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Consensus for management of portal vein thrombosis in liver cirrhosis (2020, Shanghai)

Hepatobiliary Disease Study Group, Chinese Society of Gastroenterology, Chinese Medical Association

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Portal vein thrombosis (PVT) is a common and severe complication of liver cirrhosis. So far, there have been few consensuses or practice guidelines on the management of PVT in liver cirrhosis. In this expert consensus, we systematically review the epidemiology, risk factors, imaging examinations, diagnosis, assessment of disease severity, and treatment strategy of PVT in liver cirrhosis, based on the most recent evidence and expert opinions, to further standardize the diagnosis and treatment of the disease in clinical practice.

KEYWORDS

anticoagulation, liver cirrhosis, portal vein, thrombosis, transjugular intrahepatic portasystemic shunt

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1 | BACKGROUND

Portal vein thrombosis (PVT) refers to the development of thrombosis within the main trunk of portal vein and/or left and right intrahepatic portal vein branches, with or without the involvement of mesenteric and splenic veins. Acute PVT may lead to mesenteric ischemia and even severe adverse outcomes, such as intestinal necrosis; chronic PVT can cause portal vein occlusion or portal cavernoma, thereby resulting in secondary portal hypertension. Among patients with liver cirrhosis, the onset of PVT is generally insidious and it is usually diagnosed accidentally during routine imaging examination. PVT should also be differentiated from tumor thrombosis. Due to cirrhosis-related coagulation disorder and a high risk of hemorrhage, it is often difficult to give anticoagulation therapy to cirrhotic patients with PVT. Although accumulating studies have revealed that anticoagulation therapy can promote portal vein recanalization and improve liver function, the optimal timing and type of anticoagulants in such patients have not yet been determined. Transjugular intrahepatic portosystemic shunt (TIPS) has been employed for the treatment of PVT in liver cirrhosis; however, the candidates for TIPS should be further identified. So far, there have been few consensuses or practice guidelines on the management of PVT in liver cirrhosis. Therefore, the Hepatobiliary Disease Study Group of the Chinese Society of Gastroenterology of the Chinese Medical Association invited experts in this field to discuss and draft the present consensus based on the most recent evidence and expert opinions from representative original researches and meta-analyses.

2 | EPIDEMIOLOGY

Statement 1. PVT is a common complication of liver cirrhosis.

The prevalence of PVT in patients with liver cirrhosis is 5%–20%,[1,2] with an annual incidence of 3%–17%.[3-6] The prevalence and incidence of the disease vary among studies due to the differences in patients' demographic characteristics, etiology, clinical manifestations, severity of liver dysfunction, and diagnostic approaches.

In two cohort studies in which a majority of included patients had Child–Pugh A cirrhosis, the 1- and 3-year cumulative incidence of PVT was 4.6% and 8.2%, and 3.7% and 7.6%, respectively.[3,4] In another two cohort studies that mainly included patients with Child–Pugh B or C cirrhosis, the 1-year cumulative incidence of PVT was 16.4% and 17.9%.[5,6] A large-scale multicenter retrospective study in China demonstrated that cirrhotic patients with acute decompensation events had a significantly higher prevalence of PVT than those without (9.36% vs 5.24%).[7] Taken together, PVT is a common complication of liver cirrhosis and is associated with the severity of liver dysfunction.

3 | IMPACT OF PVT ON THE PROGNOSIS OF LIVER CIRRHOSIS

Statement 2. PVT negatively influences patient prognosis in liver cirrhosis.

PVT may increase the risk of long-term mortality, hemorrhage, ascites, acute kidney injury, and post-transplant mortality.[8,9] Therefore, the stage, grade, and extension of PVT should be considered for the assessment of patient prognosis in liver cirrhosis. But the impact of PVT on patient prognosis of liver cirrhosis may depend upon the severity of underlying liver diseases. Senzolo et al found that unrecanalized PVT after anticoagulation therapy increased the mortality of patients with Child–Pugh B and C cirrhosis only.[10] However, another study in which only patients with Child–Pugh A and B cirrhosis were included showed that PVT did not increase the risk of hepatic decompensation or death.[3] Taken together, PVT may primarily affect the prognosis of cirrhotic patients with poor liver function. Additionally, when PVT affects the mesenteric vein, liver transplantation would become more technically complicated.

4 | RISK FACTORS OF PVT IN LIVER CIRRHOSIS

Virchow triad includes decreased blood flow, local vessel injury, and hypercoagulable state,[11] which can also be used for the interpretation of the pathogenesis of PVT in liver cirrhosis.

4.1 | Decreased portal vein velocity

Statement 3. Decreased portal vein velocity increases the risk of PVT in liver cirrhosis.

Patients with liver cirrhosis often have fibrous tissue proliferation, hepatic sinusoid destruction, and vascular distortion and occlusion, thereby leading to decreased portal vein velocity into the liver. Several studies have shown that portal vein velocity of <15 cm/s detected by Doppler ultrasound increases the risk of developing PVT by 10–20 folds.[5,6,12] Nonselective β-blocker, one of the most commonly used drugs for portal hypertension in liver cirrhosis, can reduce the portal vein velocity, leading to a 4-fold higher risk of PVT.[13,14]

4.2 | Local vessel injury

Statement 4. Splenectomy is the most common cause of local vessel injury for PVT in China.

Abdominal surgery is the most common cause of local vessel injury for liver cirrhosis-related PVT. In China, splenectomy is a major surgical approach for the treatment of portal hypertension and hypersplenism

in liver cirrhosis.[15] The incidence of PVT after open or laparoscopic splenectomy is approximately 22%. Splenectomy can lead to a 10-fold increased risk of developing PVT.[16] Therefore, whether splenectomy should be performed in patients with gastroesophageal varices (GEV) and hypersplenism must be considered with caution; preventive strategies against post-splenectomy PVT needed to be considered as well.

4.3 | Thrombophilia

Statement 5. Inherited thrombophilia may not be a major risk factor for cirrhosis-related PVT in China, while acquired thrombophilia may be a potential risk factor in some of the patients. Screening for myeloproliferative neoplasms is recommended for patients with splenomegaly but normal or elevated platelet count.

Thrombophilia refers to inherited or acquired hypercoagulable states secondary to hemostasis defect.[17] Inherited thrombophilia associated with venous thromboembolism mainly includes methylenetetrahydrofolate reductase (*MTHFR*) C677T gene mutation, factor V Leiden mutation, prothrombin G20210A gene mutation, and inherited deficiency of natural anticoagulant proteins (ie, antithrombin, protein C, and protein S).[18-20] Meta-analyses have reported that the *MTHFR* C677T gene mutation, factor V Leiden mutation, and prothrombin G20210A gene mutation, but not the deficiency of antithrombin, protein C, or protein S, are associated with the development of PVT in liver cirrhosis.[21-23] The factor V Leiden mutation and prothrombin G20210A gene mutation are rare in the Chinese Han population; therefore, they might not be associated with the development of PVT in Chinese cirrhotic patients.[24] Acquired thrombophilia, caused by myeloproliferative neoplasms (ie, primary polycythemia, essential thrombocytosis, and myelofibrosis), antiphospholipid syndrome, pregnancy, postpartum, oral contraceptives, paroxysmal nocturnal hemoglobinuria, and hyperhomocysteinemia, and so on, are also potential risk factors for PVT in patients with liver cirrhosis.[25] Notably, if a cirrhotic patient with PVT and splenomegaly has normal or elevated platelet count, myeloproliferative neoplasms should be considered.[26]

4.4 | Inflammation

Statement 6. Inflammation or infection of portal vein, abdominal cavity, and intestine may be important risk factors for PVT in liver cirrhosis.

Patients with liver cirrhosis often have an elevated level of intestinal endotoxin, which is related to enhanced thrombin generation in the portal vein system, thus results in hypercoagulable status.[27,28] Huang et al found that PVT is associated with elevated levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-α among cirrhotic patients with GEV.[29]

5 | IMAGING EXAMINATION OF PVT IN LIVER CIRRHOSIS

Statement 7. Doppler ultrasound is the first-line approach for the diagnosis of PVT in liver cirrhosis. Contrast-enhanced computed

tomography (CT) and magnetic resonance imaging (MRI) can be used to further confirm the diagnosis.

Imaging examination can be used to diagnose and evaluate the stage and severity of PVT and collateral vessels in cavernous transformation of the portal vein, which are closely related to patient prognosis and treatment selection of PVT. Imaging examinations primarily include Doppler ultrasound, contrast-enhanced CT, MRI, and angiography.

Doppler ultrasound is feasible and readily available in clinical practice, which can be used as the first-line option for screening and evaluation of PVT in liver cirrhosis, with a reasonable diagnostic sensitivity and specificity.[30] On Doppler ultrasound, PVT is characterized as intraluminal hyper-echoic or iso-echoic fillings, or as luminal dilatation in the acute stage of PVT; cavernous transformation of the portal vein is characterized as the development of multiple fine collateral vessels around the portal vein. Doppler ultrasound can also be used to detect the portal vein velocity. However, the findings of Doppler ultrasound are significantly influenced by the operators' skills as well as the presence of abdominal fluid and gas.

CT and MRI scans, especially with portal vein reconstruction, can be used to further confirm the diagnosis of PVT. They are advantageous in assessing thrombosis within the mesenteric vein and splenic vein. PVT manifests as a filling defect within the lumen of the portal vein; whereas new onset of PVT can sometimes present as a high-density image within the lumen of the portal vein on plain CT and MRI scans. Portal cavernoma can manifest as many fine and tortuous collateral vessels around the obstructed portal vein on contrast-enhanced CT and MRI. CT scan can also be used for the evaluation of intestinal ischemia and necrosis. Due to its invasiveness, direct or indirect portal vein angiography is rarely used for the diagnosis of PVT, but mainly for the evaluation of portal vein before vascular interventional procedures. Notably, angiography may not be superior to contrast-enhanced CT for the diagnosis of mural or partial PVT.

6 | DIAGNOSIS AND ASSESSMENT OF PVT IN LIVER CIRRHOSIS

6.1 | Diagnosis and differential diagnosis

Statement 8. PVT in liver cirrhosis can be diagnosed based on the history of chronic liver disease and typical imaging characteristics. Liver biopsy should be performed when imaging examination shows the presence of PVT but without sufficient evidence for cirrhosis. Cirrhotic PVT should be differentiated from noncirrhotic PVT and portal vein tumor thrombosis based on a combination of biochemical indicators, serum α-fetoprotein levels, imaging characteristics, and pathological findings.

PVT in liver cirrhosis is usually diagnosed based on the history of chronic liver disease and typical imaging characteristics. Doppler ultrasound is the first-line examination for the diagnosis of PVT in cirrhosis. Additionally, contrast-enhanced CT and MRI scans can be used to confirm the diagnosis of PVT and to assess the grade of thrombosis. If

there is no sufficient evidence for liver cirrhosis in patients with confirmed PVT, other diagnostic approaches, such as hepatic venous pressure gradient measurement and histological examination by transjugular liver biopsy, would be useful for the diagnosis of liver cirrhosis. PVT in liver cirrhosis should be differentiated from noncirrhotic PVT and portal vein tumor thrombosis based on a combination of clinical history, imaging characteristics, and serum α-fetoprotein levels. Portal vein tumor thrombosis is often characterized as portal vein dilatation, enhancement of the thrombus, neovascularization, tumor lesions adjacent to thrombus, and/or elevated serum α-fetoprotein levels of over 1000 ng/dL. Portal vein tumor thrombosis can be considered when meeting at least three of the abovementioned characteristics, with a sensitivity of 100%, a specificity of 94%, a positive predictive value of 80%, and a negative predictive value of 100%.[25]

6.2 | Assessment

6.2.1 | Staging

Statement 9. Cirrhotic PVT can be classified as acute symptomatic and non-acute symptomatic stages.

Statement 10. Acute symptomatic PVT should be considered in a cirrhotic patient suffering from acute abdominal pain regardless of fever or intestinal obstruction.

Staging of PVT is critical for the establishment of subsequent antithrombotic therapeutic strategy. PVT in liver cirrhosis is mainly identified accidentally during routine imaging examination for the assessment of the severity of liver cirrhosis or liver cancer surveillance. Therefore, it is often difficult to accurately determine the time of onset of PVT. Thus, classifying acute and chronic cirrhotic PVT based on the timing of the disease onset is not recommended. Instead, such classification is recommended to be performed based on PVT-related clinical manifestations. Acute symptomatic PVT is considered when a patient with liver cirrhosis manifests acute abdominal pain (symptoms and signs may be inconsistent at the disease onset), nausea, and vomiting, etc; otherwise, non-acute symptomatic PVT should be considered. In clinical practice, when acute abdominal pain lasts for over 24 hours in a cirrhotic patient regardless of fever or intestinal obstruction, acute symptomatic PVT should be highly suspected and imaging examinations are needed to confirm the diagnosis. If a cirrhotic patient presents with fever and chill with or without abdominal infection, blood culture should be routinely performed.

6.2.2 | Grade

Statement 11. Grade of cirrhotic PVT can be classified as mural, partial, complete obstruction, and fibrotic cord.

The Yerdel classification, which is currently the most commonly used system for grading PVT,[31] includes the following: (a) thrombus occlusion of less than 50% of the portal vein, with or without minimal extension of the mesenteric vein; (b) thrombus occlusion of more than 50% of the portal vein, including complete thrombosis, with or without minimal extension of the mesenteric vein; (c) complete thrombosis of the portal vein and proximal mesenteric vein; and (d) complete thrombosis of the portal vein and proximal and distal mesenteric veins. Notably, the Yerdel classification is proposed to predict primarily the technical complexity and risk of postoperative complications before liver transplantation, but its role in the selection of antithrombotic strategy still needs to be clarified. The Baveno VI consensus has also proposed a grading system for PVT.[32] However, this grading system is not designed particularly for PVT in liver cirrhosis, but involves nearly all conditions related to PVT, such as malignant, non-cirrhotic, and post-transplant PVT. Currently, PVT in liver cirrhosis is classified as mural, partial, and complete obstruction, and fibrotic cord, which seems to be more convenient and helpful to guide clinical decisions. Mural PVT refers to thrombus occlusion of less than 50% of the portal vein. Complete PVT refers to complete thrombosis of the portal vein.[33] Partial PVT refers to the grade of thrombosis between mural and complete PVT. And fibrotic cord refers to the portal vein completely obliterated and organized, in which the lumen of the portal vein cannot be identified by imaging examination.[34] Portal cavernoma can be frequently observed in cases of complete PVT and fibrotic cord.

6.2.3 | Evolution

Statement 12. Evolution of PVT in liver cirrhosis includes new onset, partial recanalization, complete recanalization, progression, stability, and recurrence.

Development and progression of PVT in liver cirrhosis should be dynamically evaluated to modify the treatment strategy in a timely fashion. Definition of changes of cirrhotic PVT is important for the standardization of the end-points in future studies. According to the development and changes in the grade of PVT, the evolution of cirrhotic PVT is defined as follows. New-onset PVT refers to the development of de novo PVT in the absence of thrombosis on prior imaging examination. Partial recanalization refers to the improvement of severity of persistent PVT by no less than one grade. Complete recanalization refers to the disappearance of prior PVT. Progression refers to the deterioration of severity of persistent PVT by no less than one grade. Stability refers to the persistence of prior PVT without any change of PVT grade; while recurrence refers to recurrent thrombus after the disappearance of prior PVT.

7 | STEPWISE TREATMENT STRATEGY OF PVT IN LIVER CIRRHOSIS

Statement 13. When a cirrhotic patient with acute symptomatic PVT develops intestinal ischemia or necrosis, surgeons should be actively consulted.

Statement 14. For a cirrhotic patient with non-acute symptomatic PVT, the initiation of antithrombotic therapy should depend on the grade, extension, and dynamic evolution of PVT.

When deciding whether and when to start treatment for cirrhotic PVT and what treatment strategy is to be used, the stage, grade,
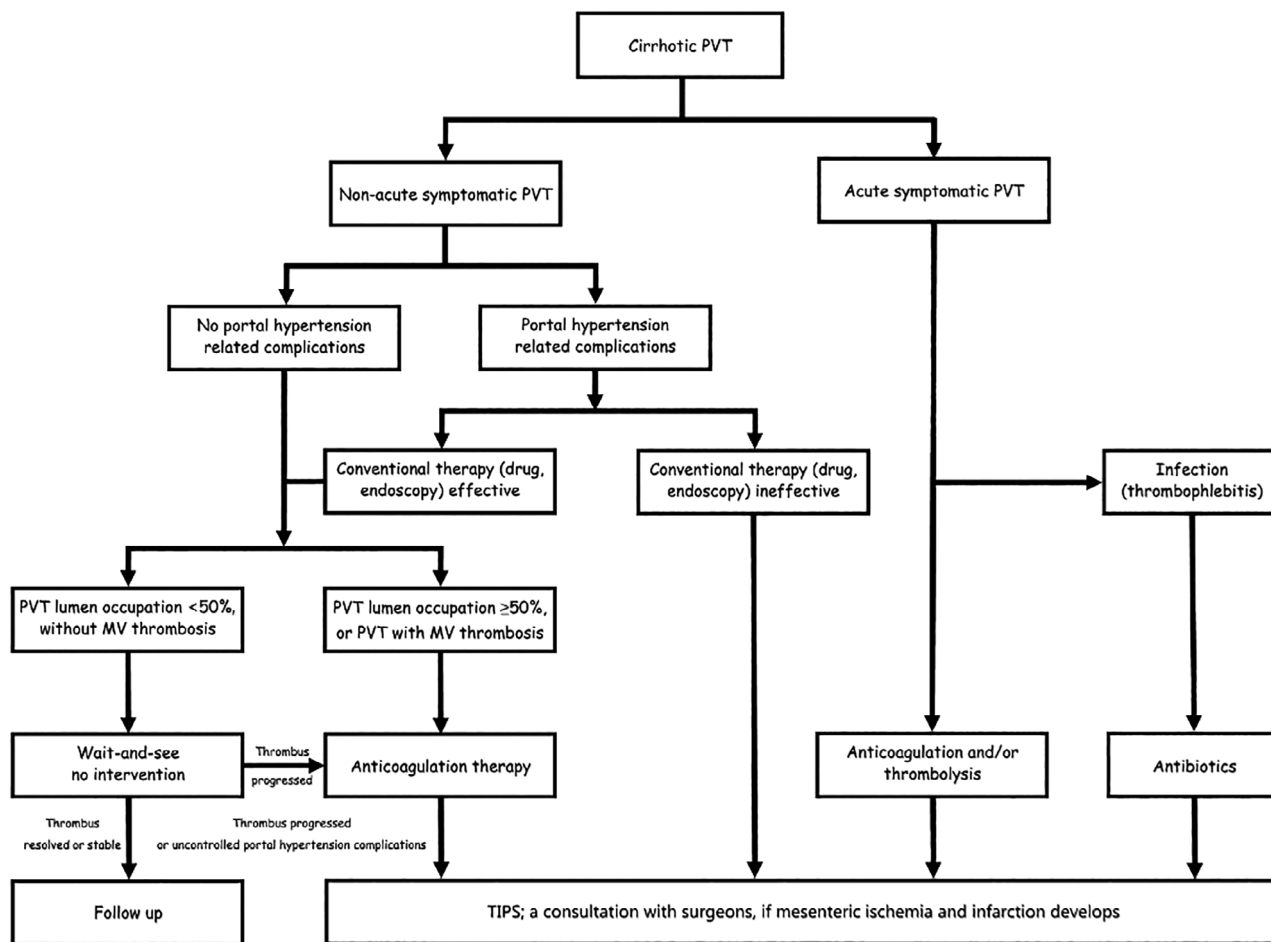
FIGURE 1 A stepwise treatment strategy of cirrhotic portal vein thrombosis (PVT). Abbreviations: MV, mesentreric vein; TIPS, transjugular intrahepatic portosystemic shunt

extension and changes of PVT, clinical manifestations, complications of portal hypertension, and risk of bleeding need to be considered.[35] A preliminary stepwise treatment strategy of PVT in liver cirrhosis has been proposed by the present consensus (Fig. 1). Acute symptomatic PVT should be treated with antithrombotic agents in a timely fashion to recanalize the portal vein and prevent thrombus extension. If antithrombotic therapy is ineffective for acute symptomatic PVT, and intestinal ischemia and necrosis develop, surgeons should be actively consulted to identify the necessity and feasibility of surgery. Gastroesophageal variceal bleeding or high-risk GEV should be treated before anticoagulation therapy. TIPS should be considered for cirrhotic patients with PVT who still suffer recurrent gastroesophageal variceal bleeding after conventional pharmacological and endoscopic therapy. A "wait-and-see" strategy can be employed for mural PVT without involvement of mesenteric veins, since some of them may spontaneously improve or even disappear without anticoagulation therapy; while PVT may progress in others, necessitating the use of anticoagulation therapy. Additionally, anticoagulation therapy should be given to patients with partial PVT with involvement of mesenteric vein.

8 | TREATMENT FOR PVT IN LIVER CIRRHOSIS

The mainstay treatment for cirrhotic PVT includes anticoagulation, thrombolysis, and TIPS. In some cirrhotic patients with PVT, thrombosis will be spontaneously recanalized without the use of antithrombotic therapy or other interventional vascular therapy, which is termed transient PVT in liver cirrhosis.[25,36] However, it is still difficult to identify such patients or to define the interval of follow-up imaging examinations. On the other hand, a higher recanalization rate of PVT is positively associated with a shorter interval between the diagnosis of PVT and initiation of anticoagulation therapy.[37,38] Therefore, the optimal timing of treatment for PVT should be further explored in more studies.

8.1 | Anticoagulation

Statement 15. Major indications for anticoagulation therapy include acute symptomatic PVT, candidates for liver transplantation, and thrombosis extension into the mesenteric veins. However,

anticoagulation therapy should be postponed for patients with a recent history of bleeding, high-risk GEV, and severe thrombocytopenia.

Statement 16. Endoscopic examination and blood coagulation test should be performed to evaluate the risk of bleeding before initiation of anticoagulation for PVT in cirrhosis.

Statement 17. Before anticoagulation therapy, nonselective β-blockers and/or endoscopic variceal therapy should be considered as the primary prophylaxis of variceal bleeding in patients with cirrhotic PVT and high-risk GEV.

Statement 18. Before anticoagulation therapy, nonselective β-blocker combined with endoscopic variceal therapy should be considered as the secondary prophylaxis of variceal bleeding in patients with cirrhotic PVT and a previous history of gastroesophageal variceal bleeding.

The efficacy and safety of early anticoagulation therapy for acute nonmalignant and noncirrhotic PVT have been widely recognized.[39,40] By comparison, cirrhotic patients are at a high risk of bleeding from gastroesophageal variceal rupture and other sources, and often manifest as coagulation disorders, such as prolonged prothrombin time, elevated international normalized ratio (INR), and decreased platelet count. Therefore, whether and when to start anticoagulation therapy, as well as the methods of anticoagulant administration, should be cautiously evaluated. Two meta-analyses have reported that in cirrhotic PVT, the rate of portal vein recanalization, complete portal vein recanalization, and thrombus progression after anticoagulation therapy is 66%–71%, 41.5%–53%, and 5.7%–9%, respectively.[41,42] Both meta-analyses suggested that anticoagulation therapy significantly increases the rate of portal vein recanalization and complete portal vein recanalization, and reduce the rate of thrombus progression, while the risk of bleeding did not significantly differ between patients who received anticoagulation therapy and those who did not. Additionally, cohort studies have demonstrated survival benefits of anticoagulation therapy in cirrhotic patients with PVT, especially in those who have achieved complete portal vein recanalization.[43,44] However, there is a potential bias in the selection of patients who receive anticoagulation therapy among these studies. The patients receiving anticoagulation are often diagnosed with nonocclusive PVT and have relatively normal coagulation function and platelet count, no history of bleeding, no or low risk of GEV, and more preserved liver function, etc. By comparison, patients who have high-risk GEV and/or severe thrombocytopenia are less likely to receive anticoagulation therapy. Therefore, risk assessment and prophylaxis of bleeding by nonselective β-blocker and/or endoscopic variceal therapy should be given before anticoagulation therapy.

8.1.1 | Indications and contraindications for anticoagulation therapy

Anticoagulation therapy for cirrhotic PVT should be individualized. Major indications for anticoagulation therapy include acute symptomatic PVT, candidates for liver transplantation, and thrombosis extension into the mesenteric veins. Major contraindications for anticoagulation

therapy often include recent history of bleeding, high-risk GEV, and severe thrombocytopenia. However, the cut-off value of severe thrombocytopenia remains controversial. Even though some studies have revealed that a platelet count of $<50 \times 10^9$/L increases the risk of bleeding in cirrhotic patients,[17,32] others reported that the risk of bleeding was not increased in such patients. Moreover, anticoagulation therapy should be cautiously given in patients with advanced liver cirrhosis, especially those with Child–Pugh C cirrhosis.[17]

8.1.2 | Types of anticoagulants

Statement 19. Low-molecular-weight heparin and direct oral anticoagulants are relatively safe and effective in patients with compensated liver cirrhosis and PVT. But the safety and efficacy of direct oral anticoagulants in cirrhotic patients with Child–Pugh C cirrhosis need further evaluation.

Anticoagulants include vitamin K antagonists, heparins, and direct oral anticoagulants. Warfarin is a major type of vitamin K antagonist. The therapeutic dosage of warfarin can be achieved with close monitoring of INR. Traditionally, the level of INR should be elevated to $2–3 \times$ upper limit of normal (ULN). Notably, INR is often high in patients with end-stage liver disease in the absence of warfarin use. Therefore, how to accurately monitor the use of warfarin in patients with liver cirrhosis is still uncertain. In addition, the INR may easily be influenced by food and drugs, which further increases the difficulty in assessing the efficacy of warfarin.

Heparins mainly include unfractionated heparin, low-molecular-weight heparin (LMWH), and fondaparinux. The therapeutic dose of unfractionated heparin can be achieved with close monitoring of activated partial thromboplastin time (APTT). Traditionally, the level of APTT should increase to $1.5–2.5 \times$ ULN. Notably, heparin-induced thrombocytopenia (HIT) often occurs within 5 days after the use of unfractionated heparin. Therefore, it has been recommended that platelet count should be monitored within 3–10 days after the use of unfractionated heparin. LMWH leads to a lower risk of HIT and bleeding compared with unfractionated heparin. Therefore, it is often unnecessary to monitor platelet count in patients receiving LMWH, while LMWH should be used with caution in those with renal insufficiency. Because LMWH needs to be injected subcutaneously, LMWH followed by oral anticoagulants can be given to patients with a poor compliance to the medication. A recent randomized controlled trial has revealed that 1-month subcutaneous injection of nadroparin calcium followed by 5-month oral administration of warfarin is effective and safe.[45] Fondaparinux has been reported to successfully recanalize PVT in seven patients with decompensated liver cirrhosis without bleeding complication or HIT.[46]

New direct oral anticoagulants include direct factor Xa inhibitors (ie, rivaroxaban and apixaban) and direct factor IIa inhibitors (ie, dabigatran). The safety and effectiveness of direct oral anticoagulants may be superior to those of traditional anticoagulants.[47,48] Direct factor Xa inhibitors can be safely given to patients with mild and moderate renal dysfunction. A multicenter survey of 38 cirrhotic patients by the Vascular Liver Disease Interest Group

Consortium demonstrated that the most commonly used type of direct oral anticoagulants was rivaroxaban, followed by dabigatran and apixaban, and that the selection of direct oral anticoagulants was primarily due to no need of monitoring INR.[49] An Egyptian randomized controlled trial compared the efficacy and safety of rivaroxaban with those of warfarin for acute non-neoplastic PVT secondary to splenectomy for splenomegaly (n = 76) or portal pyemia (n = 4) in patients with chronic hepatitis C. Rivaroxaban has significantly higher rates of complete (85% vs 45%) and partial (15% vs 0%) portal vein recanalization than warfarin, with significantly lower rate of gastrointestinal bleeding (0% vs 43.3%) and mortality (0% vs 36.4%).[50] These findings suggest that rivaroxaban is superior to warfarin for patients with liver disease-related PVT, but should be cautiously interpreted because of the limitation in patient selection. It should be noted that rivaroxaban, which is mainly metabolized by the liver, is suitable for Child–Pugh A cirrhotic patients, but should be used with caution for those with Child–Pugh B or C cirrhosis.

8.1.3 | Dosage of anticoagulants

The Chinese practice guideline for management of deep vein thrombosis recommended subcutaneous injection of LMWH at 100 U/kg every 12 hours.[51] The dosage of LWMH for cirrhotic PVT differ among studies, including nadroparin 5700 UI/day, nadroparin 85 IU/kg every 12 hours, and enoxaparin 200 U/kg·d^{-1}.[52-54] A clinical trial revealed that there was no significant difference in the rates of portal vein recanalization and variceal bleeding in cirrhotic PVT between enoxaparin 1 mg/kg every 12 hours and enoxaparin 1.5 mg/kg per day, while a dose of 1.5 mg/kg per day led to a higher risk of nonvariceal bleeding.[55] By comparison, rivaroxaban can often be administered at a fixed dose, with no need to adjust the dose according to the diet, body weight, and mild liver and kidney damage.

8.1.4 | Duration of anticoagulants

Statement 20. Long-term anticoagulation therapy should be considered in patients with mesenteric vein thrombosis or previous history of intestinal ischemia and necrosis, candidates for liver transplantation, and those with hereditary thrombophilia.

The Baveno VI consensus and the European Association for the Study of the Liver (EASL) clinical practice guideline recommend the followings: (a) duration of anticoagulation therapy should be more than 6 months; (b) anticoagulation therapy should be maintained for several months after complete portal vein recanalization or until liver transplantation; (c) long-term anticoagulation therapy should be considered in patients with mesenteric vein thrombosis or history of intestinal ischemia and necrosis, candidates for liver transplantation, or those with hereditary thrombophilia.[32,56] Six-month anticoagulation therapy may be insufficient to achieve portal vein recanalization in some cirrhotic patients with PVT; for such patients, the duration of

anticoagulation should be prolonged to 12 months.[37] Therefore, if portal vein recanalization has not been significantly improved after the first 6-month anticoagulation therapy, an extended anticoagulation protocol to 12 months should be attempted.

8.1.5 | Management of bleeding during anticoagulation therapy

Statement 21. If a bleeding event develops during anticoagulation therapy, the use of anticoagulants is recommended to be delayed or discontinued according to the severity of bleeding. Diagnostic and therapeutic endoscopy for gastrointestinal bleeding should be performed as soon as possible. Antagonists should be used for major/fatal bleeding, and transfusion of red blood cells, fresh-frozen plasma, and platelets should be given as replacement therapy.

When a bleeding event develops during anticoagulation therapy, the type and dosage of anticoagulants, and time of last anticoagulant administration should be reviewed first, and the tests of red blood cell, hemoglobin, and hematocrit, as well as liver, renal, and coagulation function should be performed to assess the severity of bleeding. Monitoring of blood drug concentration should also be done if possible. For patients with minor bleeding, anticoagulants should be delayed or discontinued, symptomatic treatments should be given, and type and dose of anticoagulants should be adjusted. If bleeding is not fatal, anticoagulants should be discontinued, mechanical compression on the bleeding site, fluid replacement, and transfusion of red blood cells, fresh-frozen plasma, and platelets should be employed; antagonists may be considered as well. If a patient develops gastrointestinal bleeding, endoscopy should be performed as early as possible to identify the source and etiology of bleeding, and the patient should be treated in accordance with the practice guidelines. If a fatal bleeding develops, anticoagulants should be immediately discontinued, a rescue treatment should be initiated, and antagonists should be prescribed.[54]

8.1.6 | Surveillance and follow-up after anticoagulation therapy

Statement 22. Portal vein patency should be under surveillance after successful anticoagulation therapy.

There is a risk of rethrombosis after portal vein recanalization is achieved by anticoagulation therapy. The rate of PVT recurrence after the discontinuation of anticoagulation is 27% and 38% during a median follow-up duration of 1.3 and 4 months, respectively.[37,54] Therefore, it is necessary to monitor the portal vein patency within 3 months after anticoagulation is discontinued.

8.2 | Thrombolysis

Statement 23. Efficacy and safety of thrombolysis for cirrhotic PVT should be further evaluated by more high-quality studies.

Evidence of thrombolysis for cirrhotic PVT is scarce. Thus, a thrombolysis protocol should be established according to the practice guidelines regarding management of deep vein thrombosis. In detail, several issues need to be clearly estimated before thrombolysis. First, the contraindications for thrombolysis should be avoided, such as recent history of major surgery and trauma, uncontrolled active bleeding, severe hypertension, and aortic dissection. Second, the patient's willingness and physical condition should be assessed, such as age, nutritional status, liver and kidney functions, as well as blood coagulation function. Finally, the indications for thrombolysis should be considered. The optimal indication for thrombolytic therapy is acute symptomatic PVT with an elevated D-dimer level. Notably, thrombolytic therapy is not indicated for either fibrotic cord or extensive portal cavernoma.

There are two major approaches of thrombolysis: local and systemic. Local catheter-directed thrombolysis can be performed via a percutaneous transhepatic, transjugular, or transmesenteric approach. Notably, a percutaneous transhepatic approach should be cautiously employed due to its potential risk of bleeding.[57] During thrombolytic therapy, the D-dimer level and coagulation function of the patients should be closely monitored to evaluate the risk of hemorrhagic complications. Portal vein patency should be evaluated at 3–5 days after thrombolytic therapy, and the duration of thrombolytic therapy should be 2 weeks at most. A continuous use of anticoagulants after thrombolysis and the duration of anticoagulation should be decided based on portal vein recanalization and the patient's overall condition.

In an Italian single-center study, nine cirrhotic patients with recent PVT received a continuous intravenous infusion of recombinant tissue plasminogen activator with a dose of 0.25 mg/kg·d^{-1} in combination with LMWH for a maximum duration of 7 days, of whom four achieved complete portal vein recanalization, four achieved partial portal vein recanalization, and the remaining one was stable; no clinically significant adverse events were reported.[58] Indirect thrombolysis via the superior mesenteric artery or direct thrombolysis via the portal vein may be effective and safe for the treatment of acute or subacute portal and mesenteric vein thrombosis in liver cirrhosis.[59,60] A randomized controlled trial also compared the efficacy of continuous infusion of urokinase with a dosage of 15 000 IU/kg·d^{-1} via the superior mesenteric artery with that of TIPS for cirrhotic PVT.[60] The rate of recanalization of main portal vein thrombosis was similar between the two groups, but urokinase infusion achieved a significantly higher rate of recanalization of superior mesenteric vein and splenic vein thrombosis with a lower incidence of hepatic encephalopathy.[60] Considering a potential risk of bleeding secondary to thrombolysis, its safety in cirrhotic patients with PVT should be confirmed by more high-quality studies.

9 | TIPS

Statement 24. Indications of TIPS for cirrhotic PVT include poor response to or contraindications for anticoagulation, ineffective conventional therapy for gastroesophageal variceal bleeding, or acute symptomatic PVT accompanied with gastroesophageal variceal bleeding.

TIPS can accelerate the portal vein inflow, which is beneficial for PVT recanalization.[61] The technical feasibility of TIPS in the settings of PVT has been widely recognized, but it remains technically difficult in patients with extensive obliteration of intrahepatic portal vein branches and fine collateral vessels. TIPS should be indicated for cirrhotic PVT if the treatment efficacy of anticoagulation is poor or there is a contraindication for anticoagulation; if conventional therapy is ineffective for gastroesophageal variceal bleeding in cirrhotic patients with PVT; or if acute symptomatic PVT is accompanied with gastroesophageal variceal bleeding. The role of early TIPS in cirrhotic patients with high-risk GEV and PVT should be further explored.

The efficacy and safety of TIPS for recanalization of PVT in liver cirrhosis have been widely confirmed in China. Compared with conventional endoscopy in combination with propranolol and anticoagulation, TIPS can significantly increase the rate of portal vein recanalization and decrease the rate of rebleeding, but without any survival benefit.[34,62-68] Considering the potential risk of peritoneal bleeding and pulmonary embolism, TIPS should be performed at highly experienced centers. Additionally, it should be recognized that TIPS would increase the technical difficulty of liver transplantation in the future.

10 | UNRESOLVED ISSUES

1. Early identification of cirrhotic patients at a high risk of PVT helps initiate the prophylactic strategy in a timely fashion. However, no model has been established so far to accurately predict the risk of PVT. Rotation thromboelastometry, thromboelastography, and thrombin generation assay can comprehensively assess the coagulation function, and their values in the prediction of the risk of PVT in liver cirrhosis should be further explored.

2. Early initiation of antithrombotic therapy can increase the rate of recanalization in cirrhotic PVT, but a proportion of patients with cirrhotic PVT can achieve spontaneous portal vein recanalization in the absence of antithrombotic therapy. Therefore, it is critical to identify the optimal timing of antithrombotic therapy for cirrhotic PVT.

3. The type, dosage, and duration of anticoagulants may influence the treatment outcomes of PVT in liver cirrhosis. Therefore, an anticoagulation strategy for cirrhotic PVT should be further optimized.

4. Hemorrhage is one of the most common adverse events of anticoagulants. On the other hand, cirrhotic patients are at a risk of gastrointestinal bleeding and often have thrombocytopenia. Taken together, early prediction and effective monitoring of bleeding in cirrhotic patients with PVT receiving anticoagulation is important. However, no specific approach has been established yet. Future studies should identify the cut-off value of thrombocytopenia for the prediction of bleeding after anticoagulation therapy and further explore the method to monitor the risk of bleeding in such patients.

5. Considering that thrombolytic therapy leads to a high risk of bleeding, further studies should be conducted on how to prevent bleeding in cirrhotic patients with PVT who receive thrombolysis.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

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