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EDITORIAL

Portal vein thrombosis in cirrhosis: Controversies and latest developments

Damian J Harding, M Thamara PR Perera, Frederick Chen, Simon Olliff, Dhiraj Tripathi

Damian J Harding, M Thamara PR Perera, Dhiraj Tripathi, Liver Unit, Queen Elizabeth Hospital, Birmingham B15 2TH, United Kingdom
Frederick Chen, Department of Haematology, Queen Elizabeth Hospital, Birmingham B15 2TH, United Kingdom
Simon Olliff, Department of Imaging and Interventional Radiology, Queen Elizabeth Hospital, Birmingham B15 2TH, United Kingdom

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Correspondence to: Dr. Dhiraj Tripathi, Liver Unit, Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Edgbaston, Birmingham B15 2TH,
United Kingdom. dhiraj.tripathi@uhb.nhs.uk
Telephone: +44-121-3714645
Fax: +44-121-4141833

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Abstract

Portal vein thrombosis (PVT) is encountered in liver cirrhosis, particularly in advanced disease. It has been a feared complication of cirrhosis, attributed to significant worsening of liver disease, poorer clinical outcomes and potential inoperability at liver transplantation; also catastrophic events such as acute intestinal ischaemia. Optimal management of PVT has not yet been addressed in any consensus publication. We review current literature on PVT in cirrhosis; its prevalence, pathophysiology, diagnosis, impact on the natural history of cirrhosis and liver transplantation, and management. Studies were identified by a search strategy using MEDLINE and Google Scholar. The incidence of PVT increases with increasing severity of liver disease: less than 1% in well-compensated cirrhosis, 7.4%-16% in advanced cirrhosis. Prevalence in patients undergoing liver transplantation is 5%-16%. PVT frequently regresses instead of uniform thrombus progression. PVT is not associated with increased risk of mortality. Optimal management has not been addressed in any consensus publication. We propose areas for future research to address unresolved clinical questions.

Key words: Portal vein thrombosis; Liver cirrhosis; Anticoagulation; Transjugular intrahepatic portosystemic stent-shunt

Core tip: Portal vein thrombosis is a complication of liver cirrhosis. Optimal management of portal vein thrombosis in cirrhosis has not been addressed in any consensus publication. There has been recent interest in the impact of portal vein thrombosis on the natural history of cirrhosis, and several authors have now described specific treatments for portal vein thrombosis, particularly with transjugular intrahepatic portosystemic stent-shunt and anticoagulation. We review current literature on portal vein thrombosis in cirrhosis and propose areas for future research to

address unresolved clinical questions.

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INTRODUCTION

Portal vein thrombosis (PVT) is a relatively common finding in advanced cirrhosis, often found in asymptomatic subjects as part of routine ultrasonography. There has been no published consensus on non-malignant PVT in cirrhosis.

We aim to provide an analysis of the current literature and explore options for optimal management of non-malignant PVT in cirrhosis. Literature was identified by a search strategy using MEDLINE and Google Scholar using search terms that included "liver cirrhosis" OR "cirrhosis" AND "portal vein" AND "thrombosis" OR "venous thrombosis" OR "embolism and thrombosis." Eligible studies referred to aspects of the incidence and prevalence, pathophysiology, aetiology, diagnosis and management of PVT in cirrhosis. Because liver transplantation is an important treatment for cirrhosis, studies that referred to PVT and liver transplantation were also eligible. Studies that referred to non-cirrhotic or hepatocellular carcinoma-related PVT were excluded. We identified 2967 search results with MEDLINE and 2860 results with Google Scholar.

ANATOMY

The portal vein is a valveless, approximately 6-8 cm long conduit that arises from the confluence of the superior mesenteric and splenic veins posterior to the neck of the pancreas. It accounts for 75% of the blood supply to the liver. In the porta hepatis, the portal vein divides into right and left branches that ultimately empty into the hepatic sinusoids of the right and left lobes respectively[1].

PVT is a condition caused by the formation of blood clot within the extra-hepatic portion of the portal vein. In the presence of cirrhosis, PVT is most commonly associated with portal vein stasis, or caused by tumour invasion from hepatocellular carcinoma or portal vein occlusion by cholangiocarcinoma in patients with primary sclerosing cholangitis. PVT may also occur following ablative therapy for hepatocellular carcinoma or fine needle aspiration of pancreatic mass[2,3]. PVT can also occur as an unusual condition in non-cirrhotic individuals: in the Western Hemisphere there is commonly an underlying pro-thrombotic aetiology or local intra-abdominal inflammation, such as pancreatitis or cholangitis. In Southern Asia omphalitis from neonatal umbilical sepsis or cannulation is a cause of childhood PVT[4]. Tumour-related and non-cirrhotic PVT is not further discussed in this review.

INCIDENCE AND PREVALENCE

There have only been limited studies of the incidence and natural history of PVT in cirrhosis. A prospective study of 1243 patients with Child's A and B cirrhosis found the cumulative incidence of new PVT after 1 and 5 years 4.6% and 10.7% respectively[5]. Another prospective study of 73 cirrhotics, with a mean baseline MELD score of 15.1, showed an annual incidence of 16%[6]. In one cohort of 251 patients with cirrhosis listed for transplantation the incidence of new PVT was 7.4% during a mean follow up of 12 mo[7]. The cumulative incidence of PVT after 1 year was 12.8% in a study by Maruyama *et al*[8] that followed 150 patients with viral hepatitis-related cirrhosis and no baseline PVT. The risk of developing PVT has been related to the severity of liver disease, with a risk less than 1% in those with well-compensated cirrhosis[9].

The prevalence of PVT in cirrhotic populations is between 0.6% to 26%[10]. In studies published since 2000 the prevalence of PVT in patients undergoing transplantation or evaluation for transplantation is between 5% to 16%[11-16].

PATHOPHYSIOLOGY

Acute phase

In acute PVT there is new formation of either partially or completely occlusive thrombosis in the portal vein. The episode may be asymptomatic, or may be associated with abdominal pain - particularly if the superior mesenteric vein is involved. Acute obstruction of the superior mesenteric vein and mesenteric arches can lead to intestinal ischaemia, and life-threatening infarction: this seldom occurs in patients with cirrhosis where the onset and progression of PVT is a more gradual and slower process, allowing alternative venous drainage to be established.

Following acute complete occlusion of the portal vein there is intense compensatory hepatic arterial vasodilatation ("arterial rescue") that stabilises liver function.

Chronic phase

After the period of arterial vasodilatation a phase of "venous rescue" follows with formation of venous collaterals that bypass the occluded segment, forming a "cavernoma" in 3 to 5 wk. For practical purposes an acute PVT can be differentiated from chronic PVT by the absence or presence of a cavernoma of porto-portal collateral vessels on imaging[17,18].

Complications of PVT

Complications of PVT include variceal haemorrhage, intestinal ischaemia and portal biliopathy (enlarged collateral veins on the surface of the common bile duct causing partial or complete bile duct obstruction)[19]. There is conflicting evidence regarding the role of PVT in the natural history of cirrhosis (see below). It has been reported that subjects with cirrhosis and PVT are at an increased risk of variceal haemorrhage compared with cirrhotics without PVT[20]. The incidence of intestinal ischaemia following PVT is not widely reported. Harki *et al*[21] prospectively assessed for symptoms and clinical evidence of ischaemia (by measuring small intestinal mucosal saturation measurements with visible light spectroscopy). In their small cohort (n = 17) of subjects with non-malignant, non-cirrhotic PVT, 67% had both exercise-induced abdominal pain and low visible light spectroscopy findings consistent with ischaemia. No similar studies have been reported. The risk of intestinal infarction has not been well characterised for reasons explained earlier. Prospective studies have not identified cases of intestinal infarction[8,22]. A retrospective study of databases from 11 hospitals in Sweden reported on 176 patients with PVT over a median 2.5 years. Abdominal pain was less common in cirrhotic than non-cirrhotic patients. 3% of the cohort required bowel resection for intestinal ischaemia or infarction[23].

AETIOLOGY OF PVT IN CIRRHOSIS

Venous stasis

Cirrhosis is associated with increased intra-hepatic vascular resistance and reduced portal blood flow into the liver[24]. Low portal blood flow seems to be the most important risk factor for PVT in cirrhosis and has been found to be predictive of future PVT[6,25,26].

Many patients with cirrhosis are treated with non-selective beta-blockers, which reduce portal blood flow and velocity[27]. The role of non-selective beta-blockers in influencing survival in patients with decompensated cirrhosis remains controversial; whether they are implicated in the pathogenesis of PVT has not been evaluated with the exception of Nery *et al*[5] who did not find any association between the use of non-selective beta-blockers and the development of PVT[10,28-30].

Thrombophilia

Levels of both pro- and anti-coagulation proteins are reduced in cirrhosis with impaired synthetic function, usually with maintained haemostatic balance and no tendency for bleeding or thrombosis[31]. Thrombin generation in cirrhosis is only impaired in the presence of severe thrombocytopenia[32]. The international normalized ratio (INR) in liver disease likely overestimates the risk of bleeding because the international sensitivity index used is determined by means of plasma from patients on vitamin K antagonists[33]. Other conventional coagulation tests in patients with cirrhosis do not take into account the reduction in anti-coagulant proteins[34].

Several large population studies have demonstrated that the incidence of venous thromboembolism (deep vein thrombosis, pulmonary embolism) in individuals with cirrhosis is at least similar to that in subjects without liver disease[35-38].

Factor Ⅷ is an important pro-coagulant involved in thrombin generation. Concentrations of factor Ⅷ increase progressively with worsening cirrhosis[39]. Protein C is an important anti-coagulant: levels of protein C are often reduced in cirrhosis[40]. The ratio of factor Ⅷ to protein C may be predictive of a hypercoagulability[41].

Some pro-thrombotic genotypes, including factor V Leiden G1691A mutation, methylenetetrahydrofolate reductase (MTHFR) C677T mutation and prothrombin G20210A mutation may be more frequent in cirrhotic patients with PVT compared with cirrhotic patients without PVT[42-44].

Anticardiolipin antibodies may be more common in PVT in cirrhosis[45]. Bacteraemia from bacteroides fragilis has been associated with an increased risk of PVT due to transient appearance of anticardiolipin antibodies[46]. However in a prospective longitudinal study of cirrhotic patients in France and Belgium the presence of G20210A prothrombin or factor V mutations was not associated with the development of PVT[5].

Endotoxinaemia

Bacterial translocation and endotoxinaemia are common with worsening liver disease, as a result of intestinal mucosal barrier damage[47-50]. Inflammation from bacterial infection increases portal pressure[51-53].

Portal endotoxinaemia may facilitate activation of the coagulation cascade within the portal venous system[54]. Villa *et al*[55] demonstrated that the use of enoxaparin in cirrhosis was associated with reduced bacterial translocation, and proposed that this was because of improvements in intestinal microcirculation sufficient to ameliorate portal hypertensive enterocyte damage[55]. Reducing portal pressure with non-selective beta blockers is associated with a reduced risk of spontaneous bacterial peritonitis or bacteraemia[56,57].

HISTORICAL RISK FACTORS FOR PVT IN CIRRHOSIS

Reported historical risk factors for PVT in cirrhosis include complications of, and previous treatments for complications of portal hypertension (previous variceal haemorrhage, endoscopic sclerotherapy, splenectomy, shunt surgery) and the presence of hepatocellular carcinoma[7,15,26]. The presence of hepatocellular

carcinoma (in the absence of macro-vascular invasion) appears to be a risk factor for non-neoplastic PVT[13]. Severity of underlying cirrhosis, and time spent on a waiting list for liver transplantation are risk factors for PVT[7,58].

Low platelet count, and the development of collateral vessels have been associated with increased risk of developing PVT[7,8]. These findings are compatible with the presence of reduced portal blood flow in cirrhosis with portal hypertension, likely the most important causative factor for PVT in cirrhosis[6].

DIAGNOSIS AND SCREENING

Imaging is appropriate as part of the initial evaluation of subjects with cirrhosis, and periodically during follow up. Because of the risk of hepatocellular carcinoma in cirrhosis computed tomography (CT) or magnetic resonance imaging (MRI) evaluation is advisable following new ultrasound diagnosis of PVT, to look for the presence of liver tumour. Endoscopic screening for varices should also take place because of the increased risk of varices in the presence of cirrhosis with PVT.

Ultrasound and Doppler ultrasound

Ultrasound and Doppler ultrasound are usually sufficient to diagnose PVT according to published series, however the incidence of PVT is much higher than that is routinely detected by above means[59,60]. Ultrasound may demonstrate hyperechoic material in the vessel lumen, but there is variation and operator dependent aspect to this diagnosis. Most of the diagnosis is reliant on Doppler scan that demonstrates absence of flow in part of, or all of the lumen. It can also show flow velocity and direction. "False negatives" have been reported with ultrasound at the time of transplantation[14]. Such findings may occur because of *de novo* thrombus formation between imaging and transplantation or false negatives. Different grades of PVT (discussed below) further complicate these findings. Using three-monthly Doppler ultrasound on their cohort of 251 cirrhotic patients awaiting transplantation, Francoz *et al*[7] diagnosed PVT in 9 patients at the time of transplantation. Eight of these patients had only partial thrombosis: transplantation was technically feasible in all cases. Data from 1491 patients who underwent liver transplantation at Queen Elizabeth Hospital Birmingham between January 2000 to August 2012 show a PVT prevalence of 119 (8%). Thirty-four (29%) of these cases were diagnosed at the time of surgery. For these subjects the mean interval from last screening imaging to transplantation was 2.25 mo. This suggests that some of the PVTs diagnosed are "interval" thromboses. Overall there were no survival differences between "diagnosed", "incidental" PVT cases and matched controls without PVT[61].

Cross-sectional imaging

Multiphase CT is alternatively recommended to diagnose PVT during evaluation of cirrhosis. Ultrasound is accurate detecting thrombus in the trunk of the portal vein and intrahepatic branches. CT better assesses the superior mesenteric vein, the presence of porto-systemic shunts, renal veins and inferior vena cava, and the extent of thrombus. CT can help diagnose hepatocellular carcinoma and intestinal ischaemia[62,63].

MRI is an alternative to CT, although has reduced definition in the presence of significant ascites[64].

MRI with contrast is helpful for demonstrating the portal venous system flow and thrombus like CT. MRI is advised for repeated imaging in younger patients to avoid the radiation associated with repeated CTs.

EFFECTS OF PVT ON THE NATURAL HISTORY OF CIRRHOSIS

The effects of PVT on the natural history of cirrhosis, including its effects on survival may not be deleterious. The risk of PVT appears to increase with severity of cirrhosis[9], but there is little data to demonstrate that PVT is an independent prognostic factor in cirrhosis[16,65].

Effects on survival

A review, using UNOS registry data from 2002 to 2013 of 66506 patients without hepatocellular carcinoma who were awaiting liver transplantation, found that the presence of PVT was not associated with an increased risk of death or reduced chance of undergoing transplantation[66].

Maruyama *et al*[8] followed up 150 patients with viral hepatitis-related cirrhosis, without PVT at baseline. Of the 42 (28%) patients who developed PVT the thrombus progressed in 7.2%, was unchanged in 45.2% and improved in 47.6%. The cumulative survival rates were similar between the thrombosis and non-thrombosis groups[8].

Effects on disease progression

In a prospective study of 1243 patients with cirrhosis and a mean follow-up of 47 mo, the development of PVT was not associated on multivariate analysis with the risk of disease progression. 118 subjects developed a new PVT, of which 87 were non-occlusive (one year cumulative incidence 4.6%). Non-occlusive thrombus varied over time, disappearing on follow-up in 70% of cases[5].

Natural history studies have identified relatively high rates of PVT regression instead of uniform thrombus progression. One study of 42 consecutive patients with cirrhosis (mean MELD 12.1; range 7-20) and untreated extra-hepatic, non-malignant PVT followed up subjects for a mean 27 mo. PVT worsened

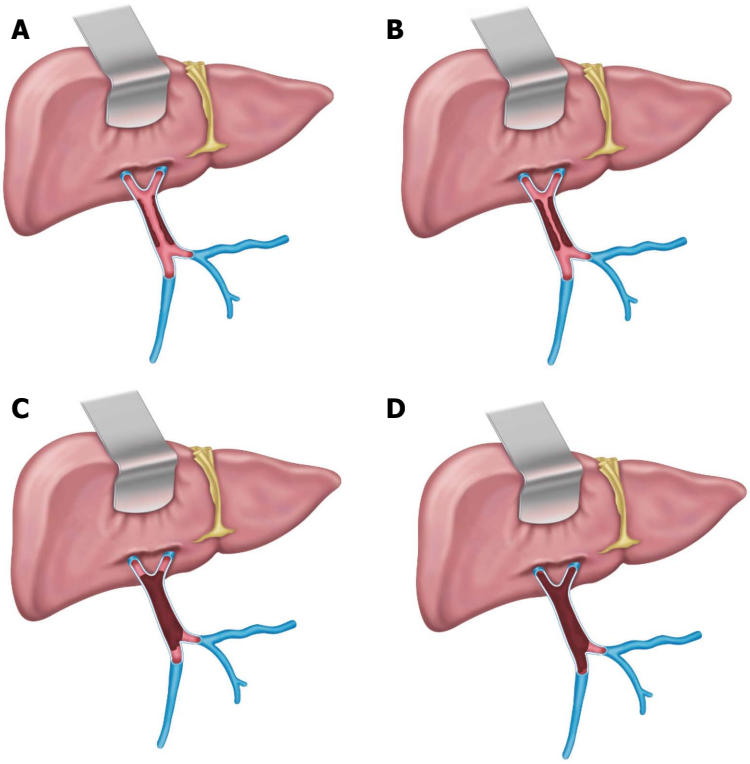

Figure 1 Yerdel's Classfication of portal vein thrombosis[15]. A: Grade Ⅰ portal vein thrombosis. Partial portal vein thrombosis (< 50% lumen) with or without minimal extension in to the superior mesenteric vein (SMV); B: Grade Ⅱ portal vein thrombosis; > 50% occlusion with or without minimal extension into the SMV; C: Complete thrombosis of both portal vein and proximal SMV. Distal SMV is open; D: Complete thrombosis of portal vein, proximal and distal SMV.

in 48% of patients and improved in 45%. There was no clear association between progression or regression of PVT and clinical outcome, with baseline Child-Pugh score the only independent predictor of survival or hepatic decompensation[22].

The positive findings of a study that examined the effects of primary prevention of PVT with anticoagulation in subjects with cirrhosis might suggest that PVT does have a role in the progression of cirrhosis: improved survival and less episodes of hepatic decompensation were seen in the study's active arm[55]. However the study's authors did not attribute the difference in hepatic decompensation to the prevention of PVT: they postulated that enoxaparin therapy lead to improved intestinal microcirculation and endothelial function, which had a protective effect on the course of the liver disease by reducing bacterial translocation. No other published studies have confirmed their findings.

Complications

The presence of PVT has been associated with a longer time to achieve endoscopic eradication of varices, but once achieved did not influence their recurrence[67].

The potential for life-threatening intestinal infarction in the presence of complete thrombus occlusion of the portal and superior mesenteric veins is known, although the actual risk of this event is not known.

Sudden clinical deterioration in a cirrhotic patient, such as the development of diuretic resistant ascites or bacterial peritonitis is suggestive of the development of PVT and should be thoroughly evaluated. The PVT may be the cause of, or the consequence of such events. A stable patient on diuretics may develop a PVT leading to diuretic resistance, leading to SBP. On the other hand bacterial infection in the peritoneum may lead to development of PVT.

IMPACT OF PVT ON LIVER TRANSPLANTATION

PVT, particularly complete thrombosis affects rates of complications, and possibly survival with liver transplantation. It was historically seen as a contraindication to transplantation.

Surgical considerations

The Yerdel classification of PVT is widely used to describe PVT because it correlates thrombosis extent with surgical technique and risk of complications (Figure 1)[15].

Pre-existing knowledge of a patient's PVT and use of the Yerdel classification allows appropriate graft selection and planning of the transplant surgical procedure. (Intra-operative diagnosis of incidental PVT may cause problems of added surgical explant time, increased risk of significant bleeding and prolonged cold ischaemia time for the selected graft). For Yerdel grades Ⅰ to Ⅲ, operative techniques include thrombectomy, with

Table 1 Key studies of portal vein thrombosis and liver transplantation

	Number of patients	Prevalence PVT, *n* (%)	PVT characteristics	Outcomes
Englesbe *et al*[65]	22291 (2001-2007)	897 (4.02)	Not described	PVT was not predictive of waiting list mortality (HR = 0.90, *P* = 0.23) PVT was predictive of post-transplant mortality (HR = 1.32, *P* = 0.02)
Sringeri *et al*[61]	1491 (2000-Aug 2012)	119 (8.0)	Not described	Prolonged theatre timea, increased blood transfusion rates[1]. No difference mortality up-to 140 mo
Ravaioli *et al*[13]	889 (1998-2008)	91 (10.2)	Partial 51 (56%)	No difference 1 yr (85% *vs* 86%) and 5 yr (68% *vs* 73%) survival between PVT and non-PVT subjects
			Complete 40 (44%)	Survival improved significantly for patients with complete PVT in the second era (2003-2008) (57% *vs* 89% at 1 yr[1])
Yerdel *et al*[15]	779 (1987-1996)	63 (8.1)	Grade 1: 24, Grade 2: 23, Grade 3: 6, Grade 4: 10	Reduced 5 yr survival between PVT and non-PVT subjects (65.3% *vs* 76.3%[1]) But improved 5 yr survival from 1st to 2nd era in all patients (from 72% to 83%[1])

[1]The *P* value is < 0.05. PVT: Portal vein thrombosis.

or without creation of an interposition graft, followed by direct porto-portal anastomosis. In cases where the lumen of the portal vein has been narrowed by cicatrisation of the thrombus, the narrowed segment can be resected and a donor iliac vein graft used as an interposition graft, resulting in a patent, larger diameter vein. Thrombectomy is still possible with Yerdel grade Ⅲ PVT as long as the portal vein is carefully examined down to the junction of the superior mesenteric and splenic veins with extraction of all thrombus.

Cases of Yerdel grade Ⅳ and some grade Ⅲ cases may be considered as contraindications to transplantation in some centres, while taken on by experienced high volume centres. Complex vascular reconstruction techniques may be necessary with meso-portal "jump grafts" from donor veins or synthetic vascular grafts, creation of porto-caval shunt or portal vein arterialisation. Such complex procedures for extensive or grade Ⅳ PVT carry a high (approximately 50%) risk of post-transplant portal hypertension[16]. There are a few case series of patients with diffuse PVT who have undergone multivisceral transplantation[68]. The procedure is only offered in a few centres, but should be considered in patients with severe bowel dysfunction due to porto-mesenteric venous ischaemia or refractory portal hypertensive gastrointestinal bleeding where diffuse PVT is present.

Outcomes of liver transplantation with PVT

A large American series described outcomes post-liver transplantation between September 2001 and December 2007 in 22291 subjects where the prevalence of PVT was 4.02% (*n* = 897). PVT was not classified according to grade, or whether occlusive/non-occlusive. The presence of PVT was associated with higher post-transplant mortality only during the first year of follow up in this cohort (HR = 1.32, *P* = 0.02)[65]. Our own institution's experience of 1491 transplants between January 2000 and August 2012 found the presence of PVT was associated with significant increases in intra-operative blood product use and theatre time, but no difference in survival[61].

Several papers describe outcomes based upon the classification of thrombosis. In subjects with non-occlusive PVT, post-transplant mortality outcomes are no different from non-PVT patients[15,69,70].

Mortality rates likely increase in the presence of occlusive PVT, but may be better in larger centres with greater experience of PVT-surgical management. In a review of 25753 transplants performed in different centres between 1984 and 2008 the 30 d and 1 year mortality rates for subjects with PVT were higher than for those without PVT (10.5% and 18.8% *vs* 7.7% and 15.4%): only complete PVT accounted for this difference[69]. Mortality rates were higher still in subjects with grade Ⅳ PVT. Studies of transplant recipients where end-to-end portal anastomoses were not feasible describe high rates of post-operative morbidity due to persistent portal hypertension, and higher rates of early post-operative mortality (25%)[71-73]. More recent data from high volume centres with specific experience in PVT-surgical treatment do not show any effect of PVT on survival. Two studies provide analysis of outcomes for patients with Yerdel grades 3 and 4 PVT. Outcomes for these centres have improved: Ravaioli *et al*[13] showed no survival differences for patients with complete PVT when their 10 year data were restricted to the last 5 years (Table 1)[13].

PVT following liver transplantation

Thrombosis of the portal vein, particularly early following transplantation carries a poor prognosis[74]. The rate of PVT occurrence post-transplantation in subjects without a history of preceding PVT is between 0%-2%[12,14,15,75]. PVT post-transplantation can occur at the anastomosis site when there is significant mismatch of the donor: recipient vein diameters[76]. The rate of post-transplant PVT recurrence in subjects with previous PVT is higher: 2%-3%[14,61,77,78]. It is not clear whether thrombosis rates are greater following more complex procedures. There are no standardised approaches to post-liver transplant prevention of re-

thrombosis. It is expected that the risk of recurrent PVT should be reduced by the correction with transplantation of the haemodynamic abnormalities associated with cirrhosis and portal hypertension. In considering approaches to managing the risk of PVT recurrence, they should be weighed against risks of post-operative bleeding.

LIVING DONOR TRANSPLANTATION AND PVT

Living donor transplantation is performed in many centres because of a shortage of cadaveric donors. For the safety of donors partial grafts obtained from living donors have only a very short length of portal vein. To complete the anastomosis it is vital that there is an adequate length of recipient portal vein, which is not always feasible, particularly in the presence of recipient PVT[79]. Procurement of additional vessels to allow complex interposition or jump grafts is also limited, making living donor liver transplantation for patients with complete PVT technically more difficult with high reported mortality. Outcomes in the presence of partial PVT are similar to those in recipients without PVT[80]. For cases of complete PVT the use of re-canalised umbilical vein, saphenous vein of the donor or the recipient, or the hepatic veins of the explanted cirrhotic liver have all been used. Another option is to use the cryopreserved vessels from cadavers or cadaveric donors but their use has been associated with worse outcomes due to an increased risk of re-thrombosis[81].

MANAGEMENT OF PORTAL VENOUS THROMBOSIS IN CIRRHOSIS

The natural history of PVT in cirrhosis remains controversial: this has affected the ability to provide clear management consensus. The presence of PVT does affect liver transplantation surgery and potentially outcome. In candidates for transplantation the main objective of management is to achieve at least partial recanalisation to allow portal flow to the graft with a conventional end to end PV anastomosis. If recanalisation cannot be achieved the objective is to prevent extension of thrombus, particularly to the superior mesenteric vein. Careful screening during evaluation and throughout follow up is important to achieve these aims. In patients with PVT there are different possible approaches to treatment: anticoagulation, transjugular intrahepatic portosystemic stent-shunt (TIPSS), and endovascular procedures with fibrinolysis. The use of primary preventative strategies could also be considered for patients at risk of developing PVT.

PVT in cirrhosis is associated with a higher risk of variceal haemorrhage than in cirrhotic individuals without PVT: assessment with upper gastrointestinal endoscopy is warranted to assess for oesophageal varices[82].

ANTICOAGULATION

Six published studies describe anticoagulation in 199 cirrhotic patients using warfarin (with target INR 2-3) or low molecular weight heparin for means of between 6 mo to 302 d[7,55,83-86] (Table 2). Two case reports describe the use of rivaroxaban, an oral factor Xa inhibitor, in the management of acute PVT in six subjects with well-compensated Child's A cirrhosis[87,88]. With the exception of studies reported by Villa *et al*[55] and Senzolo *et al*[85], all of the reported studies are case-control or retrospective series of subjects with cirrhosis and partial or occlusive acute PVT. These published studies do not describe treatment of chronic PVT associated with cavernoma.

Primary prevention

Villa *et al*[55] performed a randomised, controlled study of enoxaparin (4000 IU daily) for 48 wk in 70 patients with Child's B7 to C10 cirrhosis and no PVT (34 active arm, 36 controls). The study's primary outcome, prevention of PVT in subjects with cirrhosis, was successful: there were no PVTs in the active arm at the end of follow up (at 2 years), compared with the 27.7% rate of PVT in the control arm. Of clinical importance, rates of hepatic decompensation (ascites, encephalopathy, bacterial peritonitis, portal hypertensive bleeding) were significantly lower in the treatment arm (38.2%) compared with controls (83%, $P < 0.0001$). Treatment with enoxaparin was associated with a reduction in bacterial translocation, which was thought at least partly responsible for the lower rates of decompensation. No relevant side effects or haemorrhagic events were reported.

Secondary prevention

Senzolo *et al*[85] prospectively evaluated treatment with low molecular heparin (nadraparin) for at least 6 mo compared with standard care in 35 actively treated and 21 control subjects. The patients had cirrhosis (mean MELD 12.6 active arm) and either partial or complete acute PVT. In the active arm the incidence of complete recanalisation was 60%, with stabilisation or partial recanalisation achieved in 20%. Amongst controls recanalisation occurred in only one subject (5%) with partial recanalisation or stabilisation in 5 (24%): the incidence of thrombus progression in controls was 71.4%.

Amongst the reported studies of anticoagulation therapy for secondary prevention, treatment was associated with recanalisation rates of between 39.3% to 75%, and an incidence of thrombus progression between 0% and 14.3%. This compares favourably with rates of recanalisation or thrombus progression reported for control subjects by Senzolo *et al*[85].

Table 2 Summary of studies reporting the use of anticoagulation for portal vein thrombosis in cirrhosis

	Study type	*n* (controls)	Baseline severity liver disease	Duration and type of anticoagulation	PVT characteristics (none/partial/complete occlusion)	Recanalisation	Partial recanalisation/ stabilisation	Progression	Bleeding complicaitons
Francoz *et al*[7]	Prospective case control	19 (10)	mean MELD 12.8	Warfarin (INR 2-3) Mean 8.1 mo	0/18/1	8/19 (42%) *vs* 0/10 non-anti-coagulated (P = 0.002)	0	1	1 bleeding episode following endoscopic variceal band ligation
Amitrano *et al*[83]	Prospective	28	?	Enoxaparin 200 IU/kg per day: 6 mo for responders and non-responders. Partial responders continue until end of follow up.	0/23/5	21 (75%) at median 11 mo	5 (17.9%)	2	Mild anaemia in patient with portal hypertensive gastropathy
Delgado *et al*[84]	Retrospective	55	mean MELD 12.8 +/- 3.8	Warfarin (INR 2-3) or enoxaparin mean 6.8 mo	0/41/14	25 (45.5%)	30 (54.5%)	0	6 variceal bleeds, 1 lower GI bleed, 1 obscure GI bleed, 1 oral bleed post-dental extraction, 1 severe vaginal bleed
Senzolo *et al*[85]	Prospective case control	33 (21)	MELD 12.6 (controls MELD 13.7)	Nadraparin low molecular weight heparin until end of follow up, or until 6 mo following complete recanalisation.	0/24/11	12/33 (36%) active arm *vs* 1/21 (5%) controls	Partial: 9/33 active arm. Stabilisation: 7/33 active arm. Partial recanalisation or stabilisation in 5/21 controls.	5/33 (14.3%) active arm *vs* 15/21 (71.4%) control arm (P < 0.001)	Active arm: 1 cerebral haemorrhage, 1 epistaxis, 1 haematuria, 1 variceal bleed Control arm: 5 variceal bleeds
Werner *et al*[86]	Retrospective	28	MELD 7-29	Warfarin Mean 302 d	not described	11 (39.3%)	17 (60.7%)	0	1 significant vaginal bleed
Villa *et al*[55]	Prospective randomised controlled trial	34 (36)	Child's 7-10	Enoxaparin 4000 IU/d 48 wk treatment. Follow up to 2 yr	Primary prevention study: No PVTs at baseline	N/A	N/A	Treatment arm: No PVT at 2 yr. Control arm: PVT in 10/36 (27.8%) at 2 yr (P = 0.001)	Active arm: 2 variceal bleeds, 2 epistaxis Control arm: 1 variceal bleed, 1 epistaxis

PVT: Portal vein thrombosis.

Amitrano *et al*[83] and Senzolo *et al*[85] reported a mean time until venous recanalisation of 6.5 and 5.5 mo respectively. Delgado *et al*[84] reported that that up to 39% of subjects who had achieved portal vein recanalisation developed re-thrombosis after stopping anti-coagulation. Where assessed for, the prevalence of thrombophilic abnormalities was between 5 and 16% (Werner and Delgado)[84,86].

Complications

With the exception of the study reported by Delgado *et al*[84], all study patients were screened for large varices, with endoscopic obliteration provided before commencement of anticoagulation. Patients with cavernoma were generally excluded. Patients in the study by Delgado *et al* received standard primary or secondary management of varices following recognised international guidelines[89]. In the studies of patients who received pre-emptive endoscopic obliteration of varices (n = 144) there were 4 episodes of variceal haemorrhage on treatment. There were 6 episodes of variceal haemorrhage amongst the 57 control subjects.

Senzolo *et al*[85] report one cerebral haemorrhage leading to hemiparesis on treatment. Other bleeding complications on treatment were: 2 epistaxis (1 epistaxis in a control subject), 1 haematuria, 2 significant vaginal bleeding, 1 obscure and 1 lower gastro-intestinal haemorrhage. Among the control subjects there were 2 episodes

Table 3 Summary of new oral anti-coagulants

Name	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Clearance	80% renal clearance	73% hepatic 27% renal clearance	50% hepatic 50% renal clearance	65% hepatic 35% renal clearance
CYP3A4 interaction?	No	Yes (minor)	Minimal	Yes
Absorption with food?	No effect	No effect	Up to 20% more	40% more therefore intake with food
Elimination half life	12-17 h	12 h	9-11 h	8-9 h young 11-13 h elderly

of intestinal ischaemia (one fatal), and two subjects went on to have liver transplantation that required caval hemi-transposition. Delgado *et al*[84] identified baseline platelet count of < 50 × 10^9/L as a risk factor for bleeding complications.

In the study reported by Senzolo *et al*[85] control patients experienced greater rates of complications than the active arm: 2 of the 21 controls developed intestinal ischaemia (one fatal), and 2 required caval hemitransposition at liver transplantation. Delgado *et al*[84] study showed that complications associated with deteriorating cirrhosis were more common in patients who did not achieve recanalisation.

New oral anti-coagulants

These agents work by direct inhibition of thrombin or activated factor Xa, and are licenced for the prevention of primary or recurrent venous thromboembolism, or prevention of stroke in non-valvular atrial fibrillation[90-93]. Their practical advantages include oral administration, the lack of any requirement for monitoring with blood tests, and no effect on INR, an important component of the MELD score. The new oral anticoagulants have no antidote: of clinical importance when considering individual patients' risks of bleeding complications[94]. However specific antidotes, such as Andexanet Alfa (Clinicaltrials.gov: NCT01758432) are under development. The new oral anti-coagulants can be affected by drugs that are P-glycoprotein substrates. Drugs that inhibit or induce CYP3A4 can significantly affect concentrations or effects of rivaroxaban[95]. The potential for drug interaction is important to consider for patients intending to commence new directly acting antiviral therapies for hepatitis C (Table 3)[96].

Recent case reports describe the use of rivaroxaban to treat acute PVT in well-compensated cirrhosis. Unfortunately for patients with severe liver disease the drug has not been evaluated in decompensated cirrhosis, where concerns exist that its pharmacological effects will be altered[97,98].

From these small studies and series it is clear that anticoagulation with warfarin or low molecular heparin is feasible in cirrhosis, may prevent the onset of PVT or its extension once present, and may even slow down progression of liver cirrhosis. Further controlled studies with larger numbers are indicated to validate these findings. These published experiences may justify the current use of anticoagulation in some settings such as cirrhotics with partial or occlusive PVT who are on transplant waiting lists. There is no consensus on which anticoagulant is best: low molecular weight heparin can be given until transplantation, but requires administration of an injection. Warfarin impacts upon patients' MELD scores and requires monitoring of INR. Rivaroxaban cannot be provided to patients with decompensated cirrhosis (Table 2).

TIPSS

TIPSS (with bare or covered stents) may be a treatment option to manage PVT as an alternative to anticoagulation, particularly in the presence of severe complications of portal hypertension (recurrent or refractory variceal haemorrhage or ascites), or contraindications to anticoagulation. The goal of TIPSS is to repermeate the portal vein and restore portal flow through the low resistance shunt, thereby preventing recurrent thrombosis. TIPSS may have a role in liver transplant candidates in maintaining portal vein patency, avoiding PVT propagation, and enhancing the feasibility of transplantation. TIPSS may even be feasible in some patients with cavernoma[99,100]. TIPSS can prevent total portal vein occlusion in liver transplantation candidates with partial PVT[101]. There are no studies that compare anticoagulation, TIPSS, or conservative treatment in the management of PVT in cirrhosis.

Outcomes

Experience of TIPSS in more than 200 subjects with cirrhosis and PVT has been published[99-106]. Rates of feasibility between 70% to 100% are described. Successful TIPSS placement is associated with clinical improvement, low rates of re-thrombosis, and low rates of recurrent portal-hypertensive bleeding. Because of the low rates of re-thrombosis following complete portal vein recanalisation, systemic anticoagulation following TIPSS is probably only indicated in the presence of a documented pro-thrombotic state[101-103].

The use of TIPSS has been described in cirrhotic patients with PVT and complications of portal hypertension, bleeding or ascites. A small number of individuals have undergone TIPSS with the aim of preventing complete occlusive PVT while awaiting liver

transplantation[102,105]. D'Avola *et al*[101] describe TIPSS in 15 cirrhotic subjects with partial PVT waiting for transplantation. These individuals were compared with 8 matched controls who did not undergo TIPSS. There were no significant complications associated with the TIPSS procedure. There were no differences between the groups' post-transplantation outcomes, transplant operating times or use of blood products. Wang *et al*[105] compared a group of 25 patients with cirrhosis and PVT who were treated successfully with TIPSS with a cohort of 25 patients with cirrhosis and PVT who were managed conservatively including endoscopic variceal ligation). Successful TIPSS was associated with portal vein recanalisation and not surprisingly lower rates of variceal bleeding. Interestingly there were no differences in survival between the two groups, which were followed up for a mean of 25.1 mo (Table 4).

While elective TIPSS use in cirrhosis carries a higher risk with high MELD scores[107], between 16% to 33% of cases where baseline severity of liver disease was recorded had baseline Child's C disease severity.

Complications and technical failure

Technical failure has been associated with extensive main PVT[100], and the absence of a patent intra-hepatic portal vein branch that can be punctured[101,103,105]. TIPSS placement may compromise an intended liver transplant procedure if it is sited distally into the portal vein trunk and superior mesenteric vein[108]. Lower rates of success are reported in the presence of cavernoma[100,101]. Reduced rates of TIPSS dysfunction have been reported with the use of covered stents[103].

Unlike anticoagulation, TIPSS is associated with a risk of developing hepatic encephalopathy[109]. Han *et al*[99] and Luca *et al*[102] reported rates of post-TIPSS encephalopathy between 25% to 32%, although Senzolo *et al*[104] reported only one out of 28 subjects developing encephalopathy in their series of both cirrhotic and non-cirrhotic patients.

ENDOVASCULAR FIBRINOLYSIS

Results from published experiences of thrombolysis in non-cirrhotic patients have been disappointing with high incidence of major bleeding complications and low rates of recanalisation[110-112]. Experience of thrombolysis, alone or in conjunction with TIPSS, in cirrhotic patients with PVT is limited[113,114].

CONCLUSION

PVT is a common problem in patients with advanced cirrhosis, with diagnosis occurring more frequently because of the greater prevalence of ultrasound screening in cirrhosis. While PVT has been associated with some important clinical complications, including worsening portal hypertension (at least in the short term), mesenteric infarction and portal biliopathy; its overall prognostic significance is still not fully understood. PVT is clinically relevant where liver transplantation is anticipated.

While reduced portal vein velocity is likely the most important risk factor for PVT in cirrhosis, other causes such as thrombophilic disorders and endotoxinaemia may play an important role in some individuals. Future studies examining the impact of more targeted use of non-selective beta-blockers in advanced cirrhosis, or strategies aimed at reducing bacterial translocation in cirrhosis may demonstrate a beneficial impact on the incidence of PVT[28,115-117]. Larger studies are warranted to repeat the work of Villa *et al*[55] to establish whether primary prevention of PVT with anticoagulation has a role in selected subjects with cirrhosis.

When PVT is first diagnosed in a cirrhotic individual, it is important to ensure that the thrombosis is not associated with the presence of hepatocellular carcinoma: this can be assessed with the use of multiphase CT or MRI liver[118]. Endoscopic screening for varices is warranted. A thrombophilic disorder may be a contributing causative factor -and should be looked for if diagnosis will have longer term clinical implications, for example in liver transplant candidates.

The increasing experience of using specific therapies to prevent or to treat PVT in cirrhotic patients is very interesting. It has been argued that there is sufficient evidence or experience to warrant the use of anti-coagulation in patients with cirrhosis and PVT who are listed for liver transplantation, following prophylactic management of oesophageal varices[20,119]. However in our opinion there remains a lack of adequately powered, randomised studies to demonstrate clearly the role, benefits and risks of anticoagulation or TIPSS to manage PVT in cirrhosis, and whether such interventions are appropriate in all cirrhotics, or appropriate in only certain groups, such as potential liver transplant candidates. There is no clear evidence to support the routine use of anticoagulation or TIPSS in primary prevention.

Prospective cohort studies are warranted to assess the impact of PVT on patients referred for liver transplantation; to evaluate its impact on eligibility for transplantation, on the natural history of patients waiting for transplantation and on outcomes of transplantation.

Randomised controlled studies are warranted to compare current conservative management with the use of anticoagulation or TIPSS to treat acute PVT in cirrhosis. To evaluate outcomes it may be preferable to perform a study in patients referred for or waiting for transplantation. Outcomes of interest should include incidence and maintenance of portal vein recanalisation, survival and effects on MELD or progression of underlying liver disease, effects on portal hypertensive complications, and effects on transplant surgery and outcomes. Future study should compare the use of warfarin, low-molecular weight

Table 4 Summary of retrospective case series reporting the use of transjugular intrahepatic portosystemic stent-shunt for portal vein thrombosis in cirrhosis

	Study type and stent characteristics	*n*	Baseline severity liver disease: Child's A/B/C (%)	TIPSS indication (%)	PVT characteristics: Complete/ partial/ cavernoma (%)	Successful cannulation (%)	Outcome	Significant complications/ notes
Luca *et al*[102]	Series 2003-2010 13 bare Wallstent, 57 covered Viatorr ePTFE covered (*WL Gore* and *Associates*)	70	A: 17 (24) B: 42 (60) C: 11 (16)	Bleeding: 48 Ascites/ hydrothorax: 18 Specific treatment of PVT: 4	Complete: 24 Cavernoma: 2	70/70 (100) cannulation. Complete recanalisation or significant reduction in thrombosis: 61 (87)	Complete recanalisation in 40 (57%): 38 maintained patency at mean follow up 20.7 mo.	
Perarnau *et al*[100]	Series 1990-2004 Palmaz (*Cordis*) or Wallstent (*Boston Scientific*) bare stents	34	A: 3 (14) B: 11 (52) C: 7 (33) (incomplete details)	Bleeding: 27 (79) Ascites: 5 (15) Other: 2	Complete acute: 15 Complete + cavernoma: 19	No cavernoma: 15/15 (100) Cavernoma: 12/19 (63)	Mean F/U 30 mo. 26/34 (72%) long-term patency	Failed cannulation in presence of thrombosed intrahepatic PV branches or peri-hilar cavernoma
Senzolo *et al*[104]	Series 1994-2005 26 Memotherms (*Angiomed*) bare stents, 3 Viatorr covered stents	28 (15 non-cirrhotic)	Not stated	Bleeding: 15 Ascites: 5 Portal biliopathy: 3 Specific treatment PVT: 1	Complete: 8 (3 with, 5 without cavernoma) Partial: 5	19/28 (73%)	Primary patency mean 18 mo in 14/19. Stent thrombosis in 2 non-cirrhotic subjects (Budd-Chiari syndrome)	
Han *et al*[99]	Series 2001-2008 Uncovered stents in all patients	57	A: 25 (44) B: 26 (46) C: 6 (30)	Bleeding: 56 Ascites: 1	Complete: 14 Cavernoma: 30 Partial: 35	Overall: 43/57 (75) Complete PVT: 8/14 (57) Partial PVT: 35/35 (100) Cavernoma: 16/30 (53%)	Primary patency maintained in 26/43 (17 required shunt revisions to maintain patency)	Failure related to presence of cavernoma. 1 case of delayed severe intra-abdominal haemorrhage following percutaneous trans-hepatic approach.
Van Ha *et al*[106]	Series 1995-2003 12 bare Wallstent (*Boston Scientific*), 1 bare Zilver stent (*Cook*)	15	B: 11 (73) C: 4 (27)	Bleeding: 10 Ascites: 5	Complete: 4/partial: 7/complete with cavernoma: 4	Overall: 13/15 (87) Cavernoma: 3/4 No cavernoma: 10/11 (91)	Mean F/U 17 mo. 1 stent occlusion	
D'Avola *et al*[101]	Series 1995-2009 Bare and covered stents	15 (+ 8 controls with PVT)	Mean Child's 8	Prevention of complete PVT pre-liver transplant: 8 Bleeding: 6 Ascites: 1	All partial PVT	Series describes only patients who successfully underwent TIPSS	3/15 TIPSS thrombosis: all successfully treated. Median time TIPSS to transplant: 185 d. 100% portal vein patency at time of transplant *vs* 50% patency at transplant in controls ($P = 0.008$)	
Bauer *et al*[103]	Series 1999-2005 3 covered stents: others bare stent	9	Cirrhosis: disease severity not stated	Primary indication: maintain PV patency for future liver transplantation	Complete: 7 Partial: 2 Cavernoma: 4	Series describing only patients who successfully underwent TIPSS	1/9 re-thrombosed. 2 patients transplanted with no PVT present	
Blum *et al*[114]	Case series All bare stents	7	Cirrhosis: disease severity not stated	Bleeding: 7	PVT severity not stated. No cavernoma.	Series of successful cases		

PVT: Portal vein thrombosis; TIPSS: Transjugular intrahepatic portosystemic stent-shunt; F/U: Follow up.

heparin and new oral anti-coagulants.

Some centres routinely provide anti-coagulation to patients with cirrhosis and acute PVT who are waiting for transplantation. It would be useful to combine and publish the available efficacy and safety data from these centres.

Management of PVT in cirrhosis at present remains an individualised decision, according to the risk of thrombus extension, the likelihood of transplantation, and whether there are other clinically significant issues, such as intractable ascites or portal hypertensive bleeding that would warrant use of TIPSS.

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