

Portal Vein Thrombosis: A Detailed Review of Etiology, Diagnosis, and Treatment

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ABSTRACT

Portal vein thrombosis (PVT) is a complicated vascular condition resulting from genetic, metabolic, and environmental risk factors. This review underlines current evidence on PVT pathogenesis, clinical management, and emerging therapeutic strategies. Multiple causes of PVT include liver cirrhosis, hepatocellular carcinoma, intra-abdominal infections, and systemic hypercoagulable states, including COVID-19-related thrombosis. Diagnostic challenges persist due to asymptomatic presentations and overlapping imaging findings with other conditions; however, advancements in imaging have improved detection and risk stratification. Anticoagulants remain the cornerstone of treatment, and surgical interventions are reserved for non-responders. Prognosis is influenced by underlying liver disease, thrombus extent, and timely intervention, with cirrhotic PVT linked to higher mortality. Emerging therapies, including miRNA-modified stem cells and radiotherapy for tumor thrombi, show promise but require further validation. Future research must address gaps in genetic predisposition, optimized DOAC dosing in advanced cirrhosis, and the role of gut microbiota in thrombogenesis. This review highlights the importance of personalized, multidisciplinary approaches to enhance outcomes in this clinically diverse condition.

Keywords: Portal Vein Thrombosis (PVT); Hypercoagulability; Oral Anticoagulants (DOACs); Biomarkers; Gut-Liver Axis; Thrombolytic Therapy

Introduction

Portal vein thrombosis (PVT) is a noteworthy vascular disorder marked by the development of a blood clot in the portal vein and its branches, extending up to the splenic vein (SV) and superior mesenteric vein (SMV) [1,2]. It is characterized by partial or complete obstruction of the portal vein, which supplies 3/4th blood to the liver. This obstruction results in compromised hepatic perfusion, potential liver dysfunction and gastrointestinal bleeding [3-5]. This condition is also associated with severe complications such as increased portal venous pressure, variceal bleeding, intestinal ischemia, and liver failure, significantly impacting survival and prognosis [6]. PVT also presents significant challenges in liver transplantation, increasing both perioperative risks and technical difficulties. It is most common-

ly seen in patients with liver cirrhosis, where it often results from portal hypertension, making individuals susceptible to complications like acute esophageal variceal bleeding [7]. In non-cirrhotic cases, PVT often stems from portal and splenic vein thrombosis, leading to variceal bleeding and splenomegaly [8]. PVT is also associated with malignancies, inflammatory conditions, and myeloproliferative neoplasms (MPNs), broadening its clinical context [9,10]. In neonates, PVT is typically asymptomatic and often remains undiagnosed during this early stage of life [11]. Neonatal PVT is recognized as a key factor in the development of portal hypertension [11]. PVT is frequently asymptomatic and often discovered incidentally during routine imaging, particularly during the surveillance of hepatocellular carcinoma (HCC) or during hospitalization due to complications related to portal hypertension, such as esophageal variceal bleeding [12]. In cirrho-

sis, PVT serves as a marker of disease severity and is associated with worsened liver function, portal hypertension, and complications such as esophagogastric varices and ascites [13-15]. PVT is often asymptomatic and typically detected incidentally during routine surveillance imaging of hepatocellular carcinoma (HCC) or hospitalization due to complications of portal hypertension [12]. Diagnostic tools

such as Doppler ultrasonography are crucial for confirming the diagnosis, as they offer high sensitivity for detecting portal vein occlusion [16]. A holistic overview of Portal Vein Thrombosis (PVT) for clinical research reference and described in (Figure 1), followed by details sections below:

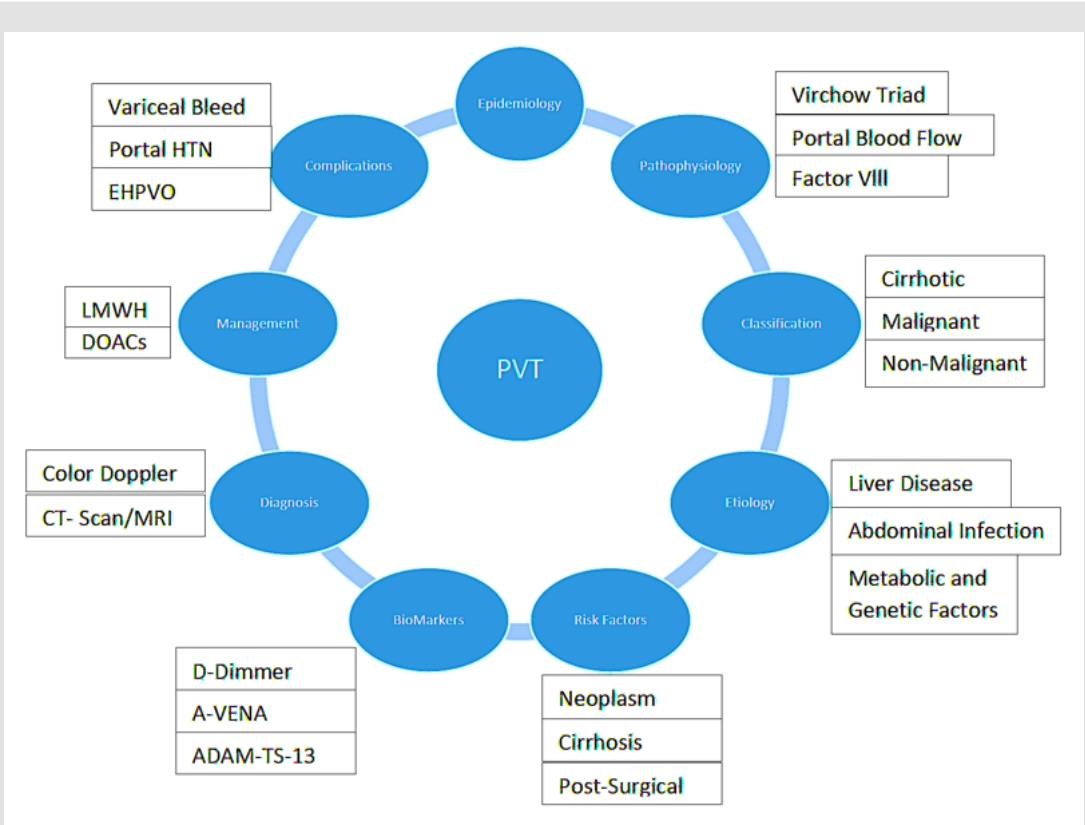


Figure 1: Overview of Portal Vein Thrombosis (PVT): This diagram illustrates the key domains involved in the understanding and clinical management of Portal Vein Thrombosis (PVT). PVT is encircled by following interconnected components: Epidemiology, Pathophysiology, Classification, Etiology, Risk Factors, BioMarkers, Diagnosis, Management, and Complications. Each domain lists specific contributing factors or tools relevant to PVT, such as the role of Virchow’s Triad and Factor VIII in pathophysiology, cirrhotic and malignant categories in classification, color Doppler and CT/MRI for diagnosis, and anticoagulation therapies like LMWH and DOACs for management.

Epidemiological Burden

PVT is especially prevalent among patients with advanced liver disease, especially cirrhosis and HCC, with rates ranging from 5% to 26% among those with cirrhosis and up to 40% in HCC cases. The prevalence ranges between 0.6% and 16% among patients with compensated cirrhosis. [17-23]. Meta- analyses suggest a pooled prevalence of around 14%, although this figure varies depending on the population and diagnostic techniques used [24-26]. The neonatal intensive care units (NICU) patients are at higher risk for developing PVT [27]. The incidence of neonatal PVT varies widely, ranging from

1.3% to 43% [27]. Studies also indicate that the incidence of PVT increases in more advanced stages of cirrhosis, with annual rates ranging from 3% to 25%. [28]. PVT is considered rare in the population without chronic liver disease, with an incidence of 2-4 per 100,000 individuals [29]. Studies have shown that PVT is responsible for 5% to 10% of all portal hypertension cases in developed countries, while in developing nations, it accounts for up to 33% of cases [8,30,31]. Autopsy studies indicate a prevalence of PVT between 6% to 64%, while studies based on ultrasound report percentages between 5% and 24% [32]. Remove this reference [25,33].

Pathophysiological Insights

The development of PVT is a complex, multifactorial process involving Virchow’s Triad [17,34,35]. In cirrhotic patients, the primary contributors are decreased portal blood flow, elevated intrahepatic vascular resistance, along with increased factor VIII levels and diminished protein C levels [18,36]. The reduction in portal blood flow is particularly pronounced in patients with advanced cirrhosis (Child-Pugh class C) compared to those with milder forms of the disease (Child-Pugh A/B) [37,38]. Genetic factors and systemic conditions, such as endotoxemia, further increase the thrombotic risk [18]. The pathophysiology of cirrhosis involves complex hemostatic alterations due to liver synthetic dysfunction, portal hypertension, and endothelial activation [39]. The mechanism of PVT in cirrhosis is distinct from other thrombotic conditions, such as deep vein thrombosis (DVT) or pulmonary embolism (PE) [16,40]. Unlike the thrombi found in DVT or PE, which primarily consist of fibrin, platelets, and red blood cells, portal vein thrombi are mainly composed of intimal hyperplasia [41,42]. This suggests that terms like “portal vein obstruction” or “portal vein stenosis” may be more appropriate in describing PVT in

cirrhosis [16,43]. Further contributing factors to PVT include portal hypertension, endothelial injury, the presence of esophageal varices, and a history of variceal endoscopic treatments [32]. The prothrombotic nature of PVT is also linked to the involvement of neutrophil extracellular traps (NETs), which promote clot formation. NETs, composed of DNA and histones, provide a scaffold for thrombus development and possess strong procoagulant activity [44-46]. Additionally, propranolol, a nonselective β-blocker (NSBB) commonly used in cirrhosis management, has been shown to enhance NET formation by increasing the production of reactive oxygen species (ROS) and NADPH oxidase activity [47,48]. This highlights the paradoxical role of NSBBs in potentially contributing to PVT despite their effectiveness in reducing variceal bleeding [38].

Classification of PVT

“PVT can be classified into cirrhotic PVT, malignant thrombosis, and non-malignant-non-cirrhotic PVT.” [35]. This line provides a basic classification framework for PVT, which is essential in understanding its different types based on etiology (detail given in Table 1) [49-54].

Table 1: Classification of PVT.

Classification	Description	References
Cirrhotic PVT	Liver cirrhosis is responsible for about 33% of all PVT cases. The elevated incidence of PVT in advanced cirrhosis is attributed to the Virchow’s triad.* Among patients with compensated cirrhosis, the prevalence is around 1%.	[49,50]
Malignant Thrombosis:	Malignant PVT is typically linked to the advancement of underlying malignancies. According to some studies, PVT was identified in 14.3% of patients with primary liver cancer accompanied by cirrhosis, and in 11.5% of those diagnosed with pancreatic cancer.	[35,51,52]
Non-malignant-non-cirrhotic PVT:	Non-malignant and non-cirrhotic PVT is attributed to prothrombogenic conditions. For example, 20-50% of the patients with NMNC PVT have reported myeloproliferative neoplasias. Similarly, In a meta-analysis of 855 patients with PVT, 30% of the patients had underlying myeloproliferative neoplasms.	[53,54]

Note: Portal Vein Thrombosis (PVT). Virchow’s triad* (hypercoagulability, endothelial injury, stasis)

Etiological Factors and Risk Contributors

PVT can arise from various etiological factors, encompassing both inherited and acquired conditions. These factors disrupt normal blood flow and lead to thrombogenesis in the portal venous system. The primary causes of PVT include liver diseases (such as cirrhosis and non- alcoholic steatohepatitis), infections, abdominal surgeries, and systemic inflammatory states. Other etiological factors include:

Schistosomiasis-Induced PVT

The pathophysiology of PVT in schistosomiasis is associated with chronic pelvic adhesions and inflammation, which contribute to thrombogenesis [55]. Risk factors for schistosomiasis-induced PVT

include cirrhosis, systemic inflammation, reduced portal vein velocity (PVV), wider portal vein diameter (PVD), and the presence of gastro-esophageal varices (GOV) [16,56,57].

Intra-abdominal Infections

Intra-abdominal infections are significant contributors to PVT, with pylephlebitis (suppurative thrombophlebitis of the portal vein) being a key complication. Conditions such as appendicitis, diverticulitis, inflammatory bowel disease (IBD), cholecystitis, and pancreatitis have been implicated in the development of PVT. Among these, diverticulitis is a notable risk factor, with an incidence of approximately 3% in colonic diverticulitis [58-67].

COVID-19 and Thrombosis

The hypercoagulable state induced by COVID-19 significantly increases the risk of thrombosis, including PVT and mesenteric vein thrombosis. COVID-19 induces a cytokine storm and endothelial dysfunction, both of which promote thrombosis in unusual sites [68]. Vaccine-induced immune thrombotic thrombocytopenia (VITT), which has been associated with the COVID-19 vaccines, can sometimes result in thrombosis within weeks of vaccination [69].

Systemic infections and Thrombosis

Systemic Infection associated inflammatory responses can lead to a hypercoagulable state, thereby increasing the risk of venous thromboembolism (VTE), including PVT. Infections such as acute toxoplasmosis and bacterial infections with hypervirulent strains of *Klebsiella pneumoniae* contribute to thrombosis formation through inflammatory mediators and disseminated intravascular coagulation (DIC) [70-75].

Inflammatory Bowel Disease (IBD)

Patients with IBD, particularly those with ulcerative colitis (UC) and Crohn's disease (CD), have a significantly higher risk of developing PVT and other VTE-related conditions. A nationwide study has shown a 20% increase in VTE-related hospitalizations among IBD patients, with UC linked to an elevated risk of thrombosis [76,77]. This underscores the need for preventive strategies in IBD patients to reduce thrombosis risk.

Cirrhosis and Liver Dysfunction

Cirrhotic patients are in a hypercoagulable state due to elevated von Willebrand factor (vWF) and reduced ADAMTS-13, leading to platelet aggregation and thrombus formation [78]. Factor VIII and deficiencies in Protein C and S also contribute to increased thrombin generation and PVT risk [79-81]. The presence of cirrhosis complicates the diagnosis of PVT, with debates surrounding its role in exacerbating cirrhosis progression or merely reflecting disease severity [82].

Liver Hypoplasia

Liver hypoplasia, a rare condition leading to elevated intrahepatic portal venous pressure, can contribute to PVT. This is particularly relevant for diagnosis in patients undergoing liver transplantation or other surgical procedures [83-85].

Clomiphene Citrate Use

Clomiphene citrate (CC), a drug commonly used for ovulation induction and male infertility treatment, has been associated with an increased risk of thrombosis, including PVT and splanchnic vein thrombosis (SMVT). The drug's effect on hormonal levels and coagulation pathways may increase the likelihood of venous thromboembolism. Clinical case studies have demonstrated that patients using

clomiphene, with no other apparent risk factors, developed PVT and SMVT, suggesting a potential causative role of the medication [86-88].

Metabolic Comorbidities

Patients with non-alcoholic fatty liver disease (NAFLD) are at an elevated risk for developing PVT due to associated metabolic comorbidities such as obesity, type 2 diabetes, and dyslipidemia [89]. Additionally, individuals with COVID-19, particularly those with severe disease or elevated D-dimer and lactate dehydrogenase (LDH) levels, have been found to have an increased incidence of thromboembolic events, including PVT [90,91].

Genetic Factors

Genetic predispositions significantly influence the risk of PVT. Mutations such as Factor V Leiden and prothrombin G20210A have been implicated in increasing thrombotic risk in affected individuals [92,93]. Additionally, the MTHFR TT genotype is associated with an earlier onset of PVT due to elevated homocysteine (HC) levels, which contribute to oxidative damage and thrombosis [94,95].

Hypercoagulable States

Hypercoagulability during pregnancy significantly increases the risk of PVT, especially when compounded by obesity (BMI >30 kg/m²). Pregnancy-induced changes, such as increased coagulation activity after 28 weeks of gestation, contribute to a heightened thromboembolic risk [96-99].

Risk Factors for Portal Vein Thrombosis

Myeloproliferative Neoplasms and Thrombophilia

Clonal hematopoiesis in myeloproliferative neoplasms (MPNs) like polycythemia vera and essential thrombocythemia significantly raises thrombotic risks, including splanchnic vein thrombosis. The JAK2V617F mutation is particularly linked to PVT [9,100,101]. Thrombophilic disorders and low ADAMTS13 activity further exacerbate thrombotic tendencies [16,102].

Post-Surgical and Environmental Risks

PVT has been documented following bariatric surgeries such as sleeve gastrectomy, where the incidence reaches 0.5%, attributable to hypercoagulability and inflammation [103]. Splenectomy, often performed to manage portal hypertension, is another notable risk factor, with PVT incidence rates post-surgery ranging between 18.9% and 57% [104,105].

Metabolic and Virological Factors

Metabolic conditions, including advanced cirrhosis and virological diseases like hepatitis B, heighten PVT risk. Hepatic tuberculosis, though rare, can directly affect the portal vein, leading to thrombosis [106,107]. Sustained virological response via direct-acting antivirals reduces hypercoagulability in cirrhotic patients but does not entirely eliminate the risk in advanced cases [108].

Risk Factors in Neonates

The placement of umbilical venous catheters (UVCs) in neonates has been identified as a significant risk factor for PVT. This triggers bacterial dissemination, which activates the coagulation cascade and leads to thrombus formation [109,110]. Malpositioned UVCs contribute to vessel wall irritation and clot formation. Studies have demonstrated that a notable proportion of neonates with UVCs develop PVT, and prolonged follow-up is essential for children with this risk factor [111,112].

Cancer-Related Risk Factors

Hepatocellular carcinoma (HCC) and cirrhosis contribute significantly to the development of PVT due to a combination of tumor-induced hypercoagulability, liver inflammation, and altered coagulation dynamics. Tumor-induced cytokine release, platelet activation, and extracellular matrix remodeling further promote thrombosis [113-116]. Additionally, cancer stem cells, particularly those expressing

EpCAM and CD133, are linked to PVT and metastasis [117,118].

Other Risk Factors

Alterations in gut microbiota, such as reduced Bacteroides abundance, have been linked to PVT progression in cirrhotic patients, with interventions aimed at restoring the microbiota showing promise in improving outcomes [119]. Additional risk factors for PVT include older age, splenomegaly, ascites, elevated INR, low albumin levels, and high MELD scores [120-122].

Biomarkers and Molecular Predictors

The identification of reliable biomarkers for predicting portal vein thrombosis (PVT) is essential for early detection, risk stratification, and monitoring disease progression. Several clinical and laboratory biomarkers have shown promise in aiding the diagnosis and prognosis of PVT in various patient populations (detail given in Table 2) [123-131].

Table 2: Biomarkers in Portal Vein Thrombosis.

Biomarkers	Description	References
D-Dimer:	Higher levels of D- dimer and a larger portal vein diameter have been associated with an increased risk of thrombus formation, whereas lower platelet counts may reflect a compromised hemostatic response	[123,124]
A-VENA Criteria and PIVKA-II:	The A-VENA criteria, which incorporate clinical variables and biomarker data, have proven useful in identifying high-risk individuals. One key biomarker, Protein Induced by Vitamin K Absence or Antagonist II (PIVKA-II), has been shown to help in identifying patients at high risk of developing PVT, particularly in those with liver disease	[125,126]
ADAMTS-13 and VWF	Low levels of ADAMTS-13 activity (<18.8%) and an imbalanced ADAMTS-13/VWF# ratio have been identified as strong predictors of PVT, especially in cirrhotic patients. A ratio of ADAMTS-13 to VWF less than 0.4 has been suggested as a reliable marker for PVT prediction.	[102,127,128]
Systemic Inflammatory Markers	Inflammatory indices, such as the Albumin-to-Neutrophil Ratio Index (ANRI), Platelet-Lymphocyte Ratio (PLR), and Neutrophil-Lymphocyte Ratio (NLR), have emerged as useful markers in predicting PVT. Elevated levels of these markers are associated with an increased risk of PVT, particularly in cirrhotic and critically ill patients	[124,129,130]
Intestinal Microbiota	Emerging research has highlighted the role of the gut-liver axis and intestinal microbiota in the development of thrombosis, including PVT. Imbalances in the gut flora may contribute to thrombogenesis, influencing coagulation pathways and exacerbating the hypercoagulable state.	[131]
Validation of Biomarkers	While these biomarkers are promising, larger prospective studies are needed to validate their clinical utility. Standardization and reproducibility of these markers across different patient populations and clinical settings are crucial for their widespread adoption in clinical practice	[124]

Note: Von Willebrand Factor (VWF)#

Diagnostic Approaches

Accurate and timely diagnosis of PVT is crucial for appropriate clinical management. Several diagnostic techniques are employed to detect PVT and assess its severity, with imaging modalities playing a central role in confirming the diagnosis. These techniques include

ultrasound, contrast-enhanced imaging (CT and MRI), and advanced diagnostic methods that help identify thrombus presence, associated complications, and underlying conditions such as cirrhosis or malignancy (detail given in Table 3) and diagnostic challenges in Portal Vein Thrombosis have been described in Supplementary Table 1 [132-146].

Table 3: Diagnostic Methods in Portal Vein Thrombosis.

Methods	Description	References
Color Doppler Ultrasound:	Color Doppler ultrasound is the first-line diagnostic tool for PVT due to its accessibility and non-invasive nature. This technique is particularly effective for detecting the presence of thrombus and assessing portal vein patency. It typically shows high-level echoes, non-visualization of the portal vein, and serpiginous vascular channels in cases of thrombosis. Sensitivity ranges from 60% to 100%, depending on the operator's expertise, and it is especially useful for detecting complications like portal hypertension, varices, and splenomegaly. However, Doppler ultrasonography may miss early-stage PVT, especially in cirrhotic patients.	[120,132-134]
Contrast-enhanced CT and MRI scans:	Contrast-enhanced CT and MRI scans are preferred for confirming PVT, as they provide superior sensitivity and specificity compared to ultrasound. They are also essential for detecting complications of thrombosis, which can occur within 6–20 days. MRI, in particular, has demonstrated high sensitivity (100%) and specificity (98%) in detecting PVT. (PMID:1853809, PMID: 8816536)	[135-137]
Contrast-enhanced ultrasound (CEUS)	CEUS has become an increasingly valuable tool for diagnosing PVT, particularly in differentiating between benign and malignant thrombi. CEUS is particularly useful for detecting thrombi in patients with hepatocellular carcinoma (HCC), depicting rapid arterial-phase hyper-enhancement and slow portal venous washout. Studies have shown CEUS to have 100% sensitivity and 98% specificity for tumor-related PVT. However, the diagnostic accuracy of CEUS can vary based on operator expertise.	[138,139]
EGD	Esophagogastroduodenoscopy (EGD) plays a critical role in evaluating complications of PVT, particularly for variceal detection. The procedure allows for the direct visualization of gastroesophageal varices, which are commonly associated with portal hypertension resulting from PVT.	[140]
Contrast-enhanced CT-Scan for Pylephlebitis	Pylephlebitis, an infection of the portal vein, presents with nonspecific symptoms, making its diagnosis challenging. Contrast-enhanced CT is the imaging modality of choice for detecting pylephlebitis, revealing portal vein dilatation, thrombus, wall thickening, and complications such as hepatic abscess or mesenteric ischemia.	[141,142]
Portal-phase imaging	Portal-phase imaging, particularly with CT and MRI, is crucial for identifying thrombosis and its complications, such as hepatic abscesses or intestinal ischemia. However, definitive evidence of infectious thrombi can be challenging to obtain, underscoring the diagnostic complexities involved in PVT management.	[62, 72,143]
Imaging for Hepatic TB	Hepatic tuberculosis (TB) can present with imaging findings that overlap with PVT. Ultrasound and CT may suggest hepatic TB, but their lack of specificity can lead to diagnostic challenges. Miliary lesions on CT appear as microabscesses, while local hepatic TB manifests as larger nodules that may resemble neoplastic or granulomatous diseases. Histopathological or bacteriological confirmation is often required for a definitive diagnosis of hepatic TB, with liver biopsy revealing granulomas.	[144,145]
PCR Testing for Hepatic TB	PCR testing targeting the IS6110 sequence has demonstrated higher sensitivity (86%) and specificity (96%) for diagnosing hepatic TB.	[146]
Portal-phase imaging	Portal-phase imaging, particularly with CT and MRI, is crucial for identifying thrombosis and its complications, such as hepatic abscesses or intestinal ischemia.	[62,65]

Supplementary Table 1: Diagnostic Challenges in Portal Vein Thrombosis.

Methods	Description	References
Asymptomatic and Underdiagnosed Cases	One of the major challenges in diagnosing PVT is the lack of symptoms in many patients, particularly in the early stages. In asymptomatic cases, PVT may go undetected until complications arise. For example, in COVID-19 patients, PVT may be underdiagnosed due to the primary focus on respiratory symptoms, leaving thrombotic complications like PVT underappreciated.	(PMID: 36402911)
Diagnosis in NAFLD Patients	In patients with non-alcoholic fatty liver disease (NAFLD), diagnosing PVT can be particularly difficult. Doppler ultrasound is commonly used to diagnose PVT in these patients, as it helps visualize thrombus formation and portal vein obstruction. However, the diagnosis can be complicated by the presence of other liver abnormalities, such as fatty infiltration, which may interfere with the accuracy of ultrasound imaging. Furthermore, liver biopsy is not routinely performed for diagnosing PVT, limiting the ability to fully evaluate the extent of liver involvement and thrombotic complications	(PMID: 33474605) (PMID: 33708916).
Delayed Presentation in Children	In pediatric populations, the delayed presentation of PVT symptoms adds another layer of complexity to diagnosis. The signs of PVT in children may not become apparent until later in life, making early detection challenging. In these cases, imaging studies, genetic screening, and a detailed history of neonatal interventions (such as umbilical venous catheter [UVC] placement) are critical for identifying children at risk.	(PMID: 35174113, PMID: 12861528, PMID: 18955865).
Advanced Laboratory Techniques for Diagnosis	In addition to imaging, advanced laboratory techniques are important in diagnosing PVT, particularly in cases with an infectious component. The MALDI-TOF MS (Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry) technique has significantly enhanced the identification of anaerobic pathogens, complementing traditional culture methods.	(PMID: 33968791, PMID: 17714522).
Challenges in Routine Screening and Early Detection	Routine screening for PVT is not universally applied, particularly in high-risk populations like cirrhosis, malignancies, or COVID-19. This results in missed opportunities for early detection, which could prevent complications such as portal hypertension, varices, and splenomegaly.	

Note: Portal vein thrombosis (PVT) presents significant diagnostic challenges, primarily due to its often asymptomatic nature, the diversity of its clinical presentations, and its overlap with other conditions. Below listed are the factors that complicate the identification of PVT.

Initial Management Strategies

The management of PVT involves a comprehensive approach tailored to the underlying cause, severity, and patient-specific factors. Initial treatment typically includes rapid anticoagulation with Low Molecular Weight Heparin (LMWH) or unfractionated heparin, followed by a prolonged course (≥6 months) to prevent thrombus progression. Once stabilized, patient is transitioned to oral antico-

agulants like warfarin (target INR: 2–3) or direct oral anticoagulants (DOACs) such as apixaban, rivaroxaban, or dabigatran [65,147-151]. DOACs often preferred due to their safety profile and ease of use. In cases where anticoagulation fails or is contraindicated, interventions like Trans-jugular Intrahepatic Portosystemic Shunt (TIPS) or surgical thrombectomy may be necessary. Adjunct therapies such as endoscopic variceal ligation and beta blockers are essential for preventing variceal bleeding [152-158] (detail given in Table 4) [159-192].

Table 4: Management of PVT.

Management type	Description	References
Thrombolysis and Surgical Intervention		
Thrombolysis	Thrombolytic therapy (e.g., urokinase, streptokinase, tissue plasminogen activator [TPA]) can be considered in acute cases within 14–30 days of diagnosis. Mechanical thrombectomy, often used during bowel infarction surgeries, is still not definitively effective, as recurrent thrombosis and the need for further interventions are common.	[159,160]
Surgical Intervention	Surgical thrombectomy is reserved for cases involving bowel infarction but carries a high risk of re-thrombosis. For severe or refractory cases, consider transjugular intrahepatic portosystemic shunt (TIPS) or liver transplantation.	[161-163]
Endoscopic variceal ligation (EVL)	Endoscopic variceal ligation (EVL) and beta blockers are essential for primary and secondary prophylaxis of acute variceal bleeding in Extrahepatic Portal Vein Obstruction (EHPVO)	[164]
Anticoagulation Post-Splenectomy	Anticoagulation is crucial after splenectomy to prevent PVT complications, particularly in patients with esophageal varices.	[103]
Antibiotic Therapy		
Broad Spectrum IV Antibiotics	Initiate broad-spectrum intravenous antibiotics immediately upon diagnosis and transition to oral antibiotics after two weeks for a total treatment duration of six weeks. Early antibiotic intervention is crucial for reducing complications and preventing progression	[65,148, 165]
Management of Specific Conditions		
Splenic Vein Thrombosis (SVT)	In cases of SVT secondary to acute pancreatitis, anticoagulation is used to aid recanalization, though it does not significantly affect mortality.	[166]
Myeloproliferative Neoplasms (MPNs):	Long-term anticoagulation with DOACs is effective, and adding aspirin may help prevent recurrence	[9,167,168]
Hepatic Tuberculosis (TB):	Combine anti-tuberculosis therapy (ATT) with anticoagulation, with DOACs preferred due to their safety and ease of use.	[104, 168]
COVID 19 Considerations		
LMWH Prophylaxis:	Prophylactic LMWH reduces thromboembolic events in COVID-19 patients, though its impact on PVT incidence is unclear.	[90,169].
Anticoagulation in Hemophilia		
Extended Half-Life FIX Concentrates:	Used in hemophilic patients with PVT to maintain coagulation balance and reduce bleeding risks.	[17-172]
Mesenchymal Stem Cells (MSCs):	miRNA-25-3p-modified human umbilical cord MSCs promote endothelial repair by enhancing cell proliferation, migration, and angiogenesis, potentially aiding in PVT management.	[17-175]
Exosomal miRNAs:	MSC-derived exosomes have anti-inflammatory and tissue repair properties, reducing thrombotic events and promoting endothelial function via exosomal miRNAs like miRNA-126-3p and miRNA-342-3p.	[17-181]
Therapeutic Potential:	The PTEN/KLF4/ AKT/ERK1/2 signaling pathway mediates the beneficial effects of miRNA-25-3p-modified hucMSCs, underscoring their potential as a therapy for PVT.	[182,183]
Anticoagulation in Pylephlebitis		
Heparin and DOACs:	Heparin and DOACs (e.g., apixaban) are effective for managing pylephlebitis, with DOACs preferred due to their lower bleeding risk. Optimal duration remains unclear	[63]
Antibiotic Selection:	Antibiotics should account for the infection's origin and bacterial resistance, with ceftriaxone and ampicillin-sulbactam being successful, while cefmetazole should be avoided	[184]
Emerging Therapies		
Systemic Therapies in HCC	Combination therapies like atezolizumab and bevacizumab provide superior survival outcomes compared to sorafenib in advanced HCC with PVT. Studies also suggest the effectiveness of immune checkpoint inhibitors (ICIs).	[18-187]
Trans-arterial radioembolization (TARE)	Emerging therapies, such as TARE with Yttrium-90 (Y-90) and stereotactic body radiation therapy (SBRT), offer better tumor control while preserving liver tissue, showing potential in improving outcomes in PVT management.	[18-190]
Portal Vein Recanalization (PVR) in Children	PVR is an emerging alternative to traditional surgical methods like Meso-Rex bypass in children with EHPVT, offering the advantage of restoring the native portal venous system and avoiding complications associated with portosystemic shunts. Predictors of success for PVR remain unclear, but it avoids complications like hepatic encephalopathy	[191, 192]

Prognosis and Outcome Predictors

Impact of Anticoagulation and Underlying Conditions

The prognosis of PVT is majorly influenced by the timely initiation of anticoagulation therapy and management of underlying conditions. In cirrhotic patients without anticoagulation therapy, approximately 22% experience progression of PVT, while 77.7% have stable or improved conditions. Notably, 29.3% of cases experience regression of PVT, but complete recanalization occurs in only 10.4%, and recurrence is observed in 24% of patients [193].

Effect of Liver Disease and Coexisting Conditions

The underlying liver disease is a key factor in determining prognosis. Cirrhotic patients with PVT experience a significant decrease in two-year survival rates, primarily due to impaired liver function and associated complications [194]. In contrast, patients with non-alcoholic fatty liver disease (NAFLD) related PVT generally have a better prognosis when treated with anticoagulation therapy. The NAFLD patients showed complete recanalization within six months without long-term complications with the use of edoxaban to prevent recurrence [195]. Factors such as a higher MELD score and the presence of ascites are linked to worse outcomes in cirrhotic patients with PVT [193]. For non-cirrhotic, non-malignant PVT, the 1-year mortality rate is lower (8%) compared to malignancy- or cirrhosis-associated PVT, which has a higher 1-year mortality rate (~26%) [196].

Acute PVT with Intestinal Ischemia

Acute PVT complicated by intestinal ischemia has a particularly poor prognosis, with mortality rates ranging from 20% to 50% [30,197]. Early intervention and anticoagulation therapy can improve survival rates in these cases, highlighting the importance of prompt diagnosis and management.

PVT and Venous Thromboembolism (VTE)

PVT is strongly associated with venous thromboembolism (VTE), including pulmonary embolism (PE), with an increased risk of VTE in PVT patients, particularly in those with idiopathic PVT [198]. The risk of PE is concerning due to its high mortality rates, especially when associated with cardiac arrest, as 70% of fatal cardiac arrests occur within the first hour of PE onset [199,200]. Therefore, early preventive measures and monitoring for VTE and PE in PVT patients are critical to improving prognosis.

Prophylaxis and Long-Term Monitoring

For cirrhotic patients, prophylactic anticoagulation therapy may decrease the incidence of PVT and improve long-term outcomes [201]. Long-term anticoagulation therapy has been shown to reduce the frequency of variceal bleeding episodes, improve outcomes by

lowering microvascular thrombosis, and reduce portal vein pressure [202]. However, patients with cirrhosis and low platelet counts (below 50,000/mL) may be at higher risk for bleeding, with major bleeding rates reaching up to 9% [150,203].

Extrahepatic Portal Vein Obstruction (EHPVO)

In patients with Extrahepatic Portal Vein Obstruction (EHPVO), long-term survival can be improved with individualized care, including primary and secondary prophylaxis for variceal bleeding [140]. Proximal splenorenal shunts offer an 80% survival rate, while Rex surgery boasts nearly 100% long-term survival [140]. Post-surgical monitoring is critical to detect complications such as variceal recurrence and portosystemic encephalopathy.

Vascular Invasion in Hepatocellular Carcinoma (HCC)

Vascular invasion, particularly in HCC with PVT, significantly impacts survival. Patients with vascular invasion (Vp1-Vp4) exhibit progressively worse survival rates, with Child-Pugh A patients undergoing hepatic resection showing median survival rates of 34 months [204]. Survival decreases as the degree of vascular invasion increases (Vp1: 42.7%, Vp2: 25.2%, Vp3: 22.3%, Vp4: 9.8%) [204].

Pylephlebitis and Long-Term Monitoring

Pylephlebitis, when left untreated, can lead to severe complications such as hepatic abscess, mesenteric ischemia, portal hypertension, and pulmonary embolism, which significantly worsen prognosis. Regular follow-up imaging is essential to monitor thrombus resolution and prevent complications [63,205]. Aggressive management, including anticoagulation and long-term monitoring, is critical for improving patient outcomes and reducing morbidity and mortality associated with this condition [148].

Portal Hypertension (PHT)

Portal hypertension plays a crucial role in the prognosis of PVTT, exacerbating complications such as refractory ascites and esophago-gastric varices, which can lead to gastrointestinal bleeding. Managing PHT through interventions like portal vein stenting and radiofrequency ablation (RFA) can improve survival outcomes in PVTT patients by reducing the risk of bleeding and worsening liver dysfunction [206].

Survival and Prognostic Indicators in PVT

Survival in PVT is significantly influenced by the extent of thrombosis and the presence of vascular invasion, with survival times being particularly short when the main portal vein is involved (MPVTT). Median survival in such cases ranges from 2.7 to 4 months [185,207,208]. This highlights the importance of early detection, aggressive management, and personalized treatment strategies to improve prognosis, especially in high-risk patients.

Complications and Clinical Challenges

Variceal Re-Hemorrhage

Chronic PVT significantly heightens the risk of variceal re-hemorrhage [209]. Patients with cirrhosis and cavernous transformation of the portal vein generally have better outcomes, including lower mortality rates, compared to those without cavernous transformation [210]. A recent study revealed that TIPS is more effective than anticoagulation alone in achieving portal vein recanalization and improving survival, with reduced rates of variceal rebleeding and refractory ascites in the TIPS group [211].

Portal Hypertension and Its Effects

Portal hypertension in PVT can lead to the development of varices, splenomegaly, and hypersplenism, all of which require careful management [212,213].

Extrahepatic Portal Vein Obstruction (EHPVO)

In patients with Extrahepatic Portal Vein Obstruction (EHPVO), variceal bleeding, particularly from ectopic varices, is a significant clinical challenge [214,215].

Septicemia and Bacterial Translocation

A rare but serious complication in PVT patients is *Clostridium paraprutificum* septicemia, typically observed in immunocompromised individuals or those with gastrointestinal pathology [216,217]. In cases of ischemic bowel disease, the disruption of the mucosal barrier facilitates bacterial translocation into the bloodstream [218]. The introduction of MALDI-TOF mass spectrometry has enhanced the detection of anaerobic infections, improving diagnostic accuracy in these cases [219,220].

Complications in Neonates

In neonates, long-term complications of PVT include liver lobe atrophy, splenomegaly, and portal hypertension, necessitating ongoing monitoring [27].

Future Direction and Research Gap

Further investigation is needed to explore the role of coagulation markers and portal vein velocity in identifying cirrhotic patients at risk for PVT, especially in those who achieve sustained virological response (SVR) [42,221,222]. Focused research into diagnostic advancements, targeted therapies, and optimized anticoagulation protocols is essential to improve outcomes in PVT management [42]. Additionally, the potential role of NSBBs in promoting PVT via NETs and neutrophil activity in cirrhosis warrants further exploration [42,221,222]. Similarly, future studies should also investigate the mechanisms behind clomiphene-associated thrombosis and enhance management strategies for cirrhotic PVT and drug-related thromboembolic events. The limitations of current studies include small sample sizes, which

affect the generalizability of findings. The absence of comparison across different disease stages restricts insights into how disease progression influences treatment outcomes. The retrospective nature of many studies and single-center settings introduce potential biases. To address these issues, future prospective clinical trials with larger, multicenter populations are needed to validate findings, biomarkers, optimize thrombolytic regimens, and explore the role of gut-liver interactions in PVT development along with the efficacy of combined therapies for PVTT in HCC [102,131,159,206].

Research into miRNA-modified human umbilical cord-derived mesenchymal stem cells (hucMSCs) holds promise for endothelial repair and vascular health [173,174]. Future studies should explore the molecular mechanisms behind miRNA-modified therapies and their broader applications in vascular diseases [180,181]. Similarly, genetic predisposition, especially MTHFR genotypes, highlights the need for early screening and personalized therapies for PVT [94,95]. While radiotherapy, including stereotactic radiotherapy (SRT) and hypo-fractionated radiotherapy, shows potential for managing PVTT in HCC, challenges remain in determining the optimal radiation dose and fractionation schedule for external beam radiotherapy (EBRT) and SRT. Further studies are necessary to establish the best anticoagulation regimens and minimize side effects to improve therapeutic outcomes for PVT.

Conclusion

PVT is a complex thrombotic condition influenced by a range of genetic, metabolic, and environmental risk factors. Key contributors include hormonal therapies like clomiphene citrate, underlying comorbidities such as obesity and NAFLD, genetic predispositions, and surgical procedures. Additionally, cancer, particularly HCC, liver cirrhosis, infections, and mechanical factors such as bariatric surgery, play significant roles in the pathogenesis of PVT. Advances in the understanding of infections, gut microbiota, micro-vesicles, and cancer stem cells offer opportunities to improve diagnostic tools and therapeutic strategies, thereby reducing thrombotic risk and enhancing patient outcomes [154,223,224]. The treatment of non-cirrhotic PVT (NCPVT) primarily includes anticoagulation therapy, with direct oral anticoagulants (DOACs) becoming the preferred choice due to their safety and convenience [154]. Endovascular interventions are increasingly utilized in refractory cases, while careful management of portal hypertensive complications remains essential, especially in chronic PVT [223,224]. The complex and multifactorial nature of PVT demands a thorough and individualized approach to diagnosis and treatment. Ongoing research is needed to better understand the molecular basis of PVT, refine management strategies, and develop predictive models to improve patient outcomes. The development of more effective therapies, coupled with early detection and intervention, will be key to addressing the challenges posed by PVT in both cirrhotic and non-cirrhotic patients [59].

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Conflict of Interest

No.

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