Journal of Clinical and Translational Hepatology **2025** vol. 13(10) | 857–868
DOI: 10.14218/JCTH.2025.00124

Review Article

Portal Vein Thrombosis in Liver Cirrhosis: A Review of Risk Factors and Predictive Indicators

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Received: March 13, 2025 | **Revised:** June 17, 2025 | **Accepted:** July 03, 2025 | **Published online:** July 29, 2025

Abstract

Actively identifying the risk factors and predictive indicators associated with portal vein thrombosis (PVT) in liver cirrhosis (LC) can enable early diagnosis and treatment, which is of great significance for prolonging the survival of patients with LC. Hemodynamic disturbances, advanced LC, vascular endothelial injury, and mutations in thrombophilic genetic factors are established risk factors for PVT-LC. Venous dilatation and decreased blood flow velocity contribute to hemodynamic disturbances. The severity of LC can be assessed by the degree of portal hypertension, liver metabolic function biomarkers, and validated liver scoring systems. Iatrogenic interventions, endotoxemia, and metabolic syndrome may induce vascular endothelial injury and hypercoagulability, the latter of which can be quantified via coagulation-anticoagulation-fibrinolysis biomarkers. Mutations in thrombophilic genetic factors, such as Factor V Leiden, MTHFR C667T, and JAK2 V617F, disrupt coagulation-anticoagulation homeostasis and predispose patients to PVT-LC. This review specifically focuses on comprehensively delineating established risk factors and predictive indicators for PVT-LC, thereby providing a theoretical foundation for the construction of clinically applicable PVT predictive models to guide early interventions and improve the prognosis. Future research should further validate the associations between recently proposed risk factors and PVT-LC, while simultaneously establishing cutoff values for indicators with robust predictive value to construct a clinically applicable PVT prediction framework.

Citation of this article: Yang Z, Zhao Y, Chen H, Zhang H, Tan M, Li X, *et al*. Portal Vein Thrombosis in Liver Cirrhosis: A Review of Risk Factors and Predictive Indicators. J Clin Transl Hepatol 2025;13(10):857–868. doi: 10.14218/JCTH.2025.00124.

Introduction

Liver cirrhosis (LC) represents the terminal stage of chronic liver disease, pathologically characterized by extensive hepatocyte degeneration and necrosis, fibrous tissue proliferation, and the formation of pseudolobules. Clinically, it is accompanied by a variety of complications, such as ascites, esophagogastric varices, hepatic encephalopathy, and portal vein thrombosis (PVT).[1] PVT is defined as the presence of a thrombus within the main portal vein and may be accompanied by thrombosis in the intrahepatic and extrahepatic branches (mesenteric vein and splenic vein) of the portal vein.[2]

Historically, PVT-LC has been considered a relatively uncommon condition in clinical practice. Nevertheless, the development of imaging diagnostic techniques in recent years has led to a marked increase in the detection rate of PVT-LC.[3] Previous studies have shown that the estimated incidence of PVT-LC ranges from 0.6% to 26%,[4] with incidence positively correlating with disease severity. The incidence of PVT in patients with compensated LC is approximately 10%, while in candidates for liver transplantation, it can be as high as 26% to 30%.[2,5]

PVT can exacerbate portal hypertension (PH) in patients with LC, further inducing or aggravating other complications such as refractory ascites, esophagogastric variceal hemorrhage (EVH), and hepatic encephalopathy.[2] Unfortunately, PVT-LC often has an insidious onset, with only a very small number of patients diagnosed and treated promptly due to symptoms arising during hospitalization. The majority of patients have already missed the optimal treatment window by the time the condition is discovered, resulting in shortened survival and poor prognosis. Therefore, actively identifying risk factors and predictive indicators associated with PVT-LC can enable early diagnosis and treatment, which is of great significance for improving the prognosis of patients with LC.

We categorize the risk factors for PVT-LC into four aspects (Fig. 1) in an attempt to elucidate its mechanisms of occurrence and uncover potential predictive indicators.

Hemodynamic disturbance

Vascular dilation and decreased blood flow velocity can induce PVT by causing hemodynamic disturbances, with specific mechanisms primarily including blood stasis and vortex formation.

Keywords: Hemodynamics; Hypertension; Liver cirrhosis; Metabolic syndrome; Portal vein thrombosis; Prediction algorithms; Risk factors; Thrombophilia.

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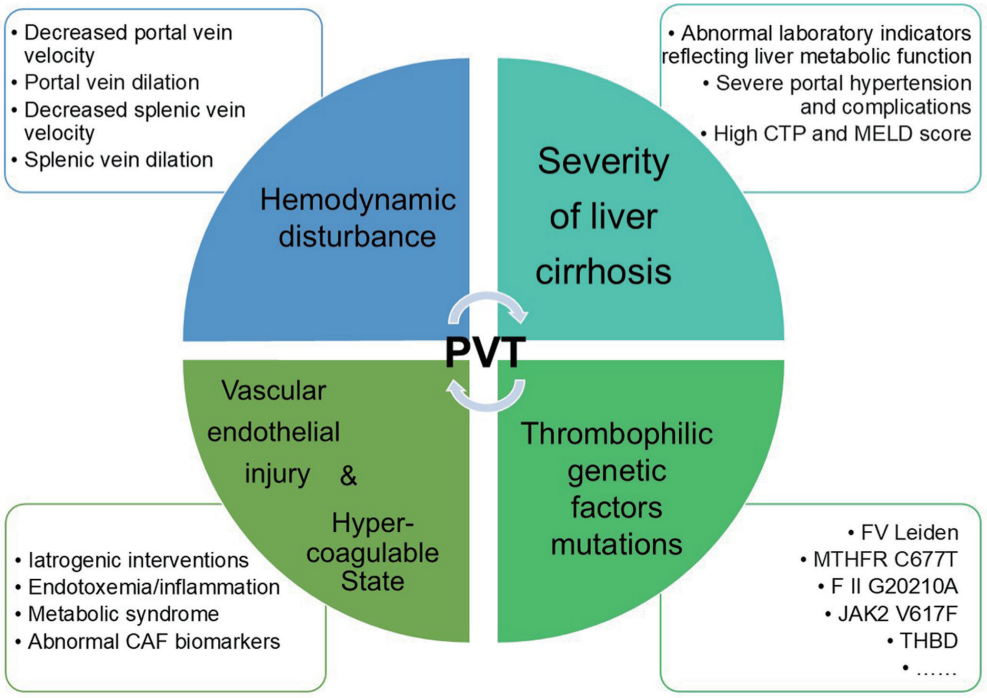

Fig. 1. Risk factors for PVT-LC. CAF, coagulation-anticoagulation-fibrinolysis; CTP, Child-Turcotte-Pugh; F II G20210A, factor II gene mutation at position 20210 (G→A); FV, factor V Leiden; JAK2 V617F, Janus kinase 2 valine-to-phenylalanine mutation at position 617; LC, liver cirrhosis; MELD, model for end-stage liver disease; MTHFR C667T, methylenetetrahydrofolate reductase gene mutation at position 677 (C→T); PVT, portal vein thrombosis; THBD, thrombomodulin gene.

Decreased portal vein velocity (PVV)

Decreased PVV is one of the most extensively studied and widely recognized risk factors for PVT-LC.[6] A matched case-control study conducted by Stine *et al*.,[5] which included 100 cirrhotic patients, demonstrated that PVV is an independent risk factor with the highest predictive value among the factors examined. Patients with PVV < 15 cm/s had a significantly increased risk of PVT compared to those with PVV ≥ 15 cm/s (HR = 6.00, 95% CI: 2.20–16.40, $P \leq 0.001$). A meta-analysis conducted by Giri *et al*.[7] also confirmed that PVV < 15 cm/s was the most commonly used cutoff for predicting PVT. In another case-control study involving 562 cirrhotic patients undergoing splenectomy combined with esophagogastric devascularization, the incidence of PVT was significantly higher in patients with PVV ≤ 16.5 cm/s compared to those with PVV > 16.5 cm/s (76.2% vs. 8.5%, $P < 0.0001$).[8] These results indicate that decreased PVV remains an independent risk factor for PVT even in patients who have undergone surgical interventions.

According to Virchow's triad, blood stasis caused by decreased blood flow velocity leads to an increased concentration of local coagulation factors and prolonged contact time between platelets and the vessel wall, thereby promoting thrombus formation. Researchers have speculated that certain medications that reduce PVV may also be associated with PVT development. Zampino *et al*.[9] suggested that non-selective beta-blockers (NSBBs), used to treat PH and prevent variceal bleeding in patients with LC, might contribute to PVT by reducing PVV ($P = 0.0003$). A prospective longitudinal study conducted by Nery *et al*.[10] confirmed that NSBB use is a risk factor for PVT, although this effect does not appear to be directly related to decreased PVV.

A recent prospective study investigated the relationship between relative residence time measured by 4D flow MRI and PVT-LC, suggesting that decreased relative residence time could serve as a novel indicator reflecting portal flow stasis, with potential predictive value.[11]

Portal vein dilation

Reducing PVV is considered the primary mechanism by which portal vein dilation induces PVT-LC. Furthermore, other researchers believe that the normal physiological function of the portal vein valve is to prevent backflow of blood into the portal vein from the liver. When the portal vein dilates, the valve becomes relatively insufficient, leading to an increase in the volume of blood flowing back into the portal vein and the formation of vortices. These vortices prolong the contact time between thrombin and the vascular endothelium, increasing the risk of developing PVT.[12,13]

Previous studies focusing on portal vein dilation have primarily revealed its close association with PVT after splenectomy. Qian *et al*.[14] conducted a case-control study involving 130 post-splenectomy patients, which showed a statistically significant difference in preoperative portal vein diameter (PVD) between the PVT and non-PVT groups (14.8 ± 1 mm vs. 13.1 ± 1.9 mm, $P = 0.000$). A recent study by Wang *et al*.[8] indicated that portal vein dilation significantly increases the risk of PVT (OR = 3.33, 95% CI: 1.81–6.13, $P < 0.001$). The study also proposed that PVD > 14.5 mm serves as a cutoff value for predicting PVT, consistent with the research of Nie *et al*.[15] Additionally, a meta-analysis by Giri *et al*.[7] demonstrated that for every 1 mm increase in PVD, the probability of PVT increases by 1.7 times.

Decreased splenic vein velocity and splenic vein dilation

In addition to hemodynamic disturbances within the portal vein, the relationship between hemodynamic disturbances in

the splenic vein and PVT-LC after splenectomy has also become a focus of current research.

Previously, Kuroki *et al*.[16] found that all cirrhotic patients postoperatively developed splenic vein thrombosis (SVT). However, only half of these patients had thrombosis in both the splenic vein and the portal vein. Notably, there were no patients who developed thrombosis solely in the portal vein without concurrent SVT. Therefore, thrombosis in the portal system after splenectomy initially occurs in the splenic vein and subsequently extends to the portal vein. In this single-center retrospective analysis, researchers also determined that splenic vein dilation is the strongest predictor for isolated SVT and for progression of SVT to PVT, with cutoff values of 10 mm and 14 mm, respectively. Later, Li *et al*.[17] demonstrated that the splenic vein diameter in the PVT group (11.59 ± 1.65 mm) was significantly larger than in the non-PVT group (10.46 ± 1.67 mm) following laparoscopic splenectomy ($P < 0.001$). More recently, a single-center retrospective study by Katano *et al*.[18] indicated that splenic vein dilation is an independent risk factor for PVT after combined liver and spleen resection (OR = 1.53, 95% CI: 1.156–2.026, $P = 0.003$). Although these latter two studies confirmed the association between increased splenic vein diameter and PVT after splenectomy, the cutoff values proposed by Kuroki *et al*. require further validation.

Vascular endothelial injury and hypercoagulable state

Factors that damage the vascular endothelium include iatrogenic interventions, portal vein inflammation caused by endotoxemia, and metabolic syndrome, all of which can also contribute to a hypercoagulable state.

Iatrogenic interventions

When LC is complicated by conditions such as PH, ascites, or EVH, endoscopic or surgical interventions are often required. These procedures have been identified as potential risk factors for PVT-LC.[19–21]

Splenectomy not only reduces portal venous pressure, effectively alleviating complications of LC, but also increases hepatic arterial blood flow by cutting off the splenic artery, thereby improving liver function.[22] Consequently, it is one of the most commonly used surgical treatments for LC and its associated complications. A retrospective study involving 113 cirrhotic patients showed that splenectomy increased the risk of PVT by at least 10-fold.[23] A case-control study by Xu *et al*.[24] also found that a history of splenectomy was significantly associated with PVT (OR = 7.565, 95% CI: 1.514–37.799, $P = 0.014$). Proposed mechanisms by which splenectomy promotes PVT include: (1) Blood stasis: Splenectomy reduces portal venous blood flow and pressure, slowing portal circulation. Additionally, ligation of the splenic vein creates a residual blind end prone to blood pooling. (2) Vascular endothelial injury: Surgical manipulation, such as traction and ligation of the splenic pedicle, can damage the vascular endothelium, thereby activating the coagulation system. (3) Hypercoagulable state: After surgery, reduced platelet destruction due to hypersplenism leads to a rebound increase in platelet count and enhanced platelet aggregation.[25–28]

Beyond splenectomy, researchers have extensively studied the association between endoscopic treatments and PVT-LC. Endoscopic variceal ligation (EVL) and sclerotherapy are both standard treatments for EVH and effectively achieve hemostasis.[29] A retrospective study in Spain found that EVL and sclerotherapy increased the risk of PVT (OR = 2.3, 95% CI: 1.2–4.5, $P = 0.01$).[30] A case-control study by Wang *et al*.[31] showed that, compared to the non-PVT group, the PVT group had a significantly higher proportion of patients who underwent EVL alone (19.3% vs. 9.2%, $P = 0.033$) or EVL combined with endoscopic cyanoacrylate injection (24.8% vs. 5.5%, $P < 0.001$). Endoscopic treatments primarily increased the risk of thrombosis in the extrahepatic portal system (main portal vein, superior mesenteric vein, and splenic vein), with minimal impact on the intrahepatic portal system (left and right branches of the portal vein). Some researchers have suggested that endoscopic treatments can obstruct blood flow from the portal vein to the esophagogastric collateral circulation, which increases portal venous pressure and promotes vortex formation.[31] Others proposed that ligation of esophageal varices or injection of sclerosing agents can mechanically damage the vascular endothelium, activating the coagulation system.[32] Therefore, when employing invasive measures to treat complications of LC, clinicians should strictly adhere to indications and carefully weigh the risks and benefits.

Endotoxemia and inflammation

Patients with advanced LC are prone to portal vein endotoxemia due to bacterial translocation from the gut and spontaneous bacterial peritonitis, making the portal system an inflammatory vascular bed. Current research suggests that inflammation caused by endotoxemia may induce PVT-LC through the following mechanisms: (1) Vascular endothelial injury: Neutrophils activated by inflammation can severely damage the membranes of vascular endothelial cells via strong oxidative bactericidal effects.[33] (2) Hypercoagulable state: Endotoxin has been described as a trigger for the coagulation cascade, activating platelets and increasing thrombin levels. Cytokines induced by endotoxin can also stimulate endothelial cells to produce factor VIII.[34–36] (3) PH: Endotoxemia can promote liver fibrosis and angiogenesis by activating hepatic stellate cells and Kupffer cells, as well as pro-inflammatory cytokine signaling, thereby increasing intrahepatic portal pressure.[37]

Previous studies have shown that whether endotoxemia can induce PVT depends on the source of the endotoxin in the portal system. An early study involving 49 cirrhotic patients found that endotoxemia caused by intestinal barrier disruption and endotoxin translocation from the gut was not a risk factor for PVT-LC,[38] consistent with a recent cross-sectional study.[39] In contrast, Koumar *et al*.[40] found that endotoxemia due to spontaneous ascitic fluid infection was significantly associated with PVT.

Bacterial endotoxins induce a range of inflammatory cell and cytokine responses in the body. Accordingly, researchers are exploring the relationship between post-infection inflammatory markers and PVT to identify potential predictors. A matched case-control study by Nie *et al*.,[15] involving 572 LC patients, combined plasma aspartate aminotransferase activity (reflecting local hepatic inflammatory damage) with neutrophil count (reflecting systemic inflammation) to develop the aspartate aminotransferase-to-neutrophil ratio index. The study found that the aspartate aminotransferase-to-neutrophil ratio index was significantly higher in the PVT group compared to the non-PVT group (40.18 vs. 27.31, $P = 0.011$). Xing *et al*.[41] conducted a retrospective study on the relationship between systemic inflammatory markers and PVT, using univariate and multivariate logistic regression analyses. Univariate analysis revealed that a high systemic immune-inflammation index, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio (PLR) were significantly associated with PVT. Multivariate analysis identified NLR and PLR as independent

Table 1. The association between DM and PVT-LC: an overview of case-control studies

First author, year	DM% in PVT group	DM% in no PVT group	*P*-value	OR, 95% CI	*P*-value
Abdel-Razik,[13] 2015	76.5% (13/17)	42.3% (33/78)	<0.001	2.15, 1.315–6.013	0.01
Ghabril,[47] 2016	29.2% (953/3,321)	22% (9,813/45,249)	<0.001	1.21, 1.07–1.36	0.002
Eshraghian,[48] 2018	37.7% (63/174)	22.7% (189/833)	<0.001	1.366, 0.382–1.996	0.748
Montenovo,[49] 2018	31.3% (1,665/5,319)	23.9% (13,865/58,012)	<0.001	1.22, 1.13–1.32	<0.001
Faccia,[21] 2022	20.94% (80/382)	13.66% (952/6,968)	0.0001	1.68, 1.27–2.22	0.0001
Koumar,[40] 2023	6.3% (1/16)	20% (20/77)	0.108		

CI, confidence interval; DM, diabetes mellitus; OR, odds ratio; PVT, portal vein thrombosis; LC, liver cirrhosis.

risk factors for PVT ($P < 0.05$). The researchers proposed using a practical nomogram based on NLR and PLR to predict PVT accurately.

Novel inflammatory markers have also emerged as a current research hotspot. Serag *et al*.[42] proposed that phosphatidylserine-positive microparticles (PS+MPs) mediate pro-inflammatory responses, vascular endothelial injury, and a hypercoagulable state during liver fibrosis. Hepatocyte damage caused by inflammation and endotoxemia can further elevate PS+MP levels. In their study, cirrhotic patients with PVT had higher PS+MP levels than those without PVT. Recent studies have also highlighted the critical regulatory role of neutrophil extracellular traps (NETs) in shaping the inflammatory microenvironment and inducing a hypercoagulable state. Plasma markers of NETs include cell-free DNA, histone-DNA complexes, and deoxyribonuclease activity. Han *et al*.[43] found that an imbalance in NETs homeostasis (characterized by elevated cell-free DNA and histone-DNA complex levels and reduced deoxyribonuclease activity) was significantly associated with PVT in patients with decompensated LC. A recent study also hypothesized that NSBBs may promote PVT development by stimulating neutrophils to release NETs.[44] Although the predictive utility of these novel inflammatory markers for PVT-LC requires further validation, clinicians should begin closely monitoring inflammatory indicators in cirrhotic patients to aid in early PVT prevention.

Metabolic syndrome

Metabolic syndrome, which significantly impacts health, is defined as a clinical condition characterized by the clustering of abdominal obesity, abnormal blood glucose, dyslipidemia, and hypertension.[45] A considerable proportion of cirrhotic patients are found to have metabolic syndrome,[46] and numerous studies have identified a close relationship between metabolic syndrome and PVT.

Diabetes is the most extensively studied risk factor in previous research (Table 1).[13,21,40,47–49]

Possible mechanisms by which diabetes induces PVT include: (1) Vascular endothelial injury: Normal vascular endothelial cells exert anticoagulant effects by synthesizing thrombomodulin. Hyperglycemia can damage vascular endothelial cells via the oxygen free radical pathway, weakening their anticoagulant function.[50] (2) Hypercoagulable state: Chronic hyperglycemia leads to glycation of various proteins, inducing peripheral mononuclear cells to produce tissue factor. In addition, diabetic patients often exhibit elevated plasma levels of coagulation factors V and VIII, and enhanced platelet aggregation.[51,52] Blood clots formed under hyperglycemic conditions are also more resistant to plasmin and oxidative degradation.[12]

Some scholars believe that the shear stress generated by turbulent blood flow in hypertension can damage vascular endothelial cells, potentially inducing PVT.[53] A recent study showed no significant difference in hypertension between PVT and non-PVT groups (OR = 0.78, 95% CI: 0.59–1.03, $P = 0.079$).[54] Previous studies have reported that visceral fat and abdominal obesity are independent risk factors for PVT.[55,56] Basaranoglu[57] proposed that abdominal obesity may induce PVT through pro-inflammatory factors released by abdominal adipose tissue, but this hypothesis requires further validation.

Abnormal coagulation-anticoagulation-fibrinolysis biomarkers

The hypercoagulable state of blood can be reflected by coagulation-anticoagulation-fibrinolysis biomarkers. Variations in these biomarkers can be used to determine whether a patient is prone to thrombosis and thus predict PVT-LC (Fig. 2).

D-dimer and fibrin degradation products (FDP) are specific biomarkers formed after the degradation of fibrin in thrombi. Elevated levels reflect both a hypercoagulable state and secondary hyperfibrinolysis.[58,59] D-dimer participates in the early stages of thrombus formation, accelerating PVT development.[60] Multiple studies have confirmed that D-dimer is an independent risk factor for PVT-LC and can serve as an effective predictor.[58,59,61–63] A recent retrospective study by Yang *et al*.[60] quantified D-dimer levels associated with PVT-LC and found that levels exceeding 0.87 μg/mL were an independent risk factor (OR = 1.925, 95% CI: 1.538–2.410, $P = 0.000$). It is important to note that D-dimer levels can also rise in various stress conditions such as pregnancy, major surgery, and infections, making it non-specific. Therefore, diagnosing PVT using D-dimer requires comprehensive analysis in conjunction with other diagnostic markers.[28] In contrast, research on FDP remains relatively limited. A single-center case-control study by Lin *et al*.[64] found that higher FDP levels were associated with a greater incidence of PVT (18.57 ± 19.46 μg/mL vs. 5.45 ± 6.00 μg/mL, $P < 0.05$), a finding that requires further validation in larger, multi-center studies.

Platelets, one of the main components of thrombi, also play a crucial role in the coagulation process. Activated platelets not only provide a catalytic surface for coagulation-related enzymes to promote clotting but also release antifibrinolytic factors (such as α-antiplasmin) to inhibit fibrinolysis and stabilize clots. Multiple studies have observed lower platelet counts in cirrhotic patients with PVT,[13,27,64] likely due to increased platelet destruction by the hyperactive spleen. A recent study demonstrated that cirrhotic patients exhibit highly activated platelet function, which promotes thrombus formation.[65] Therefore, platelet activation, rather than platelet count, better explains PVT in the context of low platelet levels.

Researchers have thus turned to biomarkers reflecting platelet activation to predict PVT. An early prospective study

Fig. 2. Variations in CAF biomarkers used to predict PVT-LC. ↑ indicates the increased level of a biomarker can predict PVT, ↓ indicates a decreased level can predict PVT. The dashed white box represents the physiological balance between vWF and ADAMTS-13 under normal conditions. ADAMTS-13, a disintegrin and metalloproteinase with thrombospondin motifs 13; AT III, antithrombin III; CAF, coagulation-anticoagulation-fibrinolysis; CD62P, P-selectin; FDP, fibrin degradation products; F VIII, factor VIII; MPV, mean platelet volume; PC, protein C; PS, protein S; TGF-β1, transforming growth factor-β1; vWF, von Willebrand factor; PVT, portal vein thrombosis; LC, liver cirrhosis.

found that mean platelet volume (MPV) was significantly higher in the PVT group compared to the non-PVT group (8.3 ± 0.54 fL vs. 7.7 ± 0.65 fL, $P < 0.001$).[13] Elevated MPV indicates enhanced platelet function, which leads to the release of more thromboxane A_2, promoting thrombus formation.[13] A subsequent meta-analysis by Lin *et al*.[66] supported this conclusion, suggesting MPV is an early marker of platelet activation. Additionally, Jiang *et al*.[67] found that elevated platelet-derived transforming growth factor-beta 1 may induce PVT-LC by interfering with vascular endothelial cell function. Some researchers also believe that P-selectin (CD62P), a marker of platelet activation on the platelet surface, may serve as a predictor of PVT-LC.[68]

Fibrinogen, the most abundant coagulation factor in plasma, plays a critical role in coagulation. Previous studies suggest that it is not fibrinogen levels but its structural and functional changes that are closely related to PVT.[69] Hugenholtz *et al*.[70,71] proposed that oxidative modifications in chronic liver disease alter fibrinogen's structure, leading to the formation of fibrin clots with reduced permeability and diminished interaction with plasmin, resulting in thrombi less susceptible to degradation.

Cirrhotic patients, due to decreased liver synthetic function, experience reduced synthesis of both coagulation and anticoagulation factors, placing the body in an unstable coagulation-anticoagulation balance that can be disrupted by various risk factors.[19] Reduced synthesis of anticoagulation factors such as antithrombin III, protein C (PC), and protein S can induce PVT-LC, as confirmed by related studies.[58,72] A meta-analysis incorporating 10 original studies demonstrated that cirrhotic patients with PVT have a significantly higher F VIII/PC ratio (factor VIII to protein C) ($P = 0.00$).[73]

von Willebrand factor (vWF), a plasma glycoprotein involved in hemostasis, primarily functions in platelet adhesion and aggregation. A disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS-13) is a protease that cleaves vWF, preventing platelet aggregation and thrombus formation. Under normal conditions, a balance is maintained between vWF and ADAMTS-13. A prospective study by Sacco *et al*.[74] found that imbalance between vWF and ADAMTS-13 in LC is a significant risk factor for PVT, and an ADAMTS-13/vWF ratio < 0.4 may be a reliable predictor of PVT development, though further validation is needed.

Severity of LC

PVT is a complication of LC, and thus, the severity of LC is likely one of the risk factors for PVT. The severity of LC can be reflected by the degree of PH, laboratory indicators related to hepatic metabolic function, and liver function scoring models.

Severe PH and complications

PH is a common clinical manifestation of decompensated LC, capable of inducing severe complications such as ascites, hepatic encephalopathy, and EVH.[75] As such, PH can reflect the severity of LC. The severity of PH is considered one of the most fundamental risk factors associated with PVT-LC.[76] The mechanism by which PH contributes to PVT is primarily thought to involve compensatory splanchnic arterial vasodilation and the formation of porto-collateral vessels, which lead to blood shunting and reduced portal flow.[77] A vicious cycle may exist between PH and PVT: PH promotes the formation of PVT, while PVT induces portal vein stenosis and blood stasis, further increasing portal venous pressure. The hepatic venous pressure gradient (HVPG) is the best indirect indicator for measuring portal venous pressure. However, there is currently no consensus on the predictive cutoff

value for HVPG. In Turon's study, patients with HVPG > 20 mmHg had a higher incidence of developing PVT than those with HVPG < 20 mmHg (HR = 8.08, P = 0.015, 95% CI = 1.50–43.6).[78] Meanwhile, a recent study demonstrated that HVPG ≥ 16 mmHg can serve as an independent predictor of PVT (P = 0.011).[79]

Complications related to PH have been confirmed by many researchers to be associated with PVT-LC.[80] A single-center study found that cirrhotic patients with ascites had a higher incidence of PVT compared to those without ascites, and that incidence increased with the severity of ascites.[81] A retrospective study by Ak *et al*.,[82] which included 165 cirrhotic patients undergoing liver transplant evaluation, demonstrated that a history of EVH significantly increased the risk of PVT (OR = 3.45, 95% CI = 1.02–11.6, P = 0.046). A prospective cohort study also showed that the incidence of PVT was significantly higher in patients with hepatic encephalopathy (38.1% vs. 9.9%, P = 0.01).[83] Therefore, early clinical monitoring of portal venous pressure and proactive prevention of related complications may be effective measures to reduce the incidence of PVT-LC.

Certain laboratory indicators can indirectly reflect the presence of complications related to PH and may serve as predictive factors for PVT-LC. Hypersplenism and EVH caused by PH increase erythrocyte destruction and loss, lowering hemoglobin and hematocrit levels.[13,84] In a retrospective study conducted by Cagin *et al*.,[85] hematocrit levels in the PVT group were significantly lower than in the non-PVT group(34.32% vs. 38.4%, P < 0.001). Lopez-Gomez *et al*.[83] also observed that hemoglobin levels were significantly lower in the PVT group than in the non-PVT group (12.6 g/dL vs. 13.8 g/dL, P = 0.01).

Abnormal laboratory indicators reflecting liver metabolic function

Plasma albumin (Alb), a protein synthesized by hepatocytes, reflects the liver's synthetic function. In patients with LC, the liver's synthetic function is impaired, and although nutrient intake may be sufficient, symptoms like poor appetite lead to lower Alb levels. A retrospective study involving 98 cirrhotic patients with PVT and 101 cirrhotic patients without PVT showed significant differences in Alb levels (2.97 g/L vs. 3.2 g/L, P < 0.05),[85] consistent with the study by Gîrleanu *et al*.[86] Notably, Basili *et al*.[87] demonstrated that Alb can inhibit platelet activation by suppressing oxidative stress mediated by soluble Nox2-derived peptides, further supporting the hypothesis that hypoalbuminemia is a risk factor for PVT.

The associations between bilirubin (BIL) and low blood urea nitrogen (BUN) levels and PVT-LC remain controversial, warranting further research. Cagin *et al*.[85] found that BIL levels in cirrhotic patients with PVT were significantly higher than in those without PVT (2.805 mg/dL vs. 1.6 mg/dL, P < 0.001). Yang *et al*.[60] proposed that higher BUN levels increased the risk of PVT (OR = 1.1157, 95% CI = 1.247–1.306, P = 0.018). In contrast, a retrospective study by Li *et al*.[61] found that BIL levels were significantly lower in the PVT group compared to the non-PVT group (12.7 μmol/L vs. 15.4 μmol/L, P = 0.004), and that lower BUN levels were independently associated with PVT (4.75 mmol/L vs. 5.2 mmol/L, P = 0.006), contradicting the aforementioned studies. Additionally, Lopez-Gomez *et al*.[83] did not find a statistically significant difference in BIL levels between the PVT and non-PVT groups.

A possible explanation is that the relationship between BIL and BUN levels and the risk of developing PVT follows a U-shaped curve. Specifically, both lower and higher levels of BIL and BUN may contribute to PVT development. Urea is the primary end product of protein metabolism in the liver, and BUN levels may indirectly reflect poor overall nutritional status and decreased liver metabolic function.[61] On the other hand, in patients with advanced cirrhosis complicated by hepatorenal syndrome, BUN levels may elevate due to reduced renal clearance of urea. As for BIL, in the early stages of cirrhosis, hemolysis due to hypersplenism and decreased hepatic metabolic function from hepatocyte damage can increase the production and reduce the excretion of BIL, resulting in elevated BIL levels. In late-stage disease, the number of red blood cells declines due to prior destruction, reducing the production of BIL from its source and consequently leading to decreased BIL levels.

High Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) score

The CTP score is one of the most widely used clinical tools for assessing hepatic reserve function. It incorporates complications of cirrhosis (ascites, hepatic encephalopathy), indicators reflecting hepatic metabolic function (BIL, Alb), and a hemostatic parameter (prothrombin time) to comprehensively estimate the risk of PVT-LC. Based on the total score, liver function is classified into three grades: A, B, and C. A meta-analysis by Pan *et al*.[88] indicated that CTP B and C can predict the occurrence of PVT-LC. The liver has dual roles in synthesizing both procoagulant and anticoagulant substances. The higher the CTP score, the worse the liver reserve function, leading to reduced synthesis of both pro-coagulant and anticoagulant substances. However, the reduction in anticoagulant synthesis appears greater than that of pro-coagulant substances, resulting in a prothrombotic state. This prothrombotic tendency gradually worsens from CTP A to C.[89] Notably, a prospective study found that not all patients with advanced LC develop PVT: only about 50% of patients in CTP C had PVT. Moreover, in that study, the CTP score worsened significantly compared to baseline after the occurrence of PVT. Therefore, the researchers speculated that the elevated CTP score might be a consequence of the formation and progression of PVT.[90]

Given the limitations of the CTP classification, researchers have also explored the clinical value of the MELD, proposed by Malinchoc *et al*. in 2000, for predicting PVT-LC. Compared to the CTP score, the MELD score incorporates more laboratory indicators (serum creatinine, international normalized ratio) and excludes factors such as hepatic encephalopathy and ascites, which are influenced by subjective clinical evaluation, holding greater clinical utility. Noronha *et al*.[91] confirmed that the MELD score could independently predict decompensated LC (HR = 1.14, 95% CI: 1.09–1.19) and, consequently, the occurrence of non-neoplastic PVT. Recently, a single-center retrospective study also found significant differences in both CTP and MELD scores between the PVT and non-PVT groups (P = 0.03 and P = 0.01, respectively).[81] Overall, in assessing LC severity, the MELD score is less widely used than the CTP score due to its more complex calculation. However, because it is more objective and accurate, it may offer superior predictive value for risk stratification in certain complex cases.

Ultimately, we consolidated the diagnostic utility of the aforementioned risk factors and predictive indicators for PVT-LC (Table 2).[5,7,42,43,60,77,92]

Mutations in thrombophilic genetic factors (THRGFs)

Previous studies have shown that a significant proportion of cirrhotic patients with PVT carry THRGFs.[85] Searching for relevant genes is currently one of the major research hotspots (Table 3).[93–102]

Early studies clearly demonstrated that G20210A, FV Lei-

Table 2. The diagnostic value of risk factors and predictive indicators for PVT-LC

Risk factors	Sensitivity	Specificity	AUC	Cutoff value
NLR[42]	–	–	0.596	≥3.14
PLR[42]	–	–	0.628	≥103.4
PS+MPs[43]	83.33%	97.56%	0.917	>35.3nmol/L
PVV[5]	66.67%	78.05%	0.854	≤15cm/L
PVD[7]	–	–	0.732	≥14.5cm
D-dimmer[60]	83.3%	83.1%	0.858	>0.87g/L
Splenectomy[60]	45.4%	90.1%	0.677	1
HVPG[77]	91.7%	48.6%	0.701	≥17.52mmHg
CD62P[92]	78.57%	90.91%	0.898	>74.39ng/mL

AUC, area under the curve; CD62P, P-selectin; HVPG, hepatic venous pressure gradient; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PS+MPs, phosphatidylserine-positive microparticles; PVD, portal vein diameter; PVT, portal vein thrombosis; LC, liver cirrhosis; PVV, portal vein velocity.

den, and MTHFR C677T mutations are closely associated with PVT-LC.[103] A subsequent case-control study by Saugel *et al*.[104] revealed a significantly higher JAK2 V617F mutation rate in the PVT group compared to the non-PVT group. A cohort study by Ames *et al*.[105] also found that the MTHFR TT homozygous genotype may be associated with more severe LC and lower PC levels, leading to an earlier onset of PVT-LC. Whether other genetic factors are associated with PVT-LC requires further validation. It is generally believed that mutations in THRGFs cause decreased production of certain coagulation factors or inactivation of anticoagulant factors, inducing a hypercoagulable state.

Moreover, genetic polymorphisms in thrombophilic genes exhibit significant ethnic variations.[106] FV Leiden and G20210A mutations are major genetic risk factors for thrombosis in Caucasian populations, whereas PROC gene mutations are more prevalent among Chinese and other Asian populations.[107,108] Currently, the Caprini Risk Assessment Model includes Factor V Leiden and prothrombin G20210A mutations.[109] Notably, it may not be applicable to Chinese and other Asian populations.

Furthermore, unlike the well-established association of FV Leiden and G20210A with PVT-LC, studies suggest that PROC may not be involved in the pathogenesis of PVT in Chinese cirrhotic patients.[110] This indicates that inherited thrombophilia might not be a major risk factor for PVT-LC in the Chinese population.[111] Consequently, current genetic screening for PVT-related mutations may provide limited clinical benefits for Chinese cirrhotic patients. Future research should aim to elucidate the genetic variants causally linked to PVT development in Chinese cirrhotic patients and to establish clinically applicable genetic screening algorithms.

Clinical decision-making framework for PVT risk stratification

Based on the four major categories of risk factors described above, we propose the following clinical decision algorithm for PVT risk stratification, taking into account both the level of evidence for existing risk factors and their strength of as-

Table 3. The THRGFs currently known: an overview of previous studies and case reports

First author, year	Journal	THRGF	Mechanisms leading to PVT
Bertina,[93] 1994	Nature	FV Leiden	Leading to activated PC resistance
Frosst,[94] 1995	Nat. Genet.	MTHFR C677T	Associating with low levels of NO (a vasodilatory factor) and hyperhomocysteinemia
Ohlin,[95] 1997	Thromb Haemost.	THBD	TM is an endothelial cell cofactor for activated protein C, the lack of TM causes impaired activation of PC
Chamouard,[96] 1999	Gastroenterology	F II G20210A	Leading to elevated prothrombin levels
De Stefano,[97] 2007	Hepatol.	JAK2 V617F	Associating with myeloproliferative disorders, which increases the production of platelets and RBCs
D'Amico,[98] 2015	Gene	PAI-1	Inhibiting the fibrinolytic system
Plompe,[99] 2015	Haematol.	CALR	Associating with myeloproliferative neoplasms, especially essential thrombocythemia and primary myelofibrosis
Zhang,[100] 2020	Clin Biochem.	SERPINC1	Causing the deficiency of AT III (a natural anticoagulant)
Zou,[101] 2022	Exp. ther. med.	PROC	Causing the deficiency of PC (a natural anticoagulant)
Ye,[102] 2023	Clin. res. hepatol. gastroenterol.	PROS	Causing the deficiency of PS (a natural anticoagulant)

AT III, antithrombin III; CALR, calreticulin; FV, factor V Leiden; F II G20210A, factor II gene mutation at position 20210 (G→A); MTHFR C667T, methylenetetrahydrofolate reductase gene mutation at position 677 (C→T); JAK2 V617F, Janus kinase 2 valine-to-phenylalanine mutation at position 617; NO, nitric oxide; PAI, plasminogen activator inhibitor; PC, protein C; PROC, gene for protein C; PROS, gene of protein S; PS, protein S; SERPINC1, serpin family C member 1; THBD, gene of thrombomodulin; TM, thrombomodulin.

Table 4. Risk stratification for PVT-LC based on the aforementioned risk factors and predictors

Risk grade	Risk factors and predictors	OR	95% CI	*P*-value	Source of evidence
High-risk	PVD↑	3.330	1.81–6.13	<0.001	Meta-analysis[7]
	Splenectomy history	7.565	1.514–37.799	0.014	Multiple analysis[23–28]
	PVV↓	6.000	2.20–16.40	≤0.001	Multiple studies[7]
Medium-risk	Endoscopic treatment history	2.300	1.2–4.5	0.01	Multiple studies[29–32]
	Diabetes mellitus	1.800	1.42–2.28	<0.0001	Meta-analysis[112]
	D-dimer↑	1.925	1.538–2.410	0	Meta-analysis[88]
	CTP B/C	2.040	1.40–2.95	<0.001	Meta-analysis[88]
	F VIII/P C↑	1.580	1.17–2.14	0.0028	Meta-analysis[73]
Low-risk	CTP A, without high-risk and medium-risk factors				

(1) High-risk: proved by meta-analysis or multiple studies and OR≥3; (2) Medium-risk: proved by meta-analysis or multiple studies and OR<3; (3) Exclusion criteria: risk factors and predictors that are unvalidated, impractical, and invasive. (e.g., BIL, ANRI and HVPG). ↑, Elevated level of a risk factor or predictor; ↓, Decreased level of a risk factor or predictor. ANRI, AST-to-neutrophil ratio index; BIL, bilirubin; CI, confidence interval; CTP-A, Child-Turcotte-Pugh Class A; CTP-B/C, Child-Turcotte-Pugh Classes B and C; F VIII/PC, ratio of factor VIII to protein C; HVPG, hepatic venous pressure gradient; OR, odds ratio; PVD, portal vein diameter; PVT, portal vein thrombosis; LC, liver cirrhosis; PVV, portal vein velocity.

sociation with PVT (Table 4).[7,23–32,73,88,112] This algorithm is designed to help clinicians identify high-risk patients, tailor surveillance frequency, and optimize preventive strategies (Fig. 3). For individuals deemed at higher risk, an increased frequency of ultrasound screening is recommended, along with active consideration of anticoagulation therapy.[113]

Notably, while we present a practical approach for early screening of PVT-LC based on current evidence, this framework is not yet fully optimized. First, although predictive imaging parameters (such as PVV) and laboratory markers (such as D-dimer) have demonstrated significant correlations with PVT, their precise cutoff values remain contentious. Secondly, our review incorporates a limited number of studies. Future research should focus on establishing validated cutoff values for these predictive indicators and generating more robust evidence for early PVT screening.

Conclusions

The risk factors for PVT-LC primarily fall into four categories: hemodynamic disturbances in the portal system, severe LC, vascular endothelial cell injury and hypercoagulable state,

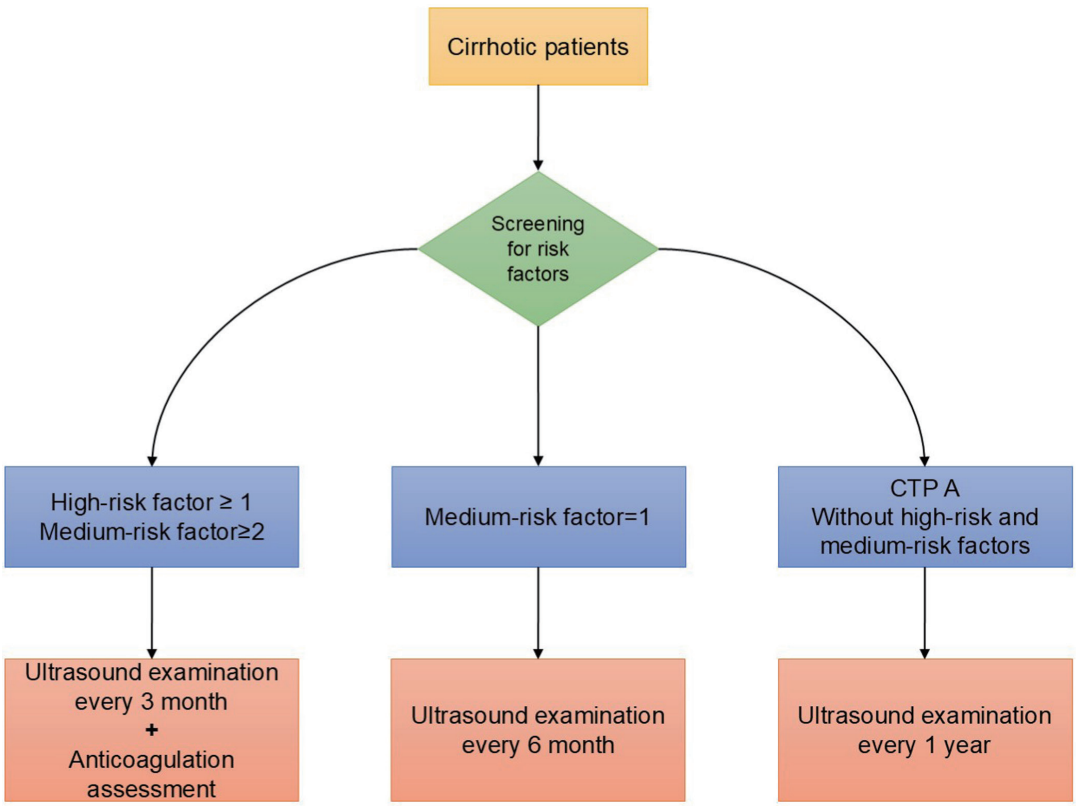

Fig. 3. Practical algorithm for early screening of PVT-LC. CTP-A, Child-Turcotte-Pugh Class A; PVT, portal vein thrombosis; LC, liver cirrhosis.

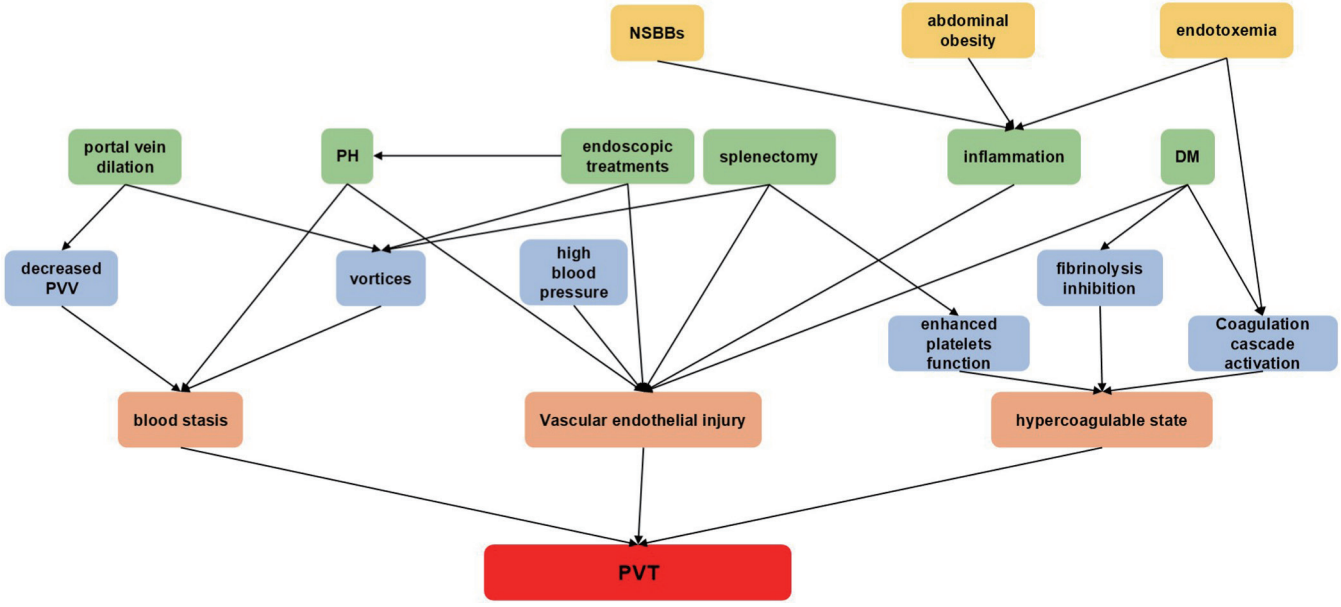

Fig. 4. Pathogenic mechanisms and interrelationships of risk factors for PVT-LC. DM, diabetes mellitus; PH, portal hypertension; PVT, portal vein thrombosis; PVT, portal vein thrombosis; LC, liver cirrhosis; PVV, portal vein velocity.

and mutations in THRGFs. It is important to note that these risk factors are not entirely independent or isolated. Instead, they are interconnected and may even mutually reinforce one another (Fig. 4). For any individual patient, the formation of PVT results from the interaction of a dominant factor with multiple additional contributing factors and mechanisms. Therefore, clinically analyzing the potential triggers of PVT-LC and preventing its occurrence requires a comprehensive consideration of all possible risk factors.

Funding

This work was supported in part by a grant from the General Program of the Chongqing Natural Science Foundation (CSTB2022NSCQ-MSX0909 to HZ); the Kuanren Talents Program of the Second Affiliated Hospital of Chongqing Medical University (No. 2021240308 to HZ); and the Group Medical Aid Project for the Tibet Autonomous Region, supported by the Natural Science Foundation of the Tibet Autonomous Region (XZ2023ZR-ZY75(Z)).

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Providing background information and outline for the draft (ZY, YZ, HZhao), literature search (HC, HZhang), data analysis (YZ, MT, XL, LT), drawing diagrams (ZY, HC), drafting of the manuscript (ZY), and critical revision of the manuscript for important intellectual content (YZ, HZhao). All authors have made significant contributions to this study and have approved the final manuscript.

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