

Evolution of Nonmalignant Portal Vein Thrombosis in Liver Cirrhosis: A Pictorial Review

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Portal vein thrombosis (PVT) is a common complication in liver cirrhosis, especially in advanced cirrhosis. It may be related to a higher risk of liver-related events and liver function deterioration. Imaging examinations can not only provide an accurate diagnosis of PVT, such as the extent of thrombus involvement and the degree of lumen occupied, but also identify the nature of thrombus (i.e., benign/malignant and acute/chronic). Evolution of PVT, mainly including development, recanalization, progression, stability, and recurrence, could also be assessed based on the imaging examinations. This article briefly reviews the pathophysiology, diagnosis, classification, and evolution of PVT with an emphasis on their computed tomography imaging features.

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INTRODUCTION

Portal vein thrombosis (PVT) is defined as a thrombus occupying the portal vein trunk and intrahepatic portal vein branches, sometimes with extension into the mesenteric vein or splenic vein (1). Owing to the progress of imaging techniques and medical awareness, PVT has been increasingly diagnosed. Liver cirrhosis is the most common cause of nonmalignant PVT (2). In turn, PVT is also a frequent complication of liver cirrhosis with a prevalence ranging from 1% to 26% (3,4), which increases with the severity of liver disease (5). The prevalence of PVT in compensated cirrhosis, decompensated cirrhosis, and liver transplantation candidates is 1%–5%, 10%–25%, and 8%–25%, respectively (5). PVT is associated with early mortality and graft failure after liver transplantation (6,7), although its effects on the outcomes of cirrhotic patients who are neither at the liver transplantation waiting list nor have undergone liver transplantations have not been fully elucidated (8,9). On the other hand, the influence of the dynamic change of PVT on the prognosis of patients with cirrhosis needs to be further elucidated. But, it seems that patients with progressed PVT have worse outcomes than those with improved or stable PVT (10,11). Early identification and assessment of PVT evolution potentially contributes to tailor treatment strategies, improving the prognosis and avoiding the potential risks related to invasive therapy. The current article aims to briefly review the pathophysiology, diagnosis, classification, and evolution of PVT, with an emphasis on imaging

features. Management of PVT in liver cirrhosis, mainly including anticoagulation, thrombolysis, and transjugular intrahepatic portosystemic shunt, has been widely discussed by recent articles and guidelines (1,2,12) and is beyond the scope of this article.

PATHOPHYSIOLOGY OF PVT IN CIRRHOSIS

Virchow's triad—mainly including hypercoagulability, portal flow stasis, and vascular endothelial injury—is the mainstay explanation for the formation of PVT in patients with liver cirrhosis (4,13). Hypercoagulability is frequently observed in liver cirrhosis (14,15), which can manifest as decreased protein C (16), plasma metalloprotease ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13) (17), and plasminogen (18), as well as increased factor VIII (19), von Willebrand factor (20), and plasminogen activator inhibitor (18). By comparison, portal flow stasis makes a greater contribution on the occurrence of PVT in liver cirrhosis (21). A reduced portal flow velocity of less than 15 cm/s increases the risk of PVT by 6- to 24-fold in patients with liver cirrhosis (22–24), but such an association is not confirmed by a prospective study (25). Factors causing direct or indirect damage to the portal vascular endothelium, such as intra-abdominal trauma or surgery (26,27), endoscopic variceal treatment (28), inflammation (29), or endotoxemia (30), can contribute to the development of PVT in liver cirrhosis.

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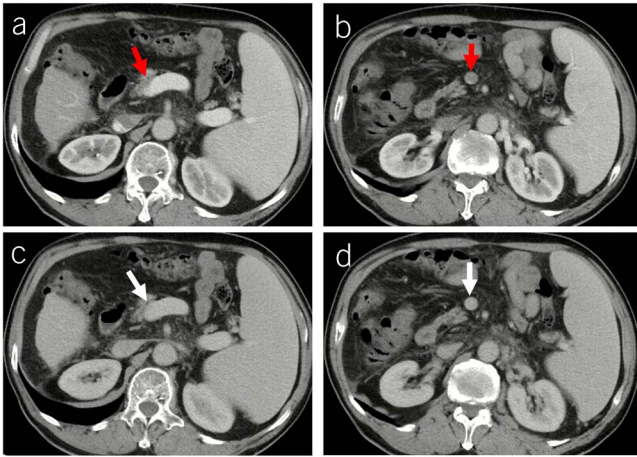


Figure 1. Diagnostic pitfalls of PVT caused by poor-quality CT images. Contrast-enhanced axial CT scans at the portal venous phase showed a mural thrombus occupying the confluence of SMV and splenic vein (red arrow, **a**) and a complete thrombus occupying the SMV (red arrow, **b**). Contrast-enhanced axial CT scans at the equilibrium phase showed patent confluence of SMV and splenic vein (white arrow, **c**) and SMV (white arrow, **d**). Therefore, mural thrombus shown at portal venous phase may be due to insufficient filling of contrast agent in the confluence of SMV and splenic vein, and complete thrombus may be due to no filling of contrast agent in the SMV. CT, computed tomography; PVT, portal vein thrombosis; SMV, superior mesenteric vein.

DIAGNOSIS OF PVT IN CIRRHOSIS

Ultrasound is the first-line screening approach for the suspicion of PVT, whereas contrast-enhanced computed tomography (CT) images are highly accurate and reliable for the diagnosis of PVT, especially for the assessment of thrombosis extension (31,32). Partial PVT often manifests as a filling defect within the portal venous system lumen and complete PVT as an absence of contrast agents within the lumen. Once acute thrombus forms, it is likely that the diameter of the obstructed vessel will be enlarged (31), and acute/fresh thrombus sometimes manifests as hyperdense on non-contrast-enhanced CT images (33). If a chronic thrombus persists, the obstructed vessel would become obliterated and evolve into a fibrotic cord. Concomitantly, multiple small and tortuous vessels would develop around the obstructed intrahepatic portal branches, portal trunk, and/or superior mesenteric vein (SMV), a radiological finding that is referred to as a cavernous transformation of the portal vein (CTPV).

In the general population, the capture of portal venous phase images needs a delay of 60–70 seconds after the injection of contrast agents, but a greater delay of 80 seconds is needed in

cirrhotic patients because of their decreased portal flow velocity (34). Failure in acquiring optimal contrast-enhanced CT images at the portal venous phase produces poor-quality images, in which contrast agents are insufficiently or hardly filled within the portal venous system lumen, leading to a false-positive radiological finding of partial or complete PVT (Figure 1). In addition, as the bile duct runs in parallel with the portal vein, a mildly dilated bile duct can be characterized as a low density near the portal vein on contrast-enhanced CT images, sometimes being mistaken as a thrombus occupying the portal vein lumen (Figure 2). For these reasons, the accuracy of the PVT diagnosis depends on the awareness about diagnostic pitfalls, which can be avoided by reviewing the images on multiple cross-sectional layers.

Malignant invasion into the portal vein lumen is a common condition in patients with a confirmed diagnosis of hepatocellular carcinoma, which sometimes mimics PVT. Unlike benign PVT, which has an 1-year survival rate of 81%–96% after liver transplantation (35–37), malignant portal vein invasion has a median survival time of only 2.7 months (38) and is often considered a contraindication to liver transplantation (39). Therefore, how to differentiate between benign thrombus and malignant invasion is very important. Because malignant invasion is composed by tumor tissue, often rich in arterial blood supply, a punctate or linear enhancement in the “thrombus” can be seen at the arterial phase of contrast-enhanced CT scans (Figure 3). Besides, venous expansion, neovascularity, adjacency to hepatocellular carcinoma lesions, and disruption of vein walls are other contrast-enhanced CT features of malignant invasion (40–46). A combination of these features with an α -fetoprotein concentration of >1,000 ng/dL can diagnose malignant invasion with a sensitivity of 100% and a specificity of 93.6% (45). Contrast-enhanced ultrasonography (47) and magnetic resonance imaging (48) are alternative approaches for identifying tumoral invasion into portal vein. Certainly, pathological evaluation is still the gold standard criterion for distinguishing benign thrombus from malignant invasion.

CLASSIFICATION OF PVT IN CIRRHOSIS

Identification of characteristics of PVT is of great significance to determine the necessity of anticoagulation therapy and feasibility of liver transplantation. Until now, at least 11 classifications have been developed to assess the degree, extent, and/or duration of PVT in patients with liver cirrhosis (46,49–59). Yerdel’s classification (53) is the most widely used to select the type of liver transplantation procedure, according to the degree of thrombotic filling of the portal lumen and the involvement of SMV. However,

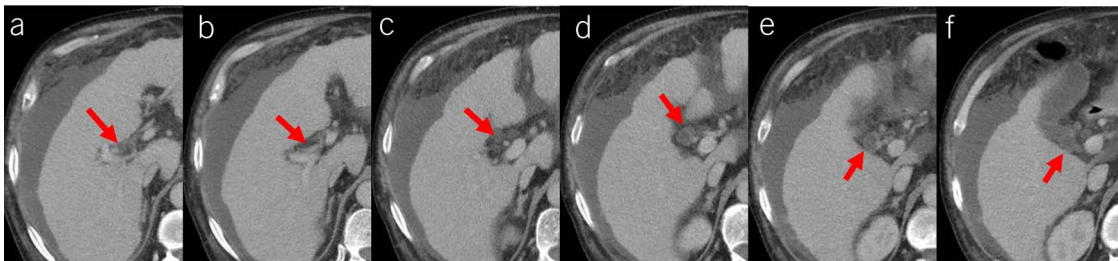


Figure 2. Diagnostic pitfall of PVT caused by a slightly dilated bile duct. Contrast-enhanced axial CT scans showed a thrombus-like hypodense occupying the right portal vein branch near the hepatic hilum (red arrow, **a**). After continuously reviewing multiple CT layers, such a thrombus-like hypodensity should be a slightly dilated bile duct (red arrows, **b–f**). CT, computed tomography; PVT, portal vein thrombosis.

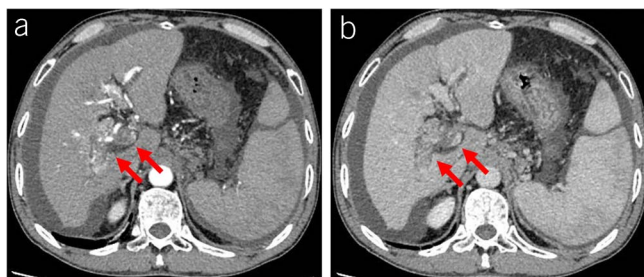


Figure 3. Malignant invasion into the portal vein in a patient with liver cirrhosis and hepatocellular carcinoma. (a) Contrast-enhanced CT scans at the arterial phase showed thread-like enhancement within the thrombus, venous expansion, and disruption of vein walls (red arrows). (b) Contrast-enhanced CT scans at the portal venous phase showed venous expansion and disruption of vein walls (red arrows). CT, computed tomography.

this classification is limited to the evaluation of inherent portal venous system vessels, rather than that of spontaneous or surgical portosystemic shunts and large collaterals secondary to portal hypertension that can also be used for portal reconstruction during liver transplantation. Accordingly, Bhangui et al. (59) proposed a novel classification, which considers the presence of splenorenal shunt, large gastric vein, pericholedochal varix, and mesocaval shunt for guiding renoportal anastomosis, gastric vein-portal anastomosis, varix-portal anastomosis, and cavoportal anastomosis, respectively.

Except for evaluating the technical feasibility and outcomes of liver transplantation, the classifications of PVT should be worthwhile for assessing the need of antithrombotic treatment in non-liver transplantation candidates with liver cirrhosis. They should also consider the need of preventive or therapeutic strategies for portal hypertension-related complications. For this reason, the

classification proposed by Sarin et al. (58) is more comprehensive in terms of the degree, extension, and duration of PVT. However, it seems a bit complicated. More recently, the Chinese consensus has proposed a simplified classification of PVT in liver cirrhosis based on the severity of thrombosis within each vessel (46) (Figure 4), which is potentially helpful to standardize the evolution of PVT and to evaluate the efficacy of anticoagulation therapy in a unanimous manner. Of course, the clinical applicability of any classification should be further confirmed.

The stage of PVT is traditionally classified as acute and chronic. Acute PVT is often considered when acute abdominal pain related to intestinal ischemia develops for a short duration of less than 60 days (56,58), which is often disproportionate to abdominal tenderness on physical examinations (60). Chronic PVT is defined as the presence of CTPV on images and/or abdominal symptoms for a duration of more than 60 days. However, it should be noted that the symptom, duration, and CTPV are not the independent criteria for staging PVT. Therefore, such a definition has been questioned (56,61). First, acute symptoms related to intestinal ischemia are noticeable only if the thrombus extends to the SMV (62). It is extremely rare in liver cirrhosis in clinical practice. Second, given that PVT is incidentally diagnosed in most patients with liver cirrhosis, it is often difficult to determine the onset of PVT. Third, CTPV rarely develops in the settings of partial PVT, despite its duration being longer than 3 months (56). By comparison, cavernous collateral vessels can develop as early as less than 6 days in the settings of occlusive PVT (63). Considering the limitations of the currently available staging system, the Chinese consensus has updated the stage of PVT as acute symptomatic and non-acute symptomatic to stratify the candidates who should undergo antithrombotic therapy and wait-and-see strategy, respectively (46). After a comprehensive evaluation

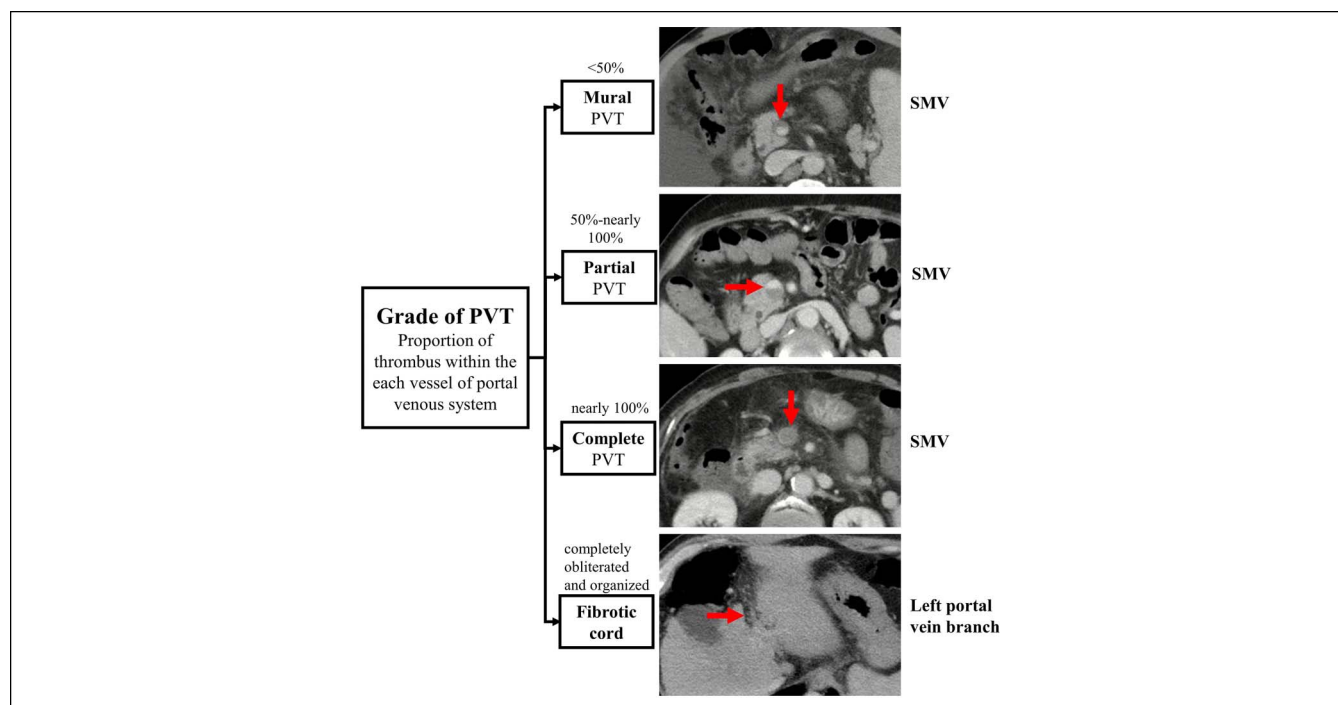


Figure 4. Classification of grade of PVT in liver cirrhosis according to the Chinese consensus. The red arrows indicate the thrombus. PVT, portal vein thrombosis; SMV, superior mesenteric vein.

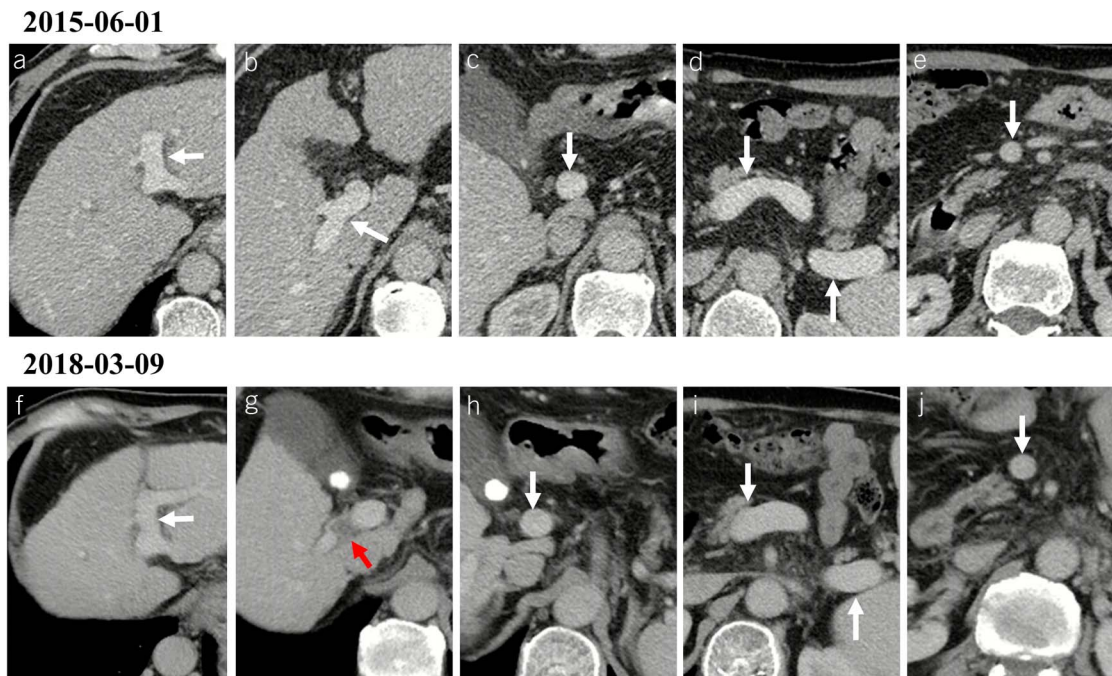


Figure 5. Development of PVT in a male patient with alcoholic liver cirrhosis. (a–e) Contrast-enhanced axial CT scans on June 1, 2015, showed patent portal venous system vessels, including left portal vein branch (a), right portal vein branch (b), portal vein trunk (c), confluence of SMV and splenic vein (d), splenic vein (d), and SMV (e). The score of each vessel was 0, 0, 0, 0, 0, and 0, respectively. (f–j) Contrast-enhanced axial CT scans on March 9, 2018, showed that *de novo* thrombus occupied the right portal vein branch (red arrow), while the other portal venous system vessels were still patent. The score of left portal vein branch, right portal vein branch, portal vein trunk, confluence of SMV and splenic vein, splenic vein, and SMV was 0, 2, 0, 0, 0, and 0, respectively. The total PVT score at baseline and during follow-up was 0 and 2, respectively, suggesting the development of PVT. Notes: The red arrows indicate the thrombus, and the white arrows indicate patent vessels. CT, computed tomography; PVT, portal vein thrombosis; SMV, superior mesenteric vein.

of disease severity and adequate prevention of gastrointestinal bleeding, antithrombotic therapy should be immediately given in cirrhotic patients with acute symptomatic PVT, and surgeons should be timely consulted in those with a suspicion of intestinal ischemia. Decision of antithrombotic treatment is closely dependent on the grade and extent of PVT in cirrhotic patients with non-acute symptomatic PVT (46).

EVOLUTION OF PVT IN CIRRHOSIS

The evolution of PVT in cirrhosis mainly includes development, complete or partial recanalization, progression, stability, and recurrence (46).

Development of PVT

Development of PVT refers to the formation of *de novo* thrombus into the portal venous system in the absence of previous PVT (Figure 5). The cumulative 1-year incidence of PVT in cirrhosis is heterogeneous among studies, ranging from 4% to 18% (22,23,64,65). Most of *de novo* PVT are partial (64,66). The most common site for *de novo* PVT is the portal vein, followed by the SMV and splenic vein (23). A decreased portal vein flow velocity has been recognized as the most important predictor for *de novo* PVT in liver cirrhosis (64–66). Presence of large-size esophageal varices (66) and high-flow collateral varices (64,67) can produce the portal vein stealing effect, thus reducing the portal flow velocity and precipitating *de novo* PVT. In addition, the use of nonselective beta-blockers (NSBBs), which can significantly decrease heart rate and cardiac output and reduce portal blood flow, may be associated with an increased risk of PVT (25,68). However, it should be noted that such a potential harmful effect of

NSBBs cannot counteract its benefits in the prevention of first variceal bleeding and variceal rebleeding which have been well confirmed by high-quality studies and recommended by mainstream practice guidelines and consensus (57,69).

Recanalization of PVT

Recanalization of PVT is classified as complete or partial. Complete recanalization is defined as complete resolution of a previous thrombus into the lumen of the portal venous system (Figure 6). The definition of partial recanalization is inconsistent among the previous studies (11,70–76). Partial recanalization often refers to more than 50% reduction of previous thrombus without thrombus extension (70,71,74–76) (Figure 6).

Among patients with liver cirrhosis, spontaneous recanalization of PVT can be observed in the absence of antithrombotic treatment, which has been recognized as “transient PVT” (77). Its incidence ranges from 0% to 57% (3,7,11,64,70,75,76,78–82). A smaller diameter and flow volume of maximum portal collateral vessels may be associated with spontaneous recanalization of PVT (64). But, there may not be any significant influence of PVT (duration, degree, and location) and patient (severity of liver cirrhosis and portal hypertension) characteristics on spontaneous recanalization of PVT (11).

Recanalization of PVT in liver cirrhosis can be further improved by anticoagulation therapy, with an overall recanalization rate of 16.7%–80% and a complete recanalization rate of 23%–72% (3,70,76,78–84). Hepatic reserve, nature of PVT, and timing of anticoagulation therapy are related to the probability of recanalization of PVT. In details, Child-Pugh class B/C, high model for end-stage liver disease score (73,83), and presence of

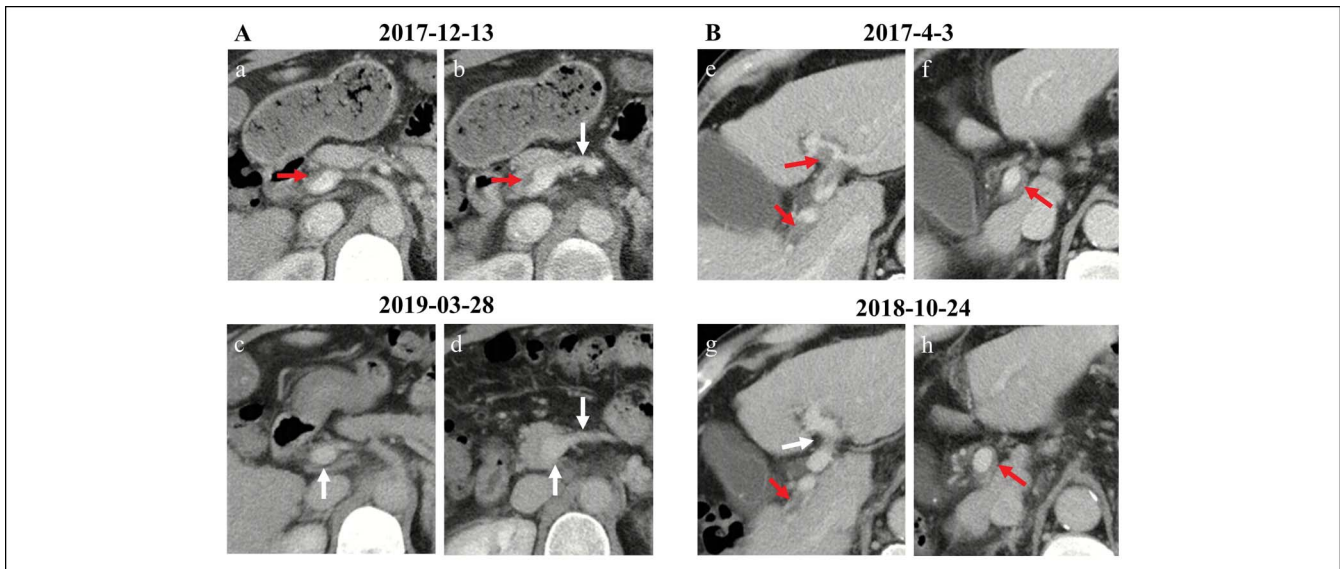
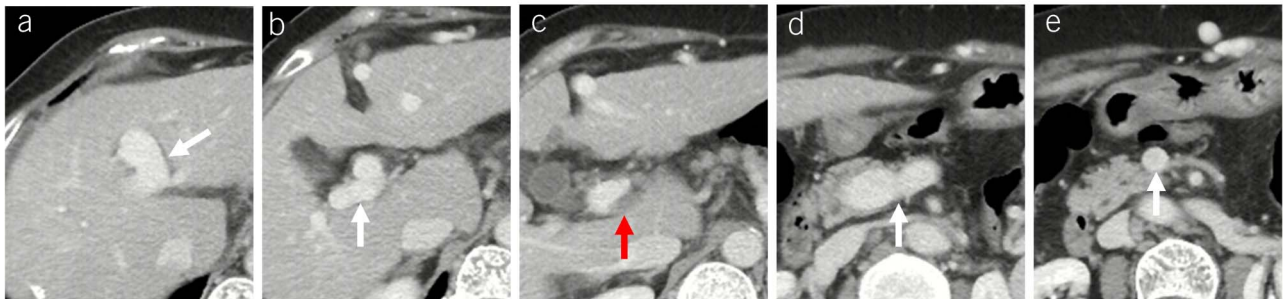


Figure 6. Recanalization of PVT in liver cirrhosis. **(A)** Complete recanalization of PVT in a male patient with hepatitis C virus–related cirrhosis. Contrast-enhanced axial CT scans on December 13, 2017, showed a thrombus occupying the portal vein trunk **(a)** and confluence of SMV and splenic vein **(b)**. Contrast-enhanced axial CT scans on March 28, 2019, showed patent portal venous system vessels **(c, d)**. **(B)** Partial recanalization of PVT in a male patient with alcoholic liver cirrhosis. Contrast-enhanced axial CT scans on April 3, 2017, showed a thrombus occupying the left portal vein branch **(e)**, right portal vein branch **(e)**, and portal vein trunk **(f)**. Contrast-enhanced axial CT scans on October 24, 2018, showed that the thrombus within the left portal vein branch disappeared, but the previous thrombus remained within the right portal vein branch **(g)** and portal vein trunk **(h)**. Notes: The red arrows indicate the thrombus, and the white arrows indicate patent vessels. CT, computed tomography; PVT, portal vein thrombosis; SMV, superior mesenteric vein.

portal hypertension (78) are associated with decreased portal vein recanalization; more extensive PVT (85), complete thrombus (86), and thrombus age of more than 6 months (86) negatively correlate with portal vein recanalization; and early initiation of

anticoagulation therapy can increase portal vein recanalization (70,78,87). In addition, recent evidence suggests that anticoagulation should improve survival (75,83,84) and hepatic function (88) in cirrhotic patients with PVT. However, whether

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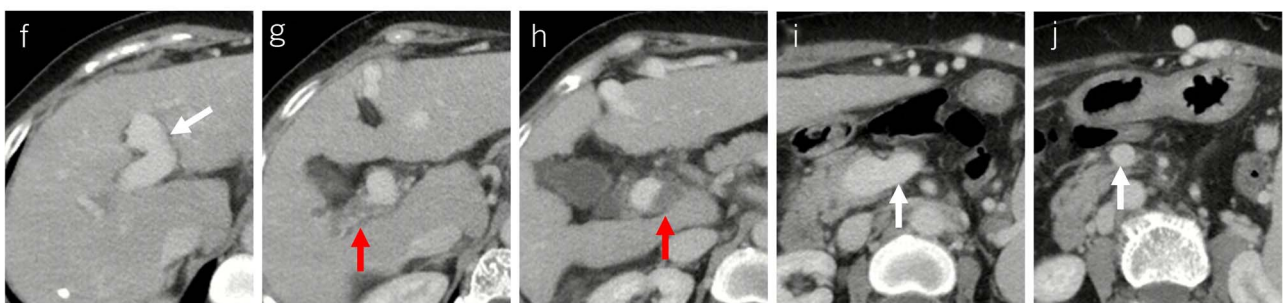


Figure 7. Progression of PVT in a female patient with liver cirrhosis. **(a–e)** Contrast-enhanced axial CT scans on May 22, 2019, showed a thrombus occupying the portal vein trunk **(c)**. **(f–j)** Contrast-enhanced axial CT scans on August 31, 2019, showed that the previous thrombus within the portal vein trunk had enlarged **(h)** with an extension to the right portal vein branch **(g)**. Notes: The red arrows indicate the thrombus, and the white arrows indicate patent vessels. CT, computed tomography; PVT, portal vein thrombosis.

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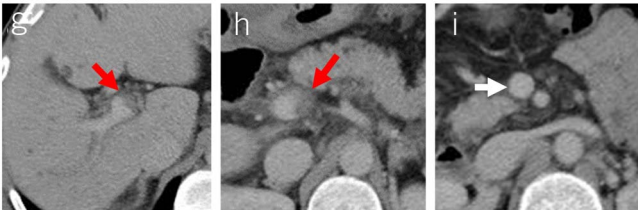


Figure 8. Recurrence of PVT after recanalization in a male patient with alcoholic liver cirrhosis. (a–c) Contrast-enhanced axial CT scans on January 19, 2018, showed a thrombus occupying the SMV (c). (d–f) Contrast-enhanced axial MRI scans on July 7, 2019, showed patent portal venous system vessels. (g–i) Contrast-enhanced axial CT scans on July 23, 2020, showed a new thrombus occupying the right portal vein branch (g) and portal vein trunk (h). Notes: The red arrows indicate the thrombus, and the white arrows indicate patent vessels. CT, computed tomography; MRI, magnetic resonance imaging; PVT, portal vein thrombosis; SMV, superior mesenteric vein.

such benefits are due to the use of anticoagulation itself or portal vein recanalization achieved by anticoagulation needs to be further explored.

Progression of PVT

Progression of PVT refers to an increase in the degree of a pre-existing thrombus in the portal venous system and/or an extension of a pre-existing thrombus into the previously patent vessels (Figure 7).

Progression is more common than spontaneous recanalization in cirrhotic patients with untreated PVT. Its incidence is approximately 0%–71% (3,11,66,70,78–81). Cirrhotic patients treated with NSBBs may have a higher risk of PVT progression than those without NSBBs (89). However, it should be noted that the evidence is insufficient from only 1 retrospective cohort study of 43 cirrhotic patients with a small number of progressing PVT events. On the other hand, cirrhotic patients who have received anticoagulation therapy have a 2- to 11-fold reduction in the risk of PVT progression (3,78,79).

Recurrence of PVT

Recurrence of PVT is defined as new thrombus development into the portal venous system after complete recanalization of a previous thrombus (Figure 8).

In cirrhotic patients who develop spontaneous recanalization of PVT, the incidence of PVT recurrence is 4.2%–45% (64,66,80). Therefore, regular imaging examination is required to monitor the patency of the portal venous system lumen. Until now, no risk factor associated with recurrence of PVT has been identified in cases of spontaneous recanalization.

In cirrhotic patients who achieve portal vein recanalization after anticoagulant therapy, the incidence of PVT recurrence after termination of anticoagulation is 3.7%–53% (74,75,82,84,87,90–92). Elder thrombus, extensive thrombus, thrombogenic gene polymorphism, and use of warfarin correlate with PVT recurrence in cirrhotic patients receiving rivaroxaban or warfarin (74).

PVT score for evaluation of PVT evolution

Dynamic change of thrombus severity is often heterogeneous among different portal venous system vessels. For example, in the same patient, the degree of thrombus may be reduced while its extension is aggravated; or the degree of thrombus is decreased in some portal venous system vessels, but increased in others. Accordingly, we have attempted to holistically quantify PVT evolution by “PVT score” (89,93), which refers to the sum of the score calculated based on the proportion of thrombus occupying each portal venous system vessel, including left portal vein branch, right portal vein branch, portal vein trunk, confluence of SMV and splenic vein, splenic vein, and SMV. In details, less than 50% occlusion (mural thrombus), 50%–80% occlusion (partial thrombus), more than 80% occlusion (complete thrombus), and fibrotic cord are counted as 1, 2, 3, and 4 points, respectively (Figure 4).

CONCLUSION

Repeated imaging examinations are useful to dynamically assess the evolution of PVT in liver cirrhosis, including development, recanalization, progression, and recurrence. However, risk factors for predicting the evolution of PVT have not been sufficiently recognized yet. In future, the role of procoagulants, natural anticoagulants, and global hemostatic status indicated by thromboelastometry and thrombin generation assay for predicting the evolution of PVT in liver cirrhosis should be further considered. In addition, the impact of PVT evolution on the mortality and decompensation in patients with liver cirrhosis remains to be explored in large-scale cohort studies.

CONFLICTS OF INTEREST

Guarantor of the article: Xingshun Qi, MD.

Specific author contributions: Shixue Xu, MS, and Xiaozhong Guo, MD, contributed equally to this work. S.X. and X.Q. drafted the manuscript. All the authors provided critical revision of the manuscript for important intellectual content. All authors are responsible for the overall contents of the article.

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