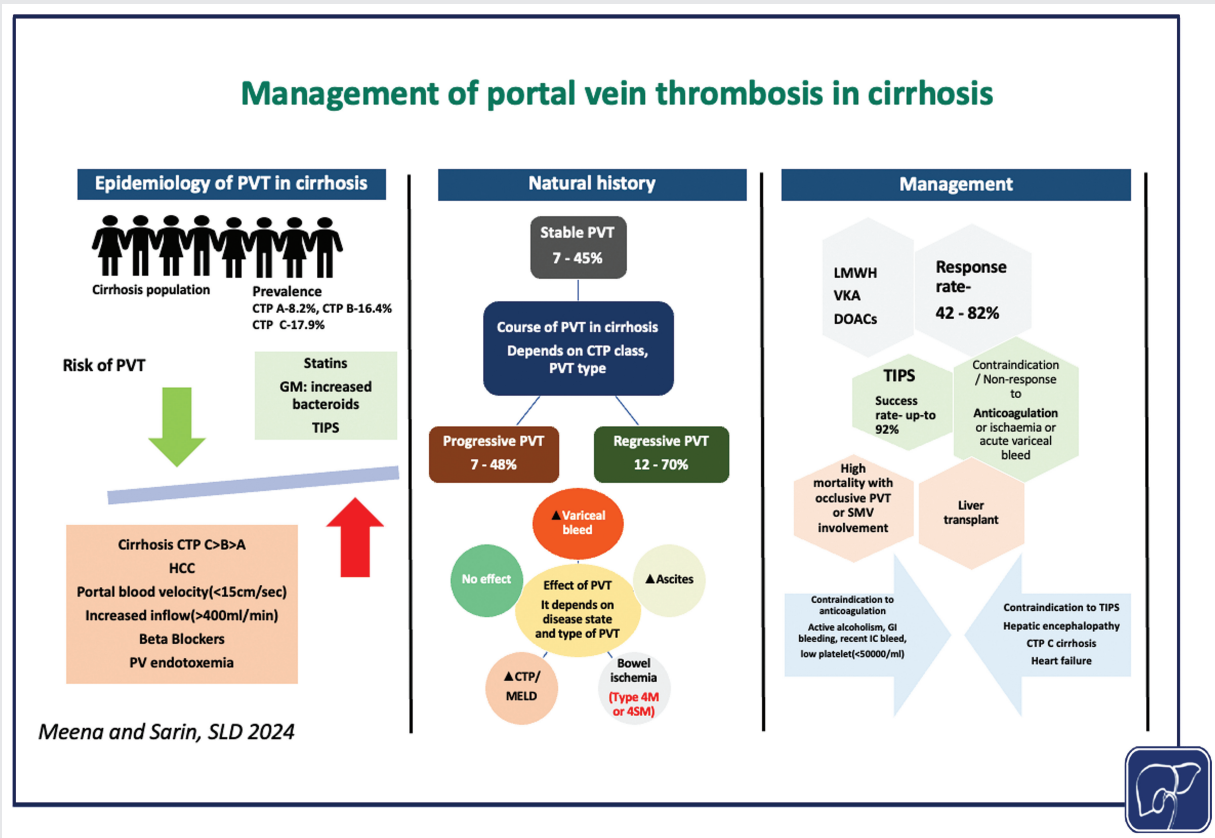
Address for correspondence Shiv Kumar Sarin, MD, DM, DSc (Hony.), Department of Hepatology, Institute of Liver and Biliary Sciences, D-1 Vasant Kunj, New Delhi 110070, India (e-mail: shivsarin@gmail.com; sksarin@ilbs.in).

Graphical Abstract



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Abstract

Portal vein thrombosis (PVT) is one of the common complications of cirrhosis. The incidence of PVT correlates with liver disease severity—higher incidence in patients with Child–Turcotte–Pugh (CTP) C, large spontaneous portosystemic shunts, hepatofugal portal flow, and in the presence of hepatocellular carcinoma. PVT may worsen ascites, increase the risk and poor control of variceal bleeding. The occurrence of PVT may increase morbidity and lower survival after a liver transplant. Using statins prevents the occurrence of PVT, whereas beta-blockers may aggravate its occurrence. Cross-sectional imaging is mandatory for the precise diagnosis and classification of PVT. Symptomatic, occlusive PVT and candidacy for liver transplantation are the main indications for anticoagulation. Vitamin K antagonists, low-molecular-weight heparin, and newer anticoagulants are effective and safe in cirrhosis. Direct-acting oral anticoagulants are agents of choice in early cirrhosis (CTP A, B). The duration of anticoagulant therapy, predictors of response, and management of complications of cirrhosis while on therapy require in-depth knowledge and individualized treatment. Transjugular intrahepatic porto-systemic shunt can be considered in nonresponsive cases or when anticoagulants are contraindicated. This manuscript reviews the latest updated knowledge about managing PVT in cirrhosis.

Keywords

- thrombosis
- EHPVO
- portal hypertension
- anticoagulants
- TIPS

Cirrhosis of the liver is accompanied by thrombocytopenia and altered levels of proteins in the hemostatic pathways. These hemostatic alterations affect both bleeding and thrombotic complications.[1] Apart from the alteration in coagulation, there is also increased portal pressure and the development of collaterals with the advancement of liver disease. This leads to portal venous blood flow becoming sluggish or hepatofugal. Such patients are more prone to develop portal vein thrombosis (PVT).[2]

PVT can be nonneoplastic or neoplastic. The term PVT is generally applied to benign or nonneoplastic thrombosis,[3] while neoplastic thrombosis is called portal vein (PV) invasion, neoplastic occlusion, or tumoral thrombosis. However, many investigators still use the term PVT, even for tumor thrombus in the PV.[4–6]

In the setting of normal liver, acute PVT can lead to the formation of collaterals, termed portal cavernoma. The cavernoma formation results from an acute portal pressure gradient, and the disease entity is recognized as extrahepatic portal venous obstruction (EHPVO).[7] PVT may be partial or complete and may extend to intrahepatic or extrahepatic venous tributaries. In patients with cirrhosis, the thrombosis of PVPV is often chronic, and cavernoma formation does not occur in the presence of existing portal hypertension (no or low-pressure gradient). The term EHPVO is also applied to the PVT in patients with cirrhosis, though this is more often used for patients without cirrhosis.

The prognosis and treatment of PVT largely depends on the rapidity of development, precipitating event, consequent impairment of blood flow and ischemia, type and stage of underlying liver disease, and the individual's genetic predisposition. A few patients with PVT manifest with complications of portal hypertension in the form of ascites and bleeding. PVT can produce technical difficulties during liver transplantation and affect patient survival. Patients with PVT face challenges in management while on anticoagulant therapy. Because of the varied manifestations and associated factors, there is a lack of clarity in the literature about the management of PVT. The present review addresses these issues in managing PVT in the context of cirrhosis and compares it at relevant places with PVT in patients without cirrhosis. The readers are expected to get an updated and focused approach towards the assessment, management, and prevention of PVT.

Contextualization

Incidence and Prevalence of PVT

Based on the autopsy data, the prevalence of PVT in general autopsies is around 1%.[3] An annual incidence of the PVT in cirrhosis ranges from 3 to 17%. The reported 1- and 3-year incidence of PVT in Child A cirrhosis is 8.2 and 7.6%, respectively. In Child B and C cirrhosis, the 1-year risk of PVT is nearly double, around 16.4 and 17.9%.[4,8] The prevalence of PVT rises to 26 to 44% in liver transplant candidates.[9] This difference could partly be due to the advanced nature of the disease, different diagnostic tools, use of different classifications, and available local expertise to manage PVT.

Pathogenesis of PVT in Cirrhosis

Although Virchow's triad was initially described for systemic vascular bed characterized by high pressure and presence of venous valves, it also finds utility for splanchnic vascular bed. The three prerequisite factors are hypercoagulation, loss of endothelial integrity, and venous stasis. According to the triad for venous thrombosis, it is applicable for PVT development.[10] Various systemic and local risk factors need consideration in the pathogenesis of PVT, which are alluded to below.

Systemic Risk Factors

- Hypercoagulable states: cirrhosis is an altered state of hemostasis with increased levels of procoagulant factors such as factor VIII and von Willebrand factor (vWF), and reduced levels of anticoagulant factors, e.g., protein C and S. The relative risk (RR) of venous thromboembolism has been reported to be 1.74 (95% confidence interval [CI]: 1.54–1.95) in cirrhosis compared with patients without liver disease.[11] Most studies have, however, not reported increased prothrombotic proteins in PVT patients. While one study showed a higher prevalence of JAK-2 V617F mutation in PVT,[12] another study involving 271 patients on the wait list for liver transplants did not corroborate it.[13,14]
- Beta-blockers and collateral vessels: Nonselective beta-blockers (NSBBs) are routinely used for prophylaxis of variceal bleeding. They have been reported to increase the risk of development of PVT up to five times (odds ratio [OR]: 4.62, 95% CI: 2.50–8.53; $p < 0.00001$).[15] This effect was primarily due to decreased portal blood flow and velocity using NSBB. The effect was more demonstrable with propranolol than with carvedilol and arkamin. However, the studies included in the meta-analysis were not powered to study the development of PVT in cirrhosis[4] and more prospective studies are required.
  The presence of portosystemic collaterals is also associated with development of PVT. A study of 108 patients with medium to large varices followed up for 19 months showed a significantly higher risk of PVT development than small varices (hazard ratio [HR]: 5.67; 95% CI: 1.49–21.63; $p = 0.011$).[16]
- Etiology of cirrhosis: there are limited data on etiology-specific incidence of PVT. The PVT risk is higher in patients with nonalcoholic fatty liver disease (NAFLD). A meta-analysis of five observational studies which included 225,571 patients, of which 26,840 (11.9%) had NAFLD, showed that the prevalence of PVT was 8.5%, and the risk was higher in NAFLD patients (OR: 1.34, 100% CI: 1.07–1.67, $p < 0{,}01$) compared with other etiologies.[17] Mandorfer et al compared hepatitis C virus (HCV)-cured ($n = 354$) versus on-therapy ($n = 179$) patients and showed that PVT occurrence was higher in patients on-therapy (4.5% over 42 months) than HCV-cured patients (2.8% over 37 months), though the difference was not significant.[18] The role of other etiological factors needs to be studied.
- Inflammatory markers, cytokinemia, and hemostatic factors: the role of inflammatory factors in the causation of PVT is debatable. Violi and Ferro have shown that high interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and platelet activation factors like p-selectin and sCD40L predispose to the development of PVT.[19] However, a study by Carnevale et al showed that none of the inflammatory (cell-free DNA, MPO-DNA, IL-6, and TNF-alpha, C-reactive protein) or homeostasis markers (sPselectin, sCD40L, Fragment 1 + 2, FVIIa, XIIa, D-dimer, and PAP) reliably predict the development of PVT.[20] Lower levels of AT-III are associated with the development of PVT and predict poor outcome.[21]

Local Risk Factors

- PV morphology: in cirrhosis, there is increased resistance to portal blood flow due to stellate cell activation, fibrosis, and low-grade endotoxemia.[20] Compliance of the PV is compromised due to the thickening of its walls. Analysis of explant of 76 patients by Driever et al showed thickened and fibrotic tunica intima of the PV covered with fibrin-rich thrombi in a proportion of cases.[22] Hence, these anatomic and hemodynamic modulations in the PV can predispose and help the progression of PVT in cirrhosis.
- Portal endotoxemia: the translocation of bacteria and bacterial toxins leads to local inflammation and endotoxemia, promoting a local hypercoagulable state in the PV. Higher lipopolysaccharide (LPS), vWF, and factor-VIII levels are seen in the portal than in systemic circulation.[23] Increased local endotoxemia causes increased platelet activation in the PV. High LPS levels cause increased endothelial secretion of factor VIII, decreased thrombomodulin activity, and increased platelet activation, leading to a hypercoagulable state.[20,24,25] However, definitive studies to prove the role of increased local inflammation in the development of PVT are lacking.
- Altered portal hemodynamics: reduced and sluggish portal flow <15 cm/s is associated with high risk of PVT development (91.7% vs. 19.7%),[26] and can predict with sensitivity and specificity of 91.2 and 85.3%, respectively.[27] On the other hand, a prospective study by Maruyama et al showed high portal blood flow (>400 mL/min) with a velocity of >10 cm/s, also as a risk factor for PVT.[28]

Predictive Model of PVT Development in Cirrhosis

A nomogram model including PV diameter, splenic vein diameter, body mass index, and platelet count for development of PVT in cirrhosis after splenectomy has been proposed. Considering these variables, the nomogram has high reliability with an area under the receiver operating curve of 0.887.[29] Another model used serum albumin, D-dimer level, PV diameter, splenectomy, and presence of esophageal and gastric varices with an area under the curve of 0.806.[30] A PVT risk index model is also proposed in decompensated cirrhosis, showing a value of 2.6 has a 94% negative predictive value and a value of 4.6 has an 85% positive predictive value for PVT occurrence.[31]

Diagnosis of PVT in Cirrhosis

Doppler ultrasound is the first imaging method to screen and diagnose PVT in cirrhosis; it detects flow velocity in the PV and in portosystemic shunts. An acute thrombus appears as a hypo- or isoechoic lesion inside the PV lumen, along with PV dilatation and absence or marked reduction of the blood flow. A chronic thrombus appears as a heterogenous hyperechoic lesion.[32] The sensitivity and specificity of Doppler ultrasound in diagnosing complete PVT are around 92 and 89%, respectively. The sensitivity is lower (14–50%) for partial PVT.[33] Contrast-enhanced ultrasound improves the

diagnostic yield of partial PVT up to 95%.[34] Ascites lower the sensitivity of ultrasound-based imaging to detect the PVT.

Cross-sectional imaging is the method of choice for diagnosing and classifying PVT in cirrhosis. The computed tomography (CT) findings of the PVT include increased attenuation in the PV in noncontrast phases without enhancement on intravenous contrast administration. Hepatic parenchyma in PVT shows increased hepatic enhancement in the arterial and decreased in the portal venous phase due to attenuated blood supply by the PV.[35,36] The PV may be dilated, and edge enhancement of the vein may be seen on CT and magnetic resonance imaging (MRI) due to the blood bypassing the thrombus.

Nonneoplastic thrombus of the PV is commonly seen in cirrhosis with hepatocellular carcinoma (HCC) and portends a poor prognosis.[3] It needs to be differentiated from neoplastic thrombus. Features of the neoplastic PVT in the setting of HCC adjacent to the PV include enhancement of the thrombus and thread and streak sign (blood-filled spaces; both artery and vein) due to arterial supply to the tumor in the PV.[37] Tublin et al showed PV diameter of more than 23 mm in the presence of enhancing thrombus as having good sensitivity (86%) and specificity (100%) for diagnosing tumoral thrombus.[38] A-VENA diagnostic criteria (alfa fetoprotein >1,000 ng/dL; venous expansion; thrombus enhancement; neovascularity; and PVT adjacent to HCC) have been shown to have 100% sensitivity and 93.6% specificity to diagnose neoplastic PVT.[39]

Classification of Portal Vein Thrombosis

Precise diagnosis and classification are essential to guide the medical management of PVT and the reconstruction of PV in liver transplantation. Yerdel's classification indicates the anatomical location of the thrombus and signifies its importance in surgically reconstructing a physiological portal inflow.[40] Several other classifications of PVT based on anatomical location, extension, and degree of occlusion have been proposed.[41,42] Baveno VII adopted a classification based on the American Association for the Study of Liver Diseases practice guidance.[42] The outcome of the PVT is based on anatomical location, extent, and underlying liver disease. Attempts are being made to further improvise it by adding newer data and achieving better consensus. A group of international experts proposed a more clinically relevant functional-anatomic classification, including the site of thrombus, duration, degree and extent of thrombosis, presence of symptoms, and presence and stage of liver disease.[43,44] More consensual and prospective studies are required to prove the clinical relevance of published classifications.

Management of Portal Vein Thrombosis

Understanding the natural history of PVT and making proper patient selection are essential for proper management of PVT. It needs to be emphasized that every patient with PVT does not require anticoagulant therapy or intervention. Therefore, it is important to be conversant with the natural history of PVT.

Natural history of PVT

The PVT can regress, remain stable, or progress depending on the disease state and portal hemodynamics.

Regression

Spontaneous recanalization of the PVT can occur in cirrhotic populations especially those with incomplete occlusion. Recent studies and meta-analyses of mainly incomplete PVT and early cirrhosis (Child–Turcotte–Pugh [CTP] A) using mainly ultrasound assessments showed that 48% of the patients have progression of the PVT, and recanalization is seen in up to 12 to 70% of the patients.[45,46] Recanalization rates range from 5 to 19%, in decompensated cirrhosis.[47,48] A study conducted by Xu et al showed ΔMELD (change in model for end-stage liver disease) score on follow-up (OR = 0.714; 95% CI: 0.512–0.995) as an independent predictor of the improvement of PVT on univariate analysis.[49]

Progression

Progression of the thrombosis is common in patients with advanced-stage and decompensated liver disease and those with mean platelet volume (MPV) involvement.[47,48] Naymagon et al observed that PVT in the left or right branch was associated with a lower extension rate than MPV involving the trunk.[50]

Stable Disease

The PVT may remain stable and cause no adverse effects on the portal hypertensive symptoms. Luca et al found that PVT remained stable in 7% of the patients over a 27-month follow-up.[51] However, a prospective study by Maruyama et al showed that PVT remained stable in 45.2% of the patients.[28]

Effect of PVT on Portal Hypertension and Complications in Cirrhosis

Morbidity and Mortality

The development and progression of PVT, especially if complete, would exert a further increase in resistance to portal blood flow, resulting in worsening of portal hypertension proximal to the thrombus. In contrast, in patients with advanced-stage cirrhosis where portal blood flow is low, PVT may result in fewer consequences. A large retrospective cohort showed that cirrhosis patients with PVT require more admissions due to gastrointestinal bleed as compared to cirrhosis without PVT.[52] PVT in patients with variceal bleeding is an independent predictor of failure to control acute variceal bleeding, higher re-bleeding, and short-term mortality.[53] Maruyama et al showed progressive PVT to be associated with worsening ascites but with no effect on variceal bleeding or mortality.[28] Similar findings were reported in a large retrospective cohort ($n = 2,597$) of patients with early-stage cirrhosis, where PVT was the consequence of splenectomy or partial splenic artery embolization; the 1-year mortality was, however, not affected by PVT.[52] The basis of such heterogeneous data is due to the selection of different cohorts of patients. A recent

prospective study of HCC with nonneoplastic PVT showed that complete or progressive PVT is associated with nonresponse to HCC treatment and lowers overall survival.[3]

Liver Transplantation in Cirrhosis with PVT

PVT in cirrhosis affects the outcome of individuals undergoing liver transplantation in the form of compromised graft and patient survival. Moreover, these patients experience complex surgery during the transplantation. Meta-analysis of the studies with PVT and cirrhosis undergoing liver transplantation showed that the presence of complete PVT limits survival both at 30 days and 1 year after liver transplantation; complete PVT causes a 5.65-fold increased risk of death related to surgical complications.[54] Moreover, in the postoperative period, early posttransplant recurrence of the thrombosis occurred in 13% of the patients when no anticoagulation was used. Hence, anticoagulation should be continued in the postoperative period.[55] Meta-analysis of liver transplantation in the presence of Yerdel grade 4 PVT has shown postoperative mortality of up to 27%.[56] Preoperative PVT, specially grade 3 and 4, is associated with increased mortality (HR: 1.45, 95% CI: 1.27–1.65) and graft loss (HR: 1.58, 95% CI: 1.34–1.85).[57]

Management of PVT in Cirrhosis

Screening for PVT is recommended in all patients who are potential liver transplant candidates at the time of screening for HCC. Also, patients with cirrhosis who develop symptoms in the form of fever, pain, recent onset or worsened ascites, or bleeding need evaluation for PVT.

Prevention of PVT in Cirrhosis

Management of PVT should start from the prevention of the development of PVT. Currently, there are three main drugs which need attention while treating an advanced cirrhosis patient: NSBBs, statins, and prophylactic anticoagulants. Varied results were reported with the use of NSBB. While some studies have shown reduced incidence, others have shown increased incidence of development of PVT with NSBB usage.[15,16] The fact that NSBB decreases portal blood flow in cirrhosis patients, in whom the flow may already be sluggish, predisposes to the risk of development of PVT. Nevertheless, it would be prudent to serially monitor the development of PVT in patients on NSBB therapy.

The use of statins may reduce the incidence of the development of PVT, as shown in a study in 2,785 cirrhosis patients.[58] However, there is a need for prospective studies to suggest the benefits of statin use for the prevention of PVT. Modulation of the gut microbiota, especially *Bacteroides*, has also been found to be a promising therapeutic approach to reduce the progression of PVT in cirrhosis.[59]

Prophylactic anticoagulant therapy is an attractive proposition to prevent development of PVT in advanced cirrhosis patients. Villa et al performed a randomized controlled trial (RCT) in patients with CTP score 7 to 10, using prophylactic enoxaparin for 48 weeks, and demonstrated that none of the patients developed PVT. Patients receiving enoxaparin faced fewer decompensating events and better survived.[60]

Goals of Treatment

The goals of treatment of PVT should be to restore the patency of the PV, prevent progression of thrombosis, enhance hepatic blood flow and perfusion, lower portal pressure gradient, and prevent portal hypertensive complications in the form of bleeding and worsening of the ascites. The choice of therapy should be determined by the grade of PVT, symptoms, possibility of recanalization, stage of liver disease, cost and duration of the treatment, and available expertise for management of patients on anticoagulant therapy. ►**Fig. 1** depicts an overview of the management of PVT in cirrhosis.

Watch-and-Treat Strategy

Some studies propose that elective anticoagulation could be deferred in asymptomatic patients or nontransplant candidates, given the possibility of spontaneous recanalization. Spontaneous recanalization has been reported in up to 40% of Child A and B patients with PVT.[61] A study by Campoverde-Espinoza et al, including 553 patients with cirrhosis with PVT, found that spontaneous recanalization can occur in up to 89% of the patients [62]. Nonprogression of PVT was reported in 21 studies with 1,160 patients. The pooled rate of PVT regression in cirrhosis was 29.3% (95% CI: 20.9–37.7; $I^2 = 91.9\%$), and the rate of complete recanalization was 10.4% (95% CI: 5.0–15.8; $I^2 = 84.1\%$). The prevalence of stable PVT was reported in 19 studies with 875 patients with a pooled event rate of 44.6% (95% CI: 34.4–54.7; $I^2 = 91.0\%$).[63] Hence, the watch-and-treat approach can be used in asymptomatic patients with incomplete PV obstruction, early-stage cirrhosis, or patients with a high risk of anticoagulation-related bleeding. During this waiting period, a complete prothrombotic workup of the patient for thrombotic events is advisable.

Treatment of PVT in Cirrhosis

Treatment for PVT in cirrhosis should undoubtedly be offered to patients with symptomatic PVT, recent-onset PVT (higher chance of recanalization), PVT with >50% occlusion of the portal venous trunk with or without involvement of superior mesenteric vein, or in liver transplant candidates. In other words, all patients with Type 2 and 3 PVT who have occlusive thrombus of recent origin need anticoagulation. Patients with PVT with involvement of the superior mesenteric vein also need treatment even with <50% occlusion.[42]

Successful treatment of PVT restores the PV patency, decreases portal and variceal pressure, and may reduce the risk of further decompensation.[64–67] A liver disease severity-matched study showed patients who achieved PV recanalization (partial or complete) had better survival than those with stable or progressive thrombosis. This effect was especially enhanced in patients with higher CTP class (B and C vs. A).[68] A meta-analysis by Wang et al, which included 33 studies and 1,696 patients, showed that anticoagulation not only improves PV recanalization (RR = 2.61; 95% CI:

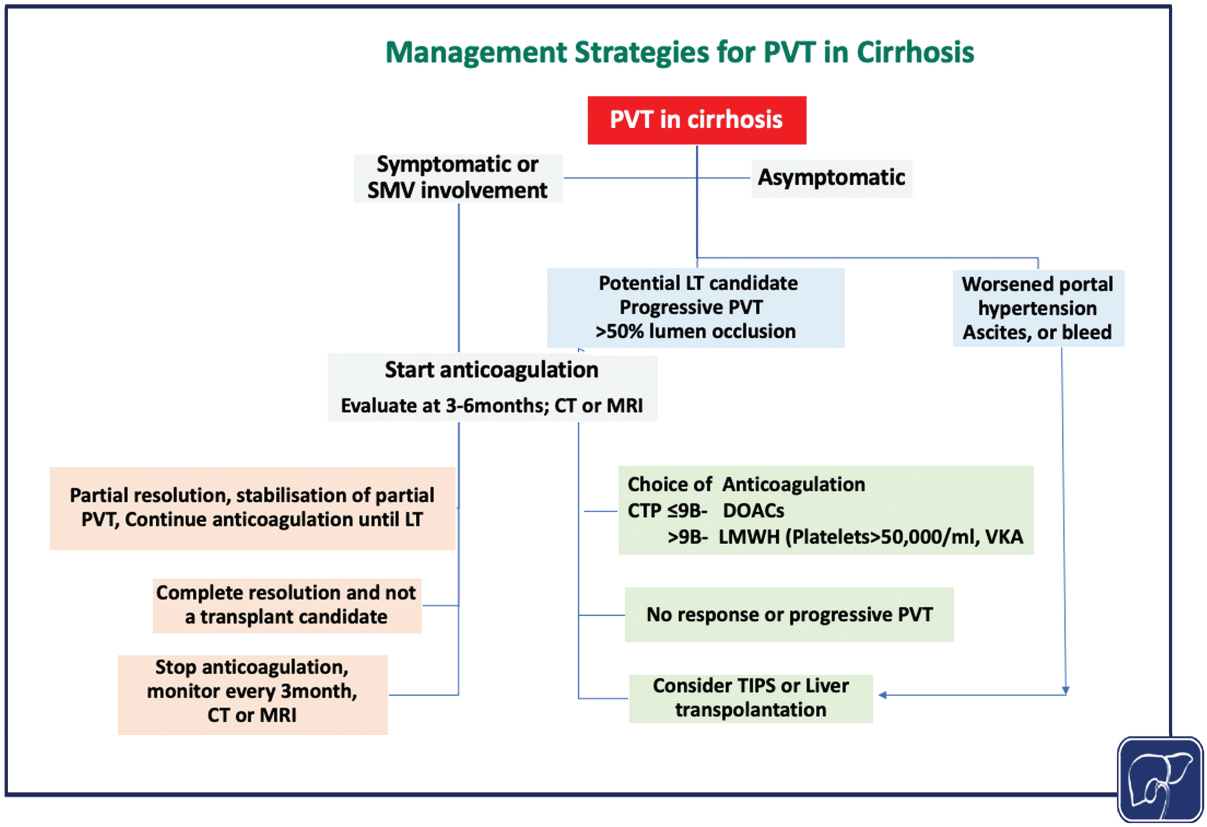

Fig. 1 An overview of the management of PVT in cirrhosis. PVT, portal vein thrombosis.

1.99–3.43; $p < 0.00001$) but it also gave a survival benefit (RR = 1.11; 95% CI: 1.03–1.21; $p = 0.01$).[69] Some studies have reported improved survival in cirrhosis patients with anticoagulation irrespective of clot resolution and even in the absence of PVT.[66,70] A recent individual patient data meta-analysis comparing anticoagulation versus no anticoagulation showed improved all-cause mortality and a reduction in liver-related mortality. The recanalization rates were higher in the anticoagulation group. Survival with anticoagulation therapy is irrespective of recanalization, but nonportal hypertensive bleeding events were higher in the anticoagulation group.[71] However, readers should interpret these findings cautiously due to potential biases inherent in meta-analyses, such as varying study designs and patient populations. Further RCTs are necessary to validate these results and establish standardized treatment protocols.

The choice of the treatment modality and the anticoagulant agent for PVT in cirrhosis is variable and evolving. The current options broadly include thrombolytic therapy, anticoagulants, and placement of transjugular intrahepatic porto-systemic shunt (TIPS).

Thrombolysis

Systemic and local thrombolysis have been attempted in patients with cirrhosis and PVT. (1) *Systemic thrombolysis*: limited small sample size studies evaluated role of systemic thrombolysis in PVT. A pilot study by De Santis et al included nine cirrhosis patients with systemic thrombolysis (using continuous recombinant tissue plasminogen activator infusion combined with low-molecular-weight heparin [LMWH]). It showed complete resolution in four and partial in another four patients.[64] In another study, using streptokinase ($n = 3$) and recombinant tissue plasminogen activator ($n = 23$) achieved recanalization in 10 of 28 cirrhosis patients with PVT.[72] (2) *Local thrombolysis*: TIPS placement followed by local thrombolysis has also been found to be useful.[73,74] A study by Jiang et al compared the efficacy of local thrombolysis using urokinase through superior mesenteric artery (SMA) with TIPS placement in 40 patients. They found that the SMA thrombolysis group achieved a higher recanalization rate (85%) than the TIPS group (70%).[75] Although these studies showed good efficacy and safety of thrombolysis in cirrhosis with PVT, the risks of serious complications such as life-threatening hemorrhage should be weighed against the likely benefits on a case-to-case basis. With the wider availability of TIPS expertise, systemic thrombolysis should be used selectively and only in expert hands.

Anticoagulation

Several cohort studies have investigated the efficacy and safety of anticoagulation for the treatment of PVT in patients with cirrhosis. The broad goal is the recanalization of the PV and prevention of further thrombus progression. Recanalization of the PV is associated with a significantly reduced risk of portal hypertensive complications.

A pooled analysis of 353 patients showed significant recanalization with anticoagulant therapy (LMWH and warfarin) as compared to no treatment (71% vs. 42%, $p < 0.0001$), without substantial increase in bleeding complications.[45] In an observational study, vitamin K antagonists (VKAs) have been shown to achieve recanalization of the PVT in event-free and transplant-free survival, with no bleeding complications.[66] All these studies showed an improvement in the outcome of patients who achieved complete resolution of the thrombus. A large registry-based prospective cohort of patients with extensive PVT (including splanchnic venous thrombosis) demonstrated a lower bleeding rate in patients receiving anticoagulation.[76] A meta-analysis, which included 1,696 cirrhosis patients with PVT, showed anticoagulation to improve recanalization and better survival, with no increased risk of portal hypertensive bleed compared to no anticoagulation therapy.[69]

Among several published cohorts, pretreatment predictive factors of anticoagulant treatment efficacy were analyzed in six studies, with better recanalization rates with early anticoagulation. The benefit of anticoagulation was shown in a single-center study when anticoagulation was started within 2 weeks from the imaging diagnosis.[67] On the other hand, chronic thrombosis (>6 months duration) and advanced liver disease are associated with poor response to treatment.[77] Recanalization of PVT is more likely to happen in patients with partial PVT. Complete PVT has a 22% lower chance of recanalization than incomplete PVT.[41] Involvement of mesenteric veins and/or the severity of baseline liver disease have also been proposed as possible predictive factors.[78]

The mean time to recanalization ranges from 5.5 to 8 months; in most cases, recanalization can occur within a year. The duration of the anticoagulation depends on the resolution of the thrombus and the risk of recurrence. Most guidelines suggest a minimum treatment course of 6 months.[34,79] However, some suggest continued anticoagulation in the patients waiting for liver transplantation even after the resolution of the thrombus.[8] The duration of anticoagulation after the thrombus' resolution, especially in nontransplant patients, remains unclear. Those with inherited prothrombotic disposition may be advised to continue anticoagulation. Recurrence of thrombosis was seen in 17 of 64 (26%) noncirrhotic patients; the cumulative incidence of recurrence reached 34% at 10 years. High FVIII (>150%) levels could predict thrombosis recurrence.[80]

Choice of Anticoagulation

Conventional anticoagulation options are VKAs and LMWH. Direct oral anticoagulants (DOACs) are relatively new for patients with cirrhosis. ►**Table 1** compares different anticoagulants in patients with cirrhosis and PVT.

Table 1 Comparison of different anticoagulants in patients with cirrhosis and PVT[11,92,112,113]

Variable	VKA	LMWH	DOACs
Mechanism of action	Inhibit factor II, VII, IX, and X	Inhibit IIa and Xa	Inhibit IIa[a] and Xa[b, c, d]
Dose	Based on INR value	Twice daily	Twice daily, *except edoxaban (once daily dose)*
Excretion (%)	Renal > biliary (92%, 8%)	Renal, biliary; 40 and 60%	Renal: 80[a], 27[b], 66[c], and 30[d] Biliary: 20[a], 73[b], and 34[c]
Initiation	Overlap with LMWH	Twice a day	[a]Overlap with LMWH after 5 days [b]10 mg twice a day for 7 days [c]15 mg twice a day for 3 weeks [d]*On next schedule dose of LMWH*
Standard dose	Target INR: 1.9–3.2	Enoxaparin 1 mg/kg twice a day or 1.5 mg/kg once a day	[a]150 mg twice a day [b]5 mg twice a day from day 8 [c]20 mg once a day from day 21 [d] *> 60 kg–60 mg once a day, <60 kg–30 mg/day*
Dose reduction	–	If CrCl < 30 mL/min, contraindicated if CrCl < 15 mL/min	[a]Age >80 years or calcium channel blocker: 110 mg twice a day [b]2.5 mg twice a day form 6 months onwards [c]10 mg once a day from 6 months onwards [d]*Crcl 15–50 mL/min, 30 mg a day*
INR monitoring	Yes	No	No
Liver disease adjustment	Yes	Yes	[a,b]Safe up to CTP B [c]Contraindicated in CTP B/C

Abbreviations: CrCl, creatinine clearance; CTP, Child–Turcotte–Pugh; DOACs, direct oral anticoagulants; INR, international normalized ratio; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.
[a]Dabigatran.
[b]Apixaban.
[c]Rivaroxaban.
[d]Edoxaban.

Low-Molecular-Weight Heparin

Generally, LMWH, given twice daily, is the initial treatment in patients with acute PVT. In a recent study of LMWH, a single dose of 1.5 mg/kg/day was found to be equally efficacious in recanalization compared to twice-a-day dose of 1 mg/kg/day, with fewer bleeding complications.[81] A challenge in cirrhosis patients is low platelet counts. A lower dose of LMWH (70% of the recommended) in patients with low platelet counts (<50,000/dL) showed equal efficacy of anticoagulation.[82] Anti-FXa assay can give an idea of the plasma LMWH levels and help monitor therapy. However, the innate anti-Xa activity can inadvertently lead to higher-than-expected anticoagulant levels, which can cause bleeding-related complications, particularly in higher CTP class cirrhosis.[65,66,83] Therefore, anti-Xa activity assays cannot be used to guide the dose of LMWH in patients with cirrhosis. Dose adjustment for LMWH is required in renal dysfunction.

Fondaparinux selectively binds to antithrombin and causes inhibition of activated factor X. It is more efficacious than LMWH.[66] As fondaparinux does not bind with platelet factor IV, the risk of heparin-induced thrombocytopenia is rare.[66] LMWH remains the drug of first choice in cirrhosis patients with acute/recent PVT with platelet counts >50,000/cmm. It can be safely given for 6 months or more, per the requirements.

Vitamin K Antagonists

These drugs have been in use as an anticoagulant for a long time. They have been found safe and effective in patients with cirrhosis as well.[84] A recent multicenter RCT showed the efficacy and safety of warfarin as the anticoagulation therapy in cirrhosis patients with nonsymptomatic PVT. The study included 64 patients and showed recanalization to be significantly higher in the anticoagulation group than in the untreated group (76.7% vs. 32.4%). No difference in bleeding and mortality was seen between the groups. Furthermore, worsening of ascites was observed in the control group. Nearly a third (34.4%) of patients achieved complete recanalization 6 months after the commencement of anticoagulation, supporting the idea that extending anticoagulation duration could offer potential benefits without increasing the likelihood of severe bleeding events.[85]

While the cost of VKA may be lower, their use in cirrhosis patients requires attention; first, maintaining a narrow therapeutic window of international normalized ratio (INR) 2 to 3 is difficult as INR is already deranged in patients with cirrhosis. The compliance of repeated monitoring and dose adjustments to maintain INR in advanced cirrhosis patients is challenging. Further, decreased protein C and factor VII levels in cirrhosis need to be accounted for while giving these agents. Also, the management of variceal bleeding or the need for endotherapies poses challenges for patients on VKA therapy.

No difference in the bleeding risk between LMWH and VKA was reported in a meta-analysis.[45] Bridge therapy of LMWH with VKA is a popular modality of anticoagulation and may be more efficacious.[77,86,87]

Direct Oral Anticoagulants

Dabigatran, rivaroxaban, apixaban, and edoxaban are the newer anticoagulants directly acting on the catalytic site of FXa or thrombin.[88] The new agents, DOACs, are equally effective as VKA and LMWH. Safety and efficacy studies involving direct anticoagulants in cirrhosis with PVT found no increased risk of bleeding complications and reasonable recanalization rates.[89] Reports suggest that DOACs have similar success rates compared with traditional anticoagulants in cirrhosis patients with PVT without an increase in adverse events or rates of discontinuation.[90,91] Hum et al compared VKA and DOACs in patients with cirrhosis and PVT. They observed significantly fewer major bleeding episodes in the DOAC group than VKAs (4% vs. 28%, $p = 0.03$).[92] For long-term anticoagulation in thrombotic disorders, DOACs are a safer alternative to VKAs. DOACs have been reported to be safe in Child A and B cirrhosis and can achieve significant recanalization of vascular thrombosis.[91] The safety of DOACs in CTP class C needs to be studied more.

Limited data showed the safety and efficacy of DOAC in cirrhosis with PVT. A retrospective study by Zhou et al included 94 patients and compared rivaroxaban and dabigatran. The complete and partial resolution rate was 75 and 79% in the rivaroxaban and dabigatran groups ($p = $ ns), respectively. Both groups showed improvement in the CTP score from baseline. Major bleeding was reported in 6% of rivaroxaban and 2% in dabigatran ($p = $ ns), and minor bleeding in 12% in each group.[93] A study of sequential therapy of danaparoid sodium followed by edoxaban or warfarin for 6 months showed edoxaban reduces the total volume of thrombus significantly as compared to warfarin, which was associated with an increased volume of thrombus.[94]

Invasive procedures can be safely performed with proper optimization of DOAC therapy. With the advent of reversal agents for certain DOACs (idarucizumab for dabigatran and andexanet alfa for rivaroxaban and apixaban), the potential for use of these agents has increased. A meta-analysis showed the successful use of these reversal agents in preoperative optimization with a good safety profile.[95,96]

Current evidence shows that DOACs have at least the same efficacy as VKAs and comparable adverse events but with ease of administration and no need for monitoring INR. They are not inferior to the LMWH as well. More studies are needed to identify the specific role of DOACs and the most appropriate one for the treatment of PVT in patients with cirrhosis. Underlying liver dysfunction severely affects the pharmacokinetics of DOACs because of plasmatic binding protein, cytochrome p450-mediated metabolism, biliary excretion, and renal clearance.[97] For this reason, the Food and Drug Administration and European Medicines Agency do not recommend using these agents in patients with CTP C cirrhosis, while they recommend caution in patients with CTP B cirrhosis and no restrictions for CTP A cirrhosis. However, there are no extensive data on safety of DOACs in these populations. DOACs are not recommended in CTP C cirrhosis; correspondingly, there is a paucity of literature reflecting safety and efficacy in this

subpopulation. In a recent meta-analysis, rivaroxaban has been classified as "unsafe" in CTP B and C based on significant pharmacokinetic alterations. Due to lack of data, apixaban, dabigatran, and edoxaban were classified as "unknown" for CTP C.[98]

Complications of Anticoagulation

Anticoagulation has a similar safety profile in cirrhosis as compared to noncirrhosis. Patients with severe thrombocytopenia, active alcoholism, recent variceal bleeding, or recent intracranial hemorrhage are not safe candidates for anticoagulation. According to a meta-analysis by Loffredo et al, which included four studies describing the rate of acute variceal bleeding, the risk of portal hypertensive bleeding was actually reduced in the anticoagulated group, which was confirmed in two subsequent studies.[45,66,68] Patients with cirrhosis receiving anticoagulation for indications other than PVT seem to have a higher risk of variceal bleeding than matched cohorts of nonanticoagulated patients with cirrhosis.[99,100] In patients treated with VKA, a study showed that patients with a platelet count <50,000/μL had a greater bleeding risk.[66] However, this cut-off value has yet to be confirmed in other studies. In settings other than PVT in cirrhosis, it has been proposed to reduce the dose of anticoagulant (i.e., LMWH) in patients with a platelet count below 50,000/μL and to consider discontinuation in patients with platelet counts below 30,000/μL.[101] Patients with low platelet count (<50,000/μL) and high-risk varices are not suitable to start upfront anticoagulation. Portal hemodynamics are different in patients with PVT, and these patients are at high risk of bleeding complications. Hence, the management of esophageal varices should follow the guidelines.[102,103] In patients with high-risk large esophageal varices, prophylactic beta-blocker treatment is to be started simultaneously with anticoagulation.[42] Small sample size studies showed no increased risk of ulcer bleed in the presence of anticoagulation. Hence, band ligation can be performed without the need for peri-procedure withdrawal of anticoagulation.[104–106] More data are required to formulate guidance on the use of anticoagulation therapy for advanced cirrhosis patients with PVT. ►**Table 2** shows the safety and efficacy of anticoagulation therapy in cirrhosis.

Endovascular Therapies

TIPS can be performed in patients with PVT, though this may require expertise. The injection of TIPS can result in a higher success rate and instant recanalization. In patients with portal cavernoma, modified trans-splenic or transhepatic approaches can achieve PV recanalization. In a series of 61 patients with cirrhosis and chronic PVT, TIPS insertion was successful in 98%, with a 92% patency rate at a median follow-up of 19.2 months. TIPS placement did not affect the posttransplant outcomes; a high proportion received favorable end-to-end anastomosis with 82% 5-year survival.[107] TIPS stenosis (22%) and transient hepatic encephalopathy (18%) were the most common issues faced after the intervention.[108] In cases of very extensive PV

Table 2 Safety and efficacy of anticoagulation therapy for PVT in cirrhosis

Study (author and ref.)	Methodology	Intervention	Success rate	Complications (bleeding)	Comment
Cui et al[113]	Randomized trial, $n = 65$, cirrhotic with PVT	Two groups, enoxaparin 1 mg/kg twice a day or 1.5 mg/kg once a day	Recanalization: 78.5% over 6 months of anticoagulation, no difference in groups	No portal hypertensive bleed	Minor nonvariceal bleeding occurred. Injection site hemorrhage, epistaxis, and hematuria.
Chen et al[86]	Retrospective analysis, $n = 66$	Warfarin, $n = 30$ No treatment, $n = 36$	Improved in 68.2% Stable in 18.2%, progressed in 13.6%	–	Warfarin improves the advanced PVT as compared to no treatment
Hum et al[92]	Retrospective study Cirrhosis with PVT, $n = 45$	DOACs, $n = 27$ LMWH or VKA, $n = 18$	Recanalization rates not reported	Major bleeding in DOACs: 4% VKA or LMWH: 28%	Similar total bleeding episodes
Loffredo et al[45]	Meta-analysis, 8 studies, 353 cirrhotic patients with PVT	LMWH or warfarin vs. no anticoagulation	72 vs. 42%	11% on both groups	High recanalization as compared to no treatment, no difference in bleeding rates
La Mura et al[66]	Retrospective, $n = 63$, cirrhotic patients with PVT	VKA	Total response: 75%, complete response: 50%	Minor: 29% Major: 24%	Bleeding episodes are related to portal hypertension
Bianchini et al[104]	Prospective analysis, $n = 265$, 553 EVL.		–	LMWH: 3.8% No LMWH: 1.6%	No increased risk of bleed after EVL with LMWH

Table 2 (*Continued*)

Study (author and ref.)	Methodology	Intervention	Success rate	Complications (bleeding)	Comment
	4 week risk of bleeding after prophylactic band ligation	169 EVL in 80 patients on LMWH vs. 384 EVL in 185 patients with no LMWH			
Ai et al[89]	Prospective cohort study, $n = 80$, cirrhosis with PVT	$n = 40$, rivaroxaban or dabigatran $n = 40$, no anticoagulation	Higher recanalization (28.5%) and improved portal velocity in the DOAC group	No difference	Higher success rate, and no difference in bleeding-related complications
Zhou et al[93]	Retrospective study, $n = 94$	Dabigatran, $n = 52$ Rivaroxaban, $n = 42$	Complete recanalization: 75%, partial: 79% No difference in between the groups	No difference	Similar efficacy and safety profile
Lu et al[85]	Multicentric randomized trial, $n = 64$, cirrhosis with PVT	Warfarin vs. no anticoagulation	Recanalization rate: warfarin: 76.7%, no anticoagulation: 32.4%	No difference in bleeding, worsened ascites in control	Anticoagulation improves PVT and prevents further worsening in the form of ascites.

Abbreviations: DOACs, direct oral anticoagulants; EVL, endoscopic variceal ligation; LMWH, low-molecular-weight heparin; PVT, portal vein thrombosis; VKA, vitamin K antagonists.

thrombus, mechanical thrombolysis during the TIPS procedure may help to achieve PV recanalization.[109]

In another meta-analysis, TIPS reduced clot burden with partial recanalization in 84% of patients and with complete recanalization in 73%.[110] Overall, 95% of patients with complete recanalization after TIPS maintained PV patency.[111] Some concerns with TIPS remain: its invasive nature, need for technical expertise, high cost, and utility in compensated cirrhosis. As nearly similar benefits can be achieved by anticoagulation, most people prefer drugs over TIPS. Studies comparing TIPS and anticoagulants in patients of cirrhosis with PVT are not available. TIPS can be beneficial in a select group of patients who have ascites or high-risk varices.[77] Referral to centers with multidisciplinary expertise in this area is usually warranted. Anticoagulation remains the mainstay of treatment in PVT.

Stopping Rule of Anticoagulation

Patients with complete recanalization and prospective liver transplantation should continue the anticoagulation indefinitely till the transplant and in postoperative period, as there is a high risk for PVT after liver transplantation. Patients who are not transplant candidates and have confirmed recanalization can stop the treatment with 3- to 6-month imaging monitoring in the form of a CT scan or MRI.[43,112] Patients who have prothrombotic genetic profiles do require life-long anticoagulant therapy.

Follow-Up

In case of incomplete PVT, monitoring with a repeat CT scan should be done every 3 to 6 months. TIPS placement can be considered in patients who do not respond to anticoagulation for 6 months, in the presence of variceal hemorrhage, challenging to treat ascites, or contraindications for the anticoagulation. Patients with complete PVT, symptomatic PVT, or involvement of superior mesenteric vein certainly merit treatment. Anticoagulation can be stopped after complete recanalization of the PV, with a follow-up every 3 to 6 months with cross-sectional imaging. In patients with existing procoagulant states, anticoagulants should be continued for life. Similarly, in patients listed for liver transplantation, anticoagulation should be continued until the posttransplant period.

Perspectives and Research Priorities

Setting up research priorities in PVT within the context of cirrhosis is crucial due to existing gaps in knowledge and lack of clear guidance for clinical practice. A clear understanding of the natural history of PVT in a large cohort of cirrhosis patients belonging to different stages of cirrhosis is needed to determine the development and progression of thrombosis and its impact on disease outcomes. Validated risk prediction models are required to identify individuals at high risk of developing PVT. Additionally, there is a need for a simple and universally acceptable classification of PVT. Future studies should focus on exploring the effectiveness of various therapies, alone or in combination, including one or more anticoagulation agents and/or interventional procedures, to

provide an algorithmic management approach. Prospective long-term evaluation of peri- and posttransplant outcomes and quality of life of cirrhotic patients with PVT would help in deciding the need and duration of anticoagulant therapy in such patients. Praiseworthy global efforts are being made by various societies and special interest groups, like the Vascular Liver Disease Group, to engage investigators to answer these challenging questions.

Conflict of Interest
The authors declare no conflict of interest.

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