Chapter 4

Portal Vein Thrombosis in Liver Cirrhosis

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Abstract

In liver cirrhosis, portal vein thrombosis (PVT), which is defined as thrombosis that occurs within the main portal vein and intrahepatic portal branches, is one of the most common complications. High incidence of PVT in the setting of liver cirrhosis is mainly due to hypercoagulable state and altered dynamic of blood flow in the portal vein. The clinical manifestations of PVT are variable among different patients, so the diagnosis of PVT is mainly dependent on the imaging examinations, like ultrasound, computed tomography and magnetic resonance imaging. The overall goal of treatment for PVT can be summarized as reducing risk factors of PVT, thus to prevent further expansion of thrombus and maintain portal patency and prevent and treat the symptoms of PVT by anticoagulants, local thrombolysis, transjugular intrahepatic portosystemic shunt and/or surgery. In future, due to the progress in vascular imaging and innovation in clinical anti-thrombotic drug, PVT could be prevented and cured effectively.

Keywords: portal vein thrombosis, cirrhosis, management, anticoagulant

1. Introduction

Portal vein thrombosis (PVT) is diagnosed when a venous thrombosis occurs within the main portal vein and intrahepatic portal branches [1, 2]. In liver cirrhosis, especially in advanced stages, PVT is one of the most common complications [3–5]. High incidence of PVT in the setting of liver cirrhosis is mainly due to hypercoagulable state and altered dynamics of blood flow in the portal vein [6–8]. Moreover, PVT will deteriorate liver cirrhosis by increasing portal vein pressure and decreasing blood flow into liver. Under severe circumstances, it will worsen symptoms of cirrhosis such as ascites, upper gastrointestinal bleeding, intestinal avascular necrosis and so on [3, 4, 9–11]. However, 30–50% patients with PVT will spontaneously

alleviate or recover without any treatment [4, 10, 12, 13]. This highlights the over-diagnosis of PVT in cirrhosis and questions whether PVT treatment will benefit cirrhotic patients, especially when they are diagnosed incidentally on imaging. Right now, there is no guideline or expert consensus on how to manage cirrhotic patients with PVT. A meta-analysis which includes 3735 cirrhotic patients demonstrated that PVT negatively influenced both mortality and hepatic decompensation, despite its limitation of including heterogeneous populations [14]. However, another prospective multicenter study which includes 863 Child-Pugh class A and 380 class B cirrhotic patients found PVT was not a prognostic factor for either mortality or hepatic decompensation [15]. A study that only investigated 42 cirrhotic patients with extrahepatic nonmalignant partial PVT reported that no association was found between progression or regression of partial PVT and clinical outcomes. The model for end-stage liver disease **(**MELD) score, rather than PVT, was the predictor of worse prognosis in cirrhotic patients [16]. So, at present, the issue of whether PVT does or does not have influence on the natural history of cirrhosis is still controversial [17–19].

2. Prevalence

The prevalence and incidence of PVT in cirrhosis often varies from 1 to 28% among different studies depending on heterogeneity in diagnosis methods, different populations and variable follow-up time [16–22]. In a retrospective study of 150 patients with viral cirrhosis, the cumulative overall incidences of PVT were 12.8% at 1 year, 18.6% at 3 years, 20% at 5 years and 38.7% at 8–10 years, respectively [23]. In another study, which includes 701 cirrhosis patients without hepatocellular carcinoma, the incidence of PVT was 11.2% since they used ultrasound for diagnosis routinely [24]. PVT is more common in advanced cirrhosis and the incidence is positively related with the stage of cirrhosis, which is only 1% in compensated patients but 8.4% in severe cirrhosis waiting for liver transplantation [21, 25–28]. However, there are some limitations in these studies which weaken the magnitude and reliability of these conclusions like different subgroup patients and follow-up times as we previously mentioned. Violi et al. reported a study aimed at evaluating the prevalence of PVT in a broad spectrum of patients with cirrhosis and found 17% of 753 cirrhotic patients had PVT [29]. A multicenter randomized trial that includes 898 well-compensated cirrhosis patients reported that the 5-year cumulative incidence of PVT was 11.9% [30].

3. Pathophysiology

3.1. Hypercoagulable state of blood flow

After liver transplantation, the number of platelets will increase temporarily for a short time, which contributes to the hypercoagulable state of blood [31, 32]. That would be one of the significant reasons for PVT formation in liver transplantation patients. The study showed that surgery not only increased blood platelets but also activated their surface glycoprotein CD62P, reflecting the degree of platelet activation and causing a hypercoagulable state [33, 34]. Postoperative-elevated CD62P is closely related with PVT, which can be used as a sensitive

diagnostic biomarker of PVT [9, 35, 36]. Toshiki Matsui also reported that soluble form of glycoprotein VI, as a platelet activation marker, was associated with PVT formation after hepatectomy and splenectomy in patients with liver cirrhosis [37]. Another study from Poland found platelet aggregability was decreased in PVT patients [31]. In another logistic regression model, incidence of PVT was highly related with D-dimer and bilirubin [38, 39]. Additionally, increased whole blood viscosity due to increased number of erythrocytes and ability of aggregation as well as decreased deformability may be reasons for increased PVT formation [34, 40]. Both procoagulant and anticoagulant proteins decreased in liver cirrhosis patients at the same time, owing to decreased synthesis function of the liver, which often largely maintained in a dynamic balance [7, 8, 34, 41]. Therefore, the body is neither to bleed nor to form thrombosis. However, after liver transplantation surgery, venous injury would reduce the flow rate of portal vein; thus, anticoagulant-associated protein S and C decreased as well as anti-thrombin III [21]. Meanwhile, surgery consumes numerous coagulation factors. Factor VIII, VII factor-related antigens and anti-cardiolipin antibody increased, which both resulted in PVT formation. Factor VIII concentration and the ratio of the most powerful procoagulant (factor VIII) and anticoagulant (protein C) were considered as markers to indicate hypercoagulability [25, 38, 42–44]. Studies showed factor VIII was related to PVT in cirrhotic patients independently. Patients with factor VIII level above 129 IU/dl had six times the probability to PVT [45]. Some researchers reported in the literature that procoagulant gene mutations, including coagulation factor V Leiden G1691A, methylenetetrahydrofolate reductase C677T and prothrombin G20210A, may be associated with PVT [46, 47]. Recent studies showed that increased hemagglutinin activated fibrinolysin inhibition gene mutation and blood coagulation factor VII, which were closely related to the occurrence of PVT [1, 2].

3.2. Hemodynamic changes in the portal vein

PVT formation is associated with intrahepatic resistance and poor portal blood flow. Moreover, portal blood flow decreases more if cirrhosis progresses. That's why the incidence of PVT is much higher in advanced-stage cirrhotic patients compared with well-compensated ones [48]. Cirrhotic patients with PVT had low portal flow volumes and high collateral vessel flow velocity. Intraoperative clamp and squeeze will cause vein intimal injury, collagen exposure and activation of the coagulation system. After liver transplantation, blood flow in portal vein is relatively slow, which is easy to form turbulence and thrombosis [9, 25, 49, 50]. Portal vein blood flow velocity and PVT have an important relationship. Studies demonstrated that patients with portal vein blood flow <15 cm/s had higher incidence of PVT [17, 27, 50–52]. So, some researchers often regarded portal vein diameter as an independent risk factor for the formation of PVT. In short, because there are various changes in portal hemodynamics, the incidence of PVT is quite high after liver transplantation.

3.3. Endotoxinemia

Cirrhosis is more likely to damage intestinal mucosal barrier which facilitates bacterial translocation and endotoxinemia [53]. Endotoxinemia not only can increase portal vein pressure but also can activate coagulation cascade. That explains why it can increase the PVT incidence in the portal system [54].

4. Diagnosis

4.1. Clinical manifestations

A study which includes 79 cirrhotic patients has shown that 57% of PVT were symptomatic and among them 39% had gastrointestinal bleeding and 70% had intestinal infarction [24]. Abdominal pain is generally the earliest clinical symptom after the acute formation of PVT. Usually, abdominal pain is limited within a specific region while few are diffuse pain and intermittent colic pain with longer durations. Nausea and vomiting occur in 50% of PVT patients [3, 4, 51, 55–57]. A few patients will have diarrhea or bloody stool. If complete intestinal obstruction occurs suddenly, abdominal pain is paroxysmal accompanied by significant nausea, vomiting without fart and defecation. Under this circumstance, there are no obvious physical examination signs, that the degree of pain is not consistent with the signs of the abdomen [19, 58, 59]. Increased anterior hepatic obstructive factors will cause decreased portal vein blood flow which aggravates liver damage, increases portal pressure, causes repeated upper gastrointestinal bleeding and refractory ascites and so on. In some severe cases, clinical manifestations of intestinal necrosis such as persistent abdominal pain, bloating, hemafecia, hematemesis, shock and peritoneal irritation will occur [18, 24, 26]. Abdominal puncture can be bloody ascites. In the event of intestinal necrosis, disease mortality rate can rise to 20–60%. Patients often suffer from persistent abdominal pain, hemafecia, abdominal cramps, ascites, multiple organ failure and so on. For chronic PVT, patients will have refractory bloating, diarrhea, upper abdominal pain and ascites due to gastrointestinal congestion and insufficient perfusion of liver portal vein [24]. The clinical manifestations of PVT are variable among different patients, so the clinical diagnosis of PVT is mainly dependent on the imaging examination.

4.2. Imaging

Ultrasound, the most common imaging way, is simple and easy to accurately evaluate PVT [60]. Thus, it is the preferred imaging method for diagnosis. Ultrasound diagnosis of PVT is characterized by abnormal echo in the portal vein, unclear boundary with the wall, CDFI: no blood flow signal, portal venous cavernous hemangioma; portal vein expansion before thrombosis site; and no display of portal vein if PVT is formed within a wide range [11, 17, 18, 60, 61]. The sensitivity and specificity of ultrasonography to diagnose PVT are up to 60 and 100% [60, 62]. Ultrasound can clearly demonstrate the blood flow, vascular diameter and the changes and the presence of thrombi. Ultrasound can also determine the formation of collateral circulation simultaneously through CDFI. But the ultrasound cannot reflect directly the situation of the portal vein and its branches, and the experience of the operator affects the accuracy of the diagnosis. Ultrasound angiography or ultrasound endoscopy can diagnose PVT more accurately that even raises the diagnostic sensitivity to 81% [24]. Some authors recommended contrasting enhanced ultrasound as the first-line imaging and "gold standard method" for the diagnosis of PVT [63, 64]. But ultrasound angiography and endoscopy also have some limitations. Firstly, they cannot evaluate the portal vein within the part of the liver and superior mesenteric vein end accurately. Moreover, they cannot assess the surrounding organs which may be affected by PVT [50, 63, 64].

Enhanced computer tomography (CT) or enhanced magnetic resonance imaging (MRI) examination by intravenous injection contrast can effectively solve the above deficiencies. By comparison with contrast, we can discover intraluminal filling defects and perfusion conditions for nearby organs at different times of the imaging process. CT angiography (CTA) and magnetic resonance angiography (MRA) greatly increase the accuracy of diagnosis. Some studies have showed that the sensitivity and the specificity for CTA were 86 and 95%. For MRA, the sensitivity was 100% and specificity was 98% [60, 65–67]. Typical CT signs of PVT are very intuitive: no-enhanced low-density intraluminal stripe or massive lesions within portal static. Occasionally, CT can also find an enhanced ring around thrombus due to nourishing small blood vessels. Moreover, CT can also help to diagnose primary liver cancer, cirrhosis and evaluate intestinal ischemia and necrosis. CTA has several advantages including short scan time, fast imaging speed and reduced motion artifact [67]. However, its main drawbacks can be related to some complications like contrast agent allergy, contrast agent nephropathy and other adverse reactions. The safety of MRA contract is significantly better than that of CTA. But MRA has the same disadvantages like motion artifacts, long-signal acquisition time and limited imaging range [66]. Therefore, patients with suspicious PVT should be enrolled in contract CT or MRI imaging, which can be more accurate for clinical diagnosis.

Angiography is the traditional method for diagnosis of PVT. It is not the routine examination of PVT because of its invasive feature. Angiography includes two categories: indirect and direct. Indirect angiography is through splenic artery and superior mesenteric artery to image [2, 65]. In this way, we can see the portal vein filling defect as well as the collateral circulation. The most important thing is we can put the catheter into the superior mesenteric artery and/or splenic artery branch to infuse thrombolytic drugs after indirect angiography. It means we can finish diagnosis and follow treatment after invasive process at one time. Direct angiography is divided into: percutaneous transhepatic portal angiography, which can display directly portal vein system and evaluate portal hemodynamics, and umbilical portal vein angiography, which is indicated for splenic vein thrombosis, spleen resection and failure of arterial portal angiography [50].

4.3. Laboratory tests

Usually, prothrombin time (PT) and activated partial thromboplastin time (APTT) were used as predictors for the coagulation state with cirrhosis, and even the predictive ability was poor [7, 34, 68]. Because they could not explain and represent natural anticoagulants such as antithrombin and protein C in vivo, the thrombin generation test, which used tissue factor as trigger and phospholipids as platelet substitutes, was considered more appropriate for evaluating thrombin generation. The test was regarded as representation of the balance between the pro- and anticoagulant proteins in plasma [33, 44]. Another test named thromboelastography (TEG) can monitor all kinds of hemostatic functions (coagulation, anticoagulation, fibrinolysis) continuously to predict thrombosis formation and dissolution dynamically. This test also emphasized the dynamic assessment of balanced status in blood coagulation and anticoagulation process [17, 18]. This is a new laboratory test to evaluate whether the blood is hypercoagulable, whether there is the formation of thrombus and whether the thrombus is stable. The effectiveness of clinical application needs to be further studied. Additionally, we

can exclude PVT patients with a 90% negative predictive value when the D-dimer level is less than 1.82 mg/l [38, 39, 69, 70]. Systemic evaluation of coagulation tests, including PT, international standardization ratio, partial thromboplastin time, and so on, could not fully assess the patient's coagulation abnormalities. Dynamic monitoring of vitamin K-related coagulation factors, fibrinogen, platelet function, fibrinolysis status as well as other coagulation factors simultaneously is essential.

5. Classification

According to PVT imaging findings preoperatively, Yerdel found a classification system as the following: grade I, <50% portal vein obstruction with or without micro-thrombus of the superior mesenteric vein; grade II, >50% portal vein obstruction with or without micro-thrombus of the superior mesenteric vein; grade III, complete portal vein and proximal superior mesenteric vein obstruction; and grade IV, complete portal vein and entire superior mesenteric vein obstruction [71].

6. PVT treatment

The overall goal of treatment for PVT can be summarized as reducing risk factors of PVT, thus to prevent further expansion of thrombus and maintain portal patency, prevent and treat the symptoms of PVT. For acute PVT, the aim is to prevent thrombus extension and intestinal infarction, whereas for chronic PVT, it is to prevent recurrent thrombosis, gastrointestinal bleeding and portal cholangiopathy [20, 35, 51].

6.1. Non-surgical treatment

The incidence of PVT is high in cirrhotic patients, but clinical studies found that 30–50% of patients with PVT could alleviate without any treatment. Longest diameter of portal vein and blood flow of the largest collateral circulation vein were closely related with the incidence of spontaneous alleviation in PVT patients [1, 21]. But another study demonstrated that untreated PVT was associated with increased mortality, especially in patients with low Child-Pugh scores. And there were strong correlations between anticoagulation therapy and lower thrombus progress rate as well as higher recanalization rate [11, 72, 73]. Furthermore, PVT has been reported as an independent risk factor for recurrent and refractory acute variceal bleeding [23, 74]. There is inconsistent guidance on the anticoagulant management of PVT. However, once the PVT is diagnosed, the optimal time of prevention and treatment often has been missed. Serious complications would increase mortality greatly for PVT patients. So, it is recommended for cirrhotic patients that routine color Doppler ultrasound assessment should be performed. Early diagnosis, early anticoagulant and thrombolytic therapy can effectively improve the prognosis of patients. A meta-analysis from Italy, which includes 8 studies comprising 353 patients with cirrhosis and PVT, demonstrated anticoagulant therapy (low-weight heparin or warfarin) could increase recanalization and reduce progression of thrombosis

effectively [75]. Meanwhile, these anticoagulants will not increase the incidence of any kinds of bleedings [75]. Another study from Italy found the benefits patients got overweighed the potential minor bleeding risk [76]. And they also concluded that portal hypertension, rather than anticoagulants, would be the real reason for the risk of major bleeding among cirrhotic patients with PVT. A prospective study from China which focused on patients with cirrhosis undergoing elective transjugular intrahepatic portosystemic shunt (TIPS) found that warfarin treatment within 12 months achieved a much higher rate of complete recanalization [77]. The commonly used drugs include warfarin, low molecular weight heparin and urokinase [78–81]. Most patients with acute PVT were recommended early anticoagulant therapy at least for 6 months. A systematic review and meta-analysis that summarized different regiments of anticoagulation has been reported [82]. In this study, the overall rate of portal vein recanalization was 37–93% and the anti-coagulation related bleeding was 0–18% [82]. In this way, we can not only reduce the incidence of PVT greatly but also increase PVT recanalization rate up to 39.3–100.0%.

In recent years, inhibitors of activated factor Xa (e.g., rivaroxaban) have been used in the prevention of clinical PVT. The advantages are convenient oral administration, no effect on the international standardization ratio and no need to monitor blood coagulation indicators. Hyeyoung Yang et al. reported a 63-year-old female who experienced complete resolution of recurrent acute PVT in liver cirrhosis after rivaroxaban treatment [83]. The disadvantage is there is no effective antagonist. When bleeding happens during anticoagulant therapy, the consequence is serious. However, some new oral anticoagulants' antidotes have been under investigation like andexanet alfa, P-glycoprotein substrates and drugs inducing CYP3A4. They all could inhibit the concentration or absorption of new oral anticoagulants and attenuate their effects remarkably [83, 84].

In short, clinical non-surgical methods are still mainly treatments of PVT in cirrhotic patients.

6.2. Local thrombolytic treatment

Local thrombolysis is divided into indirect way (femoral artery-superior mesenteric artery indwelling catheter thrombolysis) and direct way (percutaneous transhepatic portal vein thrombolysis) [13, 17, 18, 27, 35, 56, 85].

The advantages of the femoral artery-superior mesenteric artery catheter thrombolysis are simple and relative small trauma. It is just suitable for mild PVT without vascular occlusion. Because when PVT is found by this method, portal vein branches are usually in the stenosis or occlusion state by obstruction of thrombosis. Most of the drugs we injected for thrombolysis cannot reach the site of thrombus effectively. So, indications of this method are limited.

The advantages of the percutaneous transhepatic portal vein thrombolysis method are simple and show high success rates. However, we must stop this treatment when the patient has: (1) APTT significantly longer; (2) the international standardization ratio > 2; and (3) obvious abdominal pain, bloating, vomiting, hemafecia, increased puncture-point bleeding, more subcutaneous ecchymosis, hemoglobin continuing to decrease, faster heart rate, lower blood pressure and other signs of active bleeding.

6.3. TIPS

When severe PVT happened, thrombus blocked more than 50% lumen or completely blocked, anticoagulant therapy was unlikely to recanalization. Under this condition, we can choose TIPS. This method has the advantages as the following: the risk of thrombolysis is relatively small, and punctures can often reach directly to the thrombus site; at the same time intravascular technology (balloon plasty, stent replacement, thrombectomy and thrombolytic therapy surgery) can be applied to achieve the goal of treatment of PVT. A study from China which compared transcatheter selective superior mesenteric artery urokinase infusion and TIPS has found they were safe and effective for acute symptomatic PVT in cirrhosis [86]. But the operation was a relative difficult and lethal event as well as severe complications were still possible, so it is particularly important to assess the risk-benefit ratio of TIPS preoperatively. At present, the TIPS therapy methods for PVT are the following [87–89]:

A. TIPS placement → portosystemic shunt → portal vein recanalization;

B. TIPS placement through percutaneous ways portal vein recanalization;

C. TIPS placement between hepatic vein and collateral vessel → no portal vein recanalization

For cirrhotic patients with refractory variceal bleeding and ascites, TIPS was considered as one of the major treatment strategies if the patient did not have PVT. PVT has changed natural history of liver cirrhosis and affected outcomes. So, in this circumstance, TIPS should be recommended with caution. No convincing evidence has been published to verify the superiority of TIPS over traditional anticoagulants. TIPS should only be recommended for severe PVT patients although technical difficulty rose sharply when severe PVT was diagnosed [89]. That means reliable predictors for PVT progression should be further investigated in future.

6.4. Surgical treatment of PVT

Surgery is relatively high risk. The commonly used methods are (1) PVT excision; (2) portal vein stent implantation, mainly aimed to relieve portal vein obstruction; (3) liver transplantation. During treatment, if the patient has the sustained abdominal pain, abdominal distension and other signs of peritonitis, laparotomy exploration should be performed early to prevent the occurrence of intestinal necrosis. When intestinal necrosis is diagnosed, intestinal and mesangial resections should be performed. At the same time, the intestinal end-to-end anastomosis should be done. Anticoagulation was continued after surgery to prevent thrombus reformation.

7. PVT prevention

Kawanaka et al. have shown that anti-thrombin III (AT III) activity and splenic vein diameter were the risk factors of PVT after surgery. Moreover, they used those risk factors to formulate risk stratification system [90]. According to the risk stratification, doctors can decide whether to give prevention or not: low risk: AT III activity ≥70% and splenic vein straight diameter <10 mm, no preventive treatment; intermediate risk: AT III activity <70% or splenic

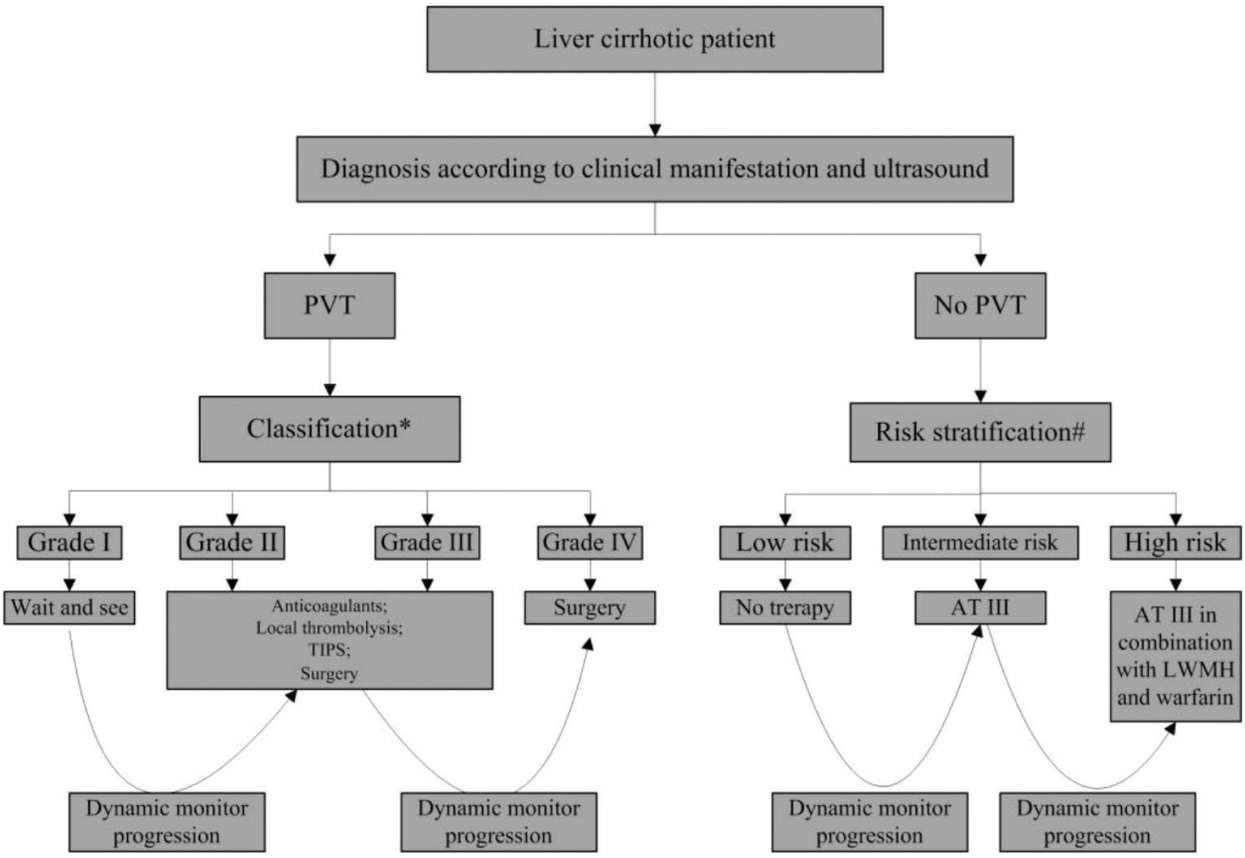

Figure 1. Algorithm for the treatment of portal vein thrombosis in liver cirrhosis. *Abbreviations*: PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; AT III, anti-thrombin III therapy; LWMH, low-weight molecular heparin; *according to Yerdel's study [68]; # according to Kawanaka's study [90].

vein diameter ≥10 mm, simple AT III prevention treatment; and high risk: splenic vein diameter ≥15 mm or from the liver collateral circulation vein diameter ≥10 mm, AT III, low molecular weight heparin in conjunction with warfarin [90].

Enoxaparin was found to prevent PVT in advanced cirrhotic patients. Daily subcutaneous enoxaparin (4000 IU/day) could significantly reduce incidence of PVT in the short and long term [91, 92]. And enoxaparin can also decrease the liver decompensation rate and improve survival of patients who received liver transplantation [52, 91, 92].

Surgery on the portal vein system should be gentle and accurate. We should prevent unnecessary damage to the vascular endothelium and avoid ligation of chunk tissue. If there is no obvious bleeding tendency, surgeons should not use hemostatic after surgery which may result in thrombosis (**Figure 1**).

8. Conclusion

PVT was a clinical rare deep venous thrombosis but highly occurred in liver cirrhotic patients. Local or systemic factors alone or in combination make contribution to the formation of PVT. In clinical, PVT should be given enough attention due to its severe threat to the patient's

life and health. The overall treatment principles are early diagnosis, early treatment and prevention combined with treatment. In the future, due to the progress in vascular imaging and innovation in clinical anti-thrombotic drug, PVT could be prevented and cured effectively.

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