

# Diagnosis and management of portal vein thrombosis in patients with cirrhosis of the liver

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## ABSTRACT

*Portal vein thrombosis (PVT) is an occlusion of the portal venous system and is a common complication of liver cirrhosis. It can present as either an acute or chronic complication. Acute PVT can present with abdominal pain, diarrhea, ileus, and bleeding. Chronic PVT is often asymptomatic; however, it can be discovered in cases of worsening portal hypertension. Portal vein thrombosis is diagnosed by imaging modalities, such as ultrasound and computed tomography. Contrast-enhanced imaging can be used in cases with difficult visualization. Despite the hemostatic imbalance in cirrhosis, anticoagulants can be safely used to recanalize the vein. Transjugular intrahepatic portosystemic shunt procedures are also an effective method for recanalization.*

**Keywords:** portal vein thrombosis, cirrhosis, anticoagulation, portal hypertension

## INTRODUCTION

Portal vein thrombosis (PVT) is a thrombotic occlusion occurring in the trunk of the portal vein, in the portal vein branches, or upstream in the splenic or mesenteric veins. This complication usually occurs in patients with cirrhosis and hepatocellular carcinoma but can occur in patients with compensated cirrhosis and, more rarely, in patients without liver disease.<sup>1,2</sup> The prevalence of PVT in cirrhosis is widely reported in the literature and occurs in up to 25% of patients with cirrhosis.<sup>2-6</sup>

Contradictory findings exist on the effect of PVT on outcomes in cirrhosis. Results from two meta-analyses indicate that PVT is associated with higher risk of hepatic decompensation, ascites, and

mortality,<sup>7</sup> and patients with complete portal vein thrombosis have increased 30-day and 1-year mortality post liver transplantation.<sup>8</sup> However, a recent retrospective study indicated that PVT alone is not predictive of mortality, but rather the Model for End Stage Liver Disease (MELD) score is predictive.<sup>9</sup> This scoring scale computes mortality risk based on laboratory values of bilirubin, INR, sodium, and the need for dialysis.

The management of PVT in patients with liver cirrhosis has been controversial. Liver cirrhosis traditionally has been thought to produce a coagulopathy characterized by thrombocytopenia due to hypersplenism and the impaired production of clotting factors II, VII, IX, and X. However, recent evidence has revised this paradigm. Cirrhosis reduces the production of both anti-thrombotic and thrombotic factors, leading to a new "hemostatic balance" in which a risk for bleeding or clot formation could exist.<sup>10</sup> This review will focus primarily on the diagnosis and management of a patient with PVT in liver cirrhosis.

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**DOI:** 10.12746/swrccc.v6i26.496

## **COAGULOPATHY IN CIRRHOSIS — NEW HEMOSTATIC BALANCE**

The reduced synthesis of pro-coagulant factors and the sequestration of platelets associated with cirrhosis should produce a coagulopathy, and anticoagulation therapy should increase the risk of bleeding. However, recent studies have shown that there is, in fact, a new hemostatic balance in cirrhosis due to the reduction in both pro-coagulant and anti-coagulant factors. This new hemostatic balance can be evaluated using laboratory measurements of these factors.<sup>10</sup>

Interesting relationships exist among cirrhosis, lipopolysaccharide (LPS), and factor VIII. The intestinal barrier becomes more permeable in liver cirrhosis,<sup>11</sup> and large amounts of LPS from the gut microbiome pass through enterocyte junctions. A recent study reported a relationship between the amount of LPS in circulation and factor VIII levels.<sup>12</sup> Lipopolysaccharides act on endothelial cells and cause the release of factor VIII and von Willebrand factor from Weibel-Palade bodies, potentially producing a hypercoagulable state. In addition, hepatocellular cancer, increased homocysteine levels, and methylene-tetrahydrofolate-reductase (MTHFR) C677T polymorphism are more prevalent in patients with liver cirrhosis who developed PVT than in patients who did not.<sup>13</sup> Methylene-tetrahydrofolate-reductase C677T polymorphism has a phenotypic effect of hyperhomocysteinemia. Homocysteine is formed in the methionine metabolism pathway and is ultimately metabolized by the liver. Hyperhomocysteinemia is associated with development of deep vein thrombosis, and the presence of elevated homocysteine levels in patients with PVT could help explain the pathogenesis of PVT.

Laboratory tests may be useful in the assessment of the risk of bleeding in cirrhotic patients.<sup>10</sup> The platelet count is the most reliable test, and counts  $\geq 50 \times 10^9/L$  can ensure normal primary hemostasis. Although the bleeding time is prolonged in cirrhosis, it should not be used to predict the risk of bleeding after invasive procedures or with esophageal varices. The prothrombin time, often reported as the INR, provides a useful test to measure liver synthetic function and is used to determine the severity of cirrhosis based

on Child-Turcotte-Pugh and MELD scoring. However, not enough information is available to determine its utility in bleeding predictions.

There is also utility in laboratory tests for of hypercoagulability in cirrhosis.<sup>10</sup> Cirrhosis impairs the synthesis of anti-thrombin and proteins C and S. Although serum levels may be low, it is not recommended to use these markers alone to determine the risk for thrombotic events. In patients with cirrhosis and a personal or family history of thrombosis, investigation of genetic mutations, such as factor V Leiden or anti-phospholipid antibodies, may help determine the risk of thrombosis. The laboratory diagnosis of anti-phospholipid antibody is difficult in patients with cirrhosis due to the baseline abnormal coagulation and the reliance of phospholipid-dependent coagulation tests to make the diagnosis. The presence of serum anti-cardiolipin and anti-Beta2-glycoprotein I could be useful in this diagnosis in patients with cirrhosis, but more information is needed.

Thromboelastography (TEG) and rotational thromboelastography techniques use whole blood to measure the time between the initiation of the clotting cascade to the initial formation of fibrin, the time between fibrin formation and clot firmness, the rate of fibrin formation and crosslinking, and maximal clot strength.<sup>14</sup> It provides a coagulation index with a negative value indicating hypocoagulability and a positive value indicating hypercoagulability. These tests can be done at the point of care and are widely used to evaluate major hemorrhage and the need for blood transfusion during liver transplantation.<sup>10</sup> Some studies using TEG have shown a tendency for chronic liver disease to be associated with a hypocoagulable state<sup>14,15</sup> delayed clot formation and reduced thrombus strength.<sup>16</sup> Thromboelastography may provide insight into the hemostatic balance seen in liver cirrhosis, but more clinical studies are needed to determine its utility, especially in patients with PVT, and to monitor treatment effects in these patients.

## **CLINICAL PRESENTATION**

Portal vein thrombosis can present as either an acute or chronic disease; patients with acute PVT are

more likely to be symptomatic.<sup>17</sup> Signs of acute PVT include abdominal pain, diarrhea, and ileus. Extension of the thrombus into the superior mesenteric artery can present as an acute abdomen. Symptoms of portal hypertension, such as variceal bleeding, can be associated with acute PVT and is reported to occur in 34-39% of cases as the presenting symptom. Chronic PVT is generally asymptomatic and is discovered incidentally on imaging; however, symptomatic portal hypertension, such as gastrointestinal and esophageal variceal bleeding or portal cholangiopathy, can be the initial presentation of an underlying chronic portal vein thrombosis.

A variety of conventions have been proposed to classify PVT. Yerdel et al proposed the extent of thrombosis of PVT can be classified from Grades 1-4.<sup>18</sup> Grade 1 is a partial occlusion of the portal vein by <50% of its lumen. Grade 2 is occlusion of the portal vein by >50% of its lumen with or without minimal extension into the superior mesenteric vein. Grade 3 is complete thrombosis of portal vein and proximal superior mesenteric vein with the distal superior mesenteric vein unoccluded. Grade 4 is complete thrombosis of the portal vein and the proximal and distal superior mesenteric veins.

Another proposed classification depends on the anatomic and functional aspects of the thrombus (Table 1).<sup>19</sup> The thrombus is classified based on the site, the degree of occlusion, duration and presentation, extent, and presence of underlying liver disease.

## DIAGNOSIS

In a suspected case of PVT, the first step in diagnostic imaging is ultrasound (Figure).<sup>20</sup> This has a low cost and good sensitivity and specificity that increase with increasing grade. The sensitivity of greyscale ultrasonography is 100% with complete PVT with an accuracy of 88-98%. False negative results can occur in incomplete PVT and isolated superior mesenteric vein thrombosis. Positive sonographic findings include recognition of a hyperechoic mass within the portal vein, portal vein distention in which the diameter is greater than its normal range of 13-15 mm, and the presence of collaterals with

**Table 1. Anatomic-functional classification of PVT in cirrhosis**

Site	Type 1 – only trunk Type 2a – only 1 branch; 2b – both branches Type 3 – trunk and branches
Degree of occlusion	O: occlusive, no visible flow in PV lumen on imaging or Doppler study NO: nonocclusive, visible flow in PV lumen on imaging or Doppler study
Duration and presentation	R: Recent – first time detected, hyperdense thrombus on imaging, absent or limited collateral circulation, or dilated PV at site of occlusion As: Asymptomatic S: Symptomatic – acute PVT features, with or without bowel ischemia Ch: Chronic – no hyperdense thrombus, previously diagnosed PVT, portal cavernoma As: Asymptomatic S: symptomatic – features of portal hypertension
Extent of PV occlusion	S: Splenic vein M: Mesenteric vein SM: both
Type and presence of underlying liver disease	Cirrhotic, noncirrhotic liver disease, post-liver transplant, hepatocellular carcinoma, local malignancies, and associated conditions

Table adapted from Sarin et al.

cavernous transformation.<sup>21</sup> There is a lack of an echogenic thrombotic mass in the portal vein lumen in 10-33% of patients; in these cases a color Doppler ultrasound should be performed.<sup>22</sup> The diagnostic finding on Doppler ultrasound would be the elimination of flow through the vein.

Contrast enhanced ultrasonography (CEUS) can be used to visualize the intrahepatic microvasculature of the portal system and can help determine if the PVT is caused by hepatocellular carcinoma (HCC) or a non-malignant disease.<sup>21</sup> Contrast-enhanced ultrasonography is recommended to confirm or exclude thrombosis in difficult cases and has a sensitivity of 95%.<sup>20</sup>

Ultrasound is limited with reduced visualization in obese patients and in patients with abundant bowel gas. In cases of insufficient visualization, contrast-enhanced computed tomography (CECT) or contrast-enhanced magnetic resonance imaging (CEMRI) should be used.<sup>20</sup> Computed tomography is preferred in unstable patients with acute abdominal pain, due to its time sensitive advantage (Figure). Contrast enhanced computed tomography and CEMRI offer the ability to detect bowel ischemia, septic foci, and malignancy and have more sensitivity in detecting thrombosis in the superior mesenteric and splenic veins.<sup>20</sup> Contrast enhanced computed tomography or CEMRI is also mandatory to evaluate the extent of

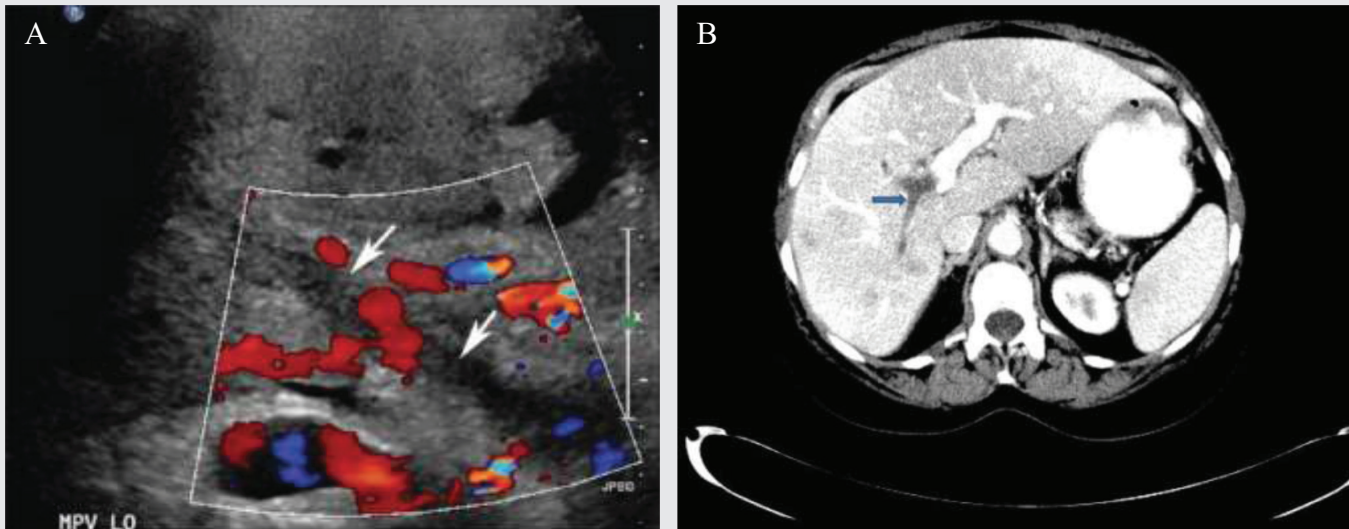
thrombosis after the diagnosis of PVT is made to map porto-systemic collaterals to plan recanalization interventions. The risks of CECT and CEMRI include ionizing radiation, allergic reactions, and nephrotoxicity; CEMRI is contraindicated in patients with acute renal failure due to an increased risk of nephrogenic systemic fibrosis. Non-enhanced MRI have shown some utility in visualizing the portal vein in studies; however, this has not yet translated into its incorporation into clinical guidelines.<sup>23,24</sup>

Myeloproliferative disorders, factor V Leiden, antiphospholipid antibody, and protein C and S deficiency are other causes to be included in the differential diagnosis of PVT.<sup>25</sup>

## MANAGEMENT

### ANTICOAGULATION

A small, randomized controlled trial at a single center with 70 patients tested the efficacy of enoxaparin



**Figure.** Images of portal vein thrombosis. A) Color Doppler ultrasound after liver transplant with arrows pointing to an echogenic thrombus in the main portal vein.<sup>1</sup> B) Contrast CT with thrombosis in the right portal vein.<sup>2</sup>

Both figures were downloaded on 9/7/2018 from the OPENi beta repository in the media collection in the Texas Tech University Health Sciences Center Library in Lubbock, Texas. Citations are <sup>1</sup> Sanyal R, et al. Postoperative doppler evaluation of liver transplants. *Indian J Radiology Imaging* 2014;24(4):360–6. and <sup>2</sup> Gajendran M, et al. Diverticulitis complicated by pylephlebitis: a case report. *J Medical Case Reports* 2011;5(1):514.

prophylaxis for patients with liver cirrhosis. At 96 weeks of the trial, zero patients in the treatment arm developed PVT compared to 10 of 36 (27.7%) control patients. In addition, liver decompensation occurred less frequently, and survival was higher in the treatment group than in the controls. There were no hemorrhagic complications reported.<sup>26</sup> The small sample size in this study introduces uncertainty about the outcome, and it is unclear if the mortality benefits of anticoagulation were due to decreased development of PVT or decreased progression of cirrhosis. One possible explanation for the benefit of prophylactic enoxaparin might involve decreased progression of cirrhosis, if the ischemic liver cirrhosis theory (ILC) is true.<sup>27</sup> The ILC is a theoretical model that postulates that chronic ischemia from disruption and damage of the microvasculature of the liver causes microvascular thrombosis which leads to hepatocyte proliferation and fibrosis. Prophylactic anticoagulation could slow this process.<sup>28</sup>

A recent meta-analysis of comparative studies analyzed data from eight different studies with 353 patients to assess the effects of anticoagulant therapy in cirrhotic patients with PVT compared to a control group not receiving anticoagulation.<sup>29</sup> In the patients who underwent anticoagulation as opposed to no therapy, recanalization rates were 71% compared to 42%, respectively. In six of the studies (225 patients), anticoagulation achieved total recanalization in 53% of patients compared to 33% in patients with no treatment. In six of the studies (257 patients), the rates of reported bleeding with either major or minor bleeds were the same at 11%. Rates of spontaneous variceal bleeding recorded in four studies (158 patients) were significantly lower in patients who received anticoagulants than those who did not; recanalization potentially reduces pressure in the portal system reducing the rate of variceal bleeding. In these studies, either warfarin or low-molecular-weight heparin (LMWH) was used. Warfarin reduced PVT progression, whereas LMWH reduced progression and was effective in resolution of clot as well. Both agents had similar safety profiles. Other non-comparative observational studies also report similar results; however, multicenter randomized controlled trials are needed to provide more information about safety in these patients.<sup>30</sup> Similarly, in a retrospective review,

danaparoid sodium was effective in reducing PVT volume with no adverse effects.<sup>31</sup> In another study, a 2 week course of danaparoid sodium followed by edoxaban had a greater reduction in volume of PVT than warfarin after 6 months.<sup>32</sup>

Two recent retrospective reviews have analyzed the safety of direct oral anticoagulants for PVT in cirrhosis.<sup>33,34</sup> In comparison with LMWH, direct oral anticoagulants caused significantly fewer major bleeding episodes (defined as fatal bleeding, bleeding in critical organs, or bleeding causing hemoglobin to fall >2 gm/dl or requiring >2 units of blood transfusion).<sup>34</sup> Although the safety data seem promising, larger studies are needed to determine the efficacy and safety of newer direct oral anticoagulants.

The timing of initiation of anticoagulation therapy could also affect recanalization rates. A prospective study of 56 patients indicated that anticoagulation started <6 months from the formation of thrombi predicted recanalization.<sup>35</sup> Similar results were seen in a retrospective review which concluded that the only factor significantly associated with recanalization was early initiation of therapy, particularly in the first 2 weeks.<sup>36</sup>

#### TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

Transjugular intrahepatic portosystemic shunt (TIPS) procedures have been used as another treatment option for PVT recanalization in cirrhotic patients. The TIPS procedure involves creating a shunt between the systemic and portal venous systems, which reduces portal venous pressures and venous stasis causing reversal of PVTs. In a prospective study of 70 patients, TIPS achieved complete recanalization in 57% of patients, a marked decrease of thrombosis in 30% of patients, and no improvement in 13%. Most patients (95%) with complete recanalization maintained a patent portal vein for 24 months.<sup>37</sup> Complications for TIPS in this study, such as hepatic encephalopathy and thrombosis of the stent, were similar to the rates of TIPS procedures in patients without PVT. Continued anticoagulation following a TIPS procedure does not provide any additional benefit to TIPS alone in maintenance of recanalization of PVT according to a recent randomized controlled

trial.<sup>38</sup> These results might suggest that venous stasis contributes more to the development of PVT than an imbalance in prothrombotic and anticoagulant factors.

Transjugular intrahepatic portosystemic shunts have been usually used in cases with acute or subacute PVT or in cases with failed anticoagulation treatment; benefit is limited in patients with extensive chronic PVT due to the difficulty of finding a placement site for the shunt.<sup>39</sup> However, a new novel approach, portal vein recanalization transjugular intrahepatic portosystemic shunt (PVR-TIPS), has shown to be a safe and effective option for treatment of chronic PVT before liver transplantation.<sup>40</sup> This procedure involves a transplenic rather than a transhepatic approach.<sup>41</sup>

## CONCLUSION

Recent studies have established diagnostic and treatment protocols for portal vein thrombosis in cirrhotic liver disease. Grey-scale and color Doppler ultrasound are low cost diagnostic tools for PVT. Contrast enhanced imaging can be used in more difficult to visualize cases. Portal vein thrombosis in cirrhotic liver disease has historically been a challenge to treat due to the concept of treating thrombosis in a coagulopathic state. Recent studies have shown that both anticoagulant treatment and TIPS procedures can safely recanalize portal veins with clots. More randomized controlled trials are needed to confirm these results and to compare the efficacy of newer direct oral anticoagulants.

**Article citation:** Adams L, Ball S. Diagnosis and management of portal vein thrombosis in patients with cirrhosis of liver. *The Southwest Respiratory and Critical Care Chronicles* 2018;6(26):10–16

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**Submitted:** 2/3/2018

**Accepted:** 8/1/2018

**Reviewer:** Sreeram Parupudi

**Conflicts of interest:** none

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