Portal Vein Thrombosis

Xingshun Qi
Weifen Xie
Editors

Springer

Portal Vein Thrombosis

Xingshun Qi • Weifen Xie
Editors

Portal Vein Thrombosis

Springer

Editors
Xingshun Qi
Department of Gastroenterology
General Hospital of Northern
Theater Command
Shenyang
China

Weifen Xie
Department of Gastroenterology
Changzheng Hospital
Second Military Medical University
Shanghai
China

ISBN 978-981-33-6537-7 ISBN 978-981-33-6538-4 (eBook)
https://doi.org/10.1007/978-981-33-6538-4

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Foreword

This book is well appreciated because it calls to mind a rare disease which is often overlooked or diagnosed late, the main reason for limited efficacy of treatment and impaired prognosis. In 1856, Rudolf Virchow (1821–1902) first described three categories of factors, known as Virchow's triad, which are thought to contribute to thrombosis: stasis, vessel wall injury, and hypercoagulability [1]. Stasis is the leading cause of portal vein thrombosis in patients with advanced liver disease. This complication is not uncommon but has probably little impact on outcomes. In contrast, non-cirrhotic portal vein thrombosis is caused by the categories of vessel wall injury mostly due to local factors (e.g., surgery, inflammation, and trauma) and hypercoagulability. Since Virchow, the knowledge of thrombogenesis has increased dramatically. Unfortunately, treatment of portal vein thrombosis is still unsatisfactory, and restitutio ad integrum remains an exception.

This book, written by experts, covers the most important topics of portal vein thrombosis. It is an outstanding achievement which will become an essential constituent for clinicians. Congratulations to the editors and the authors.

Martin Rössle
Department Innere Medizin, Klinik für Innere Medizin II, Gastroenterologie, Hepatologie Endokrinologie und nfektiologie
Universitätsklinikum Freiburg
Medizinische Fakultät
Albert-Ludwigs-Universität Freiburg
Freiburg, Germany

Reference

1. Virchow, R. (1856). "Thrombose und Embolie. Gefässentzündung und septische Infektion". Gesammelte Abhandlungen zur wissenschaftlichen Medicin (in German). Frankfurt am Main: Von Meidinger & Sohn. pp. 219–732. Matzdorff AC, Bell WR (1998). Thrombosis and embolie (1846–1856). Canton, Massachusetts: Science History Publications. ISBN 0-88135-113-X.

Preface

Portal vein thrombosis has been a major research interest for me since the initiation of my scientific activities in September 2008. Indeed, my first publication is a correspondence discussing the role of medical treatment and transjugular intrahepatic portosystemic shunt for portal vein thrombosis in liver cirrhosis with variceal bleeding (*Hepatology. 2009*). Subsequently, based on the medical records provided by Prof. Guohong Han and Prof. Daiming Fan on the Xijing Hospital of Digestive Diseases of the Fourth Military Medical University, my first original paper had been completed, which was a retrospective case series exploring the outcomes of transjugular intrahepatic portosystemic shunt for portal vein thrombosis in liver cirrhosis with variceal bleeding (*J Hepatol. 2009*), despite being a second co-first author for this paper. At that time, I was very enthusiastic about extensively reading the literature regarding management of portal vein thrombosis, and designed my first randomized controlled trial comparing the medical treatment versus transjugular intrahepatic portosystemic shunt for prevention of variceal bleeding in liver cirrhosis with portal vein thrombosis (*BMJ Open. 2010*). As known, such a time-consuming and tremendous work has been published (*Gut. 2019*), although I am a second co-author. Except for transjugular intrahepatic portosystemic shunt for portal vein thrombosis, my researches also involve the risk factors (natural anticoagulants, coagulation factors, fibrinolysis markers, and acquired thrombophilia), outcomes (risk of bleeding and death), and treatment (wait-and-see strategy and preventive and therapeutic anticoagulation) of portal vein thrombosis. Among them, two review papers, which provided more comprehensive insights on the management of portal vein thrombosis, should be particularly emphasized (*Nature Rev Gastro Hepatol. 2014*, *BMC Med. 2018*). Certainly, it should be acknowledged that these works could not be optimized without the guidance of many famous experts, including Prof. Valerio De Stefano, Prof. Dominique Valla, Prof. Eric Yoshida, Prof. Nahum Mendez-Sanchez, Prof. Andrea Mancuso, Prof. Ankur Arora, Prof. Fernando Romeiro, Prof. Frank Tacke, Prof. Aurélie Plessier, Prof. Massimo Primignani, Prof. Carlos Noronha Ferreira, Prof. Cyriac Abby Philips, Prof. Rolf Teschke, and Prof. Saurabh Chawla.

On the basis of these accomplishments, Prof. Weifen Xie, who is the head of the Hepatobiliary Disease Study Group of the Chinese Society of Gastroenterology and the co-editor of this book, appointed me to write the Chinese-language consensus for management of portal vein thrombosis in liver cirrhosis in June 2019. I

completed the first draft in September 2019. Since then, this consensus has been further improved through several rounds of face-to-face or online discussions with the members of the Hepatobiliary Disease Study Group until its publication in November 2020. During this period, Prof. Weifen Xie and I initiated the current book project *Portal Vein Thrombosis* with the support of Springer. Dozens of specialists have been invited to overview the current status and future directions in this field.

Shenyang, China Xingshun Qi
December 1, 2020

Acknowledgments

This book project cannot be completed without the contributions from so many famous experts. As known, all of them have made outstanding contributions to the management of portal vein thrombosis. Some landmark papers written by them should never be neglected, such as a randomized controlled trial regarding anticoagulation for prevention of portal vein thrombosis in liver cirrhosis by Prof. Villa (*Gastroenterology. 2012*), an excellent review paper regarding portal vein thrombosis, cirrhosis, and liver transplantation by Prof. Durand (*J Hepatol. 2012*), a large-scale longitudinal study regarding natural history of portal vein thrombosis in liver cirrhosis by Dr. Nery (*Hepatology. 2015*), a cohort study regarding natural history and management of esophagogastric varices in chronic non-cirrhotic and non-tumoral portal vein thrombosis by Dr. Noronha Ferreira (*Hepatology. 2016*), and a very comprehensive review paper regarding management of portal vein thrombosis by Dr. Intagliata (*Gastroenterology. 2019*). Besides, their enthusiastic participation in this book project, especially during the COVID-19 pandemic, should be respected and appreciated.

In order to smooth the road to publish this book project, the Springer staff, mainly including Miss Kripa Guruprasad, Miss Xianxian Sun, and Mr. James Bin Hu, gave their assistance in designing the book protocol, communicating with chapter authors, giving comments on the chapters, and formatting and publishing this book. Notably, Kripa, who is also the coordinator of my first Springer book *Budd-Chiari Syndrome*, is absolutely impressive due to her positive attitude and timely communications. Herein, I would like to pay a heartfelt tribute to her. From my side, such a conscientious staff should be praised and cherished by any publisher.

Finally, as always, I must be thankful for the lifelong support of my wife, Jun Liu, and my family.

Shenyang, China
December 1, 2020

Xingshun Qi

Contents

Anatomy of Portal Vein System

1

Ruchira Das, James Chambers, and Ankur Arora

Abstract

The abdomen is unique to have two venous systems—the systemic and portal system. The systemic venous network drains directly into the inferior vena cava, whereas the portal system delivers the blood to the liver via the hepatic portal vein. The portal venous blood gets filtered through the hepatic sinusoids to enter the hepatic veins and finally the inferior vena cava. The mesenteric and splenic veins are its main tributaries but smaller veins from the stomach, pancreas, and gallbladder also contribute to this system. The portal venous system is subject to various congenital and acquired disorders, most importantly portal venous obstruction/thrombosis and portal hypertension. Proper understanding of the anatomy of the portal venous system is imperative for the diagnosis, management, and effective treatment planning of these disorders. Variant anatomy and congenital anomalies of the portal venous system are particularly important to identify in the context of consideration of liver transplantation or hepatic resections and interventional procedures like transjugular intrahepatic portosystemic shunt, portal vein embolization, etc. In this chapter, we will review the embryology and anatomy of the portal venous system, discuss its complex tributaries, and also succinctly learn about relevant anatomical and topographical variants in light of their significance prior to surgical or interventional treatments.

R. Das · J. Chambers · A. Arora (✉)
Department of Radiology, Royal Liverpool University Hospital, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK
e-mail: Ruchira.Das@Liverpoolft.nhs.uk; James.Chambers@Liverpoolft.nhs.uk; Ankur.Arora@Liverpoolft.nhs.uk

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_1

Keywords

Portal system · Portal vein · Splenic vein · Superior mesenteric vein · Anatomic variation · Portal hypertension · Portosystemic shunts

1.1 Introduction

The portal venous system consists of all veins draining the abdominal part of the gastrointestinal tract (from the lower esophagus to the upper rectum), spleen, pancreas, and gallbladder to the liver. Unlike other solid viscera, the liver receives about 75% of its blood through the portal vein (PV), whereas the remaining 25–30% comes from the hepatic artery. The blood flows through the hepatic sinusoids and enters the systemic circulation via the hepatic veins into the inferior vena cava (IVC).

The portal venous system may be affected by a wide spectrum of congenital variants and anomalies and acquired abnormalities. It is imperative to understand the conventional anatomy and identify variant anatomy to aid diagnosis and guide appropriate management of portal vein thrombosis or portal hypertension. This chapter reviews the normal anatomy and congenital variations involving the portal venous system and their clinical significance.

1.2 Embryology of the Portal Vein System

Formation of the portal venous system takes place between the fourth and twelfth weeks of gestation. The system is formed from the paired vitelline and umbilical veins (Fig. 1.1). Initially, the right and left vitelline veins enter the liver, branch into the hepatic sinusoids, coalesce, and then drain into the sinus venosus—the primitive heart [1, 2]. These two vitelline veins form three pre-hepatic anastomoses around

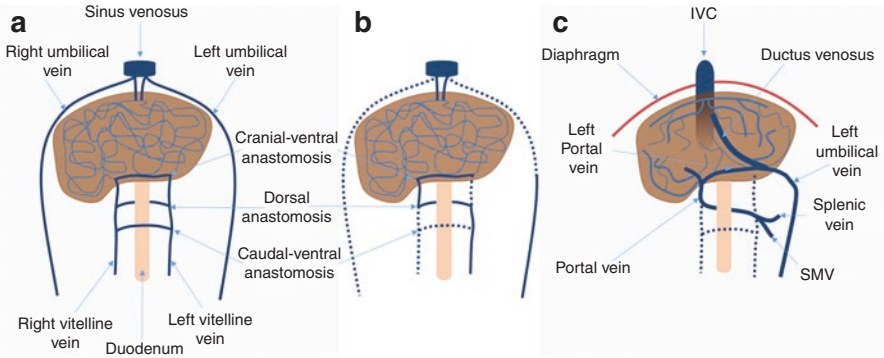

Fig. 1.1 Illustration of the development of the portal venous system, reproduced from [1]. (**a**) tomoses join the vitelline veins around the duodenum to supply the liver. (**b**) Fragmentation and involution of parts of the vitelline and umbilical veins. (**c**) Formation of the portal venous system and ductus venosus

the developing duodenum: the cranial-ventral, dorsal, and caudal-ventral. The right and left umbilical veins initially lie outside of the liver and also drain into the sinus venosus (Fig. 1.1a). As gestation advances, there is involution of parts of the vitelline and umbilical veins (Fig. 1.1b). The caudal aspect of the right vitelline vein, cranial part of the left vitelline vein, and the caudal-ventral anastomosis involute leaving the dorsal anastomosis and cranial-ventral anastomosis to become the main portal vein (MPV) and the left portal vein (LPV). The right umbilical vein and cranial aspect of the left umbilical vein involute leaving the caudal aspect of the left umbilical vein. The remaining left umbilical vein bifurcates forming a communication with the LPV and the IVC, the latter known as the ductus venosus (Fig. 1.1c). The ductus venosus transports blood from the placenta to the fetus and the communication between the left umbilical vein and LPV transports blood from the placenta to the liver. The ductus venosus and the left umbilical vein involute postpartum, becoming ligamentum venosum and ligamentum teres [1–3].

1.3 Gross Anatomy

The PV is a thin-walled, valve-less vascular structure that measures approximately 6–8 cm in length in adults with a maximum diameter of 13 mm [1, 2]. It drains the abdominal part of the alimentary tract as well as the spleen, pancreas, and gallbladder, and is formed by the confluence of the superior mesenteric and splenic veins behind the neck of the pancreas at the level of L1–L2 vertebrae (Fig. 1.2) [4, 5].

The PV contributes 40 mL/min or 72% of the total oxygen supply to the liver. Normal portal blood flow in human beings is about 1000–1200 mL/min. The normal portal pressure is about 7 mmHg.

The MPV ascends within the hepatico-duodenal ligament at an angle of 40°–90° with respect to the spine and enters the liver at the porta hepatis. The portal trunk divides in the liver hilum into two branches: LPV and right portal vein (RPV) [1–6].

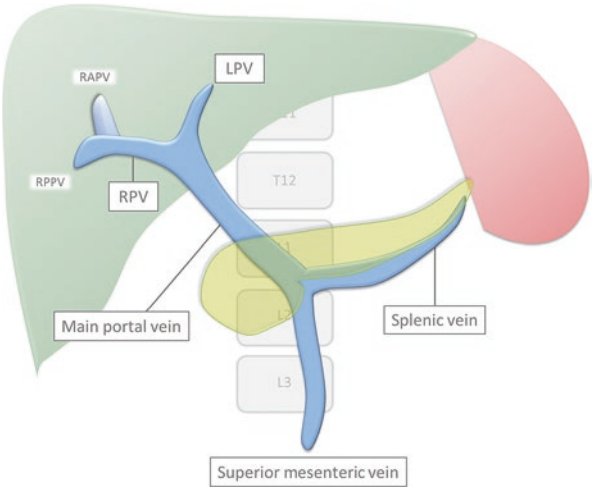

Fig. 1.2 Normal anatomy of portal venous system. *LPV* left portal vein branch, *RPV* right portal vein branch, *RAPV* right anterior portal vein, *RPPV* right posterior portal vein branch

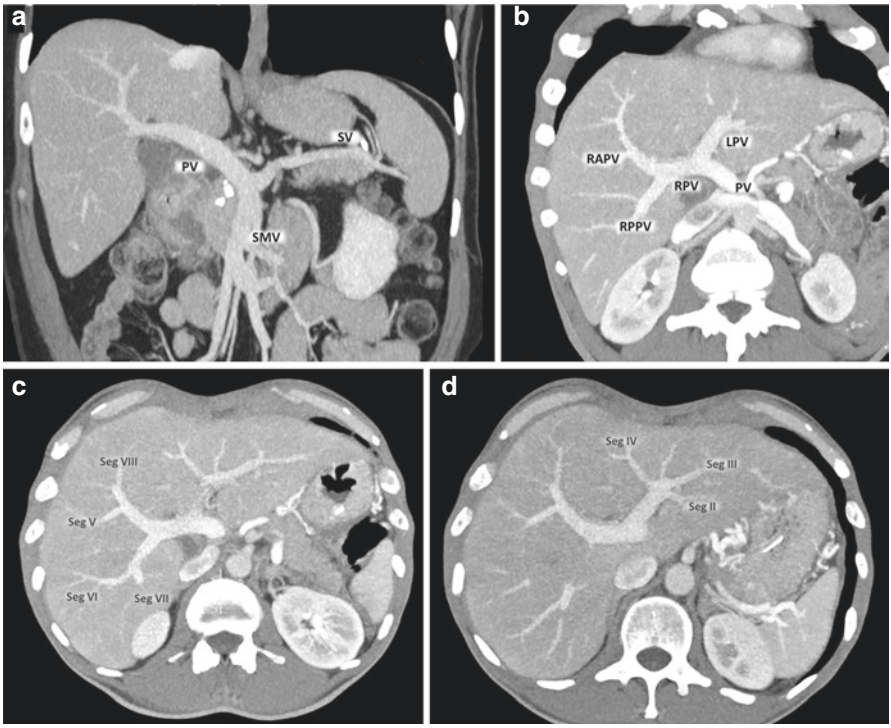

Fig. 1.3 Contrast-enhanced CT maximum intensity projection (MIP) images in coronal (**a**), reformatted coronal oblique (**b**), and axial oblique (**c**, **d**) planes demonstrating the conventional branching anatomy of the portal vein

The RPV subsequently divides into an anterior branch and a posterior branch. The right anterior portal vein branch (RAPV) supplies Couinaud segments V and VIII while the right posterior portal vein branch (RPPV) supplies segment VI and VII. The LPV supplies hepatic segments II, III, and IV and also supplies the caudate lobe (segment I) (Fig. 1.3).

These hepatic segmental branches divide further, forming smaller venous branches and finally portal venules which empty into the hepatic sinusoids. Hepatic sinusoids which are lined by endothelial cells and surrounded by hepatocytes process the blood and deliver it to the central veins. The blood then flows through the hepatic veins into the IVC [1–7].

1.4 Tributaries

1.4.1 Portal Vein

In addition to the splenic vein (SV) and superior mesenteric vein (SMV) which constitute the PV, the other tributaries of the MPV are the left gastric, right gastric,

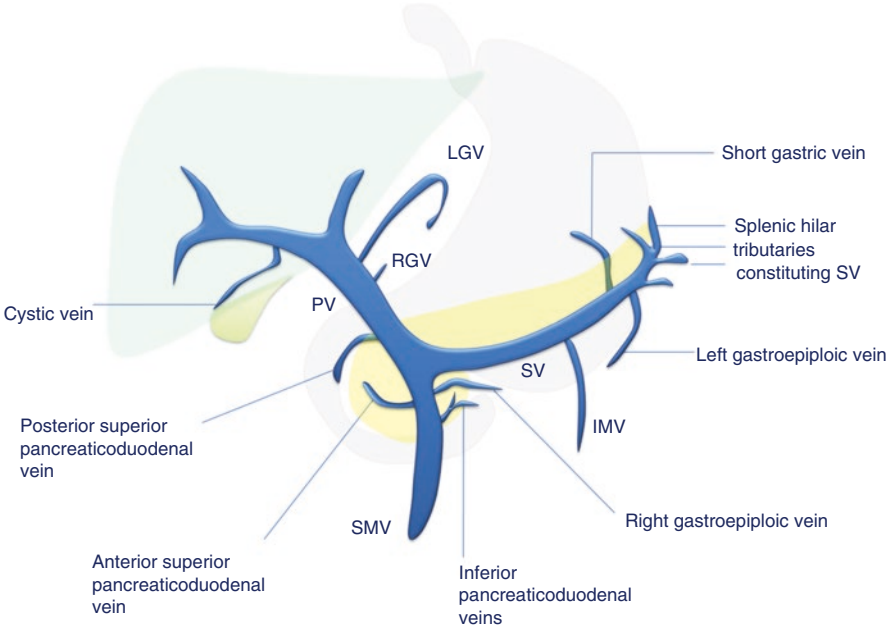

Fig. 1.4 Main tributaries of the portal venous system. *PV* portal vein, *SV* splenic vein, *SMV* superior mesenteric vein, *IMV* inferior mesenteric vein, *LGV* left gastric vein, *RGV* right gastric vein

and superior pancreaticoduodenal veins (Fig. 1.4). The cystic vein drains into the RPV while the umbilical vein drains into the LPV [5–7].

The left gastric vein (LGV) or coronary vein is one of the most important tributaries of the MPV which is responsible for the formation of esophageal and gastric fundal varices in portal hypertension [8–11]. The LGV starts from small branches of the lower esophagus and anterior and posterior gastric walls [4–6]. It passes along the lesser curvature and typically drains into the MPV (30%) or at the splenoportal junction (33%) [5]. In about 37% of cases, the LGV may instead drain into the SV [4, 5].

The RGV travels close to the gastric pylorus in the lesser curvature and separately enters into the MPV behind the duodenal cap. It drains the lesser curve of the stomach [4–6]. It also receives the prepyloric vein which drains the duodenal bulb.

The pancreaticoduodenal veins drain the second and third parts of the duodenum as well as the pancreatic head and neck. They are four in number and form a venous arcade around the duodenum. The posterior superior pancreaticoduodenal vein drains into MPV, whereas the anterior superior pancreaticoduodenal vein joins the SMV. The anterior and posterior inferior pancreaticoduodenal veins also empty into the SMV [4, 5].

The cystic vein drains the gallbladder and typically opens into the RPV while the paraumbilical vein, which drains the anterior abdominal wall, runs within the ligamentum teres to join the LPV [4, 5, 10].

1.4.2 Superior Mesenteric Vein

The SMV drains the major portion of the small bowel and the colon up to the splenic flexure. It ascends along the root of the mesentery to join the SV posterior to the pancreatic neck [1, 4–6].

The SMV receives tributaries corresponding to the superior mesenteric artery (SMA) branches, namely the jejunal vein (draining the jejunum), ileal vein (draining the ileum), ileocolic vein (draining the ileum and cecum), right colic vein (draining the ascending colon), and middle colic vein (draining the proximal two-thirds of the transverse colon) (Fig. 1.5) [4, 5].

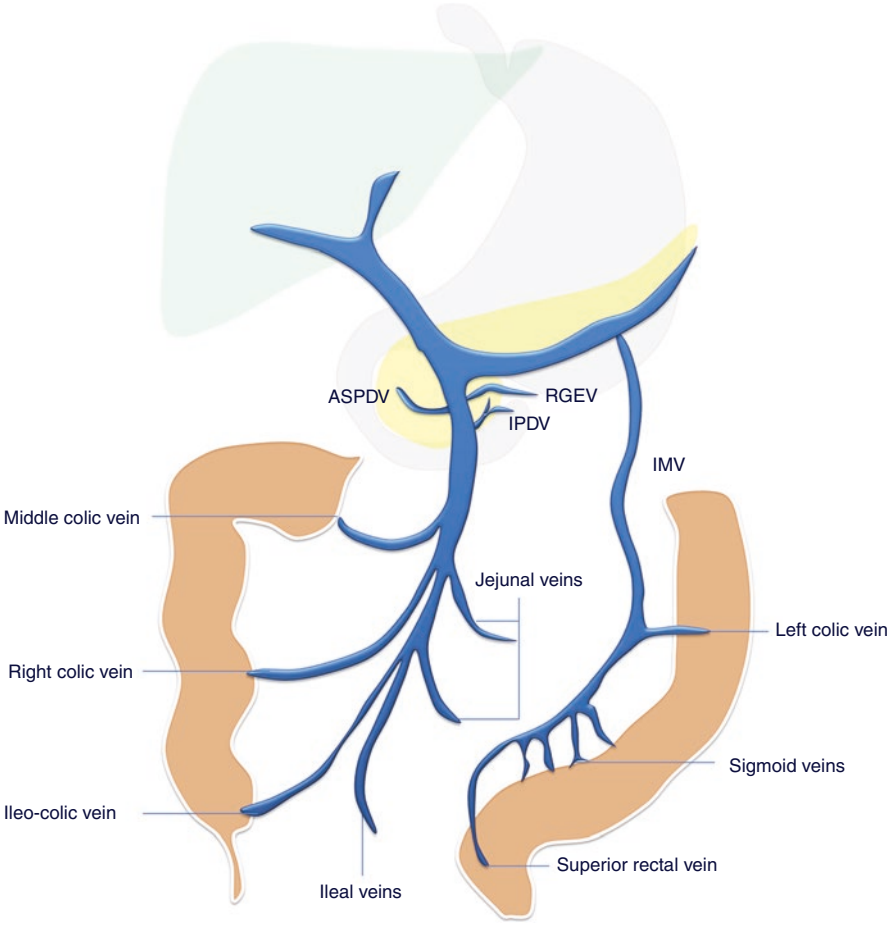

Fig. 1.5 Main tributaries of the superior mesenteric vein (SMV) and inferior mesenteric vein (IMV). *RGV* right gastro-epiploic vein, *ASPDV* anterior superior pancreaticoduodenal vein, *IPDV* inferior pancreaticoduodenal veins

In addition, it receives the right gastroepiploic vein (draining the greater curve of the stomach), and the pancreaticoduodenal veins (draining the head of the pancreas and second and third parts of the duodenum). These include the anterior superior pancreaticoduodenal vein and the inferior pancreaticoduodenal veins (anterior and posterior) [4–6].

1.4.3 Splenic Vein

Multiple small venous tributaries at the splenic hilum constitute the SV. The SV receives the short gastric veins (draining the gastric fundus), left gastroepiploic vein (draining the greater curve of the stomach), pancreatic veins (draining the neck, body, and tail of the pancreas), and typically the inferior mesenteric vein (IMV) (Fig. 1.4) [4–6].

1.4.4 Inferior Mesenteric Vein

The IMV drains into the SV in 38% of cases. In the remaining, it drains into the splenoportal confluence (32.7%), SMV (29.3%), or rarely the first jejunal vein (Fig. 1.6) [5].

IMV drains the left-sided colon starting from the splenic flexure to the mid rectum and receives blood from the left colic vein (drains the splenic flexure and descending colon), sigmoid veins (drains the sigmoid colon), and the superior rectal vein (drains the upper and mid rectum) (Fig. 1.5) [4–6].

In addition to the superior rectal vein, the rectal (or hemorrhoidal) venous plexus is constituted by middle and inferior rectal veins which in contrast to the superior rectal vein drain into systemic circulation (iliac veins) (Fig. 1.7) [4, 5, 8, 9].

1.5 Normal Portosystemic Anastomoses

Apart from the rectal (or hemorrhoidal) venous plexus wherein the portal and systemic veins anastomose, other sites of embryologically derived portosystemic anastomoses that normally exist in healthy adults are shown in Table 1.1.

1.6 Portosystemic Collateral Pathways

Resistance to normal portal venous blood flow either secondary to venous thrombosis/occlusion or due to liver parenchymal disease results in the formation of portosystemic collateral circulation. Portosystemic collateral pathways are a result of recanalization of embryonic portosystemic channels and/or reversal of flow in preexisting normal veins of the adult portal venous systems [6–11].

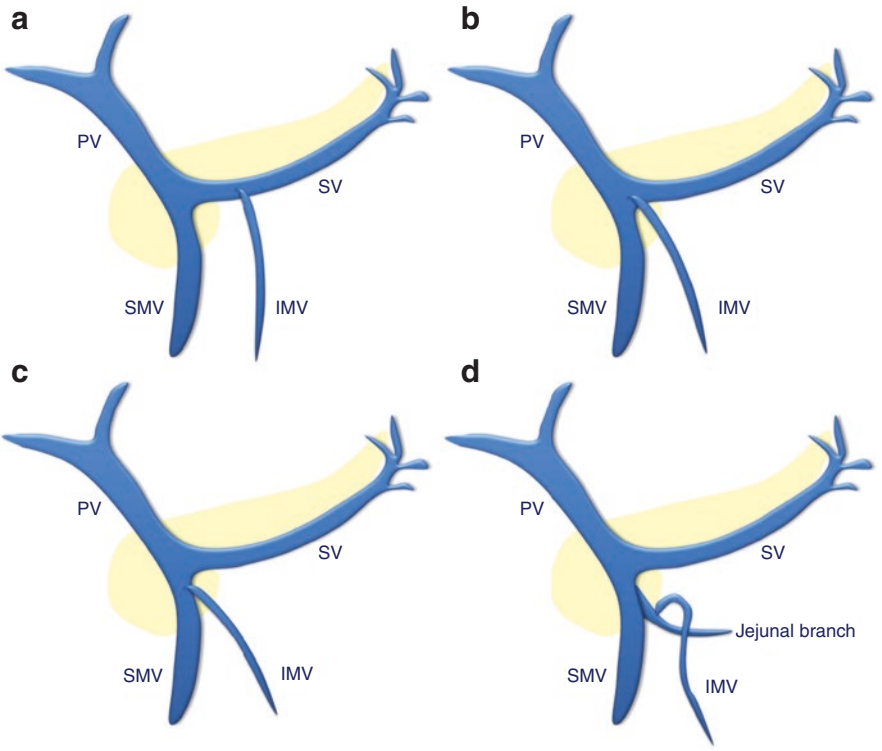

Fig. 1.6 Anatomical variants of IMV. (**a**, **b**) IMV typically drains into SV or splenoportal confluence in 38% and 32.7%, respectively. (**c**) In 29.3%, it drains into the SMV. (**d**) Rarely, the IMV may drain into the first jejunal branch of SMV

Portosystemic collateral pathways (or shunts) allow shunting of blood from high-pressure portal system to low pressure systemic vascular beds. Large volumes of blood passing through these anastomoses over a sustained period of time result in abnormal dilatation of the end-organ veins around the anastomoses—known as varices. Varices can be located outside the gut wall (para-esophageal, para-gastric, para-rectal), adjacent to the muscular layer (peri-esophageal, peri-gastric, peri-rectal) or subepithelial/submucosal in location (esophageal, gastric, rectal varices) [6].

Traditionally, the portosystemic varices have been broadly classified into two types: gastro-esophageal varices and ectopic varices [6, 8, 10, 11]. Ectopic varices encompass all varices other than those in the stomach or esophagus, e.g., duodenum, jejunum, ileum, colon, rectum, omentum, gallbladder, bile duct, bladder, uterus, vagina, diaphragm, and peristomal [6, 8, 10].

In addition to the formation of varices, spontaneous portosystemic shunts may also develop between the portal and systemic venous circulation so as to allow larger amounts of flow across them (e.g., gastrorenal or gastrocaval shunts) [8].

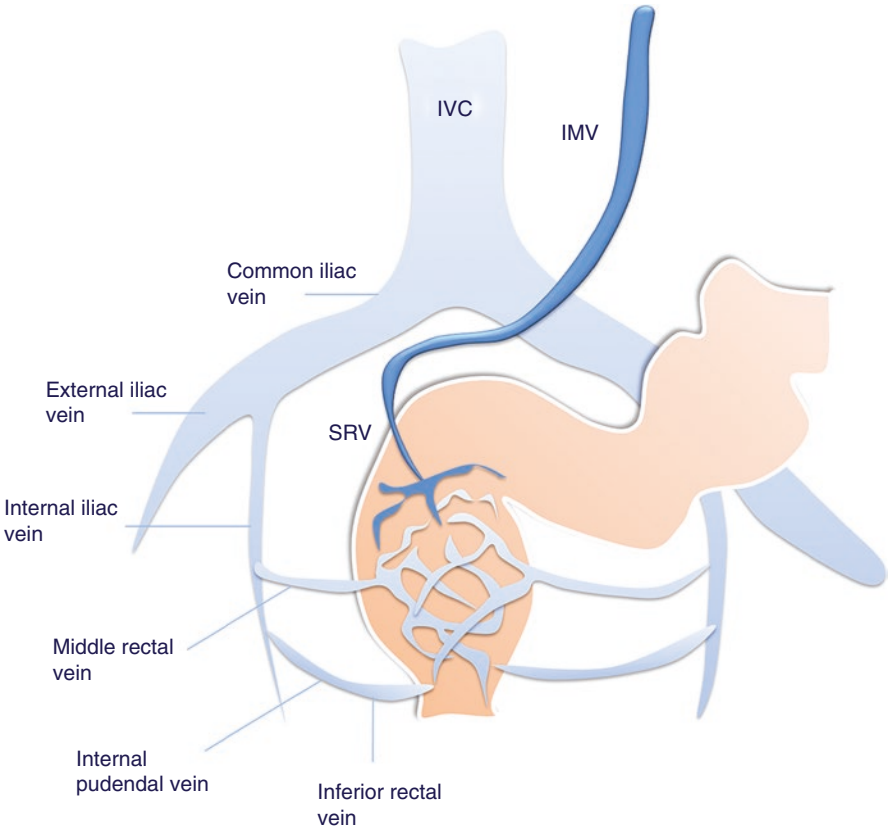

Fig. 1.7 The rectal (or hemorrhoidal) venous plexus. The upper and mid third rectum drains via the superior rectal vein (SRV) into the inferior mesenteric vein (IMV). The lower third rectum drains via the middle rectal vein into the internal iliac vein (systemic circulation). The anorectal junction and anal canal drain via the internal pudendal vein into the inferior rectal vein—a tributary of the internal iliac vein

A wide spectrum of portosystemic collateral pathways (i.e., varices and shunts) can be encountered in patients with portal hypertension [6, 8–11]. Based upon their prevalence, these can be classified into common and uncommon pathways (Tables 1.2 and 1.3) [8].

1.7 Anatomical Variants of Portal Vein

Typical PV anatomy (i.e., the MPV trunk bifurcating into RPV and LPV at the liver hilum and the RPV subsequently dividing RAPV and RPPV) is encountered in 65–80% using multi-detector CT, as has been described by published case series [3, 12, 15–17]. Any deviation from this conventional anatomy is considered an

Table 1.1 Normal sites of portosystemic anastomoses, adapted from [8]

Sites	Portal component	Systemic component
Lower esophagus	Left gastric vein	Esophageal veins (*drain into azygous vein*)
Rectum and anal canal	Superior rectal vein	Middle and inferior rectal veins (*tributaries of internal iliac and pudendal veins*)
Umbilicus	Paraumbilical vein	Superior and inferior epigastric veins
Bare area of the liver	Portal venous branches	Inferior phrenic and right internal thoracic vein
Retroperitoneum	Tributaries of splenic, pancreatic, and colic veins	Renal, gonadal, paravertebral/lumbar veins
Patent ductus venosus (rare)	Left branch of portal vein	Inferior vena cava

Table 1.2 Common portosystemic collateral pathways, adapted from [8]

Collaterals	Afferents	Efferents
Esophageal varices	Left gastric vein	Azygos-hemiazygos veins
Gastric varices	Anterior branch of the left gastric vein (gastro-esophageal varices Type 1), Short gastric and posterior gastric veins (gastro-esophageal varices Type 2)	Esophageal or para-esophageal veins
Paraumbilical vein	Left portal vein	Anterior abdominal wall veins and iliofemoral veins
Rectal varices	Superior rectal veins	Middle and inferior rectal veins, tributaries of internal iliac and pudendal veins
Gastrorenal shunt	Gastric varices or posterior or short gastric veins	Left renal vein
Splenorenal shunt	Splenic vein	Left renal vein
Pericholecystic varices	Cystic vein or a branch of the right portal vein	Hepatic vein, intrahepatic portal vein, or anterior abdominal wall collaterals
Mesenteric collaterals	Superior mesenteric vein and inferior mesenteric vein	Inferior vena cava through the retroperitoneal or pelvic veins (veins of Retzius)
Retroperitoneal collaterals	Colic or mesenteric branches (veins of Retzius)	Retrogastric varices or inferior phrenic veins to the left renal vein or directly into the inferior vena cava
Omental varices	Superior or inferior mesenteric veins	Retroperitoneal or pelvic veins or gastro-esophageal veins

Table 1.3 Uncommon portosystemic collateral pathways, adapted from [8]

Sites	Portal component	Systemic component
Tracheal and bronchial varices	Tracheobronchial plexus of veins	Pulmonary veinsBronchial veinsEsophageal/para-esophageal varices
Colonic varices	Ileocolic, right, middle colic, or sigmoid colic vein	Right gonadal vein, right renal vein, and systemic lumbar veins
Jejunal or ileal varices	Jejunal and ileal veins	Abdominal wall veins or the veins of Retzius
Duodenal varices	Superior and inferior pancreaticoduodenal veins, cystic branches of the superior mesenteric veins, gastroduodenal vein, and pyloric vein	Veins of Retzius into the inferior vena cava
Uterovaginal varices	Superior hemorrhoidal plexus	Uterine and hypogastric veins to inferior vena cava
Vesical varices	Mesenteric veins (commonly root of mesentery)	Internal and external iliac veins
Bare area of the liver	Portal venous branches	Inferior phrenic and right internal thoracic vein
Transhepatic shunt	Intrahepatic branches of the portal vein	Inferior vena cava, coronary vein, vertebral plexus, and hemiazygos vein
Mesentericorenal shunt	Mesenteric veins	Capsular renal veins or left renal vein
Mesenteric-gonadal shunt	Mesenteric veins	Right gonadal vein

anatomical variant. Due to the increasing number of liver transplants, hepatic resections, and interventional procedures, a thorough understanding of portal vasculature and potential variations is of paramount importance [13].

There are four main types of PV branching variants described in the literature [14]:

Type 1: This variant is also known as "trifurcation" pattern and has a reported occurrence of 9–11% [14]. In this variant, the MPV divides into three branches: LPV, RAPV, and RPPV (Fig. 1.8).

Type 2: RPPV originates as the first branch of portal vein (PV); this has a prevalence of 9.7–23% (Fig. 1.9).

Type 3: RAPV directly originates from the LPV (Fig. 1.10).

Type 4: This variant is the least common (<2%) and comprises of absent portal vein bifurcation (Fig. 1.11). The MPV trunk continues as a single intrahepatic arch and traverses from the right to the left liver lobe [14, 18].

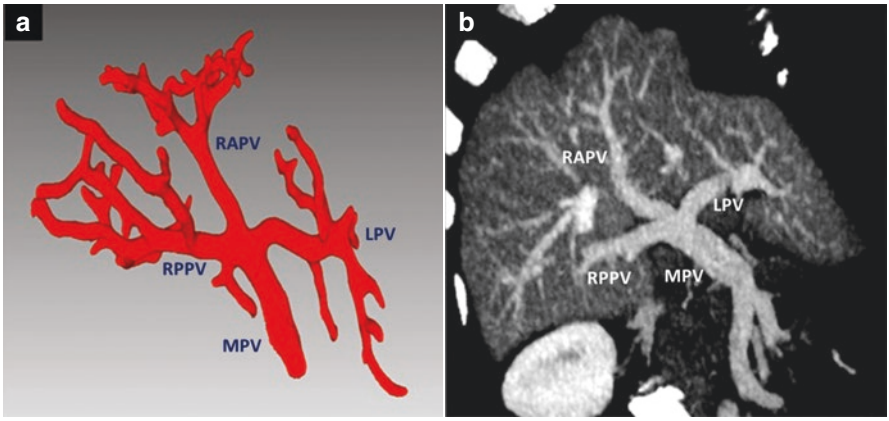

Fig. 1.8 Trifurcation variation, reproduced from [13]. (**a**) Myrian three-dimensional (3D) volume-rendered (VR) image. (**b**) CT coronal-oblique maximum intensity projection (MIP)

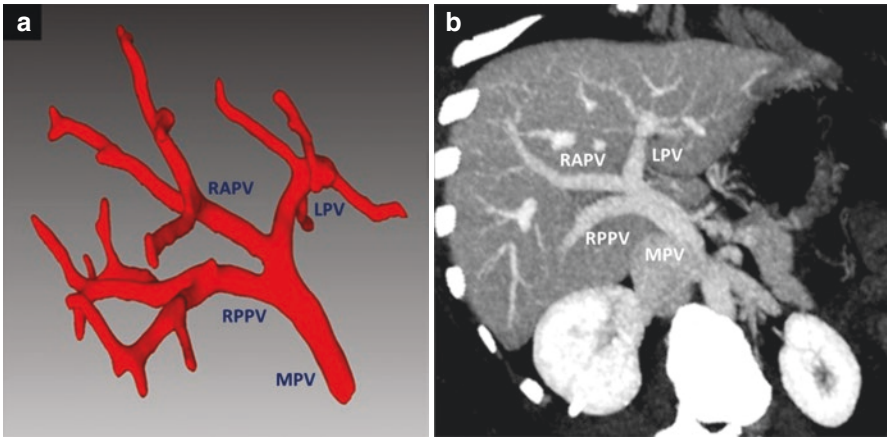

Fig. 1.9 RPPV arising from the MPV variation, reproduced from [13]. (**a**) Myrian 3D VR image. (**b**) CT coronal-oblique MIP

1.7.1 Clinical Significance

Knowledge and comprehensive understanding of these variants is extremely important for surgeons, physicians, and radiologists while planning surgeries and interventional procedures (e.g., transjugular intrahepatic portosystemic shunt [TIPS]) to avoid untoward complications.

1.7.2 Liver Transplantation

With improved diagnostic and surgical technology, PV variations can be managed rather safely; however, some variants can make surgery difficult and remain contraindications to living donor right lobectomy [19, 20]. Conventional PV branching, in

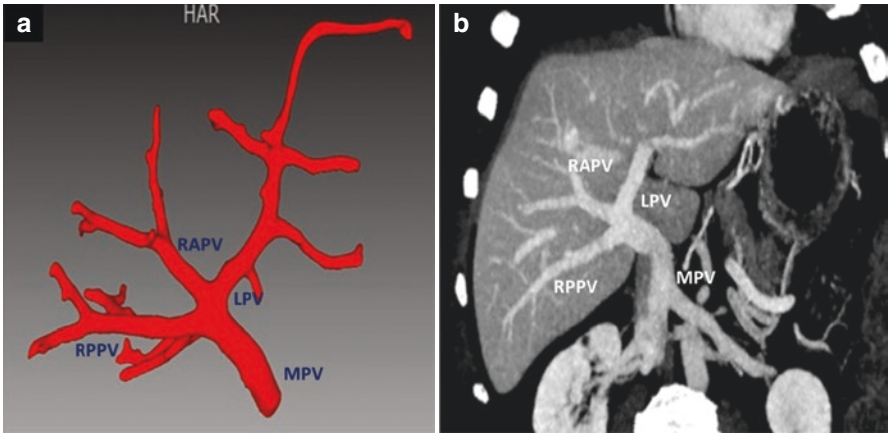

Fig. 1.10 RAPV arising from the LPV variation, reproduced from [13]. (**a**) Myrian 3D VR image. (**b**) CT coronal-oblique MIP

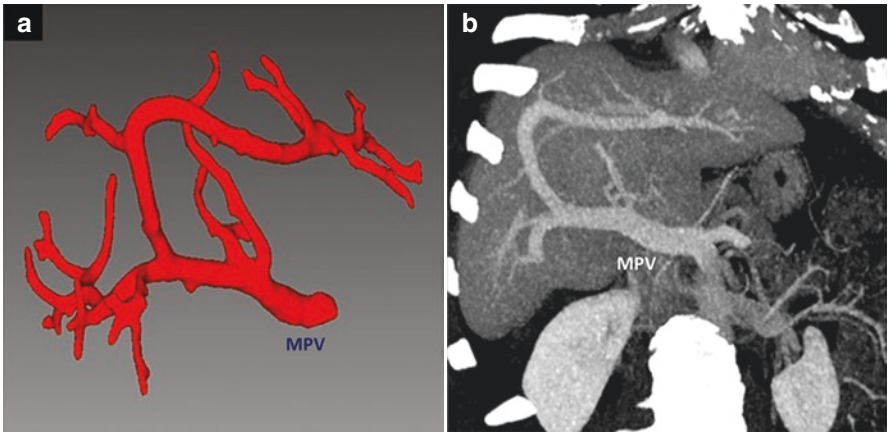

Fig. 1.11 Absence of the portal vein bifurcation variation, reproduced from [13]. (**a**) Myrian 3D VR image. (**b**) CT coronal-oblique MIP

which the RAPV and RPPV originate from the RPV, is the most suitable for living donor liver transplant. This is due to the fact that it facilitates only one surgical anastomosis between the recipient's MPV and donor's RPV. The risk of intraoperative complications increases in Type 1 (trifurcation) variant as clamping becomes difficult. In Type 2 and Type 3 variation, more than one portal vein anastomosis is required, predisposing to portal vein thrombosis [21]. If the variant RPV branches are close to each other, the recipient's PV can be bifurcated facilitating an easy reconstruction. However, when the RAPV branches from the LPV more distally, an interposed vein graft is required for reconstruction, thereby increasing the complexity of transplant manifold [20]. In Type 2 variant where the RPPV originates from the MPV, there is a high risk of unintentional ischemia/infarction of hepatic

segments V and VIII when the left lobe is harvested for liver transplantation or a left trisegmentectomy (segments II, III, and IV) is performed [22].

1.7.3 Transjugular Intrahepatic Portosystemic Shunt

The relative prevalence of PV anatomic variants mandates attentive consideration to PV anatomy prior to undertaking interventions such as TIPS. Indications for TIPS include recurrent (uncontrolled) variceal bleeding and refractory ascites in patients in whom medical treatment has failed. The procedure is often used as a bridging treatment for those awaiting liver transplantation [23–25]. It involves the percutaneous creation of an intrahepatic parenchymal shunt between a large hepatic vein and a major PV branch by inserting an expandable stent. TIPS is usually created between the RPV and the right hepatic vein, sometimes the middle hepatic vein [26, 27]. In the presence of variant PV anatomy, the direction of puncture and techniques may have to be tailored to the size, location, and direction of PV. It can also impact transhepatic access and procedural success rates, thereby reiterating the importance of cross-imaging and planning prior to TIPS [23, 28].

1.7.4 Portal Vein Embolization (PVE)

Preoperative PVE is an important tool to be considered before major hepatectomy. PVE is a minimally invasive interventional procedure which involves percutaneous selective cannulation and embolization of a peripheral branch of the PV that supplies the liver segments that are to be removed [18]. This procedure aims to reduce postoperative morbidity and mortality by producing ischemia/infarction of the embolized segment and reactive hypertrophy/hyperplasia of the remaining segments. This helps in achieving a sufficient non-tumoral future liver remnant (FLR) volume, thus preventing the occurrence of postoperative liver failure [19, 20, 29].

Diagnostic portal venography provides a road map to liver segments that require embolization and any variant anatomy that might complicate the procedure. This is to ensure that non-targeted segments are not inadvertently embolized, which might compromise the FLR. This also prevents incomplete embolization of the hepatic segments that are to be resected, which would reduce the stimulus for growth of the FLR [20].

1.7.5 Liver Resection

Embolization of both RPV and LPV branches is required in major uncommon hepatectomy procedures like extended right hepatectomy and extended left hepatectomy. PVE prior to extended right hepatectomy (which includes segment IV) is of particular significance as embolization of the segment IV branch results in better regeneration of segments I, II, and III. Preprocedural road mapping is vital to prevent reflux of the embolizing material into branches of FLR tissue [13, 18, 30].

1.8 Congenital Anomalies

As discussed, embryologically the PV is formed at 4–10 weeks via involution of the peri-intestinal vitelline venous loop. Aberrant involution and/or anastomoses of the vitelline ducts can lead to a variety of topographical variants or congenital anomalies of the portal venous system. While some are totally asymptomatic, others can have serious consequences as discussed below.

1.8.1 Congenital Agenesis of the PV

Atypical involution may cause a prebiliary, preduodenal, or duplicated PV, and excessive involution may result in agenesis of the PV. Agenesis of PV is a rare malformation characterized by the absence of the PV and anomalous drainage of SMV and SV into the systemic circulation [31–34].

In 1793, John Abernathy described the first case of congenital PV absence with a portosystemic shunt between the mesenteric vein and IVC on an autopsy of a 10-month old child [35]. Subsequently, the term "Abernethy malformations" has been used to describe and classify different varieties of extrahepatic congenital portosystemic shunts that are associated with an atretic PV. They can be classified as follows (Fig. 1.12):

- Abernethy type 1 (end-to-side) portosystemic shunt consists of either a completely atretic PV with the SV and SMV draining separately in the IVC (type 1a) or incomplete PV atresia with only a short common trunk which terminates into the IVC (type 1b) (Fig. 1.13).
- An Abernethy type 2 portosystemic shunt consists of a hypoplastic PV with partial shunting of blood into the IVC via a side-to-side shunt.

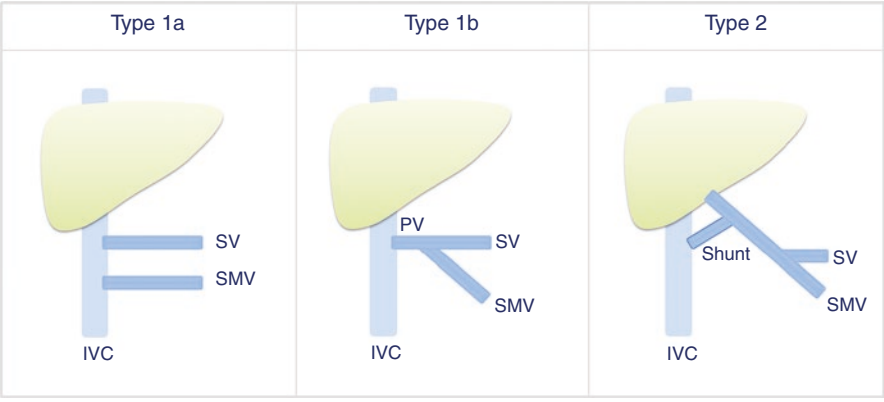

Fig. 1.12 Classification of Abernethy malformations

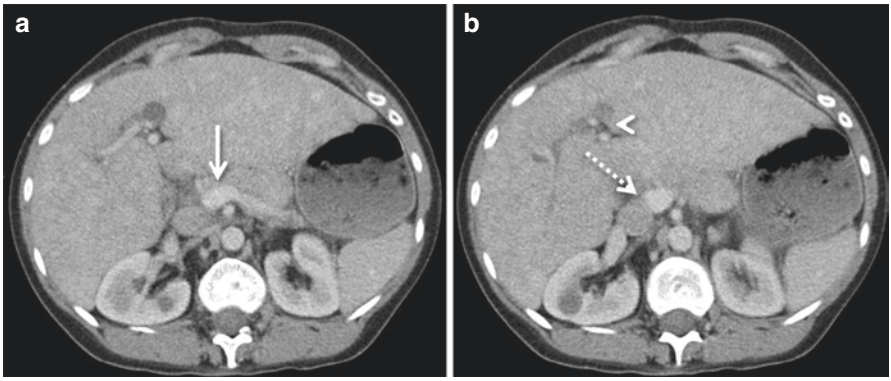

Fig. 1.13 The main portal vein is atretic except for a very short segment formed by the union of SV and SMV behind the pancreatic neck (arrow). This drains via an end-to-side portocaval shunt (interrupted arrow) into the IVC. Note the absence of PV at the liver hilum (arrowhead)

Liver morphology is generally preserved but altered hemodynamics secondary to portosystemic shunting may lead to the development of hepatic encephalopathy, hepatopulmonary syndrome, metabolic dysfunction, and cirrhosis. These patients are prone to develop focal nodular hyperplasia like liver nodules, hepatic adenomas, and HCC [31–36].

Associated visceral abnormalities include congenital cyanotic/acyanotic heart disease, duplicated SVC/IVC, hepatobiliary abnormalities like biliary atresia, congenital hepatic fibrosis, choledochal cyst, urological abnormalities like multicystic dysplastic kidney, cross-fused ectopia, hypospadias, and skeletal abnormalities like radial hypoplasia, vertebral anomalies, etc. [34].

1.8.2 Congenital Intrahepatic Portosystemic Shunt

Intrahepatic portosystemic shunts are abnormal intrahepatic communications >1 mm in caliber between branches of the PV and the hepatic veins or IVC [34, 37]. They are the result of persistent embryonic communication between the portal and vitelline veins during the fourth week of embryonic life [34].

Intrahepatic portosystemic shunts can be subdivided into the following:

- Type 1: single uniform-sized channel connecting the RPV to the IVC.
- Type 2: has one or more communications between peripheral branches of the PV and the hepatic veins, localized to one hepatic segment.
- Type 3: an aneurysmal shunt between the peripheral PV and the hepatic veins (Fig. 1.14).
- Type 4: PV branches and the hepatic veins communicating through multiple channels distributed diffusely in both lobes.

The first two varieties are the most common [34].

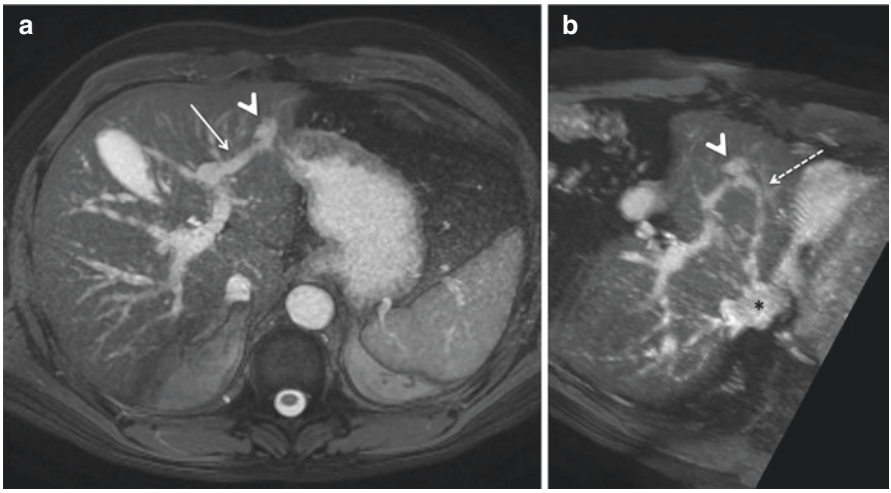

Fig. 1.14 (**a**, **b**) Congenital intrahepatic (aneurysmal) portosystemic shunt (arrowhead) incidentally detected on the liver MRI in an otherwise healthy male. It shunts blood from the LPV (arrow) into the left hepatic vein (interrupted arrow) which is draining into the IVC (asterisk)

1.8.3 Congenital Arterio-Portal Shunt

Intrahepatic arterio-portal shunts are rare and represent abnormal communication between hepatic arterial system and portal venous system. The vast majority of these shunts are acquired and associated with cirrhosis and tumors or occur secondary to penetrating trauma or iatrogenic injury (e.g., post-liver biopsy). Congenital arterio-portal shunts are extremely rare and seen in patients with hereditary hemorrhagic syndromes, total anomalous pulmonary venous return (TAPVR), etc. [36–38]. Depending on the size of the shunt, they may be completely asymptomatic or may manifest with hepatomegaly, portal hypertension, or heart failure [39, 40].

1.8.4 Portal Vein Aneurysm

Portal vein aneurysm (PVA) is increasingly being diagnosed incidentally as a consequence of increased imaging. It is a rare clinical entity described as a focal dilatation of the MPV or splenoportal confluence.

Although there is no strict size criteria, MPV diameter of more than 20 mm is considered aneurysmal (Fig. 1.15). Intrahepatic portal venous caliber more than 9 mm or any disproportionately dilated segment in comparison to adjacent segments may also be considered as aneurysms [41, 42].

PVA can be congenital or acquired. Congenital PVA may result from absent/incomplete involution of the vitelline vein in utero, which later dilates due to increased portal venous pressure. Systemic disorders like collagen vascular disorders or neurofibromatosis can also cause congenital aneurysms due to weakness in

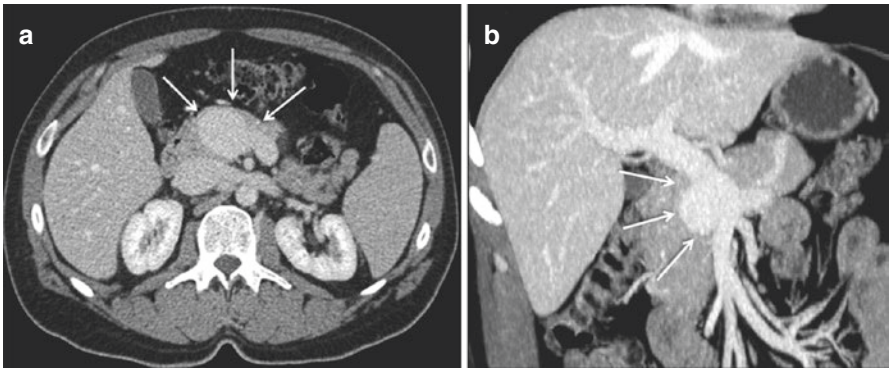

Fig. 1.15 Focal aneurysmal dilatation (arrows) of the MPV is seen just beyond the splenoportal confluence in a female patient imaged for suspected pancreatitis. The pancreas and liver appear healthy

the portal vein wall. Cirrhosis, portal hypertension, pancreatitis, and invasive malignancy have been attributed to cause acquired aneurysms. Complications include thrombosis, secondary portal hypertension, compression of adjacent structures, or rarely rupture [43].

1.9 Topographical Variants

1.9.1 Preduodenal Portal Vein

Preduodenal portal vein (PDPV) is a rare congenital anomaly due to embryonic maldevelopment of the portal venous system. As the name suggests, this results in the portal vein lying anterior to the duodenum (Fig. 1.16). Although PDPV can occur as an isolated defect, it is typically associated with other congenital anomalies, including heterotaxia or polysplenia syndrome, situs inversus, cardiac defects, malrotation, biliary or duodenal atresia, and annular pancreas [44].

Clinically, 50% of patients with this anomaly may present with symptomatic duodenal obstruction, caused by itself or coexisting anomalies such as malrotation, duodenal web, and annular pancreas. Most symptomatic cases occur in the pediatric age group [45]. In the remaining 50% of asymptomatic patients who are predominantly adults, PDPV is generally an incidental finding either at surgery or picked up on imaging.

1.9.2 Circumportal Pancreas

Circumportal pancreas (CP) is actually a rare congenital fusion anomaly of the pancreas where the pancreatic tissue at the region of the uncinate process anomalously encases the PV and/or the SMV [46]. CP is a clinically important anatomical variant as it has been associated with a higher rate of postoperative pancreatic fistula (POPF) following pancreatectomy. This is attributed to the anomalous course of the pancreatic duct which

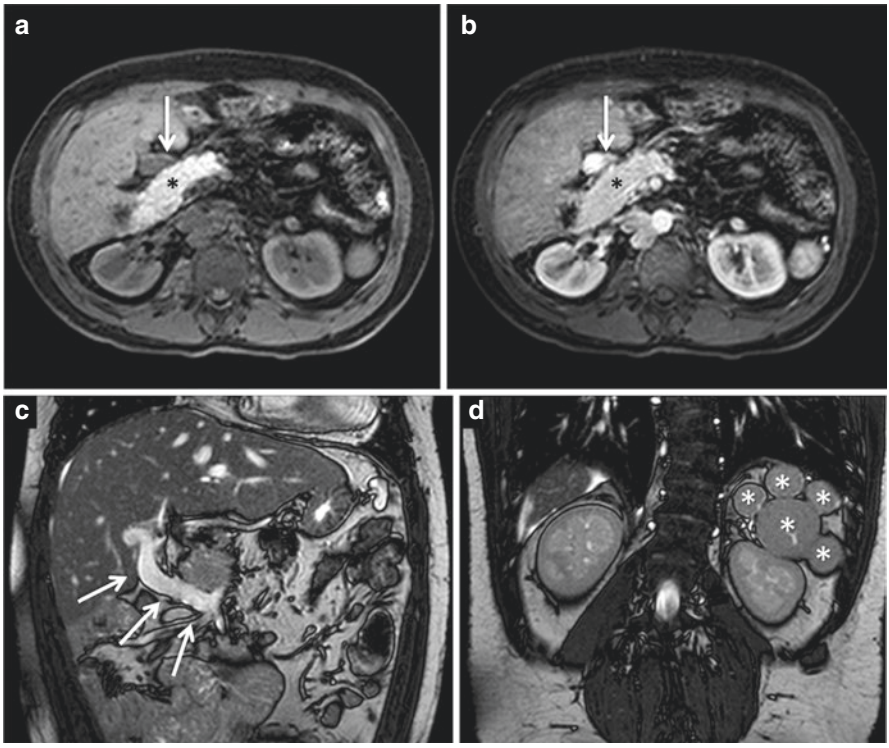

Fig. 1.16 Asymptomatic prepancreatic/preduodenal portal vein (arrows) located ventral to the pancreas (black asterisk) in a heterotaxia patient. Note polysplenia (white asterisk)

results in two cut surfaces (dorsal and ventral to the PV) following resection of the pancreatic tissue at the level of the PV–SMV junction [47, 48].

1.10 Conclusion

The complex network of veins constituting the portal venous system may be affected by a wide spectrum of anatomical variability, congenital anomalies, and acquired abnormalities. A thorough understanding of conventional and commonly seen variant anatomy of the portal vein system is essential to aid diagnosis and guide appropriate management of portal vein thrombosis and portal hypertension.

References

1. Carneiro C, Brito J, Bilreiro C, et al. All about portal vein: a pictorial display to anatomy, variants and physiopathology. Insights Imaging. 2019;10:38.
2. Collardeau-Frachon S, Scoazec JY. Vascular development and differentiation during human liver organogenesis. Anat Rec (Hoboken). 2008;291(6):614–27. https://doi.org/10.1002/ar.20679.

3. Marks C. Developmental basis of the portal venous system. Am J Surg. 1969;117(5):671–81.
4. Sharma M, Babu CS, Garg S, Rai P. Portal venous system and its tributaries: a radial endosonographic assessment. Endosc Ultrasound. 2012;1(2):96–107. https://doi.org/10.7178/eus.02.008.
5. Rameshbabu CS, Wani ZA, Rai P, Abdulqader A, Garg S, Sharma M. Standard imaging techniques for assessment of portal venous system and its tributaries by linear endoscopic ultrasound: a pictorial essay. Endosc Ultrasound. 2013;2(1):16–34. https://doi.org/10.7178/eus.04.005.
6. Sharma M, Rameshbabu CS. Collateral pathways in portal hypertension. J Clin Exp Hepatol. 2012;2(4):338–52. https://doi.org/10.1016/j.jceh.2012.08.001.
7. Rajesh S, Mukund A, Arora A. Imaging diagnosis of splanchnic venous thrombosis. Gastroenterol Res Pract. 2015;2015:101029. https://doi.org/10.1155/2015/101029.
8. Philips CA, Arora A, Shetty R, Kasana V. A comprehensive review of portosystemic collaterals in cirrhosis: historical aspects, anatomy, and classifications. Int J Hepatol. 2016;2016:6170243. https://doi.org/10.1155/2016/6170243.
9. Bandali MF, et al. Portal hypertension: imaging of portosystemic collateral pathways and associated image-guided therapy. World J Gastroenterol. 2017;23(10):1735–46. https://doi.org/10.3748/wjg.v23.i10.1735.
10. Arora A, Rajesh S, Meenakshi YS, Sureka B, Bansal K, Sarin SK. Spectrum of hepatofugal collateral pathways in portal hypertension: an illustrated radiological review. Insights Imaging. 2015;6(5):559–72. https://doi.org/10.1007/s13244-015-0419-8.
11. Abby Philips C, Sahney A. Oesophageal and gastric varices: historical aspects, classification and grading: everything in one place. Gastroenterol Rep (Oxf). 2016;4(3):186–95. https://doi.org/10.1093/gastro/gow018.
12. Smith CS, Sheehy N, McEniff N, Keogan MT. Magnetic resonance portal venography: use of fast acquisition true FISP imaging in the detection of portal vein thrombosis. Clin Radiol. 2007;62(12):1180–8.
13. Sureka B, Patidar Y, Bansal K, Rajesh S, Agrawal N, Arora A. Portal vein variations in 1000 patients: surgical and radiological importance. Br J Radiol. 2015;88:20150326.
14. Guerra A, De Gaetano AM, Infante A, et al. Imaging assessment of portal venous system: pictorial essay of normal anatomy, anatomic variants and congenital anomalies. Eur Rev Med Pharmacol Sci. 2017;21(20):4477–86.
15. Koc Z, Ulusan S, Oguzkurt L, Tokmak N. Venous variants and anomalies on routine abdominal multi-detector row CT. Eur J Radiol. 2007;61(2):267–78. https://doi.org/10.1016/j.ejrad.2006.09.008.
16. Koç Z, Oğuzkurt L, Ulusan S. Portal vein variations: clinical implications and frequencies in routine abdominal multidetector CT. Diagn Interv Radiol. 2007;13(2):75–80.
17. Akgul E, Inal M, Soyupak S, Binokay F, Aksungur E, Oguz M. Portal venous variations. Prevalence with contrast-enhanced helical CT. Acta Radiol. 2002;43(3):315–9. https://doi.org/10.1080/j.1600-0455.2002.430314.x.
18. Schmidt S, Demartines N, Soler L, Schnyder P, Denys A. Portal vein normal anatomy and variants: implication for liver surgery and portal vein embolization. Semin Interv Radiol. 2008;25(2):86–91. https://doi.org/10.1055/s-2008-1076688.
19. Nakamura TN, Tanaka K, Kiuchi T, et al. Anatomical variations and surgical strategies in right lobe living donor liver transplantation: lessons from 120 cases. Transplantation. 2002;73:1896–903.
20. Iqbal S, Iqbal R, Iqbal F. Surgical implications of portal vein variations and liver segmentations: a recent update. J Clin Diagn Res. 2017;11(2):AE01–5. https://doi.org/10.7860/JCDR/2017/25028.9453.
21. Kamel IR, Kruskal JB, Pomfret EA, Keogan MT, Warmbrand G, Raptopoulos V. Impact of multidetector CT on donor selection and surgical planning before living adult right lobe liver transplantation. AJR. 2001;176:193–200.
22. Covey AM, Brody LA, Getrajdman GI, Sofocleous CT, Brown KT. Incidence, patterns, and clinical relevance of variant portal vein anatomy. Am J Roentgenol. 2004;183:1055–64. https://doi.org/10.2214/ajr.183.4.1831055.

23. Gunasekaran SS, Gaba RC. Anatomic variations of the right portal vein: prevalence, imaging features, and implications for successful transjugular intrahepatic portosystemic shunt creation. J Clin Imaging Sci. 2017;7:14.
24. Saad N, Darcy M, Saad W. Portal anatomic variants relevant to transjugular intrahepatic portosystemic shunt. Tech Vasc Interv Radiol. 2008;11(4):203–7. https://doi.org/10.1053/j.tvir.2009.04.008.
25. Farsad K, Kaufman JA. Novel image guidance techniques for portal vein targeting during transjugular intrahepatic portosystemic shunt creation. Tech Vasc Interv Radiol. 2016;19(1):10–20. https://doi.org/10.1053/j.tvir.2016.01.002.
26. Zhuang ZW, Teng GJ, Jeffery RF, Gemery JM, Janne d'Othee B, Bettmann MA. Long-term results and quality of life in patients treated with transjugular intrahepatic portosystemic shunts. AJR Am J Roentgenol. 2002;179(6):1597–603.
27. Vignali C, Bargellini I, Grosso M, et al. TIPS with expanded polytetrafluoroethylene-covered stent: results of an Italian multicenter study. AJR Am J Roentgenol. 2005;185(2):472–80.
28. Kanterman RY, Darcy MD, Middleton WD, Sterling KM, Teefey SA, Pilgram TK. Doppler sonography findings associated with transjugular intrahepatic portosystemic shunt malfunction. AJR Am J Roentgenol. 1997;168(2):467–72.
29. Camelo R, Luz JH, Gomes FV, Coimbra E, Costa NV, Bilhim T. Portal vein embolization with PVA and coils before major hepatectomy: single-center retrospective analysis in sixty-four patients. J Oncol. 2019;2019:4634309. https://doi.org/10.1155/2019/4634309.
30. Anwar AS, Srikala J, Papalkar AS, Parveez MQ, Sharma A. Study of anatomical variations of hepatic vasculature using multidetector computed tomography angiography. Surg Radiol Anat. 2020;42:1449–57. https://doi.org/10.1007/s00276-020-02532-5.
31. Franchi-Abella S, Gonzales E, Ackermann O, et al. Congenital portosystemic shunts: diagnosis and treatment. Abdom Radiol (NY). 2018;43(8):2023–36. https://doi.org/10.1007/s00261-018-1619-8.
32. DiPaola F, Trout AT, Walther AE, et al. Congenital portosystemic shunts in children: associations, complications, and outcomes. Dig Dis Sci. 2020;65(4):1239–51. https://doi.org/10.1007/s10620-019-05834-w.
33. Bernard O, Franchi-Abella S, Branchereau S, Pariente D, Gauthier F, Jacquemin E. Congenital portosystemic shunts in children: recognition, evaluation, and management. Semin Liver Dis. 2012;32(4):273–87. https://doi.org/10.1055/s-0032-1329896.
34. Stringer MD. The clinical anatomy of congenital portosystemic venous shunts. Clin Anat. 2008;21(2):147–57.
35. Howard ER, Davenport M. Congenital extrahepatic portocaval shunts—the Abernethy malformation. J Pediatr Surg. 1997;32(3):494–7. https://doi.org/10.1016/s0022-3468(97)90614-x.
36. Eduardo Alonso-Gamarra, Manuel Parrón, Ana Pérez, Consuelo Prieto, Loreto Hierro, Manuel López-Santamaría Clinical and radiologic manifestations of congenital extrahepatic portosystemic shunts: a comprehensive review. Radiographics 2011: 31: 707
37. Bhargava P, Vaidya S, Kolokythas O, Katz DS, Dighe M. Hepatic vascular shunts: embryology and imaging appearances. Br J Radiol. 2011;84:1142–52.
38. Lupescu I, Masala N, Capsa R, Câmpeanu N, Georgescu SA. CT and MRI of acquired portal venous system anomalies. J Gastrointestin Liver Dis. 2006;15(4):393–8.
39. Zhang DY, Weng SQ, Dong L, Shen XZ, Qu XD. Portal hypertension induced by congenital hepatic arterioportal fistula: report of four clinical cases and review of the literature. World J Gastroenterol. 2015;21(7):2229–35. https://doi.org/10.3748/wjg.v21.i7.2229.
40. Norton SP, Jacobson K, Moroz SP, et al. The congenital intrahepatic arterioportal fistula syndrome: elucidation and proposed classification. J Pediatr Gastroenterol Nutr. 2006;43(2):248–55. https://doi.org/10.1097/01.mpg.0000221890.13630.ad.
41. Gallego C, Velasco M, Pilar Marcuello P, Tejedor D, De Campo L, Friera A. Congenital and acquired anomalies of the portal venous system. Radiographics. 2002;22:141–59.
42. Lopez-Machado E, Mallorquin-Jimenez F, Medina-Benitez A, Ruiz-Carazo E, Cubero-Garcia M. Aneurysms of the portal venous system: ultrasonography and CT findings. Eur J Radiol. 1998;26:210–4.

43. Laurenzia A, Ettorrea GM, Lionettib R, Meniconia LR, Colasantia M, Vennareccia G. Portal vein aneurysm: what to know. Dig Liver Dis. 2015;47(11):918–23.
44. Rusu S, Zaghal A, Choudhry MS. Surgical decision making in preduodenal portal vein: report of two cases in neonates. Eur J Pediatr Surg Rep. 2018;6(1):e40–2. https://doi.org/10.1055/s-0038-1661409.
45. Kim SH, Cho YH, Kim HY. Preduodenal portal vein: a 3-case series demonstrating varied presentations in infants. J Korean Surg Soc. 2013;85(4):195–7. https://doi.org/10.4174/jkss.2013.85.4.195.
46. Arora A, Velayutham P, Rajesh S, Patidar Y, Mukund A, Bharathy KG. Circumportal pancreas: a clinicoradiological and embryological review. Surg Radiol Anat. 2014;36(4):311–9. https://doi.org/10.1007/s00276-013-1189-y.
47. Kabir T, Xuan ZTZ, Chung AYF. Circumportal pancreas: a report of two cases. Ann Hepatobil Pancreat Surg. 2019;23(3):300–4. https://doi.org/10.14701/ahbps.2019.23.3.300.
48. Ohtsuka T, Mori Y, Ishigami K, Fujimoto T, Miyasaka Y, Nakata K, et al. Clinical significance of circumportal pancreas, a rare congenital anomaly, in pancreatectomy. Am J Surg. 2017;214:267–72.

Epidemiology of Portal Vein Thrombosis

2

Filipe Gaio Nery

Abstract

Non-malignant portal vein thrombosis may occur in patients with and without cirrhosis. Epidemiological large/nationwide studies are missing, conditioning a lack of information concerning real incidences and prevalence rates of portal vein thrombosis in both contexts. Yet, portal vein thrombosis is more often diagnosed in patients with cirrhosis than without, and in those with cirrhosis, it is most commonly perceived in patients with more severe liver disease, who are candidates for liver transplantation. Nevertheless, portal vein thrombosis in cirrhosis is also a non-negligible event in patients with a stable liver disease, with a 5-year incidence up to 11%.

Keywords

Portal vein thrombosis · Cirrhotic · Non-cirrhotic · Epidemiology · Incidence Prevalence

Portal vein thrombosis (PVT), one within a multitude of vascular disorders of the liver, may arise in patients with and without cirrhosis, expressing different milieus and specific risk factors (see Chap. 3), accordingly. Importantly, it must be differentiated from malignant invasion of the portal vein, as its etiology, clinical approach, and prognosis are different. Yet, in the past, malignant invasion of the portal vein tract and non-malignant PVT were considered somehow the same entity, which

F. G. Nery (✉)
Centro Hospitalar Universitário do Porto—Hospital de Santo António, Porto, Portugal

Instituto de Ciências Biomédicas de Abel Salazar—Universidade do Porto, Porto, Portugal

EpiUnit—Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal
e-mail: filipegaionery@gmail.com

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_2

interfered with the evaluation of the real incidence and prevalence of the latter. Also, the discrepant results of PVT's incidences and prevalence rates reflect different study designs and methodological approaches (most of them were retrospective or cross-sectional in nature), geographic regions, as well as different diagnostic procedures of PVT diagnosis. Furthermore, the indistinct use of the terms incidence and prevalence in the literature interferes with epidemiological data interpretation. This chapter reviews the epidemiology of PVT in patients with and without cirrhosis, leaving apart from malignant invasion, narrowing of the portal vein lumen due to extrinsic compression, or in the context of any other malignancy and related prothrombotic state.

2.1 Portal Vein Thrombosis (Non-cirrhotic)

There is a lack of information considering epidemiological data restricted to PVT in non-cirrhotic patients. Two population-based retrospective studies conducted in Sweden and in Italy, gathering patients with and without cirrhosis, with and without associated malignancy, and with recent and chronic PVT, found an annual incidence rate of 0.7/100,000 and a prevalence rate of 3.7/100,000 inhabitants in the first report [1], and gender-specific incidence rate of 3.78/100,000 inhabitants in males and of 1.73/100,000 inhabitants in females in the second study [2]. Another ancient Swedish report based on the study of 23,796 autopsies found an overall PVT prevalence, irrespective of the underlying etiology, to be 1.1% [3]. If excluding patients with cirrhosis or malignancy and including only patients with PVT and underlying myeloproliferative disorder, major abdominal infections/inflammation, and no attributed cause, the number lowers significantly to 0.3% [3]. Even though considered to be relatively rare, non-cirrhotic and non-malignant PVT is estimated to be the second most frequent cause of portal hypertension in the world [4].

2.2 Portal Vein Thrombosis (Cirrhotic)

There are several studies reporting incidence and prevalence rates of PVT among patients with cirrhosis (Fig. 2.1). Hitherto, there is an important discrepancy between different geographic locations, different methodologies applied to diagnose PVT, different study designs, and different grades of severity of cirrhosis. In England, in 1954, a 13% prevalence of PVT was documented in a cohort of 134 patients with portal hypertension, the majority of whom had decompensated liver disease [5]. In Hong Kong, in 1965, in a necropsy study gathering 126 patients with cirrhosis, mural thrombi involving portal vein were found in 25.4% of them [6]. In opposition to these high prevalence rates, in Japan, in 1985, a very low rate of PVT, estimated at 0.6%, was reported in 708 patients followed up for a 10-year period in a mixed population of Child–Pugh class A to C patients (the majority, Child–Pugh class C) [7]. The diagnosis was based on angiographic studies (either transhepatic or superior mesenteric arterial portography). Other ancient reports, also using

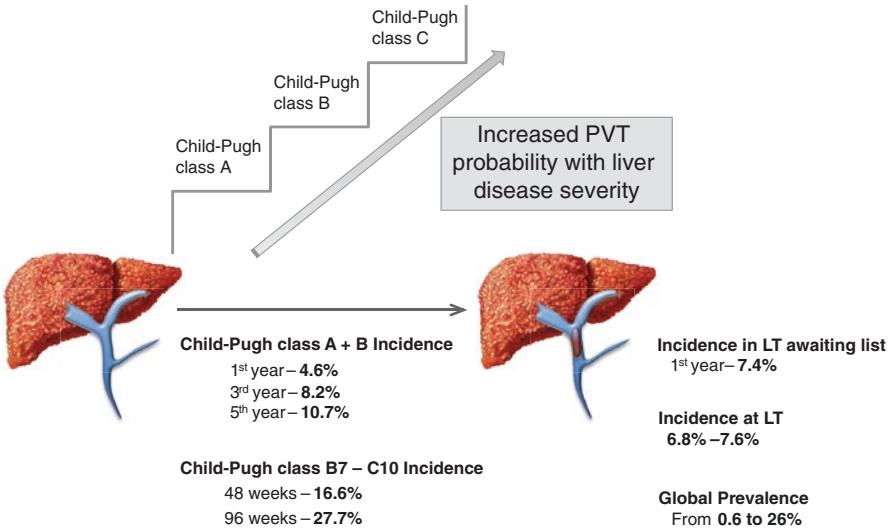

Fig. 2.1 Incidence and prevalence rates of portal vein thrombosis in patients with cirrhosis considering liver disease severity and at liver transplantation. *PVT* portal vein thrombosis, *LT* liver transplantation

invasive diagnostic tools, such as surgical technics or angiography, are in line with the heterogeneity of the aforementioned results, with prevalence rates ranging from 5.2% to 21% [8–12]. Even so, the highest prevalence rates of PVT are those reported among patients undergoing liver transplantation (LT), reflecting more severe underlying liver disease. Nonami et al. reported a 15.7% PVT prevalence by the time of LT in patients with end-stage cirrhosis [13]. Gayowski et al., in a cohort of 88 American veterans, found an even higher prevalence of 26% by the time of LT [14]. All of them were Child–Pugh class C. After excluding patients with HCC, another study documented a prevalence of PVT at LT of 17.5% [15]. In a cohort of patients listed for LT and longitudinally followed up, a 1-year incidence of PVT of 7.4% was reported, with the diagnosis made by abdominal Doppler ultrasound [16]. Most of the studies that report epidemiological data on PVT include predominantly patients with advanced liver disease, even if not on a LT waiting list. Amitrano et al. reported PVT prevalence of 11.2% in 701 patients admitted to the hospital (90% were Child–Pugh class B and C), most of them due to an acute episode of liver disease decompensation [17]. Villa et al., in a group of Child–Pugh B7-C10 cirrhotic patients, found PVT up to 16.6% per year [18]. Zocco et al., in a prospective assigned study enrolling a mixture of 81 Child–Pugh class A to C cirrhotic patients, showed a 1-year incidence of PVT of 15% [19]. More recently, Nery et al., in a cohort of patients with less severe cirrhosis (mostly Child–Pugh class A) prospectively surveyed, found a 1-, 3-, and 5-year incidence of PVT of 4.6%, 8.2%, and 10.7%, respectively [20]. An American nationwide retrospectively conducted study based on more than three million hospital discharges of patients with decompensated liver cirrhosis and clinically significant portal hypertension revealed a 1.5% global

prevalence of PVT. Importantly, the diagnosis was increasingly recognized as the years go by, with an annual percentage change of 9%, which can be related to an increased awareness for the diagnosis and the generalized use of imaging studies [21].

In short, PVT in cirrhosis has (a) different reported geographically prevalence rates, which can translate different loco-regional risk factors or reflect different diagnostic procedures or follow-up strategies of patients with cirrhosis; (b) an increased incidence and prevalence with an increase in the severity of underlying liver disease, which has been well documented particularly in patients awaiting liver transplantation; and (c) been identified to be a non-negligible event also in patients with non-severe cirrhosis with a 5-year incidence up to almost 11%.

References

1. Rajani R, Bjornsson E, Bergquist A, Danielsson A, Gustavsson A, Grip O, et al. The epidemiology and clinical features of portal vein thrombosis: a multicentre study. Aliment Pharmacol Ther. 2010;32(9):1154–62.
2. Ageno W, Dentali F, Pomero F, Fenoglio L, Squizzato A, Pagani G, et al. Incidence rates and case fatality rates of portal vein thrombosis and Budd-Chiari Syndrome. Thromb Haemost. 2017;117(4):794–800.
3. Ogren M, Bergqvist D, Bjorck M, Acosta S, Eriksson H, Sternby NH. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. World J Gastroenterol. 2006;12(13):2115–9.
4. Garcia-Pagan JC, Hernandez-Guerra M, Bosch J. Extrahepatic portal vein thrombosis. Semin Liver Dis. 2008;28(3):282–92.
5. Hunt AHWB. Thrombosis of the portal vein in cirrhosis hepatis. Lancet. 1954;263(6806):281–4.
6. Hou PC, McFadzean AJ. Thrombosis and intimal thickening in the portal system in cirrhosis of the liver. J Pathol Bacteriol. 1965;89:473–80.
7. Okuda K, Ohnishi K, Kimura K, Matsutani S, Sumida M, Goto N, et al. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. Gastroenterology. 1985;89(2):279–86.
8. Dye WS, David D, Julian OC. Successful treatment of portal vein thrombosis associated with intrahepatic obstruction. Arch Surg. 1960;80:876–82.
9. Coomaraswamy RP, Delguercio LR, Miller H, State D, Elkin M. Splenoportography and portal vein thrombosis in patients with cirrhosis of the liver. Surg Gynecol Obstet. 1964;118:560–6.
10. Sicot C, Sakellaridis D, Rueff B, Maillard JN, Benhamou JP. Portal vin thrombosis in intrahepatic block. Minn Med. 1971;54(2):87–90.
11. Sarfeh IJ. Portal vein thrombosis associated with cirrhosis: clinical importance. Arch Surg. 1979;114(8):902–5.
12. Belli L, Romani F, Sansalone CV, Aseni P, Rondinara G. Portal thrombosis in cirrhotics. A retrospective analysis. Ann Surg. 1986;203(3):286–91.
13. Nonami T, Yokoyama I, Iwatsuki S, Starzl TE. The incidence of portal vein thrombosis at liver transplantation. Hepatology. 1992;16(5):1195–8.
14. Gayowski TJ, Marino IR, Doyle HR, Echeverri L, Mieles L, Todo S, et al. A high incidence of native portal vein thrombosis in veterans undergoing liver transplantation. J Surg Res. 1996;60(2):333–8.
15. Manzanet G, Sanjuan F, Orbis P, Lopez R, Moya A, Juan M, et al. Liver transplantation in patients with portal vein thrombosis. Liver Transpl. 2001;7(2):125–31.

16. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005;54(5):691–7.
17. Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40(5):736–41.
18. Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012;143(5):1253-60.e1–4.
19. Zocco MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, et al. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. J Hepatol. 2009;51(4):682–9.
20. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015;61(2):660–7.
21. Cool J, Rosenblatt R, Kumar S, Lucero C, Fortune B, Crawford C, et al. Portal vein thrombosis prevalence and associated mortality in cirrhosis in a nationally representative inpatient cohort. J Gastroenterol Hepatol. 2019;34(6):1088–92.

Risk Factors for Portal Vein Thrombosis

3

Kamran B. Lankarani

Abstract

Portal vein thrombosis (PVT) is not uncommon in patients with chronic liver disease, but it can also occur in the absence of liver disease. In patients with liver disease, there is usually no other risk factor for development of PVT. New onset of PVT in this group may herald hepatocellular carcinoma. Severity of liver disease, large varices, and increased age have a correlation with later development of PVT. In those who develop PVT in the absence of liver disease, work-up for thrombophilia, especially for myeloproliferative neoplasm, is mandatory. Certain abdominal interventions and infections as well as malignancies are associated with an increased risk of PVT.

Keywords

Portal vein thrombosis · Thrombophilia · Cirrhosis · Hepatocellular carcinoma Myeloproliferative neoplasm

Portal vein thrombosis (PVT) is not an uncommon finding in patients with chronic liver disease. Its occurrence is not limited to these patients, and it may also occur in patients without liver disease. PVT has a wide range of presentations from totally asymptomatic to progressive liver failure depending on the underlying condition, associated risk factors, and extent of progression.

Knowing the risk factors for this condition have three potential benefits. It could guide the clinicians to intervene in high-risk patients to prevent PVT. It may also aid

K. B. Lankarani (✉)
Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran
e-mail: lankaran@sums.ac.ir

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_3

them to have a higher index of suspicion for diagnosis in those with risk factors for PVT and finally may help to predict the prognosis and guide the clinicians in planning the treatment.

In this regard, understanding the risk factors for PVT is of utmost clinical significance. Generally speaking, PVT may occur in two conditions either in the context of liver disease, especially end-stage liver disease (ESLD), or in those without liver disease. In these two settings, the risk factors might be different.

3.1 Risk Factors for PVT in Patients with Liver Disease

Chronic liver disease is the most common risk factor for PVT [1]. The incidence of PVT depends on the severity of liver disease and may range from less than 1% in compensated liver disease up to 8–25% in cirrhotic patients waiting for liver transplantation [2, 3]. The incidence is higher in those who are older or with concomitant hepatocellular carcinoma (HCC) [4].

It could be totally asymptomatic and found later as an incidental finding in imaging or it may lead to deterioration of ascites, renal function, or hepatic encephalopathy and end in progressive liver failure and death if not transplanted [5]. Liver transplantation in the presence of PVT has a higher rate of early complications and a lower rate of survival [6, 7].

There are various reports on risk factors for PVT in patients with cirrhosis. The proposed risk factors are as follows.

3.1.1 Etiology of Liver Disease

Etiology of ESLD has been considered to be a risk factor for PVT. There are reports that the incidence of PVT is higher in Asian patients with hepatitis B [8]. This was not confirmed in all reports [3, 9]. In contrast, the incidence of PVT was reported to be lower in primary biliary cholangitis, primary sclerosing cholangitis, inborn errors of metabolism affecting the liver, and biliary atresia [9].

3.1.2 Ascites and Diuretic Treatment

There are reports regarding association of ascites and diuretic treatment with later development of PVT [4]. But this was not observed in all studies [3, 5]. It has been suggested the hemoconcentration or decreased blood flow in the portal system may contribute to it.

3.1.3 Esophageal Varices

In their prospective study on PVT in cirrhotic patients, Italian researchers showed that a history of previous gastrointestinal bleeding was associated with higher occurrence of PVT [4]. In our series of PVT in patients with ESLD and PVT in

waiting list for liver transplantation, a history of variceal bleeding treated endoscopically was also a risk factor for development of PVT with an odds ratio of 2.526 (95% CI: 1.200–5.317) [3].

The presence of large esophageal varices at baseline even without a history of bleeding was shown to be associated with a higher risk of later development of PVT [5].

3.1.4 Inherited Hypercoagulable States

There are discrepancies in reported impact of inherited hypercoagulable states in the pathogenesis of PVT in the setting of chronic liver disease. While reports from Iran and other regions found no correlation with these inherited prothrombotic disorders [3, 5, 10], a recent report from Italy found that FV R506Q and FII G20210A variants had higher frequencies in patients with PVT, with an odds ratio of 2.84 (1.41–5.69) and 4.48 (2.43–8.29), respectively [11].

3.1.5 Acquired Hypercoagulable States

Although myeloproliferative disorders were a risk factor for PVT in patients without liver disease, this association was not found in patients with liver disease who develop PVT [3, 12].

3.1.6 Hepatocellular Carcinoma

The incidence of PVT is the highest in patients with ESLD and HCC occurring in up to 40% of patients with HCC at the time of diagnosis [4, 5, 13]. Not all of the PVT in HCC is due to tumor invasion, but if tumor thrombi occur, the prognosis would be grave with a median survival time of less than 4 months [13]. In a report from Southeastern Asia, HCC was the most common cause of PVT [8]. New onset of PVT in patients may be a herald sign for HCC in patients with ESLD.

3.1.7 Metabolic Diseases

There are contradictory reports on the role of obesity, hyperlipidemia, and diabetes mellitus (DM) as risk factors for PVT in patients with cirrhosis [14, 15]. While some reports indicated association, others could not find increased risk of PVT in cirrhotic patients with obesity and/or DM [16, 17].

3.1.8 Splenectomy

Splenectomy in patients with cirrhosis is associated with high risk of PVT. The incidence could be as high as 90% but is usually reported around 24–29% [16, 18]. Diameters of portal and splenic vein have a direct correlation with the risk of PVT after splenectomy in patients with ESLD [16].

3.1.9 *Helicobacter pylori* Infection and Gut Microbiota

PVT was reported to be higher in patients with ESLD and concomitant *Helicobacter pylori* infection and eradication of *Helicobacter pylori* was shown to reduce the risk [19]. This association was explained with higher serum levels of C reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), nitric oxide (NO), and vascular endothelial growth factor (VEGF) in *Helicobacter pylori*-infected patients.

Gut microbiota may cause endotoxinemia in patients with ESLD with resultant systemic inflammatory response [20]. This may contribute to thrombophilia in these patients.

Currently, there are no reports on altered gut microbiota in ESLD with PVT compared to patients with chronic liver disease without PVT.

3.1.10 Alterations in Hemostasis in End-Stage Liver Disease

In the most cirrhotic patients with PVT, there seems to be no apparent risk factor. The hypercoagulable state associated with cirrhosis itself is probably the main risk factor for development of PVT in these patients.

Liver is the site of synthesis of all coagulation factors with the exception of factor 8. Many patients with liver disease also suffer from malnutrition and impaired fat absorption leading to deficiency of fat-soluble vitamins including vitamin K. There is a state of consumptive coagulopathy which may further lead to prolongation of prothrombin time (PT) and low platelets.

Despite having prolonged PT and low platelets, apart from gastrointestinal bleeding and minor mucosal bleedings, there are no reports of bleeding tendency in patients with liver cirrhosis. Indeed, these patients are reported to be in hypercoagulable state especially on the venous side in splanchnic vasculature [21].

Production of both prothrombin and antithrombin is reduced in ESLD, but the new balance is toward thrombosis as shown by thrombin generation assays [21]. This has been reported in both systemic and splanchnic circulation in patients with cirrhosis [20].

Notwithstanding the fact that patients with ESLD have usually low platelet count, there is now accumulating evidence revealing higher rates of activation of platelets in these patients. Thrombocytes in cirrhotic patients have been shown to produce higher levels of isoprostanes, a stable eicosanoid, which itself increase platelet aggregation by activating the Gp IIb/IIIa [22].

Endotoxinemia related to altered gut microbiota in association with impaired reticuloendothelial system function reported in ESLD along with bacterial translocation in leaky bowel in these patients may lead to higher levels of lipopolysaccharides in splanchnic as well as systemic circulation in ESLD which may further activate the clotting pathway [23]. This may have a correlation with systemic inflammation reported in cirrhotic patients with PVT. This was evidenced by raised

serum level of interleukin-6 and tissue necrosis factor-α in these patients which may further contribute to the development of thrombosis in portal vein [24].

ADAMTS13 is a metalloprotease which cleaves von Willebrand factor (vWF). Its deficiency will lead to higher blood levels of vWF with resultant aggregation of platelets and thrombosis in various organs. The typical example is thrombotic thrombocytopenic purpura. But as ADAMTS13 is synthesized in the liver, patients with ESLD also have a deficiency of this factor, which may also contribute to hypercoagulable state in these patients. In concordance with this hypothesis, recent evidence shows lower levels of ADAMTS13 along with higher levels of vWF activity in patients with ESLD especially those with PVT [25]. Portal venous system endothelial damage may also have a role [26].

Low albumin may also enhance hypercoagulability in cirrhotics as it was shown that patients with cirrhosis and PVT had lower albumin level along with markers of platelet activation which were corrected with infusion of albumin [24, 27].

The low velocity of blood in portal circulation in patients with portal hypertension may increase the risk of thrombus formation [5] (Fig. 3.1).

3.2 Risk Factors of PVT in Patients without Liver Disease

While many patients with PVT in the absence of liver disease have identifiable risk factors, the risk factor may not be found in up to half of the patients especially in those with younger age [8]. As PVT could be the initial manifestation of ESLD, all these patients should be evaluated for possible underlying liver disease. In the absence of liver disease and history of abdominal surgery, a work-up for underlying disease is suggested in all of these patients.

3.2.1 Abdominal Surgery

Some surgical procedures are associated with an increased risk of PVT. Splenectomy is associated with PVT especially in the setting of cirrhosis as described above. But even in non-cirrhotics, the risk of PVT is increased after splenectomy. Although the risk is not as high as in cirrhotics, it could be as high as 3–4%. Huge splenomegaly in the setting of myelodysplastic syndrome and hereditary hemolytic anemia enhances the risk [28]. Larger splenic vein diameter will also increase the risk of PVT.

Distal pancreatectomy was found to be associated with PVT. In one study, the length of residual splenic vein after pancreatic resection was the independent risk factor for PVT in these patients [29]. Interestingly, the occurrence was more common with benign lesions and in younger patients and in those who were operated laparoscopically.

PVT may complicate almost all abdominal surgeries, especially cholecystectomy and hepatectomy [8].

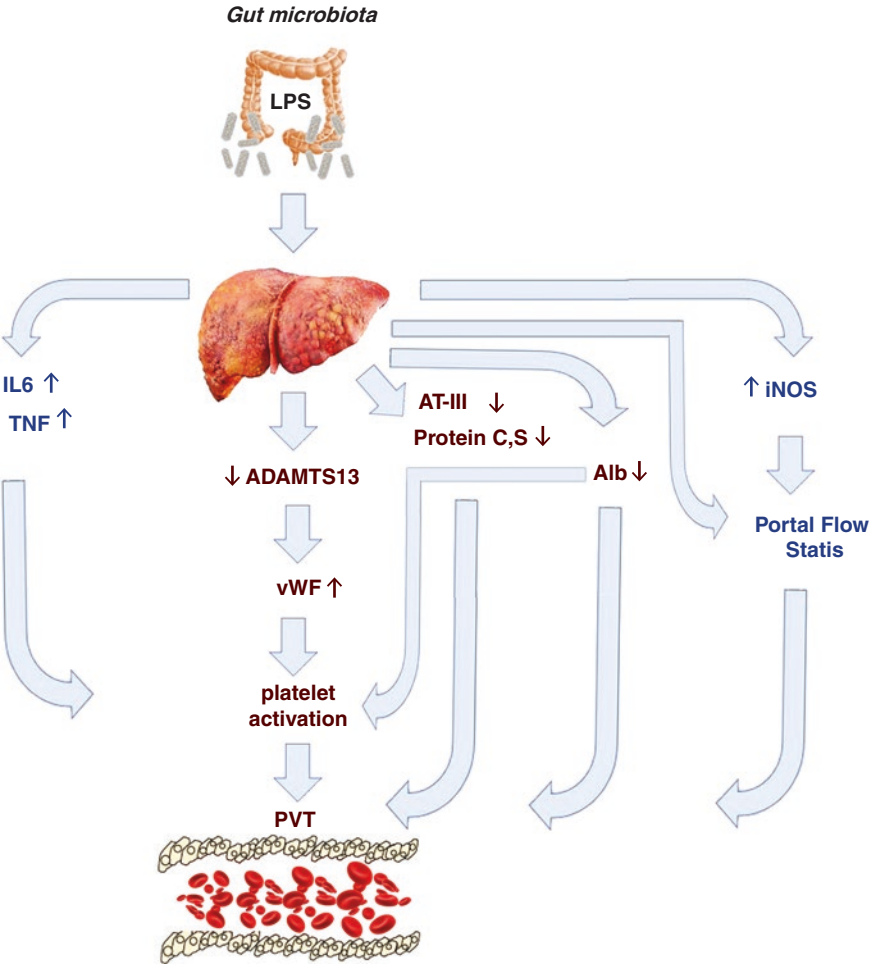

Fig. 3.1 Pathogenesis of portal vein thrombosis is liver cirrhosis. *ATIII* antithrombin III, *IL6* Interleukin-6, *iNOs* Inducible nitric oxide synthase, *LPS* Lipopolysaccharide, *TNF* Tissue necrosis factor-α, *vWF* von Willebrand factor

3.2.2 Radiologic Interventions

Umbilical catheterization, percutaneous transhepatic biliary drainage (PTBD), and T-tube insertions were reported to cause PVT [8].

3.2.3 Intraabdominal Infection and Inflammation

Several intraabdominal infections, including hepatic abscess, splenic abscess, diverticulitis, biliary tract infections, and even abdominal tuberculosis, were reported to be risk factors for PVT [8].

Inflammatory diseases in the abdomen, including inflammatory bowel disease, pancreatitis, and cholecystitis, have been reported to cause PVT [30].

3.2.4 Inherited Hypercoagulable States

Theoretically, all inherited coagulopathies could increase the risk of PVT including deficiencies of protein C and S, antithrombin III deficiency, factor V Leiden (FVL), and prothrombin (FII) G20210A mutation. A recent study in Denmark could not show an increased rate of these inherited disorders in those who had PVT as compared to the general population [31].

3.2.5 Acquired Hypercoagulable States

Myeloproliferative disorders are among the most frequent risk factors for PVT in non-cirrhotic patients [12, 32, 33]. Paroxysmal nocturnal hemoglobinuria may be a risk factor in some patients, but it is rare [33]. Antiphospholipid antibody syndrome has also been reported to cause PVT [8]. Pregnancy and use of oral contraceptive pills also have been incriminated in few cases [8, 10].

3.2.6 Malignancies

Malignancies may lead to PVT with three different mechanisms: invasion by the tumor, massive liver metastasis with resultant portal hypertension, and induction of generalized hypercoagulable state.

Several malignancies, including adenocarcinoma of the pancreas and gallbladder, cholangiocarcinoma, and ovarian cancers, were associated with PVT [8]. It has also been reported for colorectal and gastric cancers and liver metastasis from a variety of cancers [8, 34, 35].

3.3 Conclusion

PVT is not uncommon in ESLD. In this setting, there is usually no need for evaluation of risk factors except for occurrence of HCC in patients who develop PVT. Splenectomy should be avoided in ESLD as it may increase the risk of PVT. Patients with ESLD and large varices with or without bleeding need to be monitored for development of PVT.

On the contrary, all patients with PVT and no apparent liver disease need evaluation. The presence of liver disease needs to be ruled out. The most common risk factors in the absence of history of abdominal interventions and infection are myeloproliferative disorders which need to be pursued by molecular test.

References

1. Fimognari FL, Violi F. Portal vein thrombosis in liver cirrhosis. Intern Emerg Med. 2008;3(3):213–8.
2. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. Gastroenterology. 2017;153(2):480–7.e1.
3. Bagheri Lankarani K, Homayon K, Motevalli D, Heidari ST, Alavian SM, Malek-Hosseini SA. Risk factors for portal vein thrombosis in patients with cirrhosis awaiting liver transplantation in Shiraz, Iran. Hepat Mon. 2015;15(12):e26407.
4. Violi F, Corazza RG, Caldwell SH, Perticone F, Gatta A, Angelico M, et al. Portal vein thrombosis relevance on liver cirrhosis: Italian Venous Thrombotic Events Registry. Intern Emerg Med. 2016;11(8):1059–66.
5. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: Results of a longitudinal study. Hepatology. 2015;61(2):660–7.
6. Bagheri Lankarani K, Honarvar B, Seif MA, Anushiravani A, Nikeghbalian S, Motazedian N, et al. Outcome of liver transplant patients with intraoperative-detected portal vein thrombosis: a retrospective cohort study in Shiraz, Iran. Exp Clin Transplant. 2019; https://doi.org/10.6002/ect.2018.0295.
7. Malek Hosseini SA, Nikeghbalian S, Salahi H, Kazemi K, Shemsaeifar A, Bahador A, et al. Evolution of liver transplantation program in Shiraz, Iran. Hepat Mon. 2017;17(11):e60745.
8. Lertpipopmetha K, Auewarakul CU. High incidence of hepatitis B infection-associated cirrhosis and hepatocellular carcinoma in the Southeast Asian patients with portal vein thrombosis. BMC Gastroenterol. 2011;11:66.
9. Nonami T, Yokoyama I, Iwatsuki S, Starzl TE. The incidence of portal vein thrombosis at liver transplantation. Hepatology (Baltimore, Md). 1992;16(5):1195–8.
10. Parikh S, Shah R, Kapoor P. Portal vein thrombosis. Am J Med. 2010;123(2):111–9.
11. Cernera G, Di Minno A, Amato F, Elce A, Liguori R, Bruzzese D, et al. Molecular analysis of prothrombotic gene variants in venous thrombosis: a potential role for sex and thrombotic localization. J Clin Med. 2020;9:4.
12. Qi X, Zhang C, Han G, Zhang W, He C, Yin Z, et al. Prevalence of the JAK2V617F mutation in Chinese patients with budd-chiari syndrome and portal vein thrombosis: a prospective study. J Gastroenterol Hepatol. 2012;27(6):1036–43.
13. Liu P-H, Huo T-I, Miksad RA. Hepatocellular carcinoma with portal vein tumor involvement: best management strategies. Semin Liver Dis. 2018;38(03):242–51.
14. Eshraghian A, Nikeghbalian S, Kazemi K, Mansoorian M, Shamsaeefar A, Eghlimi H, et al. Portal vein thrombosis in patients with liver cirrhosis and its impact on early and long-term outcomes after liver transplantation. Int J Clin Pract. 2019;73(3):e13309.
15. Zakko A, TK P, Nankani R, Karagozian R. Obesity is not associated with an increased risk of portal vein thrombosis in cirrhotic patients. Gastroenterol Hepatol Bed Bench. 2018;11(2):153–8.
16. Yang Z-I, Guo T, Zhu D-L, Zheng S, Han D-D, Chen Y. Risk factors of portal vein thrombosis after splenectomy in patients with liver cirrhosis. Hepatoma Res. 2020;6:37.
17. Ayala R, Grande S, Bustelos R, Ribera C, García-Sesma A, Jimenez C, et al. Obesity is an independent risk factor for pre-transplant portal vein thrombosis in liver recipients. BMC Gastroenterol. 2012;12:114.
18. Song Z, Feng H, Yang C, Dai C. Prediction of the factors influencing the shengjing classification of portal vein thrombosis after splenectomy for portal hypertension in cirrhosis: a single-center retrospective case-control study. Biomed Res Int. 2020;2020:2396710.
19. Abdel-Razik A, Mousa N, Elhelaly R, Elzehery R, Hasan AS, Abdelsalam M, et al. Helicobacter pylori as an initiating factor of complications in patients with cirrhosis: a single-center observational study. Front Med (Lausanne). 2020;7:96.

20. Violi F, Loffredo L, Pastori D. Anticoagulation in patients with advanced liver disease: an open issue. Intern Emerg Med. 2021;16:61–71.
21. Lebreton A, Sinegre T, Lecompte T, Talon L, Abergel A, Lisman T. Thrombin generation and cirrhosis: state of the art and perspectives. Semin Thromb Hemost. 2020;46(06):693–703.
22. Basili S, Raparelli V, Riggio O, Merli M, Carnevale R, Angelico F, et al. NADPH oxidase-mediated platelet isoprostane over-production in cirrhotic patients: implication for platelet activation. Liver Int. 2011;31(10):1533–40.
23. Nocella C, Carnevale R, Bartimoccia S, Novo M, Cangemi R, Pastori D, et al. Lipopolysaccharide as trigger of platelet aggregation via eicosanoid over-production. Thromb Haemost. 2017;117(08):1558–70.
24. Huang X, Fan X, Zhang R, Jiang S, Yang K, Chen S. Systemic inflammation and portal vein thrombosis in cirrhotic patients with gastroesophageal varices. Eur J Gastroenterol Hepatol. 2020;32(3):401–5.
25. Lancellotti S, Basso M, Veca V, Sacco M, Riccardi L, Pompili M, et al. Presence of portal vein thrombosis in liver cirrhosis is strongly associated with low levels of ADAMTS-13: a pilot study. Intern Emerg Med. 2016;11(7):959–67.
26. Shalaby S, Simioni P, Campello E, Spiezia L, Gavasso S, Bizzaro D, et al. Endothelial damage of the portal vein is associated with heparin-like effect in advanced stages of cirrhosis. Thromb Haemost. 2020;120(8):1173–81.
27. Basili S, Carnevale R, Nocella C, Bartimoccia S, Raparelli V, Talerico G, et al. Serum albumin is inversely associated with portal vein thrombosis in cirrhosis. Hepatol Commun. 2019;3(4):504–12.
28. Maria-Theresa K, Klaus L, Edmund AMN, Ingrid P. The postoperative splenic/portal vein thrombosis after splenectomy and its prevention—an unresolved issue. Haematologica. 2008;93(8):1227–32.
29. Tanaka N, Yamada S, Sonohara F, Takami H, Hayashi M, Nakayama G, et al. An outcome analysis of predictive factors for portal or splenic vein thrombosis after distal pancreatectomy. Surg Today. 2020;50(10):1282–9.
30. Condat B, Valla D. Nonmalignant portal vein thrombosis in adults. Nat Clin Pract Gastroenterol Hepatol. 2006;3(9):505–15.
31. Kirkeby MH, Larsen JB, Gronbaek H, Hvas AM. Thrombophilia testing in patients with portal vein thrombosis. Scand J Clin Lab Invest. 2020;80:694–8.
32. Magaz M, Alvarez-Larran A, Colomer D, Lopez-Guerra M, Garcia-Criado MA, Mezzano G, et al. Next-generation sequencing in the diagnosis of non-cirrhotic splanchnic vein thrombosis. J Hepatol. 2021;74:89–95.
33. Fan J, Wang Q, Luo B, Chen H, Wang Z, Niu J, et al. Prevalence of prothrombotic factors in patients with Budd-Chiari syndrome or non-cirrhotic nonmalignant portal vein thrombosis: a hospital-based observational study. J Gastroenterol Hepatol. 2020;35(7):1215–22.
34. Tanaka A, Takeda R, Mukaihara S, Hayakawa K, Takasu K, Terajima H, et al. Tumor thrombi in the portal vein system originating from gastrointestinal tract cancer. J Gastroenterol. 2002;37(3):220–8.
35. Fujii Y, Kobayashi K, Kimura S, Uehara S, Takiguchi S. Ascending colon cancer accompanied by tumor thrombosis in the superior mesenteric vein: a case report. Int J Surg Case Rep. 2020;73:239–43.

Imaging of Portal Vein Thrombosis

4

Kumble Seetharama Madhusudhan

Abstract

Portal vein thrombosis is an uncommon condition mostly seen in association with various systemic and local pathologies. The presentation may be acute or chronic. Diagnostic imaging with modalities like ultrasonography, computed tomography, and magnetic resonance imaging is critical for proper management of these patients. In addition, imaging helps in the diagnosis of specific types of thrombosis which include septic thrombophlebitis and tumor in vein. This chapter presents the imaging features of different types of PVT in detail along with illustrations.

Keywords

Portal vein thrombosis · Computed tomography · Magnetic resonance imaging Ultrasonography · Tumor in vein · Pylephlebitis

4.1 Introduction

Portal vein thrombosis (PVT) is defined as thrombosis of a part or whole of the portal vein and/or its branches [1]. Thrombosis may extend to involve the splenic and superior mesenteric veins. Although its overall incidence is not clearly known, it is considered to be an uncommon pathology. A large population-based autopsy study by Ogren et al. found a prevalence of 1% [2]. In patients with compensated liver disease, the prevalence is in the range of 5–26%, which increases to 35% in patients with hepatocellular carcinoma (HCC) [3, 4]. PVT is the most common cause of pre-hepatic portal hypertension [4, 5].

K. S. Madhusudhan (✉)
Department of Radiodiagnosis and Interventional Radiology, All India Institute of Medical Sciences, New Delhi, India
e-mail: drmadhuks@gmail.com

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_4

The clinical presentation of patients of PVT depends on the rapidity and extent of thrombosis, and the presence of collaterals, underlying liver disease, and portal hypertension [6]. Most common symptoms include abdominal pain, fever, abdominal distension, hematemesis, and melena [1]. Frequently, patients may be asymptomatic, particularly in the chronic variety [7]. Since these presenting features are non-specific, imaging plays a critical role, not only in the diagnosis of PVT but also in defining its extent, etiology, and complications.

4.2 Etiology and Pathophysiology

Various systemic and local or regional etiologies have been defined in the development of PVT. These have been discussed in detail elsewhere in the book. Systemic causes include any conditions, either inherited or acquired, causing hypercoagulability and are responsible in 30% of the cases [1, 8]. In the remaining 70%, local and regional causes are responsible and include cirrhosis, malignancies (hepatobiliary and pancreatic), surgical or abdominal trauma, and inflammatory conditions [8]. Majority of the local and regional risk factors are identified on imaging.

A basic knowledge of the pathophysiological changes which develop due to PVT is helpful in understanding the pathological changes that are identified on imaging. Broadly, there are three types of changes which occur as a result of PVT (Fig. 4.1) [8]. The first is compensatory dilatation and increased blood flow in the hepatic artery. This occurs as a reflex due to the absence of the major component of hepatic blood flow through the portal vein. The second alteration is the development of venous collaterals, mostly around the occluded portal vein and the bile duct. This bunch of collaterals is called "cavernoma". The collateral formation begins in the initial few days after PVT and is usually complete by the fifth week [9]. The third change which occurs is in the liver parenchyma in cases with persistent portal vein occlusion by the thrombus. Due to significant reduction in the hepatic blood flow, the hepatocytes, particularly those in the peripheral segments (segments 2 and 3) of the liver which are more susceptible to ischemia, undergo ischemic apoptosis with compensatory proliferation of the hepatocytes in the central segments (segments 1 and 4) [8]. These findings identified on imaging help in making a diagnosis of chronic PVT.

4.3 Role of Imaging

Imaging assists in the diagnosis of PVT, identification of its etiology, and depiction of findings developing as a consequence, most commonly portal hypertension and hepatobiliary alterations, as discussed in the previous section. Defining the extent of thrombosis helps in planning further management [5]. In addition, this information also helps to plan vascular anastomosis in patients with cirrhosis prior to liver transplantation.

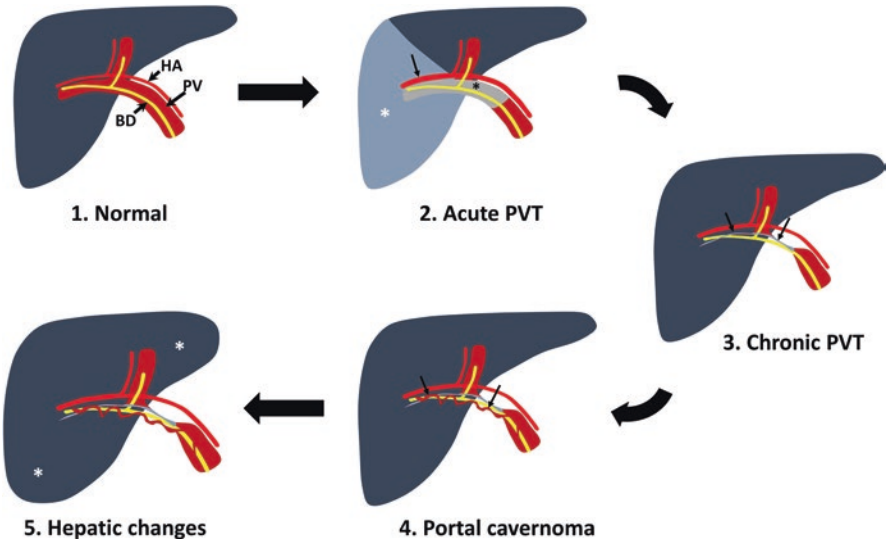

Fig. 4.1 Schematic representation of the pathophysiology of portal vein thrombosis. *1*. Normal. *2*. Development of acute PVT in the main and right portal vein (black asterisk) with resultant compensatory dilatation of the right hepatic artery (arrow) and arterial hyperperfusion and venous hypoperfusion of the right lobe of the liver (white asterisk). *3*. Chronic PVT with attenuated and thrombosed segment of the portal vein (arrows). *4*. Portal cavernoma formation due to the development of porto-portal collaterals around the common bile duct (arrows). *5*. Hepatic parenchymal changes in the form of atrophy of peripheral segments (white asterisks). *BD* common bile duct, *HA* hepatic artery, *PV* portal vein, *PVT* portal vein thrombosis

The common imaging modalities used in the evaluation of patients of PVT include ultrasonography (USG), computed tomography (CT) scan, magnetic resonance imaging (MRI), and venography. USG is the initial investigation of choice in most of the cases. CT scan or MRI is performed later to more accurately define the true extent and nature of the thrombosis, its etiology, and complications [5].

The imaging features are broadly described under three headings—(**a**) acute PVT, (**b**) chronic PVT, and (**c**) specific types.

4.3.1 Acute Portal Vein Thrombosis

Acute PVT is clinically diagnosed when the symptoms related to PVT present within 60 days of the onset of thrombosis [10]. However, this clinical diagnosis is frequently difficult due to the absence of or presence of only mild symptoms.

4.3.1.1 Ultrasonography

USG is the initial investigation of choice. It has an overall sensitivity and specificity in the range of 80–100% [5]. The sensitivity is higher for thrombosis which is complete and involves the main portal vein [11]. Adding color Doppler to USG improves

the diagnostic sensitivity and specificity [12]. Limitations of USG include its operator dependency, factors limiting visualization like obesity and bowel gas, and false positivity in cases of sluggish flow.

The acute thrombus is usually seen as a hypoechoic, isoechoic, or hyperechoic solid material filling the lumen and causing dilatation of the portal vein on B-mode scan (Fig. 4.2). The portal vein caliber is often more than 13–15 mm [6]. The thrombus may be partially or completely occluding the portal vein and often results in its dilatation [5]. The thrombus may extend from the main portal vein distally to involve its intrahepatic branches and proximally to the splenic and superior mesenteric veins. Uncommonly, the thrombosis may be localized to a lobar or intrahepatic segmental branch of the portal vein. Hyperacute thrombus may be anechoic, and it may not be possible to identify the thrombus at this stage on B-mode images [6].

Color Doppler USG (CDUSG) should be used in all cases as it confirms the presence of the thrombus in the portal vein and shows the extent to which it occupies the lumen. CDUSG has a negative predictive value of 98% [5, 12]. If the thrombus is complete, the involved segment does not show flow within the lumen (Fig. 4.2) [13]. In case of partial thrombus, the patent part of the lumen shows flow (Fig. 4.3). In cases of hyperacute thrombus, absence of color in the portal vein, with proper machine gain settings, is suggestive of thrombosis [6]. Further, CDUSG is also helpful in the detection of periportal collaterals, forming a cavernoma, when the clinical presentation is delayed (Fig. 4.4). These collateral vessels show non-undulating low velocity flow. The hepatic artery is frequently dilated with increased flow due to reflex compensatory response (Fig. 4.5).

In the acute setting, the liver usually does not show any parenchymal changes unless there is cirrhosis. There may be ascites secondary to acute portal hypertension. The etiology of PVT can also be identified in many cases. Patients with hypercoagulable states may also have associated thrombosis of the hepatic veins.

Contrast-enhanced USG (CEUS) is a technique which uses microbubble-based USG contrast agents and has shown to be useful in the diagnosis of PVT [14]. It is

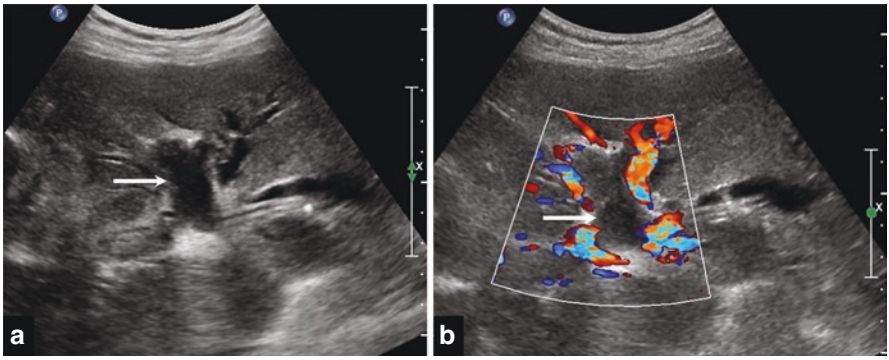

Fig. 4.2 Ultrasonography of a patient with acute left portal vein thrombosis. (**a**) B-mode image shows hypoechoic material within the left portal vein (arrow). (**b**) Color Doppler image shows no flow within the left portal vein (arrow) with multiple surrounding collaterals

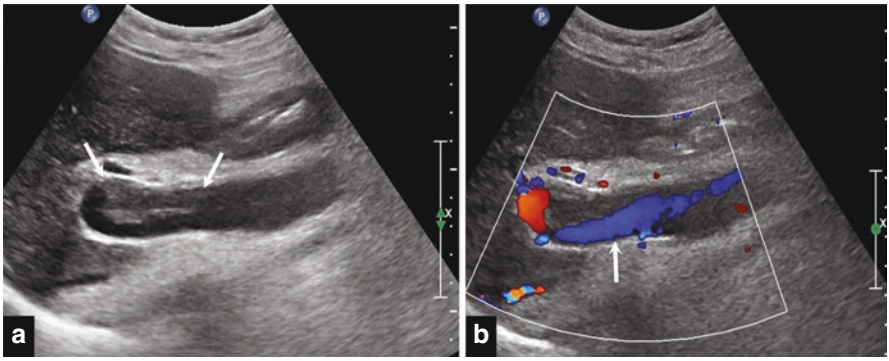

Fig. 4.3 Ultrasonography of a cirrhotic patient with acute partial main portal vein thrombosis. (**a**) B-mode image shows isoechoic material partially filling the main portal vein (arrow). (**b**) Color Doppler image shows flow within the patent part of the main portal vein (arrow)

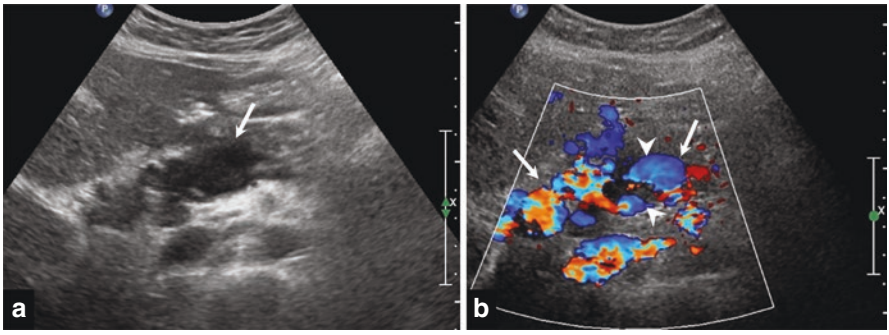

Fig. 4.4 Ultrasonography of a patient with acute portal vein thrombosis presenting late. (**a**) B-mode image shows hypoechoic material within the main portal vein (arrow). (**b**) Color Doppler image shows partial flow within the main portal vein (arrowheads) due to recanalization with multiple surrounding collaterals (arrows)

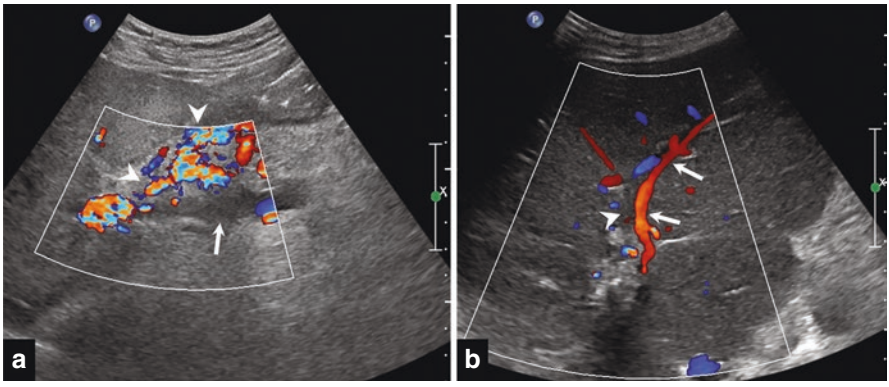

Fig. 4.5 Ultrasonography of a patient with acute portal vein thrombosis. (**a**) Color Doppler image shows hypoechoic material within the main portal vein (arrow) with surrounding collaterals (arrowheads). (**b**) Color Doppler image at a cranial level shows no flow within the left portal vein (arrowhead) with dilated accompanying segmental hepatic artery (arrows)

superior to CDUSG in the diagnosis of PVT, particularly where the obstruction is partial and flow is too slow to be detected and when the visualization of the portal vein on B-mode is poor. Another benefit of CEUS is in the differentiation of bland from malignant PVT. The sensitivity, specificity, and accuracy of CEUS in the diagnosis of malignant PVT are 100%, 66.7%, and 93.3%, respectively [15].

Endoscopic USG (EUS) is another technique which assists in the diagnosis of PVT, especially when visualization is poor on transabdominal USG [16]. This technique visualizes the portal vein through the gastric antrum and the duodenum and provides high-resolution images of the portal vein and the thrombus. Appearances on B-mode and CDUSG are similar to that seen on the standard transabdominal USG. Another advantage of EUS is in guiding interventions like sampling of the thrombus (when malignant thrombus is suspected) and intravenous thrombolysis [17].

4.3.1.2 Computed Tomography (CT)

Contrast-enhanced CT scan is the mainstay of investigation in the evaluation of PVT. It is better than USG in defining the extent of thrombosis, in detecting the etiology and complications, and in planning further interventions [5, 8]. The standard technique of CT involves a multiphasic scan, including late arterial (25–30s), portal venous (70s), and delayed (180s) phases [5]. However, often, a single portal venous phase is performed as the diagnosis of PVT is not suspected. Evaluation of the portal vein in additional planes (coronal and sagittal) through multiplanar reformation helps in better definition of the extent of the thrombus.

Acute PVT causes distension of the portal vein and is seen as an isodense or hypodense soft tissue within the lumen of the portal vein without any contrast enhancement (Fig. 4.6). The thrombus may be isodense or hyperdense on the non-contrast scan (Fig. 4.6a) [8]. In cases of partial PVT, the patent part of the lumen shows contrast filling (Fig. 4.7). There may be thickening and enhancement of the wall of the portal vein in the segment containing the thrombus, possibly due to inflammation [18]. In cases of delayed presentation, multiple collaterals are seen around the thrombosed portal vein and the bile duct (Fig. 4.8).

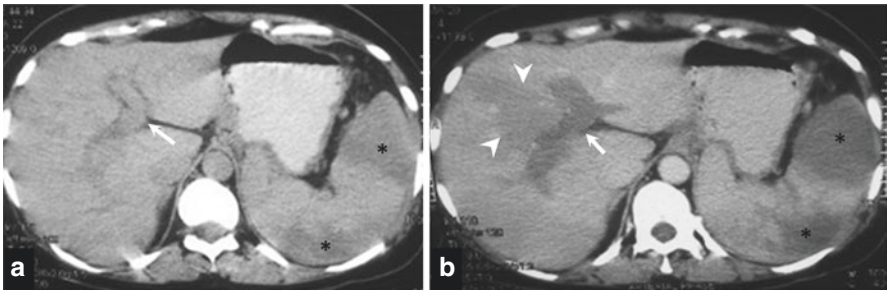

Fig. 4.6 CT scan in acute portal vein thrombosis. (**a**) Axial non-contrast image shows hyperdensity within the main and left portal vein (arrow). (**b**) Axial contrast-enhanced venous phase image shows non-enhancing thrombus within the portal vein (arrow) with adjacent parenchymal perfusion abnormality showing sharp margins (arrowheads). Multiple splenic infarcts are seen (asterisk) due to associated splenic vein thrombosis

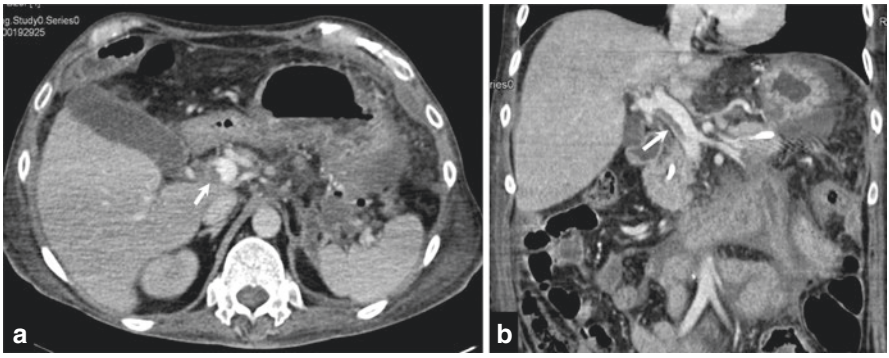

Fig. 4.7 CT scan in acute partial portal vein thrombosis. Axial (**a**) and coronal (**b**) contrast-enhanced venous phase images show non-enhancing thrombus partially filling the main portal vein (arrow) with inflammation in the surrounding regions due to acute pancreatitis

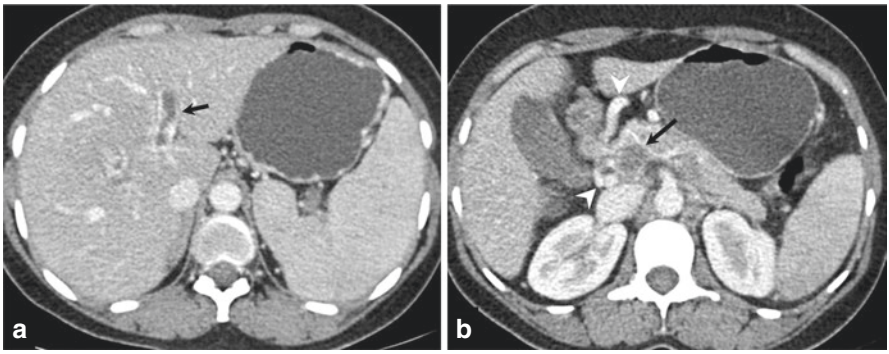

Fig. 4.8 CT scan in a patient with acute portal vein thrombosis presenting late. (**a**) Axial contrast-enhanced CT image shows thrombus within the left portal vein (arrow) with peripheral contrast filling suggesting partial recanalization. (**b**) Axial contrast-enhanced image at a caudal level shows thrombosis of the main portal vein (arrow) with multiple pericholedochal and peripancreatic collaterals (arrowheads)

The part of the liver supplied by the thrombosed portal vein appears hypodense compared to the surrounding parenchyma due to hypoperfusion (Fig. 4.6) [8]. The margin between the hypoperfused region and normal region is usually sharp. There is compensatory hypertrophy of the companion hepatic artery due to hepatic artery buffer response, and the affected liver parenchyma may show hyperenhancement in the arterial phase [19]. This area becomes either isodense or hypodense in the venous phase (Fig. 4.6). The liver then becomes homogeneous in the delayed phase due to blood flow through the collaterals. There may be ascites due to acute portal hypertension. Identification of ascites is important as percutaneous transhepatic interventions like thrombolysis are associated with a higher incidence of hemorrhagic complications in the presence of ascites.

Further, CT scan helps in identification of the etiology of PVT. These include cirrhosis of liver, inflammatory conditions like pancreatitis, liver abscess, and

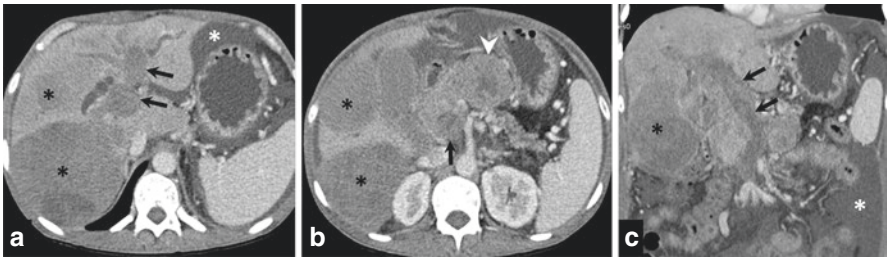

Fig. 4.9 Portal vein thrombosis in a case of pancreatic neuroendocrine tumor with liver metastases. Axial (**a**, **b**) and coronal (**c**) contrast-enhanced CT images show extensive thrombosis of the portal and mesenteric vein (arrows) due to a primary pancreatic tumor (arrowhead in **b**). Multiple hypodense liver metastases (black asterisks) and ascites (white asterisk) are noted

cholangitis, and malignant diseases like HCC, biliary cancers, pancreatic cancer, and lymphadenopathy (Fig. 4.9).

4.3.1.3 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is less frequently performed in patients with acute PVT due to its cost, long scan times, and insignificant additional benefit. The standard MRI done in the evaluation of PVT includes the T1- and T2-weighted sequences, preferably gradient echo sequences, diffusion-weighted imaging (DWI), and multiphase contrast-enhanced T1-weighted sequences [8]. Magnetic resonance cholangiopancreatography (MRCP) may be additionally done to evaluate the biliary system in cases of late presentation. Balanced steady-state sequence is useful for visualizing vessels without administration of contrast agent [20].

The acute thrombus has variable appearances on T1- and T2-weighted sequences depending on its age (Fig. 4.10) [19]. On T1-weighted images, the thrombus may be isointense or hyperintense [8]. On T2-weighted images, it appears isointense or hypointense. The thrombus may show restriction of diffusion depending on its age and variably appears hyperintense on DWI. The thrombus does not show contrast enhancement. Multiple collaterals may be seen at the porta hepatis as flow voids on T1- and T2-weighted images and as enhancing bunch of vessels on contrast-enhanced sequences [19].

The hypoperfused segments of the liver may appear hypointense on T1- and hyperintense on T2-weighted images. Contrast enhancement pattern of this part of the liver may be similar to that seen on CT scan, with arterial phase hyperenhancement, venous phase hypo-enhancement, and delayed phase iso-enhancement (Fig. 4.11). Ascites is frequently present.

4.3.1.4 Angiography

Conventional angiography is almost never performed these days for the diagnosis of PVT due to the availability of CT scan and MRI [21]. This procedure can be performed by two techniques—indirect and direct portography. In indirect

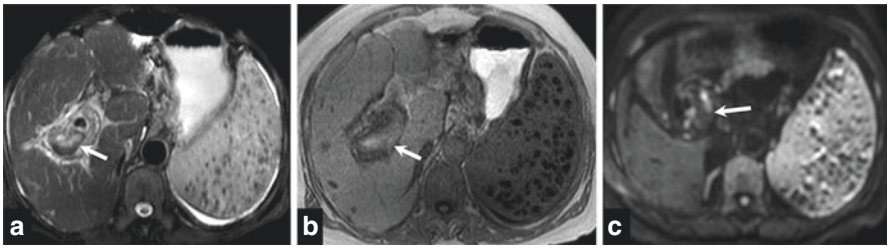

Fig. 4.10 MRI of acute portal vein thrombosis in a patient with non-cirrhotic portal fibrosis. Axial T2- (**a**), T1- (**b**), and diffusion- (**c**) weighted images show acute thrombus in the right portal vein appearing hypointense on T2- and hyperintense on T1-weighted images with focal areas of restriction of diffusion. In addition, parenchymal changes are seen in the liver with splenomegaly and Gandy-Gamna bodies

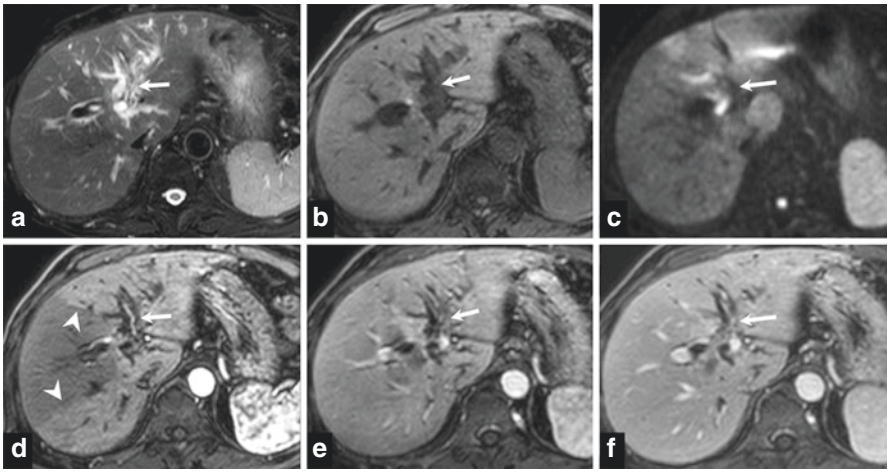

Fig. 4.11 MRI of left portal vein thrombosis in a patient with hilar cholangiocarcinoma. Axial T2- (**a**), T1- (**b**), and diffusion- (**c**) weighted images show attenuated left portal vein appearing hypointense on T2- and isointense on T1-weighted images with no restriction of diffusion. Contrast-enhanced images in arterial (**d**), venous (**e**), and delayed (**f**) phases show the characteristic perfusion abnormality in the arterial phase (arrowheads) which disappears on venous and delayed phases. Non-enhancing attenuated left portal vein is noted (arrow)

portography, also called arterioportography, contrast agent is injected into the celiac and superior mesenteric arteries and the venous phase is acquired. In direct portography, which is more invasive, portal vein is evaluated by injecting contrast agent through transhepatic, transjugular, and transsplenic routes. Currently, the arterioportography and the transjugular and transhepatic direct portographies are performed when interventional procedures like thrombectomy and thrombolysis are planned [21].

4.3.2 Chronic Portal Vein Thrombosis

Patients who are asymptomatic or have mild symptoms during the episode of acute PVT present later mostly with features of portal hypertension like hematemesis, melena, abdominal pain, abdominal lump, and jaundice. The primary thrombus is usually not visualized as it is organized and fibrotic. Imaging assists in demonstrating the complications developing as a result of previous episode of PVT and in planning further management.

4.3.2.1 Ultrasonography

Even in chronic PVT, USG is the initial investigation of choice. The portal vein is not visualized at the porta hepatis in a majority of patients; uncommonly, there may be a recanalized portal vein due to the lysis of the thrombus [22]. The thrombosed vein may be seen as a hypoechoic structure; infrequently echogenic foci of calcification may be seen. Multiple collaterals forming a cavernoma are seen at the porta hepatis and around the bile ducts, which are shown as tortuous anechoic structures with color flow on CDUSG (Fig. 4.12) [22]. Demonstration of the patency and caliber of the intrahepatic right and left portal, splenic, and superior mesenteric veins are important whenever a surgical shunt is planned.

The liver parenchyma frequently shows lobar or segmental atrophy and hypertrophy changes. As mentioned previously, the peripheral segments of the liver (usually segments 2 and 3) undergo atrophy and segments 1 and 4 undergo hypertrophy (Fig. 4.13) [23]. This is unlike cirrhosis where the segment 4 shows atrophy and segments 2 and 3 appear hypertrophic. The hepatic changes that occur in chronic PVT are due to persistent hypoperfusion, unlike in cirrhosis, where it is due to

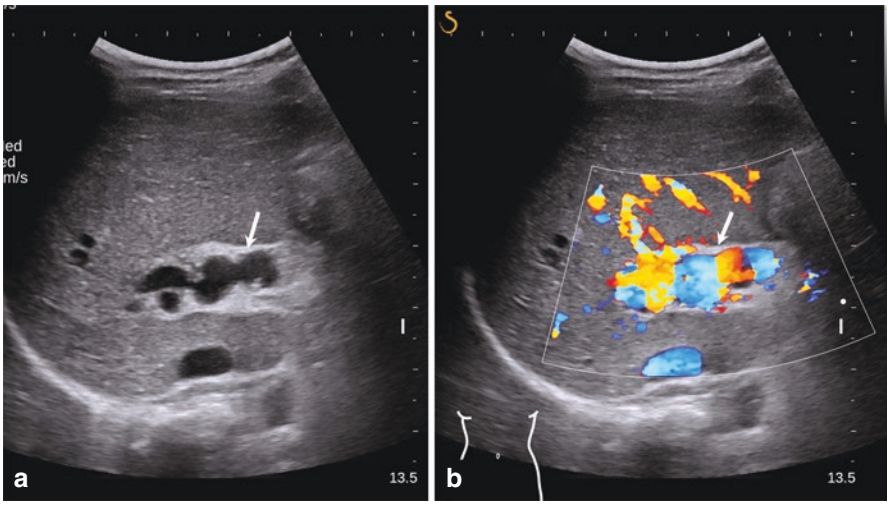

Fig. 4.12 Ultrasonography of chronic portal vein thrombosis. (**a**) B-mode image shows anechoic tortuous vascular channels with irregular outline at porta hepatis (arrow). (**b**) Color Doppler image shows marked flow within the channels suggestive of a cavernoma

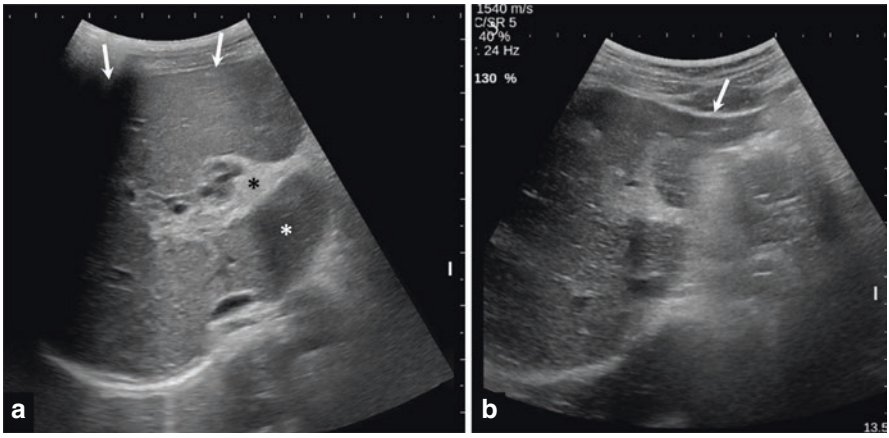

Fig. 4.13 Ultrasonography of chronic portal vein thrombosis with hepatic parenchymal changes. (**a**) B-mode image shows hypertrophy of segment 4 (arrows) and caudate lobe (white asterisk) with widened periportal space (black asterisk). (**b**) B-mode image shows atrophy of left lateral segments (segments 2 and 3; arrow)

fibrosis. Thus, measurement of liver stiffness is useful in the differentiation of these two entities and also helps in determining whether PVT is a cause or a result of parenchymal pathology. The liver stiffness in patients with chronic PVT without cirrhosis is usually normal (Fig. 4.14) [24]. Uncommonly, isoechoic or hypoechoic nodules may be seen in the liver parenchyma, which are called focal nodular hyperplasia (FNH) like nodules or benign regenerative nodules (Fig. 4.15) [25]. The USG findings are non-specific and CEUS is helpful in better characterization of these nodules, particularly in their differentiation from HCC. On CEUS, these nodules show early hyperenhancement and become isoechoic to the liver in the later phases, without any washout of contrast [26].

In addition to portal cavernoma, varices are also seen in the gallbladder wall in up to 50% of the cases [27]. Both portal cavernoma and gallbladder varices form the porto-portal collaterals. Then there are portosystemic shunts developing due to long-standing portal hypertension, which are commonly located in the peripancreatic, splenic hilum, and lienorenal regions (Fig. 4.16). Ascites is usually uncommon in the absence of cirrhosis. The spleen is often grossly enlarged [28]. Multiple echogenic foci may be seen in the parenchyma representing Gandy-Gamna bodies (Fig. 4.16). Peripheral wedge-shaped hypoechoic areas may be seen in the spleen suggesting infarcts. Chronic infarcts show scarring and calcification.

The collaterals at the porta hepatis, which are typically the epicholedochal and paracholedochal collaterals, run in and around the walls of the bile duct [29]. These collaterals compress upon the bile duct wall and cause luminal narrowing. USG, in such cases, shows dilatation of the intrahepatic bile ducts with multiple collaterals around the common bile duct. This condition is called portal cavernoma cholangiopathy (previously portal biliopathy) (Fig. 4.17). When the patient presents with cholangitis, USG may show dilated intrahepatic bile ducts, intraductal debris or calculi, thickened walls of the ducts, and abscesses in the liver.

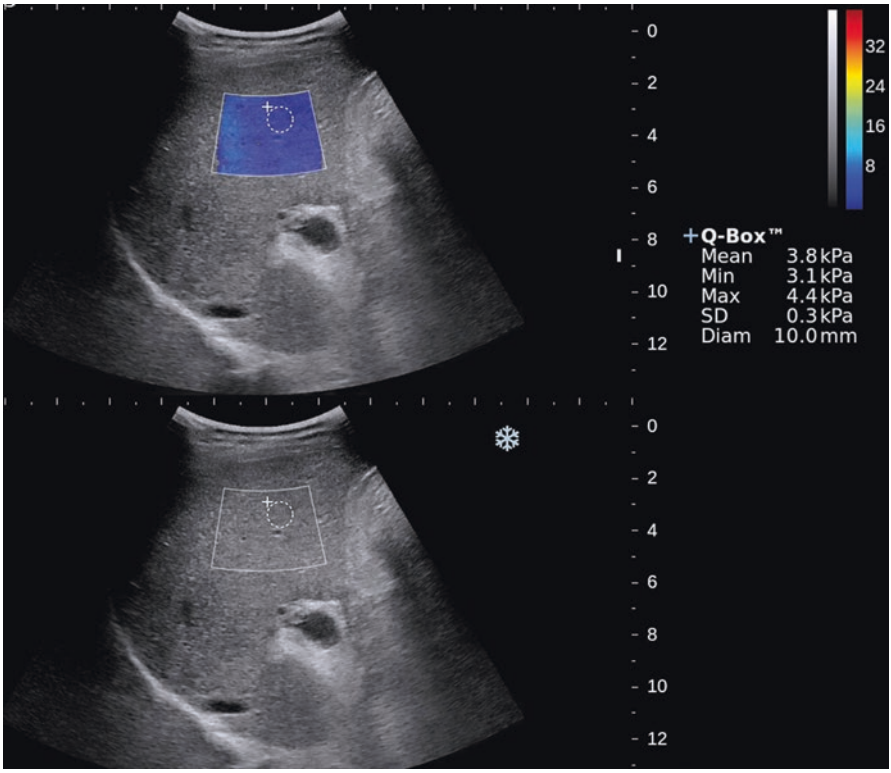

Fig. 4.14 Hepatic elastography in chronic portal vein thrombosis. Ultrasonography with shear-wave elastography in a patient with primary chronic portal vein thrombosis shows normal liver stiffness values (3.8 kiloPascals)

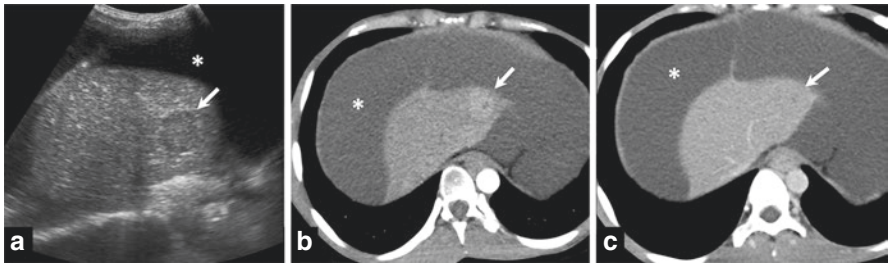

Fig. 4.15 Liver nodule in chronic portal vein thrombosis. (**a**) B-mode ultrasonography image shows a hypoechoic lesion in segment 2 of the liver (arrow). (**b**, **c**) Axial arterial (**b**) and venous (**c**) phase contrast-enhanced CT images show arterial phase hyperenhancement in the lesion (arrow) with isodense appearance in venous phase (arrow), characteristic of benign regenerative nodule. Gross ascites is noted (asterisk)

4.3.2.2 Computed Tomography

Once the pathology is suspected on USG, contrast-enhanced CT is necessary for better definition of the abnormality and its complications and to identify an etiology. In this setting, typically, a CT portography is done. Here, a single portal venous phase is acquired at 60–70s after injection of the contrast agent.

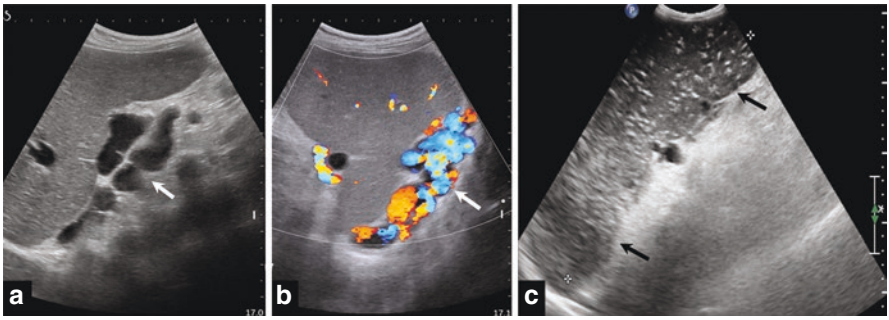

Fig. 4.16 Changes of portal hypertension in chronic portal vein thrombosis. (**a**, **b**) B-mode (**a**) and color Doppler (**b**) ultrasonography images show tortuous anechoic vascular channels with prominent flow (arrow) in the perisplenic region suggestive of lienorenal shunts. (**c**) B-mode ultrasonography image shows splenomegaly (arrows) with multiple echogenic nodules in the parenchyma suggestive of Gandy-Gamna bodies

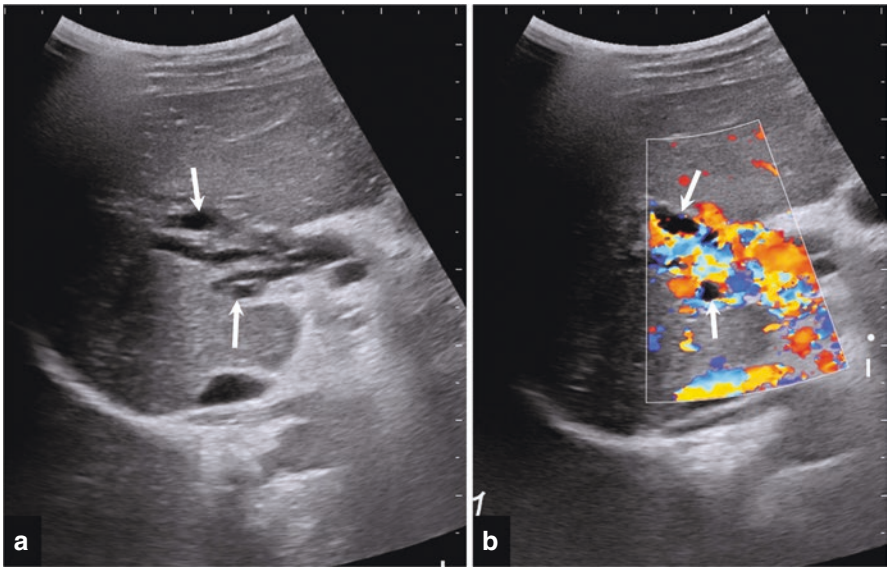

Fig. 4.17 Ultrasonography of portal cavernoma cholangiopathy. (**a**) B-mode image shows tubular wavy anechoic channels at portal hepatis (arrows) with thickened walls suggesting dilated bile ducts. (**b**) Color Doppler image shows portal cavernoma with non-filling dilated bile ducts (arrows)

The chronically thrombosed portal vein either may not be seen or seen as a hypodense non-enhancing cord [30]. Calcification of the thrombus may be seen (Fig. 4.18). Infrequently, the portal vein may become recanalized, completely or partially, due to spontaneous thrombolysis (Fig. 4.18). In such cases, the vein shows irregularly thickened walls due to peripherally organized thrombus. Calcification may be seen within the thickened walls. CT scan is better than USG in identification of shuntable veins prior to surgery [27].

As suggested under USG, CT scan also shows cavernous transformation of the portal vein [29, 31]. The collaterals are typically the porto-portal shunts (Fig. 4.19). They run

around and along the walls of the bile duct, which itself is seen as a hypodense structure. The collaterals compress the extrahepatic bile duct and may result in dilatation of the intrahepatic bile ducts. The dilatation is usually mild but, rarely, may be marked. Sludge and calculi may be seen within the dilated ducts in long-standing cases. These dilated ducts are prone to cholangitis due to bile stasis and CT scan in such cases may show thickened bile duct walls and cholangitic abscesses in the liver.

Atrophy and hypertrophy changes are seen in the liver parenchyma in chronic PVT as suggested above [23]. The portal hypoperfusion and arterial hyperperfusion induce proliferation of the hepatocytes (Fig. 4.20). In about 10% of these patients, this process may result in the formation of benign FNH-like nodules in the parenchyma [19, 32]. Whenever such nodules are found on USG, a multiphasic CT scan should be performed. These nodules show arterial phase hyperenhancement and become isodense in the venous and delayed phases (Fig. 4.15). This appearance helps in its differentiation from HCC.

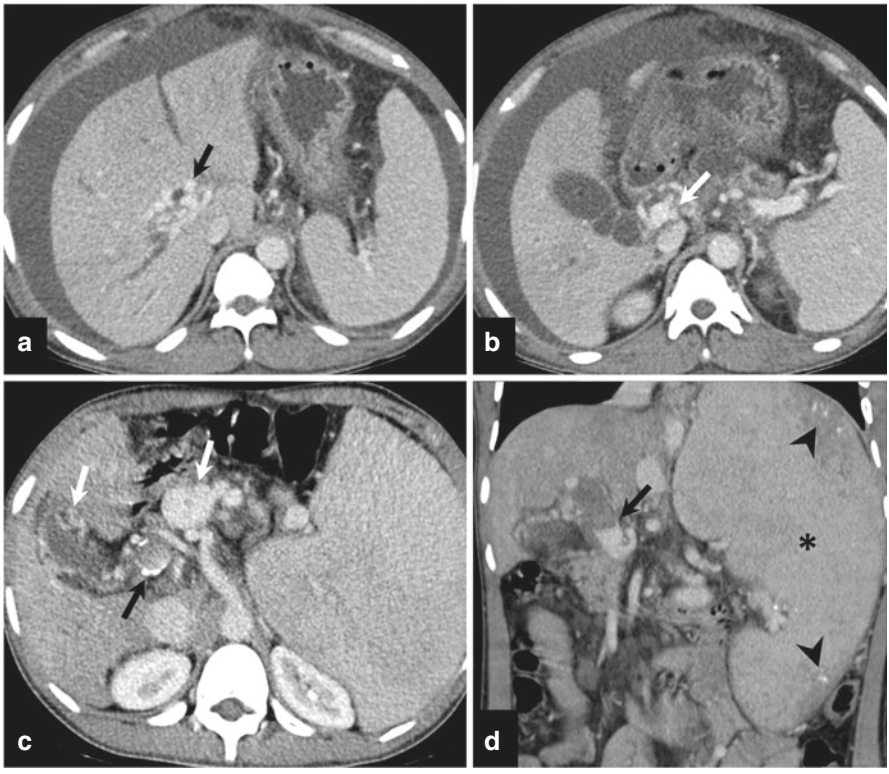

Fig. 4.18 CT scan in chronic portal vein thrombosis. (**a**, **b**) Axial contrast-enhanced CT images show portal cavernoma (arrow in **a**) with irregularly recanalized main portal vein (arrow in **b**). (**c**, **d**) Axial (**c**) and coronal (**d**) contrast-enhanced CT images show calcification in a partially recanalized portal vein (black arrows) with collaterals in the gallbladder wall and peripancreatic region (white arrows). Splenomegaly is noted (asterisk) with calcified Gandy-Gamna bodies (arrowheads)

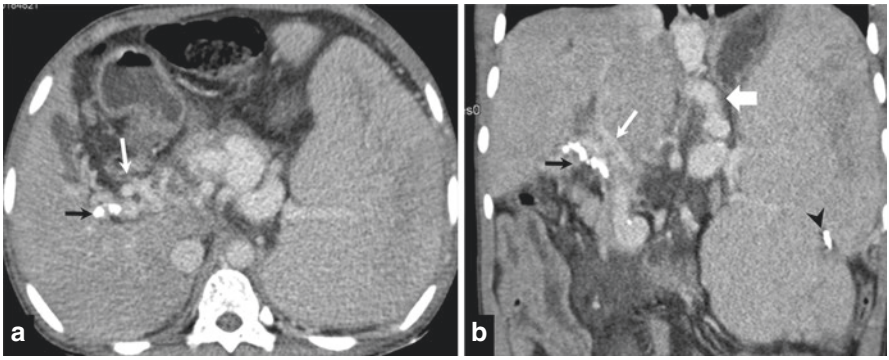

Fig. 4.19 CT scan in chronic portal vein thrombosis. Axial (**a**) and coronal (**b**) contrast-enhanced CT images show portal cavernoma (white arrows) with calcific foci (black arrows) and large perigastric shunts (block arrow in **b**). Note is made of splenomegaly with chronic infarct (arrowhead in **b**) and calcification

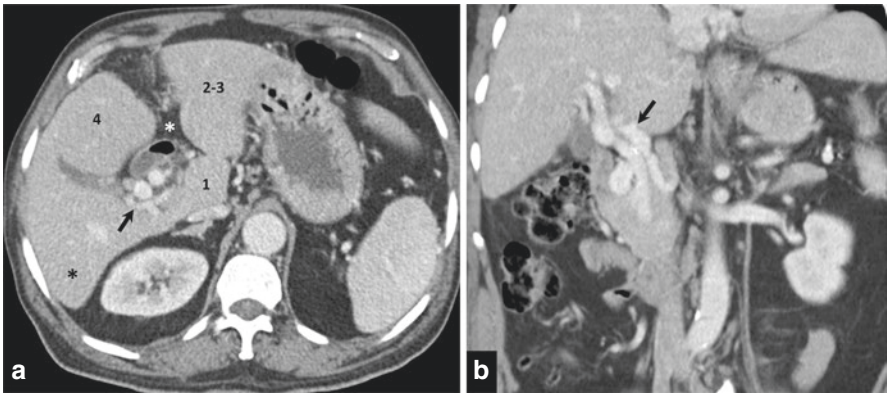

Fig. 4.20 CT scan in chronic portal vein thrombosis with hepatic parenchymal changes. Axial (**a**) and coronal (**b**) contrast-enhanced CT images show collaterals along the bile duct (black arrows). The liver shows widened fissure (white asterisk) with atrophic segments 2–3 and right posterior segments (black asterisk) and prominent segments 4 and 1

The spleen is enlarged in the majority of cases and may show infarcts, Gamna-Gandy bodies, and peripheral calcifications (Figs. 4.18, 4.19, and 4.21). Multiple portosystemic shunts may also been seen in the peripancreatic, perisplenic, and gallbladder regions (Fig. 4.21). Changes in the arteries are also seen in chronic PVT. There is hypertrophy of the hepatic artery which is a compensatory response [27]. The splenic artery is also enlarged and due to the hyperdynamic flow, true aneurysms may develop in the splenic artery.

Similar to acute PVT, CT scan in chronic PVT helps in identifying the etiology too. However, most patients who present in the chronic stage have either cirrhosis or no identifiable cause. Other mentioned etiologies mostly manifest at an early stage.

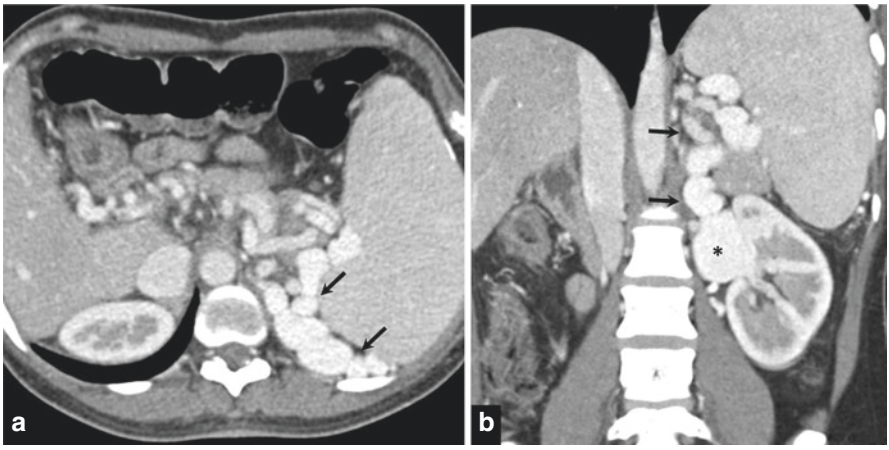

Fig. 4.21 CT scan in chronic portal vein thrombosis with portosystemic shunts. Axial (**a**) and coronal (**b**) contrast-enhanced CT images show large perisplenic collaterals (arrows) with dilated left renal vein (asterisk in **b**) suggestive of lienorenal shunts

4.3.2.3 Magnetic Resonance Imaging

MRI is uncommonly performed in the setting of chronic PVT. The sequences used are the same as those used for acute PVT. Important indications for MRI are the evaluation of portal cavernoma cholangiopathy and liver nodules.

Non-contrast sequences, like balanced spin echo sequences, show multiple collaterals (cavernoma) at the porta hepatis (Fig. 4.22). The patency of the shuntable veins is also depicted, in addition to the portosystemic shunts, splenomegaly, and hepatic parenchymal volume redistribution (Fig. 4.22) [33]. Uncommonly, the collaterals may be multiple and tiny and appear mass-like, when they may mimic a malignancy like cholangiocarcinoma [34]. Absence of diffusion restriction, presence of flow voids on plain sequences, and supplementation by CDUSG which shows high vascularity help in the differentiation.

The FNH-like nodules or benign regenerative nodules are isointense to hyperintense on T1-weighted and isointense or mildly hyperintense on T2-weighted sequences (Fig. 4.23) [19]. They do not show diffusion restriction. On multiphasic contrast-enhanced imaging, they show arterial phase hyperenhancement and appear isointense on the venous and delayed phases [19]. On the hepatobiliary phase images (when hepatobiliary contrast agent is used), they appear isointense to the liver parenchyma indicating the presence of functional hepatocytes.

Portal cavernoma cholangiopathy, seen in 70–100% of patients of chronic PVT, shows dilatation of the intrahepatic bile ducts [27, 29, 31]. The collaterals around the bile ducts indent on their walls giving a pseudo-sclerosing cholangitis appearance (Figs. 4.22 and 4.24). The strictures of the bile ducts may be either temporary when caused by indentation of the collaterals or permanent when there is fibrosis due to long-standing compression. Long-standing cases may show calculi or sludge within the bile ducts and also in the gallbladder (Fig. 4.24).

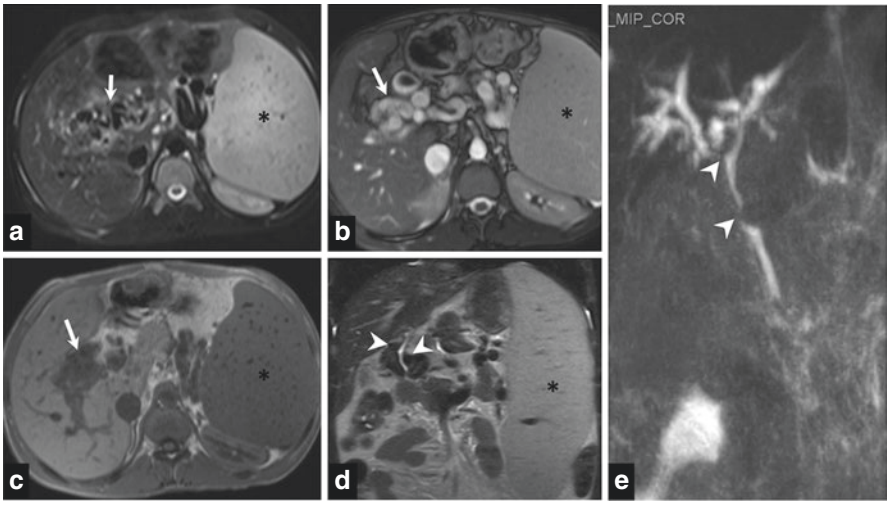

Fig. 4.22 MRI in chronic portal vein thrombosis. (**a**–**c**) Axial T2 (**a**), balanced spin echo (**b**), and T1-weighted (**c**) images show multiple channels in the porta hepatis (arrow) forming a cavernoma. (**d**, **e**) Coronal T2-weighted (**d**) and MRCP (**e**) images show flow voids in the wall of the bile duct (arrowheads in **d**) causing strictures in bile ducts (arrowheads in **e**) with proximal dilatation resulting in portal cavernoma cholangiopathy. Note is made of splenomegaly (asterisk) with multiple hypointense foci (Gandy-Gamna bodies)

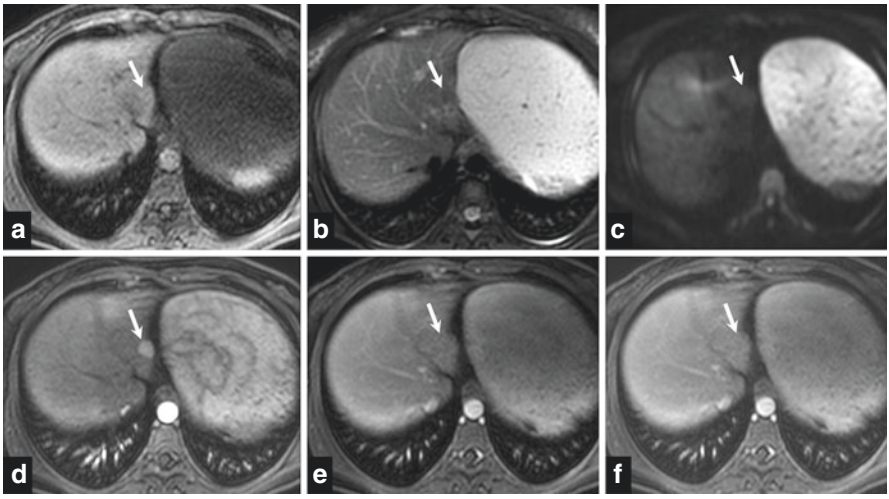

Fig. 4.23 MRI of benign regenerative nodule in chronic portal vein thrombosis. (**a**–**c**) Axial T1- (**a**), T2- (**b**), and diffusion- (**c**) weighted images show a nodule (arrow) appearing mildly hyperintense on T1- and hypointense on T2-weighted images with no diffusion restriction. (**d**–**f**) Arterial (**d**), venous (**e**), and delayed (**f**) phase contrast-enhanced images show intense arterial phase enhancement of the nodule with isointense signal in venous and delayed phases (arrows) suggestive of benign regenerative nodule

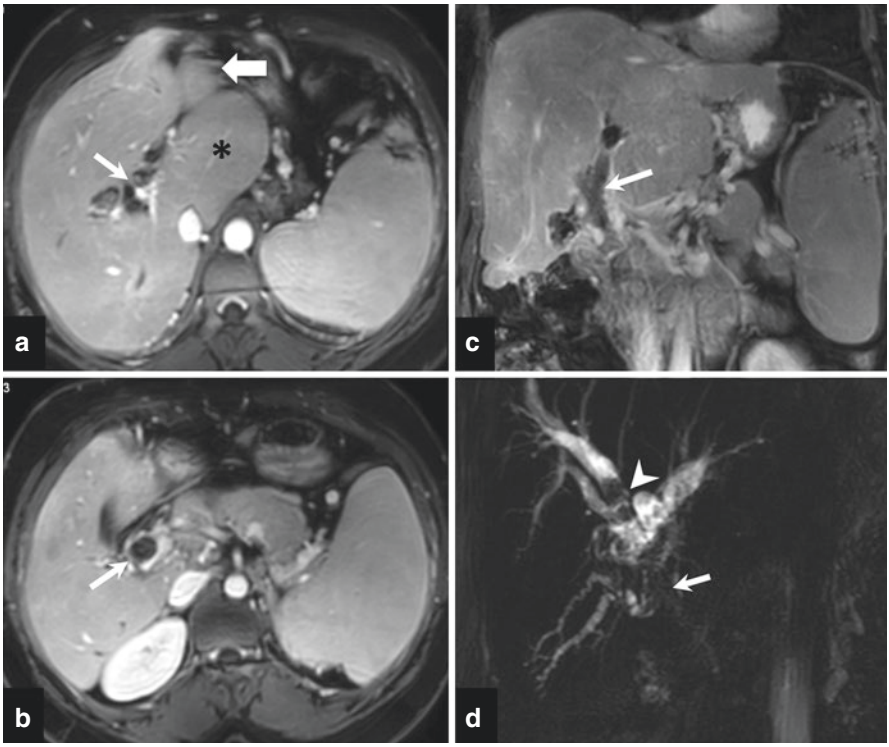

Fig. 4.24 MRI of portal cavernoma cholangiopathy. (**a**–**c**) Axial (**a**, **b**) and coronal (**c**) contrast-enhanced MR images show dilated intrahepatic and extrahepatic bile ducts (arrow) with collaterals in their walls suggestive of portal cavernoma cholangiopathy. Liver shows enlarged caudate lobe (asterisk in **a**) with atrophic segments 2 and 3 (block arrow in **a**). (**d**) MRCP image shows non-visualization of distal bile duct due to long segment stricture (arrow) with dilatation of proximal bile ducts. Signal voids are seen within the bile ducts (arrowhead) suggestive of calculi

4.3.3 Specific Types of Portal Vein Thrombosis

4.3.3.1 Septic Thrombophlebitis

Septic thrombophlebitis of the portal vein or pylephlebitis occurs when the thrombus is associated with a local or regional infection or inflammation [35]. It is a potentially lethal complication of infective or inflammatory conditions of the abdominal cavity, with a mortality rate as high as 32% due to the risk of development of early sepsis [36]. The thrombus is not bland and contains inflammatory cells like neutrophils, lymphocytes, macrophages, and eosinophils and the infective elements like bacteria or fungi. In view of the risk of septicemia and septic emboli, it is treated as an emergency.

Diagnosis of pylephlebitis may be suspected on USG when the portal vein shows echogenic contents within the lumen and the liver shows anechoic or hypoechoic lesions suggestive of abscesses. Imaging with CT scan or MRI is necessary for confirming the same. These modalities show thrombus in the portal vein, which may be associated with thickening and enhancement of its wall (Figs. 4.25 and 4.26)

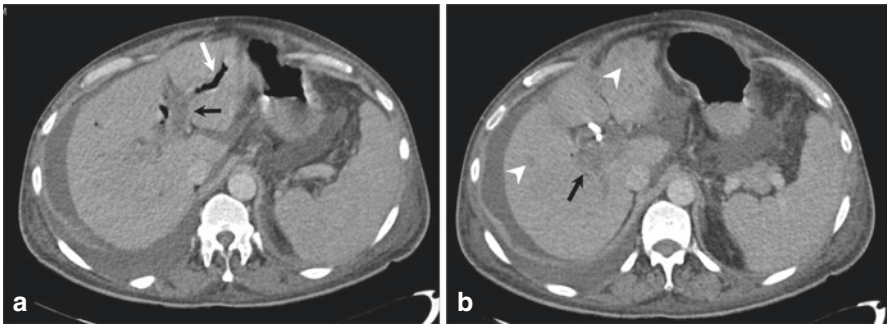

Fig. 4.25 CT scan of pylephlebitis due to cholangitis. (**a**, **b**) Axial contrast-enhanced CT images show thrombosis of the portal vein with mild peripheral wall enhancement (black arrow) and air foci in left portal vein branches (white arrow in **a**). Multiple hypodense lesions are seen in the liver (arrowheads in **b**) suggestive of cholangitic abscesses

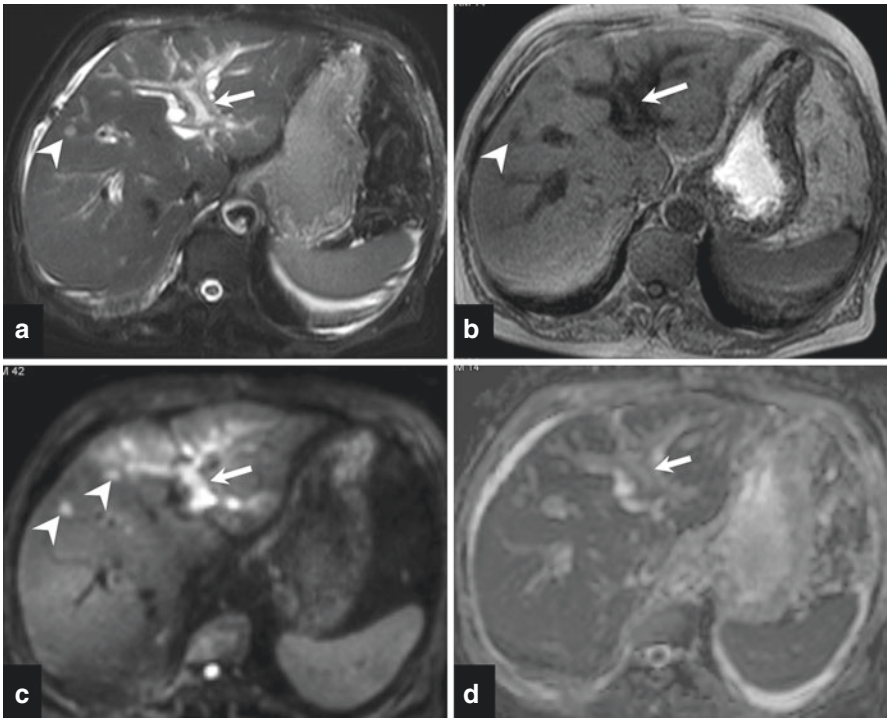

Fig. 4.26 MRI of pylephlebitis due to cholangitis. (**a**, **b**) Axial T2- (**a**) and T1- (**b**) weighted MR images show acute thrombosis of left portal vein (arrow) appearing hyperintense on T2 and mildly hyperintense on T1-weighted images with wall thickening. (**c**, **d**) Axial diffusion-weighted (**c**) and apparent diffusion coefficient (**d**) images show restriction of diffusion within the left portal vein thrombus (arrow). Note cholangitic abscesses in the liver (arrowheads)

[19, 35]. Other findings include peripherally enhancing lesions in the liver suggestive of abscesses, perfusion abnormalities in the liver parenchyma, and air foci in the portal vein [37]. More importantly, the primary source of infection or inflammation is better identified on these imaging modalities and includes pancreatitis, diverticulitis, cholangitis, appendicitis, intra-abdominal or liver abscess, and inflammatory bowel disease.

4.3.3.2 Malignant Portal Vein Thrombosis

Malignant PVT or now called "tumor in portal vein" indicates extension of a tumor into the portal vein, most commonly HCC [38]. HCC is an angioinvasive tumor and up to 33% of cases are associated with extension into the portal vein [39]. Once the tumor is in the portal vein, it occludes the portal vein leading to a few specific changes on imaging. Since this condition indicates poor prognosis, it is important to differentiate tumor in portal vein from bland PVT [40].

USG is usually the initial investigation performed in these patients. USG shows a heteroechoic material within the lumen of the portal vein causing its distension (Fig. 4.27) [41]. It is frequently associated with a tumor in the adjacent hepatic parenchyma. However, the hepatic tumor may not be seen frequently, particularly in cases of infiltrative HCC. Further, there may be disruption of the outline of the portal vein and invasion of the adjacent structures. CDUSG may show vascularity within the tumor and helps in the differentiation of a tumor from a bland thrombus [42]. Use of CEUS further increases the accuracy of this differentiation. On CEUS, the tumor shows enhancement in the early and/or late phase depending on the type of the tumor [43].

CT or MRI scan is usually necessary for better characterization of the tumor in the vein and also to assess the primary lesion in the liver parenchyma [44]. On CT scan, the tumor in the portal vein shows enhancement in the arterial phase, showing linear enhancing areas giving the "threads and streaks" appearance (Figs. 4.28 and 4.29) [45, 46]. The

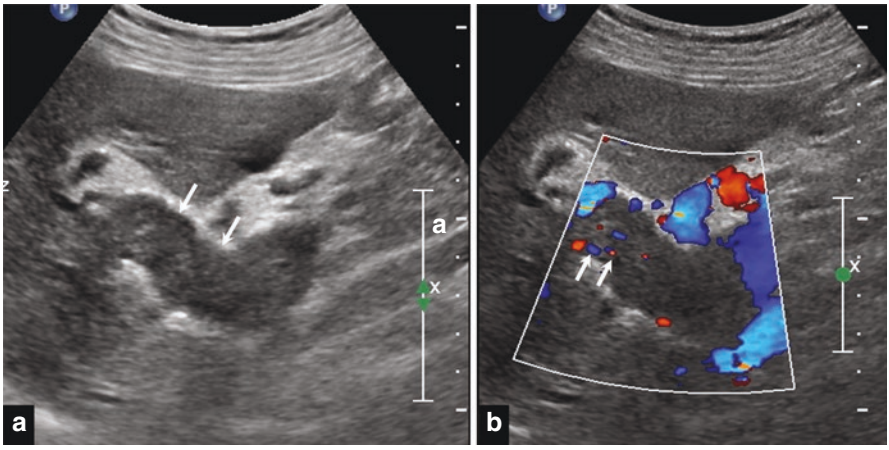

Fig. 4.27 Ultrasonography of malignant portal vein thrombosis. (**a**) B-mode image shows dilated portal vein (arrows) filled with echogenic material. (**b**) Color Doppler image shows foci of internal vascularity within the thrombus (arrows) suggesting tumor in vein

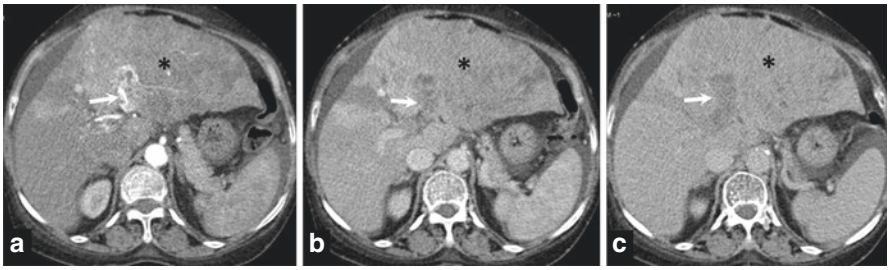

Fig. 4.28 CT scan of malignant portal vein thrombosis with infiltrative hepatocellular carcinoma. Arterial (**a**), venous (**b**), and delayed (**c**) phase contrast-enhanced CT images show thrombus in the left and proximal right portal vein (arrow) with linear and patchy enhancement (threads and streaks) in the arterial phase and washout in venous and delayed phases suggesting tumor in vein. An infiltrative variety of hepatocellular carcinoma is seen in the left lobe of the liver (asterisk)

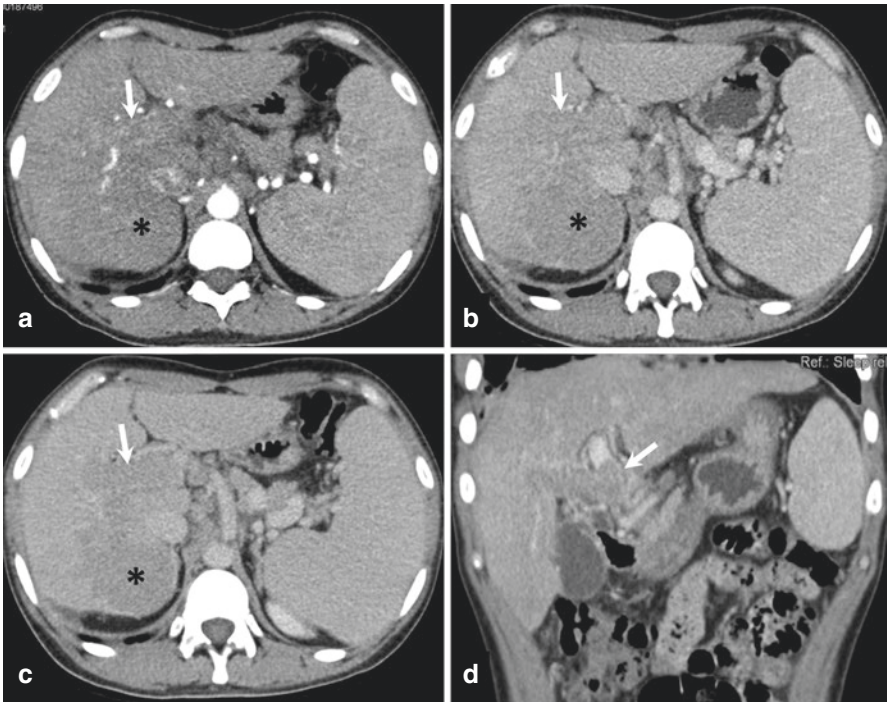

Fig. 4.29 CT scan of malignant portal vein thrombosis with hepatocellular carcinoma. (**a**–**c**) Arterial (**a**), venous (**b**), and delayed (**c**) phase contrast-enhanced CT images show thrombus in the right and main portal vein (arrow) with mild linear enhancement (threads and streaks) in the arterial phase and washout in venous and delayed phases suggesting tumor in vein. A rounded tumor with mild arterial phase enhancement and venous and delayed phase washout is seen in segment 6 (asterisk) of cirrhotic liver suggestive of hepatocellular carcinoma. (**d**) Coronal venous phase CT image shows the thrombus in the right and main portal vein (arrow)

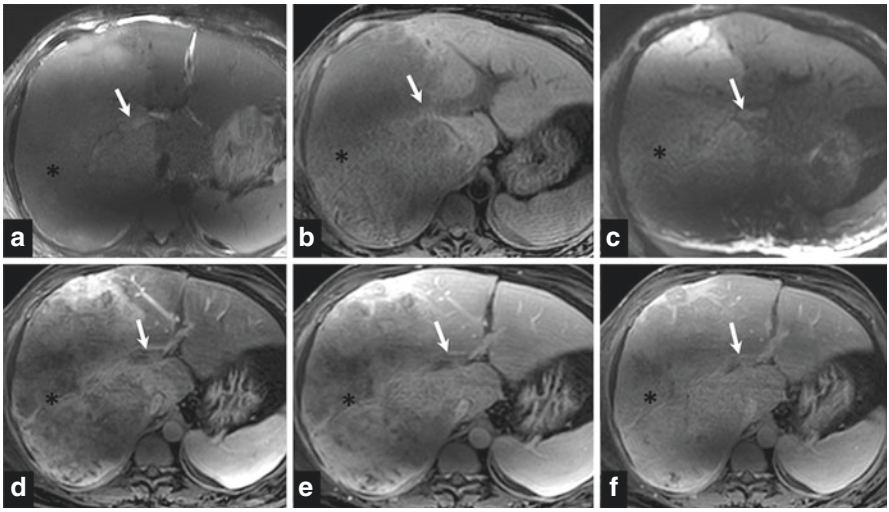

Fig. 4.30 MRI of malignant portal vein thrombosis with infiltrative hepatocellular carcinoma. (**a**–**c**) Axial T2- (**a**), T1- (**b**), and diffusion- (**c**) weighted MR images show thrombus in the right portal vein (arrow) appearing hyperintense on both T1- and T2-weighted images with restriction of diffusion. (**d**–**f**) Arterial (**d**), venous (**e**), and delayed (**f**) phase contrast-enhanced MR images show enhancing thrombus in the right portal vein (arrow) suggesting tumor in vein. A large infiltrative variety of hepatocellular carcinoma showing arterial phase hyperenhancement and venous and delayed phase washout is seen in the right lobe and segments 1 and 4 of liver (asterisk)

tumor is often seen in contiguity to the lesion in the liver parenchyma. The primary tumor and the tumor in the vein often show similar patterns of enhancement. The enhancing tumor in vein shows washout in the venous and delayed phases. In cases of infiltrative HCC, the primary tumor may not be clearly visible and the tumor in vein may not show enhancement [44]. Further, due to the parenchymal perfusion abnormalities occurring as a result of occlusion of the portal vein, the primary lesion may not show the characteristic enhancing features.

MRI is more sensitive than CT scan in the diagnosis of tumor in vein [47]. The involved vein is dilated and appears hypointense on T1- and hyperintense on T2-weighted images (Fig. 4.30). The tumor in vein may show diffusion restriction. However, these described changes on non-contrast MRI may also be seen in bland thrombus and hence differentiation is not easy [47]. On contrast-enhanced multiphasic MRI, the enhancement patterns are similar to that as described under CT scan [48].

^{18}F-FDG PET/CT has also shown promising results in the differentiation of malignant from benign PVT. A study has shown that a cutoff value of standardized uptake value (SUV) of more than 3.35 in favor of tumor in vein has a sensitivity, specificity, and accuracy of 93.6%, 80%, and 88.9%, respectively [49].

4.4 Conclusion

PVT is an uncommon complication and is associated with various local and systemic conditions, most common being cirrhosis of the liver. The clinical presentation is often non-specific. Imaging plays an important role, not only in making the diagnosis of PVT but also in assessing the extent of thrombosis, its complications, and the etiology and in planning further management. Although USG is the initial modality, most of the patients require imaging with either CT scan or MRI for complete evaluation. The imaging findings are different in acute and chronic PVT, and this differentiation is helpful in management. Septic thrombophlebitis is associated with high morbidity and mortality and an early imaging diagnosis is necessary. Tumor in the portal vein is mostly associated with HCC and has imaging features different from a non-malignant thrombus. Knowledge of these various imaging features helps in making an accurate assessment of patients with PVT and in their judicious management.

References

1. Chawla YK, Bodh V. Portal vein thrombosis. J Clin Exp Hepatol. 2015;5:22–40.
2. Ogren M, Bergqvist D, Bjorck M, et al. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. World J Gastroenterol. 2006;12:2115–9.
3. Okuda K, Ohnishi K, Kimura K. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. Gastroenterology. 1985;89:279–86.
4. Amitrano L, Guardascione MA, Brancaccio V. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40:736–41.
5. Margini C, Berzigotti A. Portal vein thrombosis: the role of imaging in the clinical setting. Dig Liver Dis. 2017;49:113–20.
6. Hidajat N, Stobbe H, Griesshaber V, Felix R, Schroder RJ. Imaging and radiological interventions of portal vein thrombosis. Acta Radiol. 2005;46:336–43.
7. Wang JT, Zhao HY, Liu YL. Portal vein thrombosis. Hepatobiliary Pancreat Dis Int. 2005;4:515–8.
8. Ponziani FR, Zocco MA, Campanale C, et al. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. World J Gastroenterol. 2010;16:143–55.
9. De Gaetano AM, Lafortune M, Patriquin H, De Franco A, Aubin B, Paradis K. Cavernous transformation of the portal vein: patterns of intrahepatic and splanchnic collateral circulation detected with Doppler sonography. AJR Am J Roentgenol. 1995;165:1151–5.
10. Gertsch P, Matthews J, Lerut J, Luder P, Blumgart LH. Acute thrombosis of the splanchnic veins. Arch Surg. 1993;128:341–5.
11. Danila M, Sporea I, Popescu A, et al. Portal vein thrombosis in liver cirrhosis—the added value of contrast enhanced ultrasonography. Medical Ultrasonography. 2016;18:218–33.
12. Tessler FN, Gehring BJ, Gomes AS, et al. Diagnosis of portal vein thrombosis: value of color Doppler imaging. AJR Am J Roentgenol. 1991;157:293–6.
13. Kaproth-Joslin K, Ashwani KS, Rubens DJ. Ultrasound imaging and interventional treatment of portal vein thrombosis. Ultrasound Clin. 2013;8:237–47.
14. Rafailidis V, Fang C, Yusuf GT, et al. Contrast-enhanced ultrasound (CEUS) of the abdominal vasculature. Abdom Radiol. 2018;43:934–47.

15. Song ZZ, Huang M, Jiang TA, et al. Diagnosis of portal vein thrombosis discontinued with liver tumors in patients with liver cirrhosis and tumors by contrast-enhanced US: a pilot study. Eur J Radiol. 2010;75:185–8.
16. Rameshbabu CS, Wani ZA, Rai P, Abdulqader A, Garg S, Sharma M. Standard imaging techniques for assessment of portal venous system and its tributaries by linear endoscopic ultrasound: a pictorial essay. Endosc Ultrasound. 2013;2:16–34.
17. Anastasiou J, Berzin TM. Endoscopic ultrasound-guided vascular interventions: from diagnosis to treatment. Saudi J Med Med Sci. 2018;6:61–7.
18. Laissy JP, Trillaud H, Douek P. MR angiography: noninvasive vascular imaging of the abdomen. Abdom Imaging. 2002;27:488–506.
19. Jha RC, Khera SS, Kalaria AD. Portal vein thrombosis: imaging the spectrum of disease with an emphasis on MRI features. AJR Am J Roentgenol. 2018;211:14–24.
20. Smith CS, Sheehy N, McEniff N, Keogan MT. Magnetic resonance portal venography: use of fast-acquisition true FISP imaging in the detection of portal vein thrombosis. Clin Radiol. 2007;62:1180–8.
21. Hauenstein K, Li Y. Radiological diagnosis of portal/mesenteric vein occlusion. Viszeralmedizin. 2014;30:382–7.
22. Ueno N, Sasaki A, Tomiyama T, Tano S, Kimura K. Color Doppler ultrasonography in the diagnosis of cavernous transformation of the portal vein. J Clin Ultrasound. 1997;25:227–33.
23. Vilgrain V, Condat B, Bureau C, et al. Atrophy-hypertrophy complex in patients with cavernous transformation of the portal vein: CT evaluation. Radiology. 2006;241:149–55.
24. Madhusudhan KS, Sharma R, Kilambi R, et al. 2D Shear wave elastography of liver in patients with primary extrahepatic portal vein obstruction. J Clin Exp Hepatol. 2017;7:23–7.
25. Bureau C, Péron JM, Sirach E, Selves J, Otal P, Vinel JP. Liver nodules resembling focal nodular hyperplasia after portal vein thrombosis. J Hepatol. 2004;41:499–500.
26. Dietrich CF. Characterisation of benign focal liver lesions with contrast-enhanced ultrasound (CEUS). In: Lencioni R, editor. Enhancing the role of ultrasound with contrast agents. Milano: Springer; 2006. p. p17–38.
27. Arora A, Sarin SK. Multimodality imaging of primary extrahepatic portal vein obstruction (EHPVO): what every radiologist should know. Br J Radiol. 2015;88:20150008.
28. Sarin SK, Khanna R. Non-cirrhotic portal hypertension. Clin Liver Dis. 2014;18:451–76.
29. Kalra N, Shankar S, Khandelwal N. Imaging of portal cavernoma cholangiopathy. J Clin Exp Hepatol. 2014;4(suppl 1):S44–52.
30. Wani ZA, Bhat RA, Bhadoria AS, Maiwall R. Extrahepatic portal vein obstruction and portal vein thrombosis in special situations: need for a new classification. Saudi J Gastroenterol. 2015;21:129–38.
31. Moomjian LN, Winks SG. Portal cavernoma cholangiopathy: diagnosis, imaging, and intervention. Abdom Radiol (NY). 2017;42:57–68.
32. Kondo F. Benign nodular hepatocellular lesions caused by abnormal hepatic circulation: etiological analysis and introduction of a new concept. J Gastroenterol Hepatol. 2001;16:1319–28.
33. Gupta P, Kalra N, Gulati A, et al. Changes in liver morphology in patients with extrahepatic portal venous obstruction: a retrospective magnetic resonance imaging study. Br J Radiol. 2019;92:20180890.
34. Ussui VM, Goldstein L, Souto E, Levy C. Portal cavernoma mimicking pancreatic malignancy. ACG Case Rep J. 2018;5:e15.
35. Choudhry AJ, Baghdadi YM, Amr MA, Alzghari MJ, Jenkins DH, Zielinski MD. Pylephlebitis: a review of 95 cases. J Gastrointest Surg. 2016;20:656–61.
36. Plemmons RM, Dooley DP, Longfield RN. Septic thrombophlebitis of the portal vein (pylephlebitis): diagnosis and management in the modern era. Clin Infect Dis. 1995;21:1114–20.
37. Ames JT, Federle MP. Septic thrombophlebitis of the portal venous system: clinical and imaging findings in thirty-three patients. Dig Dis Sci. 2011;56:2179–84.
38. Quencer KB, Friedman T, Sheth R, Oklu R. Tumor thrombus: incidence, imaging, prognosis and treatment. Cardiovasc Diagn Ther. 2017;7(Suppl 3):S165–77.

39. Sakata J, Shirai Y, Wakai T, Kaneko K, Nagahashi M, Hatakeyama K. Preoperative predictors of vascular invasion in hepatocellular carcinoma. Eur J Surg Oncol. 2008;34:900–5.
40. Takizawa D, Kakizaki S, Sohara N, et al. Hepatocellular carcinoma with portal vein tumor thrombosis: clinical characteristics, prognosis, and patient survival analysis. Dig Dis Sci. 2007;52:3290–5.
41. Rossi S, Rosa L, Ravetta V, et al. Contrast-enhanced versus conventional and color Doppler sonography for the detection of thrombosis of the portal and hepatic venous systems. AJR Am J Roentgenol. 2006;186:763–73.
42. Tarantino L, Francica G, Sordelli I, et al. Diagnosis of benign and malignant portal vein thrombosis in cirrhotic patients with hepatocellular carcinoma: color Doppler US, contrast-enhanced US, and fine-needle biopsy. Abdom Imaging. 2006;31:537–44.
43. Chammas MC, Oliveira AC, D Ávilla MJ, Moraes PH, Takahashi MS. Characterization of malignant portal vein thrombosis with contrast-enhanced ultrasonography. Ultrasound Med Biol. 2019;45:50–5.
44. Shah ZK, McKernan MG, Hahn PF, Sahani DV. Enhancing and expansile portal vein thrombosis: value in the diagnosis of hepatocellular carcinoma in patients with multiple hepatic lesions. AJR Am J Roentgenol. 2007;188:1320–3.
45. Tublin ME, Dodd GD 3rd, Baron RL. Benign and malignant portal vein thrombosis: differentiation by CT characteristics. AJR Am J Roentgenol. 1997;168:719–23.
46. Matsumoto N, Ogawa M, Abe M, et al. The thread and streaks sign. J Med Ultrason. 2009;36:99–100.
47. Sandrasegaran K, Tahir B, Nutakki K, et al. Usefulness of conventional MRI sequences and diffusion- weighted imaging in differentiating malignant from benign portal vein thrombus in cirrhotic patients. AJR Am J Roentgenol. 2013;201:1211–9.
48. Gawande R, Jalaeian H, Niendorf E, et al. MRI in differentiating malignant versus benign portal vein thrombosis in patients with hepatocellular carcinoma: value of post contrast imaging with subtraction. Eur J Radiol. 2019;118:88–95.
49. Hu S, Zhang J, Cheng C, Liu Q, Sun G, Zuo C. The role of 18F-FDG PET/CT in differentiating malignant from benign portal vein thrombosis. Abdom Imaging. 2014;39:1221–7.

Classification of Non-malignant Portal Vein Thrombosis

5

Matthew J. Stotts and Nicolas M. Intagliata

Abstract

When thrombosis of the portal vein occurs, a wide range of symptoms and clinical consequences can be seen. Management decisions can be especially challenging, as much of the research on portal vein thrombosis (PVT) has been performed on heterogeneous populations of patients, often with varying degrees of underlying liver dysfunction, portal hypertension, and clot burden. In this setting, a standardized classification of PVT is especially appealing. While no universally accepted classification system currently exists, multiple systems have been proposed over the years.

Keywords

Portal vein thrombosis · Thrombosis · Portal vein · Classification · Yerdel

5.1 Introduction

Non-malignant thrombosis of the portal vein can lead to a wide range of presentations and clinical consequences. While some individuals may be completely asymptomatic, others may develop severe abdominal pain in the setting of intestinal ischemia or symptoms related to worsening portal hypertension and synthetic liver dysfunction. When occurring in liver transplant candidates, management strategies range from routine monitoring with serial imaging to performing medical

M. J. Stotts (✉) · N. M. Intagliata
Coagulation in Liver Disease Study Group, Division of Gastroenterology and Hepatology, University of Virginia Medical Center, Charlottesville, VA, USA
e-mail: MS7KZ@hscmail.mcc.virginia.edu; NMI4D@hscmail.mcc.virginia.edu; intagliata@virginia.edu

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_5

interventions in hopes of maintaining portal vein patency, with additional considerations for significant adjustments to surgical technique.

There are multiple potential reasons for this heterogeneity in presentations and clinical implications, as both patient and thrombus characteristics play important roles. Portal vein thrombosis (PVT) can vary in regard to the actual location of thrombus (including if there is extension into the splenic vein and superior mesenteric vein), as well as the overall degree of lumen obstruction and whether or not features of chronicity are present. In addition, patients may have different symptoms and complications of portal hypertension. Given that prognosis and treatment response likely depends on the site, extent, rapidity of development, duration of thrombosis, and stage of liver disease, the "one-size-fits-all" approach for PVT is not appropriate, as the risks and benefits of treatment and transplantation likely vary widely between individuals.

Classically, clinicians classify PVT simply as acute or chronic, which may be an important consideration as more recently developing PVTs likely have higher rates of recanalization with anticoagulant therapy [1]. However, determining the time course in the absence of prior imaging can be very difficult. While cavernous transformation of the portal vein is commonly considered a sign of chronicity, duration from thrombus formation to cavernous transformation can be as little as 6 days [2]. In addition, symptoms often do not correspond to the duration of thrombosis, as the thrombus may occur long before symptoms develop.

In this setting, there is a clear need for classification systems to guide clinicians and researchers in determining the best therapeutic approach for any given patient. Over the last 30 years, multiple attempts to develop such systems have been made, each with relative strengths and limitations (see Table 5.1).

5.2 Classification Systems for PVT

PVT was previously considered a contraindication to transplantation due to concerns regarding appropriate portal inflow [3]. As experiences with transplantation grew, a variety of surgical techniques were described based on the anatomical location of the thrombosis and, in this setting, early classification systems were largely anatomical. Over time, however, attempts were made to incorporate signs of chronicity and functional components in hopes of guiding therapies and understanding prognoses.

5.2.1 Stieber Classification (1991)

In 1991, while PVT was a major technical hurdle to transplantation, Stieber and colleagues published a series of 34 subjects with PVT who were successfully transplanted between April of 1986 and October of 1989 [4]. These individuals underwent intraoperative cannulation of either the ileocolic or the inferior mesenteric vein and a venogram was performed to determine the extent of thrombosis. The thrombosis was then classified as follows:

Table 5.1 Overview of classification systems for portal vein thrombosis

	Stieber (1991)	Nonami (1992)	Gayowski (1996)	Yerdel (2000)	Jamieson (2000)	Charco (2005)	Bauer (2006)	Ma (2014)	Sarin (2016)
Description	*Type A:* segmental involvement of main PV *Type B:* main PV and SMV *Type C*: more extensive, including SV and IMV	*Grade 1*: Intrahepatic PV *Grade 2*: right or left portal branches or bifurcation *Grade 3*: partial obstruction of PV trunk *Grade 4*: complete obstruction of PV trunk	*Grade 1*: partial thrombosis of main PV trunk, residual flow *Grade 2*: complete thrombosis of main PV trunk, not extending to confluence *Grade 3*: complete thrombosis, extending to confluence *Grade 4*: complete thrombosis of main PV trunk, extending below confluence	*Grade 1*: main PV affecting < 50% of lumen, with or without minimal extension to SMV *Grade 2*: main PV affecting > 50% of lumen, with or without minimal extension to SMV *Grade 3*: complete PVT plus extension to proximal SMV *Grade 4*: complete PVT plus complete thrombosis of SMV	*1*: confined to PV beyond confluence (partial or complete) *2*: extending to proximal SMV (with patent vessel in mesentery) *3*: diffuse thrombosis of splanchnic venous system, with large accessible collaterals *4*: Extensive thrombosis of splanchnic venous system, with only fine collaterals	*1*: confined to PV (partial or complete) *2*: extending to proximal SMV (with permeability of confluence) *3*: diffuse thrombosis of splanchnic system, presence of dilated collateral veins *4*: diffuse thrombosis, presence of fine collateral veins	Thrombosis was graded as follows for the portal, mesenteric, and splenic veins separately: *Grade 1*: <25% of lumen occluded *Grade 2*: 26–50% of lumen occluded *Grade 3*: 51–75% of lumen occluded *Grade 4*: 76–100% of lumen occluded	*Type 1*: partial, without cavernoma *Type 2*: partial, with cavernoma *Type 3*: complete, without cavernoma *Type 4*: complete, with cavernoma	*Site*: Type 1: trunk Type 2a: one branch Type 2b: two branches Type 3: trunk and branch *Grade*: O: occlusive NO: non-occlusive *Duration and Presentation*: R: recent Ch: chronic As: asymptomatic S: symptomatic *Extent*: S: SV M: Mesenteric vein SM: both

(continued)

Table 5.1 (continued)

	Stieber (1991)	Nonami (1992)	Gayowski (1996)	Yerdel (2000)	Jamieson (2000)	Charco (2005)	Bauer (2006)	Ma (2014)	Sarin (2016)
Site[a]	X	X	X	X	X	X	X		X
Grade[b]		X	X	X	X	X	X	X	X
Extent[c]	X		X	X	X	X	X		X
Duration[d]								X	X
Symptoms[e]									X
Quantitative Assessment[f]							X		

PV portal vein, *SMV* superior mesenteric vein, *IMV* inferior mesenteric vein, *SV* splenic vein

[a]Site refers to venous segment which is involved by thrombosis

[b]Grade refers to whether the thrombosis is occlusive or non-occlusive

[c]Extent refers to the overall length of the portal venous system affected

[d]Duration refers to if features of chronicity on imaging or by history are accounted for

[e]Symptoms refer to the presence of associated symptoms which may include features associated with portal hypertension

[f]Quantitative assessment refers to if the classification system allowed for a means to quantitatively assess clot burden to potentially allow for monitoring response to interventions

1. Type A: segmental involvement of the main portal vein
2. Type B: involvement of the main portal vein and superior mesenteric vein
3. Type C: more extensive involvement including the splenic vein and inferior mesenteric vein

The authors described various techniques used to treat the different forms of thrombosis encountered and provided an algorithm for surgically managing these patients, including suggestions for when to perform a direct dissection and anastomosis, when to perform a jump graft, and when to manage with declotting and anticoagulation. Given the focus on surgical implications, this classification system was primarily anatomic and only accounted for the site (which venous segment was involved) and extent (the length affected) of thrombosis. It did not account for the grade of thrombosis (i.e., if it was occlusive), the duration of thrombosis, the presence of associated symptoms, or a quantitative measurement of clot burden.

Importantly, this was the first proposed classification system for PVT and the authors of the study provided evidence that individuals with thrombosis in the portal system could be technically transplanted, as their overall survival rate was 67.6% (23 of 34 subjects). Survival did vary by the extent of thrombosis, as those with thrombosis of the portal vein only had a survival rate of 73.9% (17/23), compared to 54.5% (6/11) with more extensive thrombosis.

5.2.2 Nonami Classification (1992)

In an attempt to describe the incidence of PVT in liver transplant recipients (as well as potential risk factors), Nonami and colleagues examined their experiences transplanting 885 patients with end-stage liver disease between 1989 and 1990 [5]. Of these 885 patients, they described 14 patients (1.4%) who had thrombosis of the intrahepatic portal vein branches (defined as grade 1 thrombosis), 27 patients (3.2%) who had thrombosis of the right or left portal branches or at the bifurcation (defined as grade 2 thrombosis), 27 patients (3.2%) who had partial obstruction of the portal vein trunk (defined as grade 3 thrombosis), and 49 patients (5.8%) who had complete obstruction of the portal vein trunk (defined as grade 4 thrombosis). In this large cohort, they showed that a significant proportion of those undergoing transplantation had some degree of PVT (13.8%) and described higher incidences of PVT in those with primary hepatic malignancy, chronic encephalopathy, and refractory ascites.

Similar to its predecessor, this scoring system was primarily anatomic with a focus on surgical implications—specifically if a standard end-to-end portal vein anastomosis was feasible or if additional methods, such as a vein graft (specifically a jump graft or interpositional graft) or thromboembolectomy, may be required. There were no considerations for underlying liver disease, associated symptoms, features of chronicity, or quantitative measurements to assess treatment response. An additional limitation was its focus only on the portal vein without considerations for extension into the splenic vein or superior mesenteric vein.

5.2.3 Gayowski et al. (1996)

In another study, 88 consecutive patients at a Veterans Administration Medical Center were reviewed, 23 of whom had PVT [6]. When comparing those with and without PVT, no association was found between PVT and etiology of underlying liver disease, age, Child–Turcotte–Pugh score, or prior abdominal surgery. The authors did not find differences in patient survival among those with or without PVT, although graft survival was lower (65% vs. 86%) and intraoperative blood loss was higher (median 21 units of PRBCs vs. 14 units) in the cohort with PVT.

PVT was classified according to its surgical implications, as follows:

1. Grade 1—partial thrombosis of the main portal trunk extending to or below the confluence with residual flow
2. Grade 2—complete thrombosis of the main portal trunk, not extending to the confluence of the superior mesenteric and splenic veins
3. Grade 3—complete thrombosis of the main portal trunk extending to the confluence
4. Grade 4—complete thrombosis of the main portal trunk extending below the confluence

This scoring system was used to determine surgical technique, with thrombectomy and standard end-to-end anastomosis in the 10 patients with grades 1 and 2 thrombosis versus reconstruction with jump grafts or interposition grafts in those with grades 3 and 4 PVT. Similar to its predecessors, this classification system did not account for any features of chronicity, the presence of associated symptoms, or a means to quantitatively measure clot burden.

5.2.4 Yerdel Classification (2000)

Of all the classification systems that have been proposed, perhaps the best known and most widely used one is that proposed by Yerdel and colleagues [7]. In their study, they described 63 operatively confirmed PVT in a series of 779 adult liver transplantations from 1987 to 1996. PVTs were retrospectively graded as follows:

1. Grade 1—thrombus at the main portal vein affecting less than half of the lumen (with or without minimal extension into the superior mesenteric vein)
2. Grade 2—thrombus affecting more than half of the portal vein lumen including complete thrombosis (with or without minimal extension into the superior mesenteric vein)
3. Grade 3—complete PVT plus thrombosis extending to the proximal superior mesenteric vein
4. Grade 4—complete PVT plus complete thrombosis of the superior mesenteric vein

They similarly described the surgical approaches taken, including low dissection and/or thrombectomy for grades 1 and 2, using the distal superior mesenteric vein as an inflow vessel (usually via interposition of donor iliac vein) for grade 3, and a splanchnic tributary or a thrombectomy for grade 4. Given that this classification was also designed to guide management decisions in surgical procedures, it was similar to prior classification systems in that it did not account for features of chronicity, the presence of symptoms, or a means to provide a quantitative measurement of clot burden to monitor treatment response.

Notably, this classification system has been shown to have prognostic value in those undergoing liver transplantation. In the initial study, the authors noted that those with grade 1 PVT had similar survival compared to controls (5-year patient survival of 86%), whereas those with grades 2, 3, and 4 PVT had reduced survival. In a subsequent meta-analysis, pooled data from ten studies reported that 30-day mortality was higher in those with grade 4 thrombosis [8].

5.2.5 Jamieson Classification (2000)

In the same year, an additional classification attempted to describe PVT from a practical viewpoint, specifically describing cases based on anatomical locations and their surgical implications [9]. Cases were broken down based on features including thrombosis confined to the portal vein beyond the splenomesenteric confluence, thrombosis extending into the proximal superior mesenteric vein with a patent vessel in the mesentery, diffuse thrombosis of the splanchnic system with large accessible collaterals, and extensive thrombosis with only fine collaterals. The relevant surgical techniques for each were then described, ranging from thrombectomy to jump graft to multivisceral transplantation.

This classification again focused on anatomical considerations and the associated surgical implications. While it did account for the site, grade, and extent of thrombosis, it was similar to prior scoring systems in that it did not consider any features of chronicity, the presence of associated symptoms, or a means to quantitatively measure the clot burden for monitoring treatment response.

5.2.6 Charco et al. (2005)

In a review on PVT in the setting of liver transplantation, authors similarly suggested that PVT could be classified practically to guide surgical management [10]. In it, they proposed a similar PVT classification, as follows:

1. Thrombosis confined to the portal vein (partial or complete)
2. Thrombosis extending to the proximal portion of the superior mesenteric vein with permeability of the mesenteric confluence
3. Diffuse thrombosis of the splanchnic system (with dilated collaterals)
4. Diffuse thrombosis with the presence of fine collateral veins

While accounting for the site, grade, and extent of thrombosis, this classification system was again designed to direct surgical interventions and did not account for features of chronicity, the presence of symptoms, or a means to quantitatively measure clot burden.

5.2.7 Bauer et al. (2006)

In an attempt to study the efficacy and clinical outcomes of transjugular intrahepatic shunt (TIPS) in individuals with PVT and cirrhosis eligible for liver transplantation, nine consecutive patients undergoing elective TIPS to maintain portal vein patency prior to transplantation were described [11]. The authors described successful placement of TIPS in all nine patients without complication, with eight of the nine patients having improvement in thrombosis at follow-up. To determine treatment efficacy, they estimated clot burden in the portal, mesenteric, and splenic veins at the time of their procedure as well as at follow-up, grading thrombosis in each segment as follows:

1. Grade I: less than 25% of lumen occluded
2. Grade II: 26–50% of lumen occluded
3. Grade III: 51–75% of lumen occluded
4. Grade IV: 76–100% of lumen occluded

While this classification system did not consider the presence of underlying symptoms and was limited by difficulties precisely determining the degree of occlusion, it was unique in that it provided a means to quantitatively measure clot burden, allowing for therapeutic monitoring.

5.2.8 Ma et al. (2014)

In a cohort of 60 patients (24 of whom had cirrhosis), researchers from China attempted to classify PVT using contrast-enhanced computed tomography over a 7-year period from 2005 to 2012 [12]. Two radiologists reviewed images to evaluate the location of thrombus and the presence of portal cavernoma and, using an image analysis program, determined the degree of occlusion of the portal vein, superior mesenteric vein, and splenic vein. Thrombosis was defined as complete when it reached 90% of the area of the vein lumen at the point of maximum thrombosis. They then suggested a classification based on the presence of cavernous transformation and complete thrombosis, as follows:

1. Type I—partial PVT without cavernoma
2. Type II—partial PVT with cavernoma
3. Type III—complete PVT without cavernoma
4. Type IV—complete PVT with cavernoma

In it, the authors highlight the rationality of this classification system, including the absence of ambiguous variables (such as pain) and potentially allowing easier treatment considerations based on classification. While the study did consider quantitative measurements for the burden of thrombosis, the final proposed classification system did not include the presence of symptoms, whether the thrombosis extended into other venous segments, or specific parameters quantifying the burden of thrombosis beyond complete or partial.

5.2.9 Sarin et al. (2016)

In the setting of the lack of a universally accepted classification system for PVT in cirrhosis, Sarin and colleagues published an editorial that aimed to provide a classification system assessing both the structural and functional components of thrombosis [13]. They argued for the importance of considering the precise clinical context whenever PVT occurs, including considerations for the anatomical location of the thrombosis as well as the underlying liver disease, the associated symptoms, and the duration of thrombosis.

In this setting, the authors proposed a comprehensive scoring system. They recommended the following classifications regarding the *site* of PVT:

1. Type 1—only the trunk
2. Type 2a—only one branch
3. Type 2b—two branches
4. Type 3—the trunk and branches

Regarding the *degree* of portal venous system occlusion, they recommended the following:

1. O—occlusive
2. NO—non-occlusive with flow visible on imaging

For the *duration* and *presentation*, thrombosis was classified as:

1. R—recent (described as asymptomatic and symptomatic)
2. Ch—chronic (described as asymptomatic and symptomatic)
3. S—symptomatic
4. As—asymptomatic

And regarding the *extent* of portal vein system occlusion, they recommended the following:

1. S—splenic vein
2. M—mesenteric vein
3. SM—both

In addition, they recommended describing the type and presence of underlying liver disease, including individuals with cirrhosis or non-cirrhotic liver disease, those who had previously undergone liver transplantation, and those with hepatocellular carcinoma.

While this proposed classification is likely more burdensome than many of the prior ones described, it is unique in that it accounts for both patient and thrombus characteristics and could potentially allow both clinicians and researchers to classify patients more uniformly. By doing so, it offers the potential for recruiting homogenous groups of patients which could ultimately allow an improved understanding of natural histories and treatment efficacies.

5.3 Conclusion

Over the last 30 years, multiple classification systems for PVT have been proposed, ranging from primarily anatomical systems to guide surgical management (Stieber, Nonami, Gayowski, Yerdel, Jamieson, Charco), to ones quantifying the proportion of lumen obstructed to determine treatment response (Bauer, Ma), to a much more comprehensive system evaluating both functional and anatomical components of thrombosis (Sarin). Given the heterogeneity of presentations and clinical consequences, there is a clear need to determine the natural history of PVT and the risks and benefits of potential therapies in different subpopulations of patients. With improvements in imaging modalities (including computed tomography or magnetic resonance angiography), clinicians and researchers may have opportunities to quantify the volume of PVT (and of the remaining lumen) in specific patients, potentially allowing assessment of treatment response and limiting the need to strictly classify patients. To date, there is no universally accepted classification system or strategy to quantify thrombosis that is widely used in clinical practice.

References

1. Plessier A, Darwish-Murad S, Hernandez-Guerra M, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology. 2010;51(1):210–8.
2. De Gaetano AM, Lafortune M, Patriquin H, De Franco A, Aubin B, Paradis K. Cavernous transformation of the portal vein: patterns of intrahepatic and splanchnic collateral circulation detected with Doppler sonography. AJR Am J Roentgenol. 1995;165(5):1151–5.
3. Van Thiel DH, Schade RR, Starzl TE, et al. Liver transplantation in adults. Hepatology. 1982;2(5):637–40.
4. Stieber AC, Zetti G, Todo S, et al. The spectrum of portal vein thrombosis in liver transplantation. Ann Surg. 1991;213(3):199–206.
5. Nonami T, Yokoyama I, Iwatsuki S, Starzl TE. The incidence of portal vein thrombosis at liver transplantation. Hepatology. 1992;16(5):1195–8.
6. Gayowski TJ, Marino IR, Doyle HR, et al. A high incidence of native portal vein thrombosis in veterans undergoing liver transplantation. J Surg Res. 1996;60(2):333–8.

7. Yerdel MA, Gunson B, Mirza D, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. Transplantation. 2000;69(9):1873–81.
8. Zanetto A, Rodriguez-Kastro KI, Germani G, et al. Mortality in liver transplant recipients with portal vein thrombosis—an updated meta-analysis. Transpl Int. 2018;31(12):1318–29.
9. Jamieson NV. Changing perspectives in portal vein thrombosis and liver transplantation. Transplantation. 2000;69(9):1772–4.
10. Charco R, Fuster J, Fondevila C, Ferrer J, Mans E, García-Valdecasas JC. Portal vein thrombosis in liver transplantation. Transplant Proc. 2005;37(9):3904–5.
11. Bauer J, Johnson S, Durham J, et al. The role of TIPS for portal vein patency in liver transplant patients with portal vein thrombosis. Liver Transpl. 2006;12(10):1544–51.
12. Ma J, Yan Z, Luo J, Liu Q, Wang J, Qiu S. Rational classification of portal vein thrombosis and its clinical significance. PLoS One. 2014;9(11):e112501.
13. Sarin SK, Philips CA, Kamath PS, et al. Toward a comprehensive new classification of portal vein thrombosis in patients with cirrhosis. Gastroenterology. 2016;151(4):574–577.e573.

Impact of Non-malignant Portal Vein Thrombosis on Outcomes of Liver Cirrhosis

6

Hajime Takatori, Takehiro Hayashi, Hidetoshi Nakagawa, and Shuichi Kaneko

Abstract

Portal vein thrombosis (PVT) is usually associated with cirrhosis with reduced hepatic reserve. PVT sometimes has a natural history of spontaneous disappearance or shrinkage, but in other cases, PVT volume increases and portal vein blood flow is impaired, which reduces hepatic reserve causing portal hypertension, increased ascites, variceal exacerbation, and bleeding. Prognosis often does not differ between cases with and without PVT. In patients awaiting liver transplantation, the consensus recommendation for PVT is anticoagulant therapy, given that thrombus affects outcome and prognosis post-transplantation. Prophylactic low molecular weight heparin may prevent complicating PVT in patients with cirrhosis and delaying the progression to liver failure. However, it is not clear whether PVT affects prognosis directly. In terms of the effects of PVT on varicose veins (e.g., in the esophagus), variceal bleeding may occur and endoscopic treatment takes time. Thus, prevention and treatment of PVT may improve prognosis in patients with cirrhosis. Large-scale prospective studies of PVT and treatment are needed to clarify the types and effects of PVT on liver cirrhosis prognosis and identify good treatment targets.

Keywords

Portal vein thrombosis · Liver failure · Ascites · Esophageal varices · Liver decompensation · Anticoagulant therapy · Prognosis

H. Takatori (✉) · T. Hayashi · H. Nakagawa · S. Kaneko
Department of Gastroenterology, Kanazawa University, Kanazawa, Japan
e-mail: takatori@m-kanazawa.jp

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_6

6.1 Impact of Portal Vein Thrombosis on Liver Decompensation and Prognosis

The appearance of portal vein thrombosis (PVT) is typically caused by three factors that may contribute to the progression of liver cirrhosis: stagnation of portal vein blood flow due to liver cirrhosis, abnormalities of various coagulation factors, and vascular endothelial damage. Alternatively, the appearance of thrombus may be a result of advanced liver cirrhosis or abnormal portal vein blood flow.

In Case 1, contrast-enhanced computed tomography (CECT) showed the appearance of PVT incidentally. There were no subjective symptoms, ascites, or changes in Child-Pugh score. The PVT disappeared after a short period of anticoagulant therapy (Fig. 6.1).

Case 2 was a patient with alcoholic liver cirrhosis and rupture of esophageal varices 1 year after endoscopic variceal ligation (EVL). CECT at that time revealed the appearance of PVT for the first time. At the same time, an increase in ascites was observed clinically. After hemostasis of the varicose vein, anticoagulant therapy was instituted, following which the PVT disappeared and ascites decreased (Fig. 6.2).

In Case 3, PVT was initially reduced following anticoagulant therapy, but the therapy was discontinued due to abnormal bleeding. Three years later, cavernous transformation occurred, pleural effusion and ascites worsened, and liver failure progressed (Fig. 6.3).

It can be seen then that the clinical course of PVT varies from case to case, and short-term observation of individual cases cannot conclusively determine whether PVT worsens the prognosis of liver cirrhosis. It is also unclear in the long term whether the appearance of PVT associated with advanced liver cirrhosis markedly influences the natural course of liver cirrhosis or whether it is itself the result of advanced liver cirrhosis. Opinions vary as to whether or not PVT affects the clinical course.

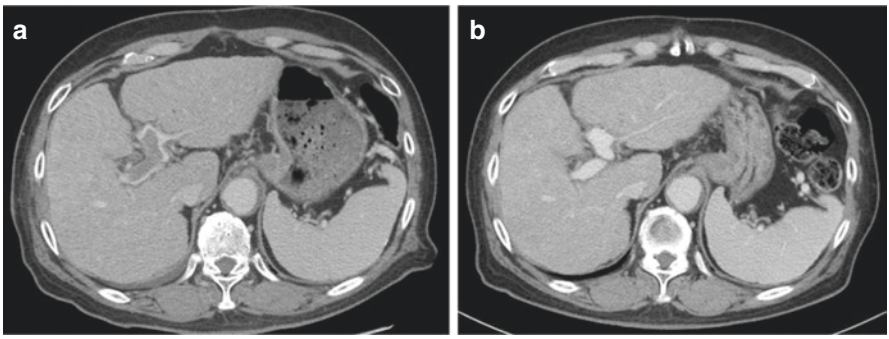

Fig. 6.1 (**a**) Thrombus first appeared from the portal vein extending to the intrahepatic portal vein, but with no ascites or subjective symptoms. (**b**) This resolved with anticoagulant therapy after 2 weeks

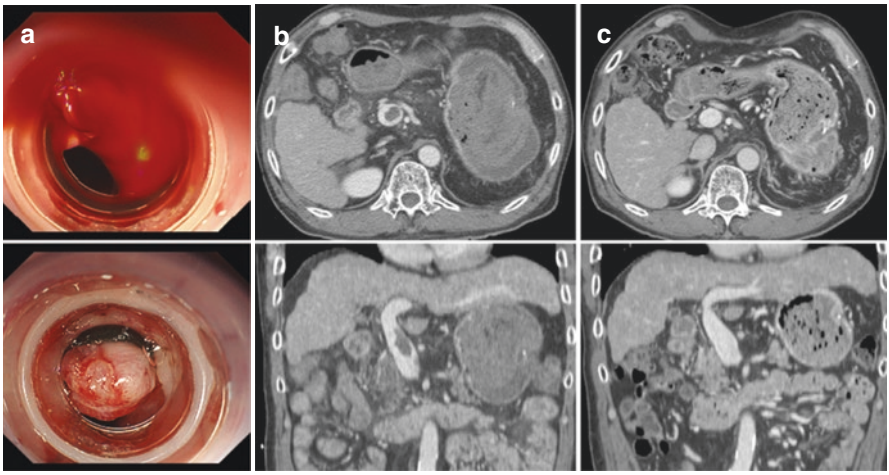

Fig. 6.2 (**a**) Ruptured esophageal varices, with bleeding stopped with ligation. (**b**) Thrombus in the main portal vein. (**c**) Decreased ascites after the thrombus disappeared

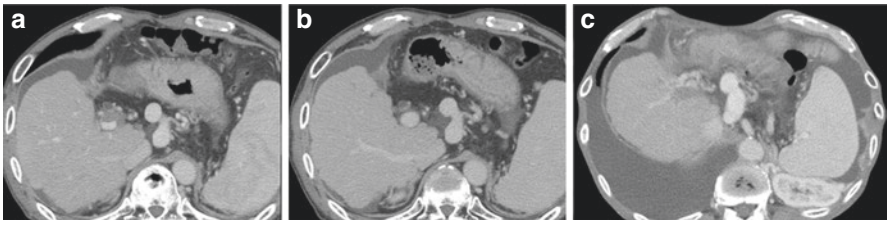

Fig. 6.3 (**a**) Thrombus on initial appearance in the main trunk of the portal vein. (**b**) Thrombus disappeared after 3 months following anticoagulant therapy; (**c**) 3 years after anticoagulant therapy was discontinued due to abnormal bleeding, collateral circulation developed with evidence of pleural effusion and ascites

To clarify this issue, a prospective study was conducted in which 1243 cases of liver cirrhosis were thoroughly observed for about 4 years using Doppler ultrasound to detect the appearance of PVT and progression of liver disease. In total, 118 subjects had newly developed PVT, and the 5-year cumulative incidence was 10.7%. Seventeen developed completely obstructive PVT, and 14 progressed from partial thrombosis to complete obstruction. Eighty-seven were non-obstructive and partial thrombosis, which disappeared in 70% of cases at follow-up. Progression of liver disease was observed in 52 of the 118 cases, while exacerbation occurred before the appearance of thrombus in 23 cases. Conversely, the thrombus appeared at the same time in five cases, and exacerbation occurred after the appearance of the thrombus in 24 cases. It was concluded that progression of liver disease was independently associated with baseline age, body mass index, prothrombin time, serum albumin, and esophageal varices, but not PVT [1]. In a study of 150 patients with viral hepatitis associated with cirrhosis followed up using Doppler ultrasonography, 42 (28%)

developed PVT, with a cumulative incidence of 12.8% per year and 20% in 5 years [2]. Thrombosis progressed in 7.2%, remained unchanged in 45.2%, and improved spontaneously in 47.6%. Cumulative survival rates were similar between the thrombotic and non-thrombotic groups. In a study of 42 patients with untreated partial extrahepatic PVT associated with cirrhosis and followed for an average of 27 months, PVT worsened in 48% of patients and improved in 45% [3]. There was no clear association between PVT progression and clinical outcome, and the baseline Child-Pugh score was the only independent predictor of survival or liver decompensation.

In each of these prospective observational studies, PVT was noted in some of the patients with cirrhosis. It has become clear that the volume of thrombus does not always increase; it may spontaneously shrink in some cases. In addition, individual studies concluded that the appearance of thrombus did not influence prognosis in patients with cirrhosis, and baseline liver reserve was associated with more advanced cirrhosis. Thus, PVT is believed to be the result, not the cause, of liver failure progression.

Conversely, the results of a meta-analysis involving 2436 cases in three studies reported that PVT was significantly associated with both mortality and decompensated ascites (Fig. 6.4) [4].

In the pathology of PVT, the original portal vein blood flow is finally occluded and collateral blood circulation, such as cavernous transformation, develops in cases where the lesion is partial (mural) and then disappears spontaneously. Previous studies include such cases, so the thrombus does not affect portal blood flow and cirrhosis to the same extent in all cases. As such, no unifying conclusions can be drawn from these studies.

In an interesting randomized controlled trial that examined the effectiveness of prophylactic anticoagulant therapy for primary prevention of PVT in patients with cirrhosis, the results suggest that the appearance of thrombus contributes to progression of cirrhosis [5]. Patients with cirrhosis with Child-Pugh scores 7–10 were randomly assigned to a treatment group ($n = 34$) administered the low molecular weight heparin enoxaparin twice daily for 48 weeks or an untreated control group ($n = 36$). The incidence of PVT was significantly lower in the enoxaparin group than in the control group, at 0% vs. 16.6% at 48 weeks, 0% vs. 27.7% at 96 weeks, and 8.8% vs. 27.7% at 192 weeks, respectively. The decompensation rate was 11.7% in the enoxaparin group and 59.4% in the control group, and the survival rate was also

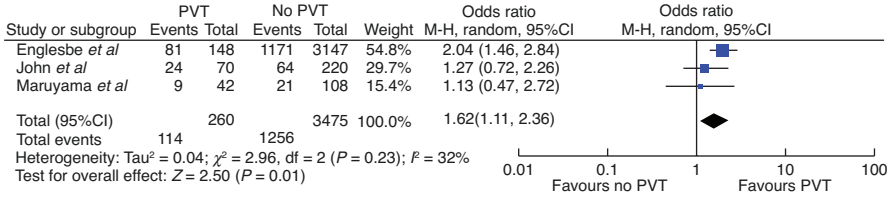

Fig. 6.4 PVT and mortality. PVT is associated with an increased pooled risk of death in the absence of significant heterogeneity. (Reproduced from [4])

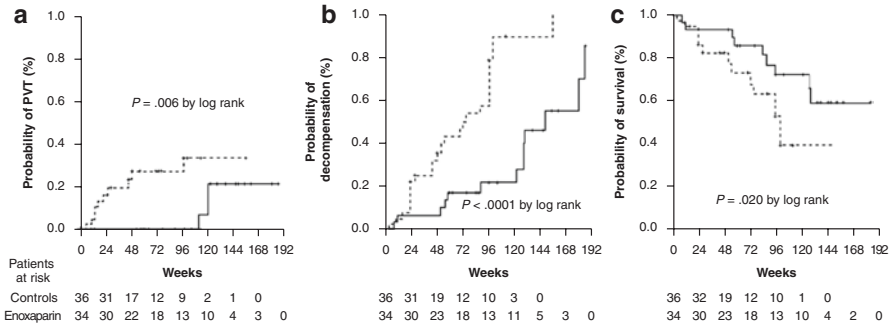

Fig. 6.5 Actuarial probability of developing PVT or hepatic decompensation, and probability of survival according to treatment group. Probability of remaining free from (**a**) PVT and (**b**) hepatic decompensation, and (**c**) probability of survival. Dashed line: controls; continuous line: enoxaparin-treated patients. (Reproduced from [5])

excellent in the enoxaparin group (Fig. 6.5). This study clarified that in patients with advanced liver cirrhosis, the absence of PVT had a better effect on delaying progression to liver failure and prognosis, even after short-term observation. However, the authors of the study hypothesized that differences in liver decompensation were not solely due to PVT, and that enoxaparin administration contributed to improved intestinal microcirculation and enterocytic damage, leading to reduced bacterial translocation. Whatever the cause, the fact that anticoagulant therapy prevented PVT, resulting in improved prognosis, had a major impact on subsequent treatment of PVT.

Thus, prognosis for all cases with PVT was not necessarily worse than for those without PVT. However, it was confirmed that the appearance of PVT is associated with poor prognosis of liver cirrhosis. Therefore, a larger and more detailed clinical study is required to clarify the type of PVT cases that carries a poor prognosis.

6.2 Impact of PVT on Liver Cirrhosis-Related Complications

Esophagogastric varices are a typical complication of cirrhosis, and ruptured varicose veins have a prognostic impact. The presence of PVT is thought to increase portosystemic shunt flow and worsen varices. Because the bleeding rate from varices is higher when cirrhosis is complicated by PVT than when it is not, it is recommended that esophageal varices be evaluated by endoscopy [6]. In a meta-analysis by Loffredo et al. [7], four studies involving 158 patients showed significantly lower variceal bleeding rates in patients receiving anticoagulants for PVT than in controls, suggesting that the presence of thrombus may cause bleeding varicose veins (Fig. 6.6c). Regarding the outcomes of treating varices associated with PVT, a retrospective study examined the effect of endoscopic varicose vein ligation (EVL) [8]. Twenty-two cases of thrombosis required 50.9 days for varices to disappear, which was longer than the 43.4 days in cases without thrombosis. This suggests that

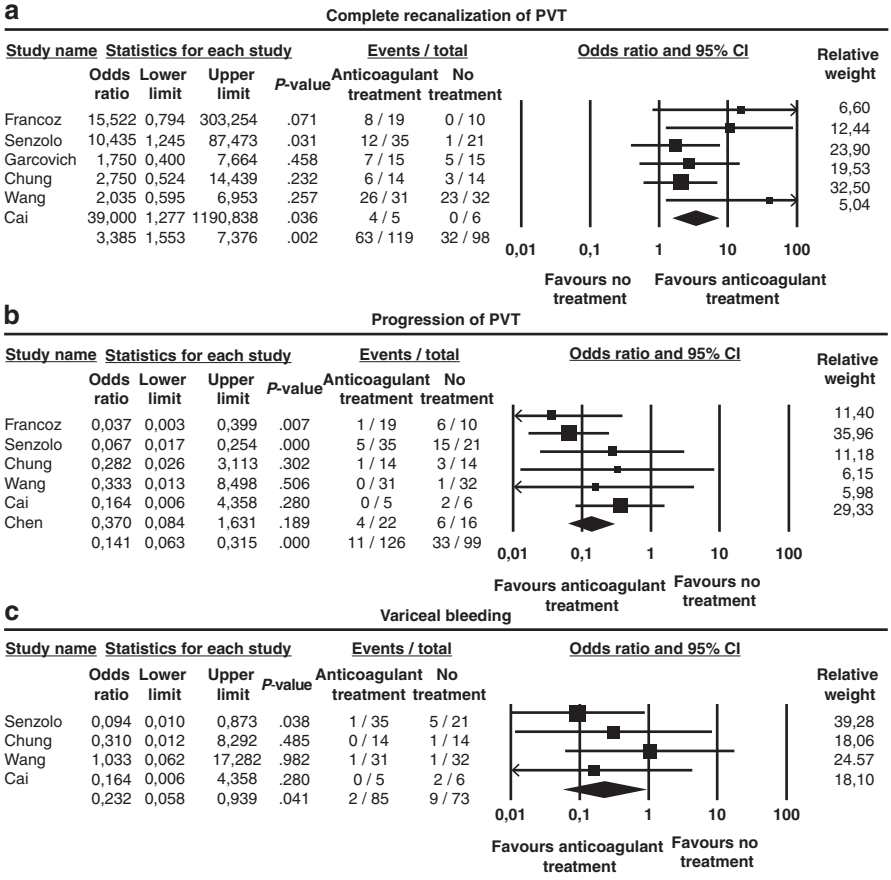

Fig. 6.6 (**a**) Meta-analysis of studies investigating complete recanalization of PVT according to anticoagulant treatment. (**b**) Meta-analysis of studies investigating progression of PVT according to anticoagulant treatment. (**c**) Meta-analysis of studies investigating variceal bleeding according to anticoagulant treatment. (Reproduced from [7])

EVL has no effect on recurrence of varices and can be performed without problems in patients with PVT.

Intestinal infarction is a rare complication associated with PVT, but it should be noted that it presents with serious symptoms. The occurrence of infarction is thought to be associated with complete occlusion of venous outflow and the contraction and occlusion of reflex arteries, in which the mesenteric arch does not function as a collateral pathway [9]. Many prospective studies of PVT do not report on the development of intestinal infarction. In a multicenter retrospective study that followed 173 cases of PVT for 2.5 years, intestinal ischemia or infarction led to intestinal resection in 3% of cases [10]. However, in this study, the majority of cases did not have liver disease, so intestinal infarction may occur less frequently in cases of liver cirrhosis. When symptoms of abdominal pain and diarrhea are observed in a case of

PVT, it is necessary to evaluate intestinal blood flow using CECT. Special attention should be paid to cases of thrombosis that progress to rapid and complete obstruction or to cases of thrombosis in the distal mesenteric vein. In addition, because intestinal ischemia is a pathological condition with poor prognosis leading to multiple organ failure, patients with a history of intestinal ischemia may be eligible for continuous anticoagulation therapy [9, 11].

6.3 Impact of PVT on Liver Transplantation

Liver transplantation is an effective treatment for cirrhosis, but its outcome can be adversely affected by PVT, and in this respect the prognosis of liver cirrhosis can also be affected. A retrospective study of liver transplant cases from 2002 to 2013 found that 3321 out of 48,570 initial liver transplants, PVT occurred in 6.8%. Complications of PVT were independently associated with 90-day mortality as well as age and Model For End-stage Liver Disease score. PVT was also associated with graft failure after transplantation (Fig. 6.7). The presence of PVT was not associated with reduced transplant rates or death from exclusion from the transplant list. There were many cases in which PVT was confirmed for the first time during liver transplantation, and other cases in which thrombosis appeared during the waiting period. Fatty liver, obesity, diabetes, and ascites were risk factors for PVT during the waiting period [12]. In a meta-analysis of 44 studies on PVT and prognosis after liver transplantation, of 98,257 liver transplants, PVT occurred in 7257 (7.3%). The mortality rate at 30 days post-transplantation was 13% in patients with thrombosis and they had a poorer prognosis than the 7% of patients with no thrombosis. The mortality rate after 1 year was also similar; 13.5% of patients had thrombosis and a poorer prognosis than 9.9% with no thrombosis. Also, patients with complete thrombosis

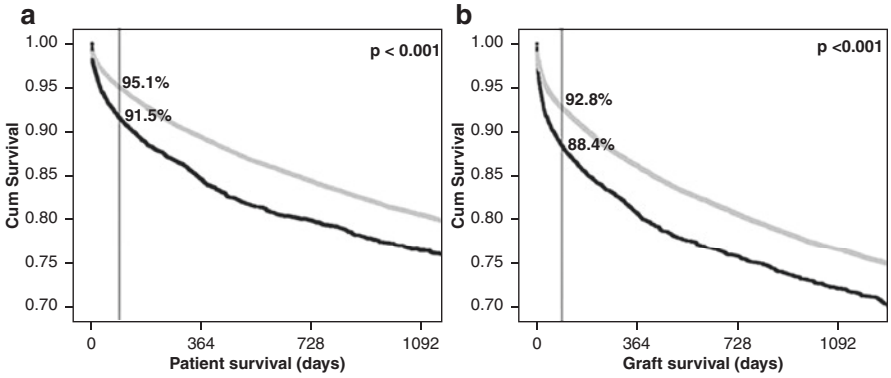

Fig. 6.7 Kaplan-Meier curves for (**a**) patient and (**b**) graft survival after liver transplantation in patients with PVT (*black line*) and without PVT (*gray line*), comparisons performed using the log-rank test. Vertical lines correspond to the 90-day timepoint after liver transplantation. (Reproduced from [12])

had significantly worse prognosis than those with partial thrombosis, especially in relation to the 30-day mortality rate [13]. The EASL guidelines recommend anticoagulant therapy for PVT while liver transplant candidates await transplantation [11].

In order to prevent deterioration of liver transplantation outcomes due to PVT, it is necessary to establish measures against PVT while awaiting transplantation.

6.4 Effect of PVT Therapy on Liver Cirrhosis

There is still no clear evidence for the prognostic impact of treating PVT and its treatment remains controversial. Historically, evidence for the management of PVT in cirrhosis is of relatively poor quality, so there is urgent need for high levels of evidence for using high-risk anticoagulant therapy [14].

Therefore, while guidelines encourage consideration of anticoagulant therapy for cases awaiting liver transplantation and those with a history of bowel infarction, other treatment strategies and methods for PVT are still under discussion. The results of relatively small studies of anticoagulant therapies, such as warfarin and heparin and low molecular weight heparin, are well documented. In a meta-analysis of 353 cases included in eight studies comparing untreated and anticoagulant-treated cases, recanalization rates were 42% in the untreated group and 71% in the treated group, which was also complete recanalization [7]. The recanalization rate was also higher in the treatment group, at 53% compared with 33% in the untreated group (Fig. 6.6a, b). It has also been reported that there is no significant increase in hemorrhagic complications.

A study on the prevention of PVT with the anticoagulant enoxaparin was shown to yield good results in terms of hepatic reserve and prognosis [5]. However, the impact of treatment for evolving PVT on prognosis remains unclear. We investigated therapeutic efficacy and prognosis in 52 cases (Child-Pugh classification: A:13, B:25, C:14) who were administered with the low molecular weight heparin danaparoid sodium for 14 days [15]. Danaparoid sodium catalyzes inactivation of factors Xa (FXa) and thrombin. The volume of PVT was measured by CECT before and after treatment, and cases in which the volume was reduced by 75% or more compared with that before treatment were designated effective. PVT volume was significantly decreased from 6.1 ± 8.9 mL to 2.5 ± 7.4 mL; effective cases comprised 53.8%. In patients with low blood antithrombin (AT) activity, the effective rate was increased by increasing AT activity to 70% or more by combining AT preparations with danaparoid sodium. In all 52 cases, better prognosis was seen in Child-Pugh class A cases than in Child-Pugh class B and C cases. When limited to 39 cases of Child-Pugh class B and C, prognosis in the effective cases was 2262 days, which was significantly better than the 818 days in the non-effective cases (Fig. 6.8).

The therapeutic effect was an independent prognostic factor that was not affected by HCC, and no hemorrhagic complications were observed. Similarly, in 90 patients who used danaparoid sodium (Child-Pugh score 5–12 points, median 7 points), the 1-year survival rate was 83% and the 3-year survival rate was 60% [16]. Prognosis was significantly better in patients who achieved

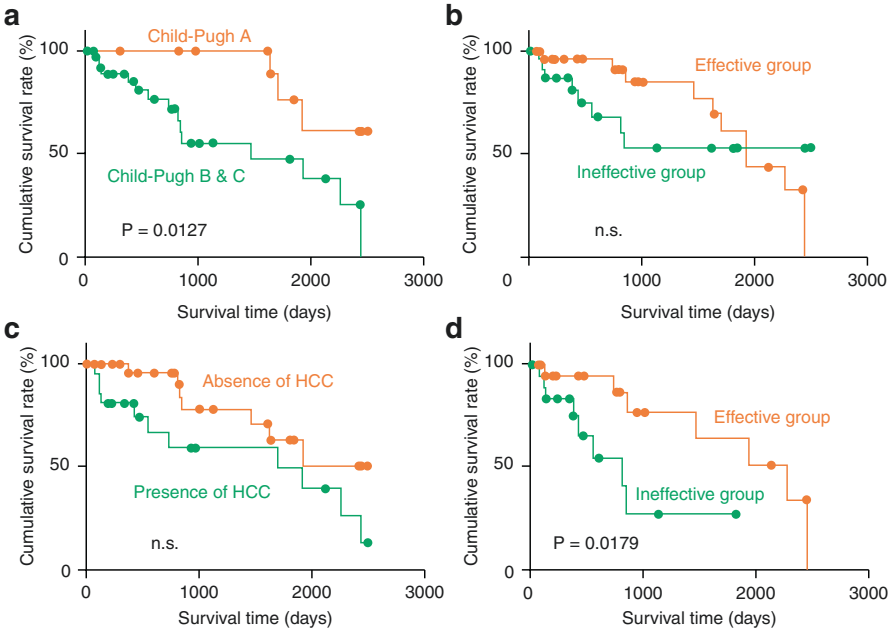

Fig. 6.8 Prognosis of cirrhosis patients with PVT. (**a**) Comparison by hepatic reserve capacity: patients with compensated cirrhosis (Child-Pugh class A, $n = 13$) show significantly better prognosis than those with decompensated cirrhosis (Child-Pugh class B and C, $n = 39$; $P = 0.0127$). (**b**) Comparison by treatment effect: no significant difference is seen between the effective group ($n = 28$) and ineffective group ($n = 24$; $P = 0.7128$). (**c**) Comparison by presence of hepatocellular carcinoma (HCC): no significant difference is seen between presence of HCC ($n = 21$) and absence of HCC ($n = 31$; $P = 0.0618$). (**d**) Comparison by treatment effect in Child-Pugh class B and C decompensated cirrhosis: effective group ($n = 20$) shows significantly better prognosis than ineffective group ($n = 19$; $P = 0.0179$). (Reproduced from [15])

complete disappearance of PVT due to treatment compared to partial responders or non-responders. Prognosis was good for patients without HCC. Recently, the results on the use of direct oral anticoagulants (DOACs) have begun to be reported. Edoxaban, which is a DOAC, has the effect of inhibiting FXa similarly to danaparoid sodium, but it does not require AT. When either warfarin or edoxaban was given as maintenance therapy for 6 months after induction therapy with danaparoid sodium, edoxaban was superior to warfarin in reducing thrombosis [17]. On the other hand, hemorrhagic complications were observed in 15% of edoxaban users and 7% of warfarin users.

Although retrospective in design, the results showed that the better the thrombosis reducing effect, the better the prognosis of patients with PVT. On the other hand, it must be recognized that anticoagulant therapy given with the aim of improving prognosis can pose a risk of worsening prognosis. Large-scale randomized controlled trials are needed to determine whether treatment of PVT can really improve prognosis and which cases are good candidates for treatment.

6.5 Conclusions

In this chapter, we have discussed the effects of PVT on the clinical course and prognosis of liver cirrhosis. In some cases of PVT, the thrombus is partial and asymptomatic, spontaneously disappears, and has no significant effect on short-term prognosis. Conversely, in many cases after the appearance of PVT, ascites increases, variceal bleeding ensues, and liver failure progresses, resulting in poor prognosis. Differences in the course of PVT are thought to result from differences in the balance and severity of the three factors (i.e., portal vein blood flow stagnation, abnormal coagulation factors, and vascular endothelial damage). Shrinkage of PVT after anticoagulant therapies well correlates with favorable prognosis. Although prevention of PVT by anticoagulants may benefit cirrhosis patients *(by improving intestinal microcirculation and inhibiting bacterial translocation)*, it is unrealistic to target all cases of cirrhosis. Future large-scale, long-term prospective studies should clarify the impact of PVT on cirrhosis and when and what therapeutic intervention is safe and effective.

References

1. Nery F, Chevret S, Condat B, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015;61(2):660–7.
2. Maruyama H, Okugawa H, Takahashi M, et al. De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. Am J Gastroenterol. 2013;108(4):568–74.
3. Luca A, Caruso S, Milazzo M, et al. Natural course of extrahepatic nonmalignant partial portal vein thrombosis in patients with cirrhosis. Radiology. 2012;265(1):124–32.
4. Stine JG, Shah PM, Cornella SL, et al. Portal vein thrombosis, mortality and hepatic decompensation in patients with cirrhosis: a meta-analysis. World J Hepatol. 2015;7(27):2774–80.
5. Villa E, Cammà C, Marietta M, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012;143(5):1253–60.
6. Tsochatzis EA, Senzolo M, Germani G, et al. Systematic review: portal vein thrombosis in cirrhosis. Aliment Pharmacol Ther. 2010;31(3):366–74.
7. Loffredo L, Pastori D, Farcomeni A, et al. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. Gastroenterology. 2017;153(2):480–7.
8. Dell'Era A, Iannuzzi F, Fabris FM, et al. Impact of portal vein thrombosis on the efficacy of endoscopic variceal band ligation. Dig Liver Dis. 2014;46(2):152–6.
9. DeLeve LD, Valla DC, Garcia-Tsao G. Vascular disorders of the liver. Hepatology. 2009;49(5):1729–64.
10. Rajani R, Björnsson E, Bergquist A. The epidemiology and clinical features of portal vein thrombosis: a multicentre study. Aliment Pharmacol Ther. 2010;32(9):1154–62.
11. European Association for the Study of the Liver. EASL clinical practice guidelines: vascular diseases of the liver. J Hepatol. 2016;64(1):179–202.
12. Ghabril M, Agarwal S, Lacerda M, et al. Portal vein thrombosis is a risk factor for poor early outcomes after liver transplantation: Analysis of risk factors and outcomes for portal vein thrombosis in waitlisted patients. Transplantation. 2016;100(1):126–33.
13. Zanetto A, Rodriguez-Kastro KI, Germani G, et al. Mortality in liver transplant recipients with portal vein thrombosis—an updated meta-analysis. Transpl Int. 2018;31(12):1318–29.
14. Qi X, Han G, Fan D. Management of portal vein thrombosis in liver cirrhosis. Nat Rev Gastroenterol Hepatol. 2014;11(7):435–46.

15. Hayashi T, Takatori H, Horii R, et al. Danaparoid sodium-based anticoagulation therapy for portal vein thrombosis in cirrhosis patients. BMC Gastroenterol. 2019;19(1):217. https://doi.org/10.1186/s12876-019-1140-8.
16. Fujiyama S, Saitoh S, Kawamura Y, et al. Portal vein thrombosis in liver cirrhosis: incidence, management, and outcome. BMC Gastroenterol. 2017;17(1):112. https://doi.org/10.1186/s12876-017-0668-8.
17. Nagaoki Y, Aikata H, Daijyo K, et al. Efficacy and safety of edoxaban for treatment of portal vein thrombosis following danaparoid sodium in patients with liver cirrhosis. Hepatol Res. 2018;48(1):51–8. https://doi.org/10.1111/hepr.12895.

Anticoagulation for Nontumoral Portal Vein Thrombosis

7

Carlos Noronha Ferreira

Abstract

The development of portal vein thrombosis (PVT) is explained by Virchows triad which includes genetic and acquired prothrombotic factors, a decrease in the velocity of blood flow and alteration in the endothelium of the portal vein.

Acquired or genetic systemic thrombophilic factors are identified in nearly 60–70% of patients with noncirrhotic PVT and local factors in 30–40%. It is now clear that patients with cirrhosis, specially those with decompensated cirrhosis (Child-Pugh class B and C), have a prothrombotic tendency. Acute PVT usually presents with abdominal or lumbar pain of sudden onset but may be paucisymptomatic or an incidental finding in partial thrombosis, which is often the case in patients with cirrhosis. There is a trend for earlier recognition of PVT at an acute stage rather than the stage of cavernoma. In patients with chronic PVT, bleeding due to ruptured varices may be the presenting feature.

The aim of anticoagulant therapy in acute PVT is to recanalize obstructed veins and prevent intestinal ischemia. Anticoagulation should be started as soon as possible in both patients with and without cirrhosis who develop nontumoral PVT. In patients with chronic PVT and those with underlying cirrhosis, upper gastrointestinal endoscopy prior to starting anticoagulation should always be performed to screen for large esophageal and/or gastric varices with high risk stigmata for bleeding and adequate prophylaxis of variceal bleeding started if indicated. Vitamin K antagonists and direct oral anticoagulants are both effective in noncirrhotic patients and those with compensated cirrhosis who develop nontumoral PVT. In patients with decompensated cirrhosis, low molecular weight

C. Noronha Ferreira (✉)
Clínica Universitária de Gastrenterologia, Faculdade de Medicina de Lisboa, Serviço de Gastrenterologia e Hepatologia, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal
e-mail: carlosnferreira@hotmail.com

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_7

heparin may be maintained with doses adjusted for thrombocytopenia and concomitant renal failure.

Anticoagulation should not be stopped in patients with genetic or aquired thrombophilic conditions and those with concomitant superior mesenteric vein thrombosis. In patients with cirrhosis and notumoral PVT, anticoagulation should be preferably maintained in those on liver transplant list and should be considered also in those who tolerate anticoagulation without adverse events to avoid rethrombosis.

Keywords

Nontumoral portal vein thrombosis · Portal cavernoma · Anticoagulation
Cirrhosis · Noncirrhotic · Varices · Bleeding

7.1 Introduction

The pathophysiology of portal vein thrombosis (PVT) is explained by Virchows triad which is characterized by alteration in the endothelium of the portal vein, genetic and acquired prothrombotic factors and a decrease in the velocity of blood [1–3].

An acquired or genetic systemic thrombophilic factor is identified in nearly 60–70% of patients with noncirrhotic PVT and local factors in 30–40% [2–4]. Contrary to previously held beliefs, it is now clear that patients with cirrhosis, especially those with decompensated cirrhosis (Child-Pugh class B and C), have a prothrombotic tendency [1, 5, 6]. The severity of cirrhosis and that of portal hypertension as reflected by a history of prior decompensations of cirrhosis and thrombocytopenia predict the development of PVT in cirrhosis [4, 7].

Acute PVT usually presents with abdominal or lumbar pain of sudden onset and in the absence of sepsis, a systemic inflammatory response syndrome (SIRS) may be present [8, 9]. PVT may be paucisymptomatic or an incidental finding in partial thrombosis which is often the case in patients with cirrhosis [4, 8, 9]. There is a trend for earlier recognition of PVT at an acute stage rather than the stage of cavernoma [4]. Rarely, bleeding due to ruptured varices may be the presenting feature in chronic PVT also termed as portal cavernoma [4].

The aim of anticoagulant therapy in acute PVT is to recanalize obstructed veins and prevent intestinal ischemia [4]. The decision for initiating anticoagulation in patients with noncirrhotic acute PVT is usually more straightforward and should be done as soon as the diagnosis is confirmed [10]. However, in patients with cirrhosis who develop PVT, prior to initiating anticoagulation, it is crucial to confirm the diagnosis and rule out tumoral invasion of PVT by hepatocelular carcinoma (HCC) as well as determine the extent and degree of luminal occlusion of the portal vein and involvement of the superior mesenteric (SMV) and splenic veins [3]. Transient and partial PVT in patients with

cirrhosis have been found in majority of patients who develop PVT and this is unlikely to have an impact on blood perfusion of the liver [4, 9].

7.2 Clinical Reality of Anticoagulation in Patients With and Without Cirrhosis

After detection of PVT with abdominal ultrasound, in both patients with and without cirrhosis, cross-sectional imaging with angio CT scan and/or MRI is recommended to determine the extent and degree of luminal occlusion of PVT, detect involvement of the SMV and splenic veins, and exclude HCC as well as detect local factors, such as acute diverticulitis or colon cancer, and features suggestive of noncirrhotic chronic PVT, including collateral circulation, enlarged caudate lobe and atrophic left lateral segment or right liver [3, 8].

Unfortunately, patients often do not receive adequate cross-sectional imaging at diagnosis of PVT due to lack of awareness of the treating physician of the importance of cross-sectional imaging and the fear of renal toxicity due to intravenous iodine based contrasts in patients with advanced cirrhosis and concomitant renal failure [11]. This ultimately results in underestimation of concomitant SMV thrombosis and inadequate baseline evaluation of the extent and degree of luminal occlusion of PVT [11, 12].

7.2.1 Noncirrhotic Nontumoral PVT

In noncirrhotic acute PVT, patients who do not recanalize the portal vein on anticoagulation may develop varices as early as 1 month after initial clinical symptoms, highlighting the importance of early diagnosis and institution of anticoagulation as well as endoscopic screening for varices within 1 year of PVT detection [13]. Successful recanalization of PVT depends on early initiation of anticoagulant therapy, and patients who do not receive anticoagulation are unlikely to develop recanalization [3].

7.2.2 Cirrhotic Nontumoral PVT

In patients with cirrhosis, de novo nontumoral PVT is incidentally detected in one third of the patients and is partial in more than two thirds of patients. In addition, it may be transient and disappear spontaneously in up to 70% of patients [4, 7, 12]. In reality, patients with cirrhosis and those with a prior history of variceal bleeding who develop nontumoral PVT are significantly less likely to receive anticoagulation [11, 12]. This is due to the misconception that these patients are naturally anticoagulated and also due to the belief that there is a higher risk of bleeding on anticoagulation, both of which have been shown to be unfounded [12, 14].

7.3 Indications for Anticoagulation in Nontumoral Portal Vein Thrombosis

Patients with chronic noncirrhotic nontumoral PVT and those with both acute and chronic PVT in the context of underlying cirrhosis, after adequate cross-sectional imaging with CT scan or MRI, should undergo upper gastrointestinal endoscopy to screen for large esophageal and/or gastric varices with high risk stigmata for bleeding and adequate primary or secondary prophylaxis of variceal bleeding either with non-selective beta blockers (NSBB) or endoscopic band ligation (EBL) when indicated [3, 8, 15]. The potential benefits and risks of anticoagulation in patients with and without cirrhosis and nontumoral PVT are shown in Fig. 7.1.

7.3.1 Noncirrhotic Nontumoral PVT

In patients without cirrhosis, PVT can present acutely with or without symptoms or after chronic progression of thrombosis that leads to development of varices due to resulting portal hypertension [3]. In patients with acute or acute on chronic noncirrhotic nontumoral PVT, anticoagulation should be started as soon as possible after adequate cross-sectional imaging studies which confirmed the diagnosis of acute PVT as well as the extent and degree of luminal occlusion, especially in those patients who are symptomatic with abdominal pain and in those with SMV thrombosis due to the risk of small intestinal ischemia [3].

In patients with noncirrhotic nontumoral PVT, anticoagulation is indicated in all patients for at least 6 months, and lifelong in patients with genetic or acquired thrombophilic conditions and in those where the SMV is involved [3].

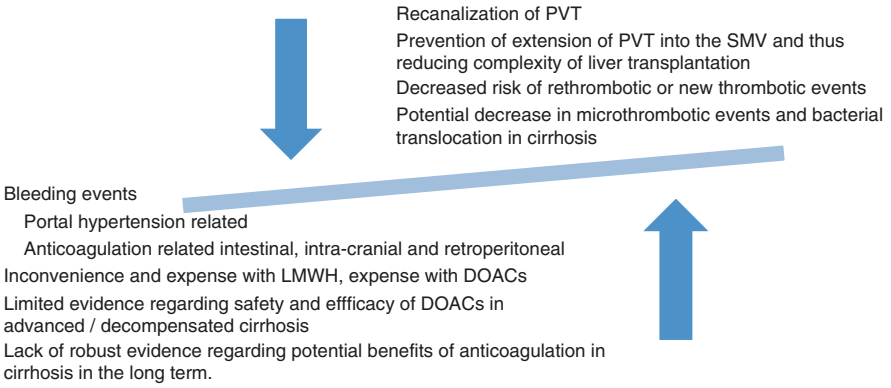

Fig. 7.1 Potential benefits and risks of anticoagulation in patients with and without cirrhosis and nontumoral PVT

Table 7.1 Imaging features and factors influencing decision to start anticoagulation in patients with and without cirrhosis who develop nontumoral portal vein thrombosis

1.	Confirm diagnosis and extent of luminal occlusion by PVT detected by abdominal ultrasound and echodoppler	
		CT or MRI to determine the degree of luminal occlusion (<50%/≥50%) and extent of PVT (trunk and/or intra-hepatic branches) involvement of superior mesenteric vein and/or splenic vein
		Rule out HCC in cirrhosis, underlying neoplasia and metastatic liver disease in non-cirrhotic PVT
2.	Endoscopic screening for esophageal and/or gastric varices	
		Patients with large esophageal and/or large gastric varices or varices with high risk stigmata for bleeding should receive primary and/or secondary prophylaxis of bleeding with NSBB and/or EBL of varices
3.	Evaluate patient frailty, risk of fall and individualize decision for anticoagulation in non-liver transplant candidates/asymptomatic non-cirrhotic PVT patients	
4.	Consider platelet count, comorbidities including renal failure, alcohol abuse and portal hypertension related decompensations prior to initiating anticoagulation	
		Avoid starting anticoagulation in patients with platelet count $<50 \times 10^9$/L due to risk of bleeding

PVT portal vein thrombosis, *CT* computerized tomography, *MRI* magnetic resonance imaging, *HCC* hepatocelular carcinoma, *NSBB* non-selective beta blockers, EBL endoscopic band ligation

7.3.2 Cirrhotic Nontumoral PVT

Among patients with cirrhosis, especially those on liver transplant list, anticoagulation is indicated in those who are symptomatic, with occlusive PVT or thrombosis with more than >50% luminal occlusion of the portal vein trunk, extensive PVT involving the portal vein trunk and branches and those with progressive PVT on follow-up imaging or thrombosis of the SMV [3]. Anticoagulant therapy should be started as soon as possible in patients with cirrhosis and nontumoral PVT, since recanalization rates are significantly higher in those patients who start anticoagulation within the first 6 months of PVT detection [16].

The points to be considered before starting anticoagulation are summarized in Table 7.1. The diagnostic evaluation and decision making flow chart for initiating and maintaining anticoagulant therapy is shown in Fig. 7.2.

7.4 Safety of Anticoagulation in Patients With and Without Cirrhosis and Nontumoral PVT

The incidence of bleeding reported in studies is difficult to interpret due to varying definitions of clinical severity and may be classified as gastrointestinal bleeding related or not to portal hypertension and nongastrointestinal bleeding which includes subcutaneaous, intracranial, pulmonary and retroperitoneal locations [3]. In order to decrease the risk of variceal bleeding, all patients with noncirrhotic chronic PVT

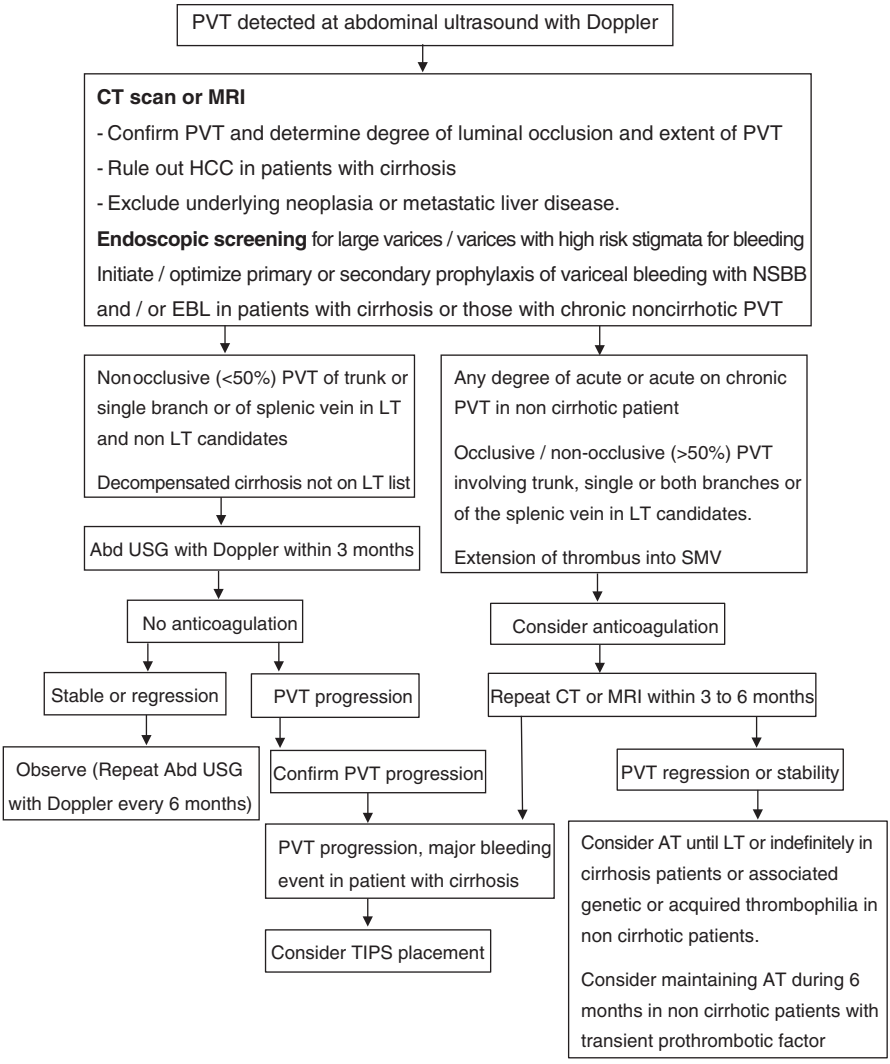

Fig. 7.2 Flowchart to aid management of anticoagulation therapy in patients with and without cirrhosis who develop nontumoral PVT

and all patients with cirrhosis and acute or chronic PVT should undergo endoscopic screening and adequate prophylaxis of variceal bleeding if indicated [8]. Bleeding episodes while on anticoagulant therapy for noncirrhotic nontumoral PVT can occur in up to 26% patients [15, 17] and varies between 10.8% and 28% in patients with cirrhosis and nontumoral PVT [11, 14, 18]. A study from Egypt in patients with cirrhosis and nontumoral PVT showed an unusually high bleeding rate of 43% in patients receiving warfarin [19]. In a meta-analysis evaluating direct acting oral anticoagulants (DOACs), major bleeding risk ranged from 4% to 15% for all DOAC

recipients and from 7% to 28% for patients receiving vitamin K antagonists (VKA) or low molecular weight heparin (LMWH) during median/mean treatment durations of 6–9 months for DOACs and 6–16 months for VKAs or LMWHs [20].

7.4.1 Noncirrhotic Nontumoral PVT

Although there has been evidence suggesting that anticoagulation in patients with noncirrhotic nontumoral PVT doubles the risk of bleeding compared to those who do not receive anticoagulation [21], a more recent study did not find an association between anticoagulation and higher risk of gastrointestinal bleeding in patients who received adequate prophylaxis of variceal bleeding [15]. In noncirrhotic nontumoral PVT, mortality in context of anticoagulant therapy has been documented in two patients who died due to gastrointestinal bleeding [21].

7.4.2 Cirrhotic Nontumoral PVT

Among patients with cirrhosis, La Mura et al. showed that the risk of bleeding seemed to be related to underlying portal hypertension rather than anticoagulant therapy [14]. A large multicentre observational study has shown that the risk of bleeding in patients with cirrhosis receiving anticoagulation for splanchnic vein thrombosis was thrice that compared to patients without cirrhosis, but was lower then that in patients with cirrhosis who did not receive anticoagulation, and this beneficial effect may have been attributable to adequate prophylaxis of variceal bleeding in patients receiving anticoagulation [12, 22].

In patients with cirrhosis, thrombocytopenia (platelet counts $<50 \times 10^9$/L), low serum albumin and prior history of variceal bleeding have been found to be significantly associated with higher risk of bleeding while on anticoagulation [23, 24]. Both thrombocytopenia and past history of variceal bleeding have been found to be independent predictors of development of PVT in cirrhosis, highlighting the complexity of management with anticoagulant therapy in these patients [25]. Anticoagulation in patients with cirrhosis has been found to be neither associated with higher rebleeding risk at 5 days nor with higher 6 week mortality [26].

Attention to potential risk factors for bleeding on anticoagulation (platelet count $<50 \times 10^9$/L, low serum albumin suggesting advanced cirrhosis) and avoiding initiating anticoagulation in patients with alcohol dependence, elderly and frail patients at risk of falls and those with advanced renal failure may maximize the potential utility of anticoagulant therapy decreasing its unnecessary use in high risk patients and consequent bleeding episodes.

Despite multiple studies suggesting a low risk of mortality due to bleeding in the context of anticoagulation in patients with cirrhosis [11, 14, 18, 23, 26], in the study by Kwon et al., two patients died due to bleeding complications related to anticoagulation, one of them due to intracranial bleed and the other due to bleeding duodenal varices with the latter patient having a baseline platelet count of 44×10^9/L [24].

These data highlight the importance of individualized approach to decision making to initiate and maintain anticoagulant therapy with adequate informed consent prior to starting anticoagulation in patients with nontumoral PVT with and wihout cirrhosis [24].

7.5 Choice of Anticoagulant, Doses and Duration of Anticoagulation

7.5.1 Noncirrhotic Nontumoral PVT

Among patients with noncirrhotic nontumoral PVT, anticoagulation should ideally be started with LMWH (enoxaparin 1 mg/kg 12/12 subcutaneous [s.c.] or tinzaparin 1.5 mg/24 h s.c. in the presence of renal impairment) which is maintained during 1 month and later switched to VKAs (i.e., warfarin, coumadin) or DOACs (i.e., direct factor × inhibitors – apixaban, edoxaban, rivaroxaban; thrombin inhibitor – dabigatran).

In noncirrhotic nontumoral PVT, anticoagulation should be maintained for at least 6 months in patients who do not recanalize the portal vein and who do not have underlying thrombophilic conditions [4, 8]. Anticoagulant therapy should be maintained indefinitely in those patients with genetic and acquired thrombophilic conditions or when there is involvement of the SMV [3, 4].

7.5.2 Cirrhotic Nontumoral PVT

In patients with cirrhosis and nontumoral PVT who are candidates for anticoagulant therapy, in the case of Child Pugh class A and B (7 points), anticoagulation should ideally be started with LMWH (enoxaparin 1 mg/kg 12/12 s.c. or tinzaparin 1.5 mg/24 h s.c. in the presence of renal impairment) which is maintained during 1 month and later switched to VKAs to maintain international normalized ratio (INR) between 2 and 3.

Alternatively, in patients with compensated cirrhosis (Child Pugh class A), DOACs may be used with dose adjustement required for patients with more advanced cirrhosis and/or those with associated renal failure. Despite the paucity of data in patients with cirrhosis, DOACs may be as effective and safe as conventional VKA and LWMH [20, 27, 28]. DOACs are not recommended for use in pregnant or lactating women as well as Child-Pugh class C cirrhosis patients, and in these patient groups, LMWHs should be used [20, 29]. Recommended doses of DOACs are suggested in Table 7.2. DOACs have been used in reduced doses in patients with cirrhosis in majority of the published studies [27].

Among Child-Pugh class B (8–9) and C patients, enoxaparin at a dose of 1 mg/kg 12/12 s.c. and adjusted to half the conventional dose or less if required, in patients with severe thrombocytopenia (platelet count $<50 \times 10^9$/L) or renal failure, may be a useful therapeutic option.

Table 7.2 DOACs and dose adjustments in patients with cirrhosis and nontumoral portal vein thrombosis

Type of DOAC	Mechanism of action	Hepatic metabolism	Dose adjustment for renal impairment	Dose recommended in cirrhosis and nontumoral PVT	Child-Pugh class	Safety in pregnant and lactating women
Rivaroxaban	Direct Factor Xa inhibitor	Yes	Yes	20 mg/24 h (CrCl > 50 mL/min) 15 mg/24 h (CrCl ≤50 mL/min)	With caution in CP B Avoid in CP C	No
Apixaban	Direct Factor Xa inhibitor	Yes	Yes	5 mg every 12 h	With caution in CP B Avoid in CP C	No
Edoxaban	Direct Factor Xa inhibitor	Yes	Yes	60 mg/24 h (CrCl > 50 mL/min), 30 mg/24 h (CrCl 30–50/ min)	With caution in CP B Avoid in CP C	No
Dabigatran	Thrombin inhibitor	Yes	Yes	110 mg every 12 h	With caution in CP B Avoid in CP C	No

DOAC direct oral anticoagulant, *PVT* portal vein thrombosis, *CP* child-pugh, *CrCl* creatinine clearance

The potential benefits of DOACs include convenience with a predictable anticoagulant effect with a daily dose which does not require regular monitoring but these drugs are significantly more expensive than VKAs [1, 3, 27, 29]. The safety and efficacy of DOACs has not been confirmed in patients with advanced cirrhosis, and therefore these patients should preferably be maintained on LMWH [3, 29]. LMWH is, however, inconvenient due to the requirement for daily injections, which decreases compliance, and is relatively expensive compared to VKAs [1].

Ideally, angio CT scan or MRI should be performed at baseline at the time of diagnosis of PVT, at 3 and at 6 months after starting anticoagulation, in order to effectively evaluate the effect of anticoagulant therapy on PVT recanalization [3].

In patients with cirrhosis and nontumoral PVT, anticoagulant therapy should be maintained for at least 6 months or until liver transplantation or indefinitely in patients with genetic or acquired thrombophilic conditions or if associated with SMV thrombosis [1, 3].

7.6 Efficacy of Anticoagulation on Recanalization of Nontumoral Portal Vein Thrombosis and Clinical Significance

7.6.1 Noncirrhotic Nontumoral PVT

Initial studies had suggested that early detection and anticoagulation in patients with acute noncirrhotic nontumoral PVT was associated with complete recanalization in 50% and partial recanalization in 40% compared to 0% in those not receiving anticoagulation [17]. Recent studies, however, suggest that the PVT recanalization rates with anticoagulant therapy in these patients are around 40% [10, 13]. The presence of ascites and occlusion of the splenic vein have been found to be factors associated with failure of PVT recanalization [10].

7.6.2 Cirrhotic Nontumoral PVT

Among patients with cirrhosis and nontumoral PVT, partial or complete recanalization rates range between 36% and 82% [1, 3, 25], with majority of these studies being relatively small and retrospective. In the meta-analysis by Loffredo et al., anticoagulant therapy was found to significantly increase PVT recanalization rates [30]. Recently, in a large study involving patients from two centres, the partial or complete recanalization of PVT on anticoagulant therapy was obtained in 56.8% (46/81) of patients with spontaneous recanalization occuring in 25.7% (26/101) of untreated patients. Factors predicting a higher probability of PVT recanalization in patients with cirrhosis include early initiation of anticoagulant therapy (<6 months), lesser severity of liver disease (Child-Pugh class A), less extensive PVT and absence of prior portal hypertensive bleeding [16, 31, 32].

7.7 Thrombosis Recurrence After Stopping Anticoagulation

7.7.1 Noncirrhotic Nontumoral PVT

In noncirrhotic nontumoral PVT, anticoagulation has a trend to decrease the risk of rethrombosis and patients with underlying prothrobotic factors have a significantly higher risk of rethrombosis and therefore anticoagulation should not be stopped [21].

7.7.2 Cirrhotic Nontumoral PVT

In patients with cirrhosis and nontumoral PVT, when anticoagulation is stopped due to portal vein recanalization or due to adverse events related to anticoagulation, rethrombosis occurs in around one third of patients [11, 18, 23]. Rethrombosis in these patients is most likely due to sluggish blood flow in the portal vein secondary to underlying cirrhosis [33]. Therefore, in the absence of contraindications or adverse events, anticoagulation should preferentially be maintained in patients with cirrhosis who develop nontumoral PVT to avoid rethrombotic events [11].

7.8 Anticoagulant Therapy and Prognosis in Nontumoral PVT in Patients With and Without Cirrhosis

7.8.1 Noncirrhotic Nontumoral PVT

The current outcome in noncirrhotic nontumoral PVT is a mortality rate of less than 5% at 5 years usually due to the classical complications of PVT (intestinal infarction or gastrointestinal bleeding) [8]. The effect of anticoagulation on survival in patients with noncirrhotic nontumoral PVT is not clear. Recurrent thrombotic events have been found to be independent predictors of mortality [21]. In addition, age, ascites, altered liver enzymes at baseline and comorbidities, especially underlying myeloproliferative disease, have been found to be associated with higher mortality [8, 9, 15].

7.8.2 Cirrhotic Nontumoral PVT

Anticoagulant therapy in patients with cirrhosis and nontumoral PVT was found to be associated with significantly longer portal hypertension event-free and transplantation free-survival times in patients who responded with complete recanalization of PVT [14]. In the study by Kwon et al., in patients with cirrhosis and nontumoral PVT who received anticoagulation, any recanalization of PVT was associated with significantly lower serum bilirubin and significantly higher platelet count post-treatment compared to pre-treatment values [24]. More recently, Pettinari et al. showed that anticoagulation in cirrhosis and nontumoral PVT was an independent predictive factor of better prognosis [18]. Anticoagulation in Child-Pugh class B and C patients with cirrhosis and nontumoral PVT was found to be associated with significantly better orthotopic liver transplant (OLT) free survival in patients receiving anticoagulation compared to those who did not [11]. This finding was significant since no difference in OLT free survival was found in patients with any recanalization compared to those without recanalization of PVT, highlighting the potential role of anticoagulation in preventing microthrombotic events within the liver parenchymal sinusoids beyond macroscopic PVT recanalization and thus contributing to

better prognosis [11]. Despite these positive findings, larger multicentre studies are required to confirm and better evaluate the potentially useful role of anticoagulation in nontumoral PVT in cirrhosis.

In conclusion, anticoagulation should be started as soon as possible in both patients with and without cirrhosis who develop nontumoral PVT. In patients with chronic PVT and those with underlying cirrhosis, upper gastrointestinal endoscopy prior to starting anticoagulation should always be performed to screen for large esophageal and/or gastric varices with high risk stigmata for bleeding and adequate prophylaxis of variceal bleeding should be started prior to anticoagulation. After initial anticoagulation with LMWH during the first month, VKAs and DOACs are both effective in noncirrhotic patients and patients with compensated (Child-Pugh class A) cirrhosis. In patients with decompensated cirrhosis, LMWH could be maintained with doses adjusted for thrombocytopenia and concomitant renal failure. Anticoagulation should preferentially be maintained in both cirrhotic and noncirrhotic patients with genetic or aquired thrombophilic conditions and those with concomitant SMV thrombosis. In patients with cirrhosis, anticoagulation should be maintained in those on liver transplant list and should be considered also in those who tolerate anticoagulation without adverse events to avoid rethrombosis.

References

1. Qi X, Han G, Fan D. Management of portal vein thrombosis in liver cirrhosis. Nat Rev Gastroenterol Hepatol. 2014;11:435–46.
2. Valla DC, Condat B. Portal vein thrombosis in adults: pathophysiology, pathogenesis and management. J Hepatol. 2000;32:865–71.
3. Intagliata NM, Caldwell SH, Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. Gastroenterology. 2019;156:1582–1599.e1.
4. Nery F, Chevret S, Condat B, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015;61(2):660–7.
5. Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, Grandone E, Balzano A. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40:736–41.
6. Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, Colombo M, Mannucci PM. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology. 2009;137:2105–11.
7. Noronha Ferreira C, Marinho RT, Cortez-Pinto H, Ferreira P, Dias MS, Vasconcelos M, Alexandrino P, Serejo F, Pedro AJ, Gonçalves A, Palma S, Leite I, Reis D, Damião F, Valente A, Xavier Brito L, Baldaia C, Fatela N, Ramalho FVJ. Incidence, predictive factors and clinical significance of development of portal vein thrombosis in cirrhosis: a prospective study. Liver Int. 2019;25:1459–67.
8. Condat B, Valla D. Nonmalignant portal vein thrombosis in adults. Nat Clin Pract Gastroenterol Hepatol. 2006;3:505–15.
9. Valla D. Splanchnic vein thrombosis. Semin Thromb Hemost. 2015;41:494–502.
10. Plessier A, Darwish-Murad S, Hernandez-Guerra M, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology. 2010;51:210–8.
11. Noronha Ferreira C, Reis D, Cortez-Pinto H, et al. Anticoagulation in cirrhosis and portal vein thrombosis is safe and improves prognosis in advanced cirrhosis. Dig Dis Sci. 2019;64:2671–83.

12. Riva N, Ageno W, Schulman S, et al. Clinical history and antithrombotic treatment of incidentally detected splanchnic vein thrombosis: a multicentre, international prospective registry. Lancet Haematol. 2016;3:e267–75.
13. Turnes J, García-Pagán JC, González M, et al. Portal hypertension-related complications after acute portal vein thrombosis: impact of early anticoagulation. Clin Gastroenterol Hepatol. 2008;6:1412–7.
14. La Mura V, Braham S, Tosetti G, Branchi F, Bitto N, Moia M, Fracanzani AL, Colombo M, Tripodi A, Primignani M. Harmful and beneficial effects of anticoagulants in patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol. 2018;16:1146–1152.e4.
15. Noronha Ferreira C, Seijo S, Plessier A, et al. Natural history and management of esophagogastric varices in chronic noncirrhotic, nontumoral portal vein thrombosis. Hepatology. 2016;63:1640–50.
16. Senzolo M, Sartori TM, Rossetto V, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosistemic shunt for the management of portal vein thrombosis in cirrhosis. Liver Int. 2012;32:919–27.
17. Condat B, Pessione F, Helene Denninger M, Hillaire S, Valla D. Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulant therapy. Hepatology. 2000;32:466–70.
18. Pettinari I, Vukotic R, Stefanescu H, Pecorelli A, Morelli M, Grigoras C, Sparchez Z, Andreone P, Piscaglia F. Clinical impact and safety of anticoagulants for portal vein thrombosis in cirrhosis. Am J Gastroenterol. 2019;114:258–66.
19. Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. Vasc Pharmacol. 2019;113:86–91.
20. Hoolwerf EW, Kraaijpoel N, Büller HR, van Es N. Direct oral anticoagulants in patients with liver cirrhosis: a systematic review. Thromb Res. 2018;170:102–8.
21. Spaander MCW, Hoekstra J, Hansen BE, Van Buuren HR, Leebeek FWG, Janssen HL. Anticoagulant therapy in patients with non-cirrhotic portal vein thrombosis: effect on new thrombotic events and gastrointestinal bleeding. J Thromb Haemost. 2013;11:452–9.
22. Ageno W, Riva N, Schulman S, et al. Long-term clinical outcomes of splanchnic vein thrombosis: results of an international registry. JAMA Intern Med. 2015;175:1474–80.
23. Delgado MG, Seijo S, Yepes I, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol. 2012;10:776–83.
24. Kwon J, Koh Y, S jong Y, Yoon JH. Low-molecular-weight heparin treatment for portal vein thrombosis in liver cirrhosis: efficacy and the risk of hemorrhagic complications. Thromb Res. 2018;163:71–6.
25. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, Denninger MH, Sauvanet A, Valla D, Durand F. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005;54:691–7.
26. Cerini F, Gonzalez JM, Torres F, et al. Impact of anticoagulation on upper-gastrointestinal bleeding in cirrhosis. A retrospective multicenter study. Hepatology. 2015;62:575–83.
27. De Gottardi A, Trebicka J, Klinger C, et al. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. Liver Int. 2017;37:694–9.
28. Intagliata NM, Henry ZH, Maitland H, Shah NL, Argo CK, Northup PG, Caldwell SH. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci. 2016;61:1721–7.
29. Weinberg EM, Palecki J, Reddy KR. Direct-acting oral anticoagulants (DOACs) in cirrhosis and cirrhosis-associated portal vein thrombosis. Semin Liver Dis. 2019;39:195–208.
30. Rank KM, Lake J. CON: anticoagulation for portal vein thrombosis in advanced cirrhosis. Clin Liver Dis. 2018;12:80–2.
31. Rodriguez-Castro KI, Vitale A, Fadin M, et al. A prediction model for successful anticoagulation in cirrhotic portal vein thrombosis. Eur J Gastroenterol Hepatol. 2019;31:34–42.

32. Chen H, Liu L, Qi X, He C, Wu F, Fan D, Han G. Efficacy and safety of anticoagulation in more advanced portal vein thrombosis in patients with liver cirrhosis. Eur J Gastroenterol Hepatol. 2016;28:82–9.
33. Riva N, Ageno W, Poli D, et al. Recurrent thrombotic events after discontinuation of vitamin k antagonist treatment for splanchnic vein thrombosis: a multicenter retrospective cohort study. Gastroenterol Res Pract. 2015;2015:620217.

Thrombolysis for Non-malignant Portal Vein Thrombosis

8

Tuba Baydas, Necat Irem Abdulhayoglu, Emine Mutlu, Leila Kianifard, and Metin Basaranoglu

Abstract

Portal vein thrombosis (PVT) is thrombosis of the portal circulation. PVT is an uncommon thrombotic condition in the general population; on the other hand, it is one of the most common vascular disorders of the liver especially among patients with underlying chronic liver diseases, malignancy, and hypercoagulable states. The natural history and clinical outcome of PVT differentiate according to the site and extension of the obstruction in the portal venous system. Causes of PVT are cirrhosis, hepatobiliary malignancy, inflammatory conditions and inherited/acquired thrombophilia. Diagnosis of PVT is made by Doppler ultrasonography as the first-line choice. Treatment modalities range from conservative management to anticoagulation, thrombolysis, and thrombectomy. The primary end point was portal vein recanalization. In this section, we describe thrombolysis for non-malignant PVT.

Keywords

Portal vein · Thrombosis · Malignant · Thrombolysis · Thromboembolism Cirrhosis

T. Baydas · N. I. Abdulhayoglu · E. Mutlu · M. Basaranoglu (✉)
Division of Gastroenterology, Department of Internal Medicine, Bezmialem Vakif University, Istanbul, Turkey
e-mail: metin_basaranoglu@yahoo.com

L. Kianifard
Beykoz Institute of Life Sciences and Biotechnology, Bezmialem Vakif University, Istanbul, Turkey

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_8

8.1 Introduction

Portal vein thrombosis (PVT) is partial or complete blood clot formation of the portal circulation. Thrombosis can extend to the portal branches to the splenic and/or the mesenteric veins. Clinical features differentiate according to the site and extension of the obstruction in the portal venous system [1, 2]. In partial obstruction, asymptomatic presentation and incidental diagnosis during routine workup is common [3]. Number of incidental PVT increases with use of abdominal imaging for other purposes [4]. If complete thrombosis occurs, it can lead to hepatic decompensation, variceal bleeding and intestinal infarction as a consequence of portal hypertension [5]. It is also divided into acute, subacute and chronic. Making this distinction is important in determining the approach to treatment [6, 7]. There are two different views in the acute/chronic distinction. Even though this is not a generally accepted definition, according to some clinicians, PVT was considered to be acute, if symptoms develop within 60 days prior to diagnosis [8, 9]. In fact, some other authors describe acute PVT as symptoms occurring within 7 days prior to diagnosis and subacute PVT if symptoms last longer than 7 days [10, 11]. Actually, acute and chronic PVT are different stages of the same disease [2]. Chronic stage definition is used when portal hypertension symptoms (collaterals/varices, ascites and splenomegaly) and portal cavernoma (formation of collateral vasculature bypassing the area of obstruction) occur [12].

8.1.1 Epidemiology

PVT was first described in 1868 by Balfour and Stewart in a 20-year-old patient with ascites, splenomegaly and esophageal varices [13]. Since then, it is a rare clinical diagnosis and the incidence of PVT is unknown. In general population, prevalence is 0.7 to 1/100,000 [14]. In certain conditions, such as cirrhosis, prevalence increases. There is a connection between the prevalence of PVT and the severity of liver disease. In compensated cirrhosis, estimated prevalence is less than 1%, meanwhile it is 8–25% in liver transplant candidates [15, 16]. According to the Sweden based study that was performed from 1970 to 1982 with 24,000 autopsies, the prevalence of PVT was 1%. This study revealed that the most common causes for PVT were cirrhosis (28%), primary or secondary hepatobiliary malignancy (23–44%), major infectious or inflammatory abdominal disease (10%), or a myeloproliferative disorder (3%). Predisposing factor was not found in 14% [17].

8.1.2 Pathophysiology and Etiology

PVT pathophysiology is similar to thrombus formation in any other vessel. In order to understand pathophysiology, Virchow's triad (endothelial damage, stasis and hypercoagulability) must be known [4, 5]. Pathophysiology changes according to the underlying etiology. Etiology of PVT can be divided into local and systemic (Table 8.1).

Table 8.1 Causes of portal vein thrombosis [4, 15, 18]

A. Local causes	*Cirrhosis*
	Malignancy
	• Hepatocellular carcinoma
	• Hepatobiliary cancer
	• Pancreatic cancer
	• Gastrointestinal cancer
	• Lymphoma
	Direct injury to portal vein
	• Surgery
	• Trauma
	• Shunts
	Inflammatory conditions
	• Pancreatitis
	• Cholecysititis
	• Diverticulitis
	• Inflammatory bowel disease
	• Connective tissue disease
	• Appendicitis and any other intra-abdominal infection
B. Systemic causes	*Inherited thrombophilia*
	• Factor V Leiden mutation
	• Protein C, S and antithrombin 3 deficiency
	• Prothrombin gene mutation
	Acquired thrombophilia
	• Myeloproliferative disorders: JAK 2 gene mutation, polycythemia vera, essential thrombocythemia, myelofibrosis
	• Paroxysmal nocturnal hemoglobinuria
	• Antiphospholipid antibody syndrome
	• Hyperhomocysteinemia
	• Pregnancy
	• Hormonal treatments

8.1.3 Clinical Presentation

PVT has a wide clinical presentation ranging from asymptomatic and incidental diagnosis, to mild to moderate abdominal pain, nausea, vomiting, to mesenteric ischemic symptoms with severe abdominal pain, hypotension, and even death [15]. Symptoms vary depending on many factors (acute/subacute/chronic; occlusive/non-occlusive; benign/malignant; and intrahepatic/extrahepatic).

In acute stage of PVT, if occlusion is partial, thrombus may be asymptomatic or may be associated with nonspecific symptoms, such as colicky pain, loss of appetite, nausea and vomiting [4, 19]. On the other hand, if occlusion is complete, it may present as acute or long-standing abdominal pain, signs of decompensated chronic liver disease (variceal bleeding, ascites, and hepatic encephalopathy), occult blood in stool, peritonitis, portal cholangiopathy, and intestinal ischemia. Sudden

worsening of the cirrhotic patient's clinic should suggest PVT development. When the extension of thrombosis reaches to the superior mesenteric vein (SMV) and mesenteric arches, life-threatening intestinal infarction risk could appear. Occlusion may extend into the splenic vein [18].

When acute PVT resolution fails, chronic PVT occurs. As a result, cavernous transformation develops [1]. Cavernous formation of portal vein (portal cavernoma) occurs between 6–20 days after unresolved PVT, and for the reason that portal vein flow stasis in cirrhosis usually prevents collateral dilatation, cavernomas are more common in patient without concomitant liver disease [5, 20]. Chronic PVT can lead to esophageal varices with bleeding, splenomegaly and ascites as a result of portal hypertension [15]. Endoscopic screening for gastro-oesophageal varices must be done within few months since varices may be seen as early as 1 month after acute PVT. If varices are not detected, endoscopic screening should be repeated 6 months later, if PVT recanalization has not been achieved [2].

8.1.4 Diagnosis of PVT

There are no specific laboratory tests to indicate PVT. Imaging methods are used in the diagnosis of PVT. In fact, PVT is an incidental finding in the majority of patients with cirrhosis. Doppler ultrasound (US) is the first-line technique for PVT diagnosis [18]. Doppler US is used commonly in screening cirrhotic patients for hepatocellular carcinoma (HCC) [21]. Contrast-enhanced imaging techniques, including contrast-enhanced ultrasound (CEUS) and contrast-enhanced computed tomography (CECT), are useful for diagnosis with higher sensitivity, allowing further characterization of PVT. These techniques allow a better definition of PVT extension and evaluation of underlying malignancy [5, 19, 22, 23]. Visualization of the entire mesenteric venous system and wide availability are advantages of a CT scan. On the other hand, risk of contrast nephropathy, radiation exposure, and technical variations should be considered. In the arterial phase of CECT and magnetic resonance imaging (MRI), intra-thrombus vascularity has been reported to be specific for malignant PVT [18, 24–28].

8.1.5 Management

Treatment of the underlying etiology of PVT is essential. For example, in the management of septic portal phlebitis, antibiotherapy and drainage of the abscess should be performed as soon as possible [3]. The primary goal of treatment is to promote portal vein recanalization and to prevent propagation of the thrombus [6, 21, 22]. Recanalization will prevent the complications of portal hypertension and mesenteric ischemia [4].

Treatment should be patient-specific and a delicate balance between thrombosis and bleeding should be maintained. The treatment of PVT ranges from close monitoring without intervention to anticoagulation, thrombolysis, thrombectomy, and

transjugular intrahepatic portosystemic shunt (TIPS). The clinician should make treatment decisions considering the involvement of other splanchnic veins, hypercoagulable states, local factors (infections, inflammatory disorders, and cirrhosis), malignancy, bleeding risk, and gastroesophageal varices [15]. Therapeutic decisions strongly depend on the etiology. When forming a treatment strategy, patients are considered in three main groups: patients with liver cirrhosis, with malignancies, and those unrelated to cirrhosis or malignancies [12]. In general, the primary treatment for acute/subacute PVT is immediate systemic anticoagulation [29, 30].

In this section, we will focus on thrombolysis for non-malignant PVT. The use of intravascular thrombolytic agents originates back to the 1960s with the pulmonary embolism treatment. By the 1970s, catheter-directed thrombolysis for vascular occlusion entered the mainstream. Nowadays, thrombolytics are used in many thrombotic conditions, including acute peripheral/visceral arterial occlusion, coronary artery thrombosis, thrombosed dialysis grafts, thrombosed intravascular catheters and deep vein thrombosis. Until now, urokinase, streptokinase, alteplase, reteplase, and anistreplase have been used as thrombolytic agents. Each of them converts plasminogen to plasmin, which then degrades fibrin and fibrinogen to their fragments and in this way accelerates lysis of thrombus. These agents have been used with or without anticoagulants, platelet-receptor antagonists, and plasminogen or thrombin inhibitors. For more efficient treatment, thrombolytic agents can be given directly into the thrombus, thus a high local drug concentration is achieved [31].

8.2 Thrombolysis

The goals of the treatment are complete recanalization of portal vein to prevent further extension of thrombus into the mesenteric veins and prevent further morbidities caused by chronic PVT [6, 32].

Current treatment options of PVT vary from a conservative approach as monitoring with no treatment to anticoagulation, thrombolysis therapy, replacement of TIPS, and surgical thrombectomy [33]. Spontaneous resolution of obstruction is extremely rare with conservative approach and higher incidences of portal hypertension associated morbidities are reported. Within acute settings, short-term complications, like bowel infarction and sepsis, can occur, and even could result in mortality [6, 33].

Suitable conditions for using thrombolysis are if the patient has intensifying abdominal pain due to extension of thrombus under anticoagulation therapy or if the risk of intestinal necrosis and infarction is high (mostly seen with multiple vessel involvement) [15].

Although there is no consensus on the initiation time of thrombolysis from the diagnosis, early detection of thrombus and initiation of treatment could possibly give benefit of increasing success due to less organized thrombus at the beginning. In a systematic review study, the interval from the initiation of the symptoms to beginning of the treatment was from up to 4–60 days [6, 31, 34, 35]. Longer intervals from diagnosis to recanalization could increase the risk of long-term

complications. In a 2-year follow up study, after 6 months of treatment, no obvious benefit of anticoagulation is observed on recanalization. If treatment delays after the second week of symptoms onset, recanalization rates are as low as 69% to 25% [4, 36, 37].

Total venous occlusion and portal hypertension at the time of diagnosis lowers the chance of recanalization [38]. Especially in cavernous transformation of PV, the possibility of recanalization is lower in chronic PVT patients [39].

Even though using systemic thrombolysis as an alternative to anticoagulation is related to higher percentages of recanalization, there is still an increased risk of hemorrhagic complications [40, 41]. Decisions on treatment options should be made on an individual basis upon a multidisciplinary approach.

8.2.1 Contraindications

Selecting patients for thrombolysis treatment with PVT, clinician should assess contraindications before the intervention, such as recent stroke, presence of CNS tumor, active bleeding, known bleeding diathesis, former ischemia with bleeding or CNS surgery in 4 weeks, major surgery in 2 week or CNS hemorrhage within 12 months prior, known allergic reaction to thrombolytic materials, platelet count lower than 50×10^9/L or fibrinogen level under 1 g/L [3, 38].

Treatment aims at achieving recanalization of the thrombosed vessel, so restoring flow and preventing the onset of early and late complications related to thrombosis progression and portal hypertension.

The recanalization rate is even lower in patients with chronic PVT, in particular in those with cavernous transformation of the portal vein.

8.2.2 Treatment Protocols

European Association for the Study of Liver (EASL) suggests that without any contraindications current first-line treatment of acute symptomatic PVT depends on anticoagulants like unfractionated (UFH) or low molecular weight heparin (LMWH) [22].

In case of asymptomatic patients without underlying malignancy, hypercoagulability or thrombus extension to mesenteric vessels, monitoring without treatment is suggested [4]. However, if the patient has intensifying abdominal pain due to extension of thrombus under anticoagulation or if the risk of intestinal necrosis and infarction is high, commonly used methods are either systemic thrombolytic therapy via central venous catheter or catheter-directed local approaches, such as chemical, mechanical thrombolysis like suction or agitation, balloon angioplasty and stenting [3, 15].

Mechanical thrombectomy can be used in patients with contraindications to thrombolytic treatment or if the clinician prefers to reduce the dose of thrombolytics

in favor of the patient's current situation. In the acute stage of clot formation, thrombus is more fragile and it can be fragmented by agitation which increases the effect of thrombolytics to dissolve thrombus. For this modality, pigtail catheters, balloon or other special devices could be used [32]. Also, among mechanical thrombectomy modalities, rheolytic thrombolysis is reported to have an easy practice and related to lesser complications and shorter hospitalization time. Rheolytic thrombolysis is practiced as saline jet infusion to break down the clot [33, 40, 42]. Pulmonary emboli from fragmented clot, restenosis, and disruption of vessel wall integrity are complications of this procedure [43, 44].

Surgical thrombectomy and resection are preferred, if there is suspected intestinal necrosis, perforation or peritonitis. Though it has a risk of surgical complications, such as short bowel syndrome, in terms of mortality, 2-year survival rate or recurrence, no difference has been shown between non-surgical and surgical approaches [45].

8.2.3 Systemic Thrombolysis

For systemic thrombolysis, a recombinant human tissue-type plasminogen activator (tPA) or urokinase could be used as thrombolytic agent. Compared to urokinase, tPA is more expensive but has a higher affinity for fibrin molecule. Immediately after attachment, tPA converts plasminogen to plasmin thus induces disintegration of clot [38, 46].

After ruling out contraindications and getting consent, IV infusion of urokinase or tPA is initiated from a central venous line. Preferred tPA dose is 0.05 mg/kg/h up to a maximum dose of 4 mg/kg. Preferred urokinase dose is 400,000-600,000 U/day [46]. Heparin is also administered at a maintenance dose of 500-1000 IU/h. Thrombolysis infusion time varies between institutional practices from a few hours to 7 days on average. During infusion follow up, imaging is made between 48–72 h by appropriate imaging methods [38].

If abdominal pain does not ameliorate during the next 48–72 h and imaging evidences suggest no improvement on recanalization, catheter directed local thrombolysis options should be revised.

8.2.4 Catheter Directed Local Thrombolysis

Catheter directed local thrombolysis is used after failure with systemic approach or when the patient has any contraindication to systemic approach.

Transhepatic approach is preferred for non-cirrhotic patients with acute or subacute PVT. It is an easy procedure with lower cost compared to other methods, but carries a greater risk for hemorrhage during thrombolysis. Herein, we would like to present a case with symptomatic acute PVT due to major abdominal surgery successfully treated by catheter directed thrombolysis, as follows.

A 34-year-old male patient with no previous chronic disease history presented to the emergency department on April 19, 2020 with complaints of abdominal pain, nausea and vomiting. Abdominal CT imaging was performed with a diagnosis of acute abdomen. The size of the liver was normal, and its contours were smooth. The spleen was normal in size and its parenchyma was homogeneous. The appearance compatible with dilated appendix was measured 10 mm and it was evaluated in favor of acute appendicitis due to the presence of significant inflammation around it. Laparoscopic appendectomy was performed.

Three weeks after the operation, the patient returned to the emergency room due to the acute abdominal pain again. His blood pressure was 120/80 mmHg and heart rate 84 beats per min. His general condition was good, conscious and cooperative. Hepatomegaly was absent. Other systems were normal. His uncle's daughter had a history of thrombus. Laboratory examinations showed that whole blood count was normal. C-reactive protein was 105 mg/L (normal: 0–5), INR: 1.07, APTT: 41.8 s, blood urea: 42 mg/dL, creatinine: 0.8 mg/dL, Na: 142 mmol/L, potassium: 4.1 mmol/L, AST: 34 U/L, and ALT: 106 U/L. Abdominal contrast CT revealed that liver size was normal with smooth contour and normal size of the pancreas and spleen and a physiological calibration at abdominal aorta. The intrahepatic branches of the portal vein were entirely thrombosed and its extrahepatic segment was nearly totally thrombosed. The thrombus has been extended to the distal branches of SMV (Fig. 8.1a, b).

Final diagnosis was SMV thrombosis and acute thrombus in the portal vein. Thrombolytic therapy was planned due to acute abdominal pain, acute thrombus appearance, and the young age of the patient. Interventional radiology was performed. A 21G needle accompanied by ultrasound was entered into the right portal vein (Fig. 8.1c, d). A hydrophilic guide wire was placed. A 20 cm long infusion catheter was placed in the SMV. On the first day, it was decided to give tPA *(alteplase)* at a dose of 2 mL/h infusion and heparin 800 IU/h infusion and aPTT was followed. It was planned to perform control portography after 20 h. The general condition of the patient was good, conscious and cooperative during the whole procedure.

Splenoportography performed at the 20th hour of treatment revealed no complete patency in the SMV and portal vein. The patient did not have any complaints of pain. On the second day of treatment, tPA (alteplase) 1 mL/h infusion and heparin 1500 U/h infusion were continued. An angiography performed on the third day of treatment showed that portal vein lumen was open (Fig. 8.1e). On the fourth day of treatment, tPA infusion treatment was discontinued and heparin was continued at 1500 U/h. The general condition of the patient was good. With the aim of advanced examination, evaluation and treatment, antithrombin III, protein C and protein S levels were requested to eliminate the conditions that may cause PVT. No significant coagulating pathological condition was detected. Then, LMWH was started while heparin was stopped. On the seventh day of treatment, LMWH was stopped and an oral anticoagulant (rivaroxaban) treatment was started and the patient was discharged to home.

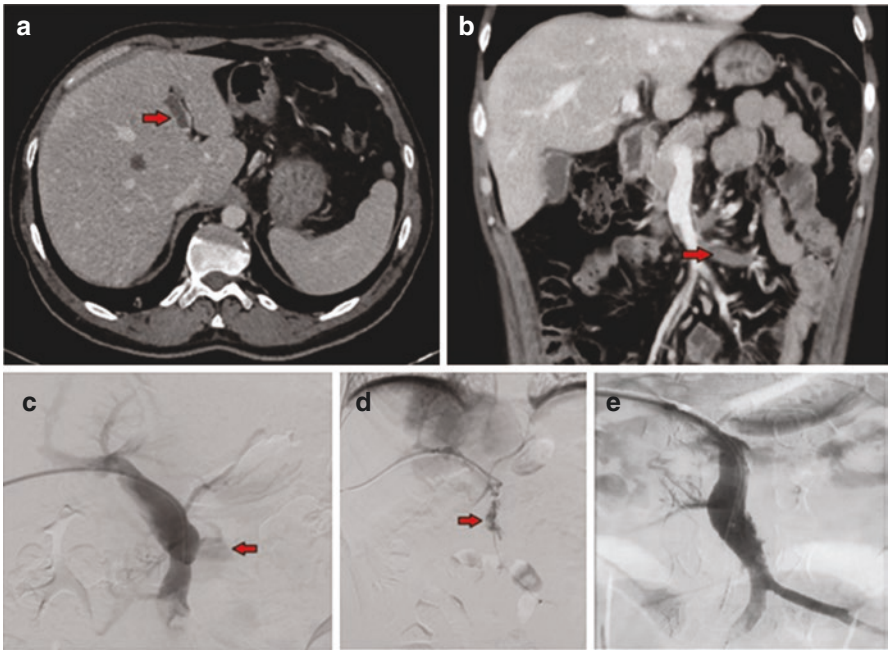

Fig. 8.1 A case with acute PVT successfully treated by catheter directed thrombolysis. (**a**, **b**) Abdominal contrast CT revealed that the intrahepatic branches of the portal vein were entirely thrombosed and its extrahepatic segment was nearly totally thrombosed. The thrombus has been extended to the distal branches of SMV (red arrow). (**c**, **d**) A 21G needle accompanied by ultrasound was entered into the right portal vein at interventional radiology. A hydrophilic guide wire was placed. A 20 cm long infusion catheter was placed in the SMV for therapeutic purpose. Splenoportography performed at the 20th hour of treatment revealed no complete patency in the SMV and portal vein. (**e**) On the third day of treatment, splenoportography showed that portal vein lumen was open

At the third month follow-up, he has no complaints, and a Doppler ultrasonography demonstrated the main portal vein diameter of 13.2 mm with mild sequelae intimal thickening, and patent portal vein and its branches, SMV and splenic vein lumens. No major recurrent thrombosis was detected. FibroScan elastography showed that median liver stiffness value was 5.6 kPa (IQR/med: 4%), suggesting F0-F1 fibrosis (no significant liver injury).

Transileocolic approach is preferred in patients with failed TIPS or PVT patients with ascites, but has less hemorrhagic risk and requires surgical intervention.

Transjugular approach requires portal venous access via inferior vena cava or hepatic veins and may be used to create a TIPS, and it has a lower risk of bleeding complication [31, 40].

Indirect approach is used in case of portal vein anatomical variations, with administration of thrombolysis to SMA via femoral artery or radial artery, and considered to be a effective and safer approach, compared to systemic thrombolysis hence being less invasive [3, 34].

8.2.5 Follow Up During Treatment

During the treatment, the patient should be evaluated for symptom improvement. Periodic complete blood count along with prothrombin time, aPTT, INR, fibrinogen, blood urea, electrolytes, and liver enzymes should be monitored every 6–12 h [38]. If fibrinogen levels drop under 1 g/L, infusion must be ceased. Before the intervention, if aPTT levels are not in a normal range, heparin infusion must be monitored with anti-Xa targeting the level 0.5–0.8 IU/mL during the infusion. Especially with UFH use, heparin induced thrombocytopenia is a life-threatening situation with falling of platelet counts over 50%, and after cessation of heparin, platelet count comes back to normal range [4, 22]. Clinicians also must be vigilant in terms of local or intracranial hemorrhages during treatment.

8.2.6 Acute and Chronic Complications

In acute stage, minor local or systemic bleeding, allergy, vessel injury, need for surgical intervention, sepsis and rarely death have been reported [6, 47].

One of the significant complications of PVT treatment is extrahepatic portal hypertension as recognized with elevation of portal venous pressure above 12 mmHg at rest. For recognizing portal hypertension with the help of clinical signs and imaging manifestations, ascites, variceal bleeding, hypersplenism and related thrombocytopenia, and hepatic encephalopathy should not be overlooked [2, 48].

8.2.7 Long Term Prognosis

Recently, survival rates are improved on account of early diagnosis and starting early anticoagulation also with new invasive approaches. Even incomplete recanalization affects prognosis positively.

Without former liver disease for acute PVT, 5-year mortality rate is up to 15%, which is mostly related to underlying disease or complications after intervention [49]. For chronic PVT, mortality for 5 years is as low as 5–10%, which is mostly related to age, underlying diseases, and etiology of PVT, rather than PVT complications [2, 50].

8.2.8 Further Imaging and Medical Follow Up

After successful treatment, the complaints of the patients are expected to decline within 2 weeks. Periodic outpatient controls should be done for signs of portal hypertension in further follow-up. If the patient has no complaints or signs of restenosis, checking for recanalization with doppler US at 3 and 6 months is sufficient. CT or MRI is suggested if the patient has signs of ischemic intestinal damage. Repeated imaging at 3 weeks is reported [2, 6, 51]. After acute PVT, if complete

patency is not achieved, endoscopic evaluation for gastroesophageal varices should be scheduled within few months and repeated 6 months following. Without sufficient evidence, further assessment with endoscopy is recommendable after 2–3 years [2, 52]. For patients with gastroesophageal variceal bleeding, prevention is provided with the use of beta blockers or endoscopic band ligation [22].

Anticoagulation treatment decision should be made considering the patient's further risk of bleeding and evaluation of each case must be made on an individual basis. On discharge, transition to warfarin after initial administration of LMWH is recommended. If the patient has JAK2 mutation, daily acetylsalicylic acid use is recommended [38].

References

1. Wu M, Schuster M, Tadros M. Update on management of portal vein thrombosis and the role of novel anticoagulants. J Clin Transl Hepatol. 2019;7(2):154–64.
2. Primignani M. Portal vein thrombosis, revisited. Dig Liver Dis. 2010;42(3):163–70.
3. Chamarthy MR, Anderson ME, Pillai AK, Kalva SP. Thrombolysis and transjugular intrahepatic portosystemic shunt creation for acute and subacute portal vein thrombosis. Tech Vasc Interv Radiol. 2016;19(1):42–51.
4. Haris M, Thachil J. Portal vein thrombosis - a primer for the general physician. Clin Med (Lond). 2017;17(3):212–9.
5. Faccia M, Ainora ME, Ponziani FR, Riccardi L, Garcovich M, Gasbarrini A, et al. Portal vein thrombosis in cirrhosis: why a well-known complication is still matter of debate. World J Gastroenterol. 2019;25(31):4437–51.
6. Hall TC, Garcea G, Metcalfe M, Bilku D, Dennison AR. Management of acute non-cirrhotic and non-malignant portal vein thrombosis: a systematic review. World J Surg. 2011;35(11):2510–20.
7. Sarin SK, Sollano JD, Chawla YK, Amarapurkar D, Hamid S, Hashizume M, et al. Consensus on extra-hepatic portal vein obstruction. Liver Int. 2006;26(5):512–9.
8. Parikh S, Shah R, Kapoor P. Portal vein thrombosis. Am J Med. 2010;123(2):111–9.
9. Ponziani FR, Zocco MA, Campanale C, Rinninella E, Tortora A, Di Maurizio L, et al. Portal vein thrombosis: insight into physiopathology, diagnosis, and treatment. World J Gastroenterol. 2010;16(2):143–55.
10. Chawla Y, Duseja A, Dhiman RK. Review article: the modern management of portal vein thrombosis. Aliment Pharmacol Ther. 2009;30(9):881–94.
11. Loss M, Lang SA, Uller W, Wohlgemuth WA, Schlitt HJ. Combined surgical and interventional therapy of acute portal vein thrombosis without cirrhosis: a new effective hybrid approach for recanalization of the portal venous system. J Am Coll Surg. 2014;218(3):e79–86.
12. Lang SA, Loss M, Wohlgemuth WA, Schlitt HJ. Clinical management of acute portal/mesenteric vein thrombosis. Viszeralmedizin. 2014;30(6):394–400.
13. Balfour GW, Stewart TG. Case of enlarged spleen complicated with ascites, both depending upon varicose dilatation and thrombosis of the portal vein. Edinb Med J. 1869;14(7):589–98.
14. Rajani R, Bjornsson E, Bergquist A, Danielsson A, Gustavsson A, Grip O, et al. The epidemiology and clinical features of portal vein thrombosis: a multicentre study. Aliment Pharmacol Ther. 2010;32(9):1154–62.
15. Sharma AM, Zhu D, Henry Z. Portal vein thrombosis: when to treat and how? Vasc Med. 2016;21(1):61–9.
16. Okuda K, Ohnishi K, Kimura K, Matsutani S, Sumida M, Goto N, et al. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. Gastroenterology. 1985;89(2):279–86.

17. Ogren M, Bergqvist D, Bjorck M, Acosta S, Eriksson H, Sternby NH. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. World J Gastroenterol. 2006;12(13):2115–9.
18. Mantaka A, Augoustaki A, Kouroumalis EA, Samonakis DN. Portal vein thrombosis in cirrhosis: diagnosis, natural history, and therapeutic challenges. Ann Gastroenterol. 2018;31(3):315–29.
19. DeLeve LD, Valla DC, Garcia-Tsao G, American Association for the Study Liver Diseases. Vascular disorders of the liver. Hepatology. 2009;49(5):1729–64.
20. De Gaetano AM, Lafortune M, Patriquin H, De Franco A, Aubin B, Paradis K. Cavernous transformation of the portal vein: patterns of intrahepatic and splanchnic collateral circulation detected with Doppler sonography. AJR Am J Roentgenol. 1995;165(5):1151–5.
21. Intagliata NM, Caldwell SH, Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. Gastroenterology. 2019;156(6):1582–99.e1.
22. European Association for the Study of the Liver. EASL Clinical practice guidelines: vascular diseases of the liver. J Hepatol. 2016;64(1):179–202.
23. Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F, et al. Concepts and controversies in haemostasis and thrombosis associated with liver disease: proceedings of the 7th International Coagulation in Liver Disease Conference. Thromb Haemost. 2018;118(8):1491–506.
24. Mathieu D, Grenier P, Larde D, Vasile N. Portal vein involvement in hepatocellular carcinoma: dynamic CT features. Radiology. 1984;152(1):127–32.
25. Taylor CR. Computed tomography in the evaluation of the portal venous system. J Clin Gastroenterol. 1992;14(2):167–72.
26. Tublin ME, Dodd GD 3rd, Baron RL. Benign and malignant portal vein thrombosis: differentiation by CT characteristics. AJR Am J Roentgenol. 1997;168(3):719–23.
27. Okumura A, Watanabe Y, Dohke M, Ishimori T, Amoh Y, Oda K, et al. Contrast-enhanced three-dimensional MR portography. Radiographics. 1999;19(4):973–87.
28. Rossi S, Rosa L, Ravetta V, Cascina A, Quaretti P, Azzaretti A, et al. Contrast-enhanced versus conventional and color Doppler sonography for the detection of thrombosis of the portal and hepatic venous systems. AJR Am J Roentgenol. 2006;186(3):763–73.
29. Hall TC, Garcea G, Metcalfe M, Bilk D, Rajesh A, Dennison A. Impact of anticoagulation on outcomes in acute non-cirrhotic and non- malignant portal vein thrombosis: a retrospective observational study. Hepato-Gastroenterology. 2013;60(122):311–7.
30. Cong L, Yu JC, Liu CW, Zhang TP, Zhao YP, Jin ZY, et al. Acute mesenteric venous thrombosis: experience of 27 cases. Zhonghua Wai Ke Za Zhi. 2008;46(6):423–6.
31. Hollingshead M, Burke CT, Mauro MA, Weeks SM, Dixon RG, Jaques PF. Transcatheter thrombolytic therapy for acute mesenteric and portal vein thrombosis. J Vasc Interv Radiol. 2005;16(5):651–61.
32. Wang CY, Wei LQ, Niu HZ, Gao WQ, Wang T, Chen SJ. Agitation thrombolysis combined with catheter-directed thrombolysis for the treatment of non-cirrhotic acute portal vein thrombosis. World J Gastroenterol. 2018;24(39):4482–8.
33. Seedial SM, Mouli SK, Desai KR. Acute portal vein thrombosis: current trends in medical and endovascular management. Semin Interv Radiol. 2018;35(3):198–202.
34. Wang MQ, Guo LP, Lin HY, Liu FY, Duan F, Wang ZJ. Transradial approach for transcatheter selective superior mesenteric artery urokinase infusion therapy in patients with acute extensive portal and superior mesenteric vein thrombosis. Cardiovasc Intervent Radiol. 2010;33(1):80–9.
35. Wang MQ, Lin HY, Guo LP, Liu FY, Duan F, Wang ZJ. Acute extensive portal and mesenteric venous thrombosis after splenectomy: treated by interventional thrombolysis with transjugular approach. World J Gastroenterol. 2009;15(24):3038–45.
36. Plessier A, Darwish-Murad S, Hernandez-Guerra M, Consigny Y, Fabris F, Trebicka J, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology. 2010;51(1):210–8.

37. Turnes J, Garcia-Pagan JC, Gonzalez M, Aracil C, Calleja JL, Ripoll C, et al. Portal hypertension-related complications after acute portal vein thrombosis: impact of early anticoagulation. Clin Gastroenterol Hepatol. 2008;6(12):1412–7.
38. Benmassaoud A, AlRubaiy L, Yu D, Chowdary P, Sekhar M, Parikh P, et al. A stepwise thrombolysis regimen in the management of acute portal vein thrombosis in patients with evidence of intestinal ischaemia. Aliment Pharmacol Ther. 2019;50(9):1049–58.
39. Rodrigues SG, Sixt S, Abraldes JG, De Gottardi A, Klinger C, Bosch J, et al. Systematic review with meta-analysis: portal vein recanalisation and transjugular intrahepatic portosystemic shunt for portal vein thrombosis. Aliment Pharmacol Ther. 2019;49(1):20–30.
40. Wolter K, Decker G, Kuetting D, Trebicka J, Manekeller S, Meyer C, et al. Interventional treatment of acute portal vein thrombosis. RöFo. 2018;190(8):740–6.
41. Malkowski P, Pawlak J, Michalowicz B, Szczerban J, Wroblewski T, Leowska E, et al. Thrombolytic treatment of portal thrombosis. Hepato-Gastroenterology. 2003;50(54):2098–100.
42. Stambo GW, Grauer L. Transhepatic portal venous power-pulse spray rheolytic thrombectomy for acute portal vein thrombosis after CT-guided pancreas biopsy. AJR Am J Roentgenol. 2005;184(3 Suppl):S118–9.
43. Ferro C, Rossi UG, Bovio G, Dahamane M, Centanaro M. Transjugular intrahepatic portosystemic shunt, mechanical aspiration thrombectomy, and direct thrombolysis in the treatment of acute portal and superior mesenteric vein thrombosis. Cardiovasc Intervent Radiol. 2007;30(5):1070–4.
44. Uflacker R. Applications of percutaneous mechanical thrombectomy in transjugular intrahepatic portosystemic shunt and portal vein thrombosis. Tech Vasc Interv Radiol. 2003;6(1):59–69.
45. Brunaud L, Antunes L, Collinet-Adler S, Marchal F, Ayav A, Bresler L, et al. Acute mesenteric venous thrombosis: case for nonoperative management. J Vasc Surg. 2001;34(4):673–9.
46. Liu K, Li WD, Du XL, Li CL, Li XQ. Comparison of systemic thrombolysis versus indirect thrombolysis via the superior mesenteric artery in patients with acute portal vein thrombosis. Ann Vasc Surg. 2017;39:264–9.
47. Tateishi A, Mitsui H, Oki T, Morishita J, Maekawa H, Yahagi N, et al. Extensive mesenteric vein and portal vein thrombosis successfully treated by thrombolysis and anticoagulation. J Gastroenterol Hepatol. 2001;16(12):1429–33.
48. Simonetto DA, Liu M, Kamath PS. Portal hypertension and related complications: diagnosis and management. Mayo Clin Proc. 2019;94(4):714–26.
49. Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. N Engl J Med. 2001;345(23):1683–8.
50. Janssen HL, Wijnhoud A, Haagsma EB, van Uum SH, van Nieuwkerk CM, Adang RP, et al. Extrahepatic portal vein thrombosis: aetiology and determinants of survival. Gut. 2001;49(5):720–4.
51. Poplausky MR, Kaufman JA, Geller SC, Waltman AC. Mesenteric venous thrombosis treated with urokinase via the superior mesenteric artery. Gastroenterology. 1996;110(5):1633–5.
52. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol. 2005;43(1):167–76.

9 Transjugular Intrahepatic Portosystemic Shunt for Non-malignant Portal Vein Thrombosis

Anshuman Elhence, Shivanand Ramachandra Gamanagatti, and Shalimar

Abstract

Portal vein thrombosis (PVT) is characterised by the presence of thrombus in the main portal vein, with or without intra-hepatic or mesenteric extension. PVT can arise in a non-cirrhotic liver, or on a background of cirrhosis. The etiologies, natural history, prognosis and therapeutic implications differ in both groups accordingly. Currently, anticoagulation is primarily recommended for those with acute PVT but is fraught with a theoretical risk of bleeding. Surgical therapy in these patients might be over-aggressive. In the past, transjugular intrahepatic portosystemic shunt (TIPS) placement was considered a relative contraindication in patients with PVT but now has been shown to be safe and efficacious in these patients, both with and without cirrhosis, with some caveats and modifications. What remains to be explored is the stage at which TIPS should be offered and whether it should be preferred over therapeutic anticoagulation. Randomized controlled trials are needed to answer this question.

Keywords

Cirrhosis · EHPVO · Anticoagulation · Intervention · TIPS · NCPF · HCC · liver Vascular · DOAC · Dabigatran · LT

A. Elhence · Shalimar (✉)
Department of Gastroenterology and Human Nutrition, All India Institute of Medical Sciences, New Delhi, India
e-mail: drshalimar@aiims.edu

S. R. Gamanagatti
Department of Radiodiagnosis, All India Institute of Medical Sciences, New Delhi, India

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_9

9.1 Introduction

Portal vein thrombosis (PVT), as the term suggests, is characterized by thrombosis in the main portal vein trunk, with or without extension into intra-hepatic portal vein branches and/or mesenteric vessels. It may occur on a background of cirrhosis, or without any evidence of chronic liver disease. Both these sub-groups differ from each other in terms of etiology, natural history and therapeutic options [1]. An important feature of PVT, which has prognostic and therapeutic implications, is the acute or chronic nature of thrombosis at the time of presentation. A stable patient of cirrhosis with new-onset PVT may present with acute decompensation (worsening of jaundice and ascites). In a patient with hepatocellular carcinoma (HCC), acute PVT may lead to acute worsening of liver function. Thus, PVT may lead to a change in the natural history of cirrhosis/liver disease.

Anticoagulation plays an important role in the management of PVT. Traditionally, transjugular intrahepatic portosystemic shunt (TIPS) has been thought to be relatively contraindicated in the setting of PVT [2]. However, over the last 2 decades, more experiences have been gained with TIPS in PVT cases, and it has been established as a valid therapeutic option [3]. A number of meta-analyses that have been published recently [4, 5] highlight the interest in the use of TIPS for PVT management.

9.2 Epidemiology

The epidemiologic data on non-cirrhotic PVT is sparse. A recent Italian study examining 3535 patients admitted in hospital over 10 years estimated the risk to be 3.8 per 100,000 inhabitants in males and 1.7 per 100,000 inhabitants in females [6]. A limitation of this study was that only symptomatic, hospitalized patients were included. The population prevalence of PVT based on autopsy series has been estimated to be around 1% [7]. The prevalence of PVT in compensated cirrhosis varies from 0.6% to 16%. In comparison, the prevalence in patients awaiting liver transplantation is around 10% (2–23%) [8]. In patients with HCC, the prevalence may be as high as 35% [9, 10]. The incidence may be affected by risk factors, which include age, gender, hypercoagulable states, study region, drugs and underlying chronic diseases. Various observational and clinical trials have also reported the incidence of PVT. Francoz et al. estimated PVT incidence to be 7% in patients waiting for liver transplantation (LT) when screened with Doppler ultrasonography [11].

9.3 Natural History and Prognosis

The natural history and prognosis of PVT differ among patients with and without cirrhosis. Another important factor that determines the outcome is the stage of presentation- acute or chronic. The data on the natural history of acute non-cirrhotic

PVT is sparse. The aim of early therapy in such a scenario is to prevent the progression of thrombus into the mesenteric vessels and promote recanalization of the portal vein, thereby preventing the development of intestinal ischemia and portal hypertension-related complications in the long term [12, 13]. Plessier et al. [13] in a prospective multicentre study included 102 patients with acute PVT without cirrhosis. Of these, 95 (93.1%) patients received anticoagulation. Over a median follow up of 234 days, anticoagulation therapy led to an increased rate of patency of the portal vein (left or right branch)- 39% vs. 13% at presentation, the splenic vein (SV)- 80% vs. 57% at presentation, and the superior mesenteric vein (SMV)- 73% vs. 42% at presentation. Progression to ischemia and infarction and death were reported in 2% of patients, each [13].

The natural history of chronic PVT in non-cirrhotic patients comes under the spectrum of extra-hepatic portal venous obstruction (EHPVO), which frequently presents as well tolerated acute variceal bleed and symptomatic moderate splenomegaly in the first decade of life, and a minority of patients may develop symptomatic portal cavernoma cholangiopathy, minimal hepatic encephalopathy (MHE), ascites, jaundice and terminal decompensation as a result of parenchymal extinction [14].

The natural history of PVT in cirrhosis is ominous and often heralds acute decompensation- worsening of jaundice, ascites, encephalopathy or detection of HCC [1]. PVT is diagnosed more frequently in patients with cirrhosis because of frequent imaging done for screening for HCC. The spontaneous recanalization rate of up to 40% has been reported [15]. The complexity of LT increases in patients with PVT, and the reported post-transplant outcomes are inferior as compared to cases without PVT [16].

9.4 Diagnostic Evaluation

Four important questions need to be answered on imaging before proceeding to the treatment of PVT. a) Is there any evidence of cirrhosis or not? b) Is the PVT acute or chronic? c) Is the thrombus bland or associated with a tumour? d) Is there an extension of thrombus into intrahepatic branches and mesenteric vessels?

Doppler ultrasonography is the first-line investigation. The thrombus appears as hypoechoic to isoechoic content within the lumen of the portal vein. Associated findings include the presence of collaterals and cavernoma. The presence of cavernoma usually indicates the chronic nature of PVT. However, cavernoma may develop within 6 days from the onset of acute PVT [17]. Doppler mode may also show the absence of flow within the portal vein. The presence of cirrhosis and other features of portal hypertension can also be inferred from the ultrasonography. Cross-sectional imaging with multiphase computed tomography is very helpful. It adds to the information given by Doppler ultrasound- the porto-mesenteric venous system can be visualized in its entirety, and the extension of thrombus into the mesenteric system with associated intestinal ischemia can also be inferred. The

presence of an enhancing, lumen-distending thrombus associated with an enhancing tumour in the cirrhotic liver, especially with high alpha-fetoprotein levels, is highly ominous for a malignant thrombus due to HCC [18].

9.5 TIPS as a Therapeutic Option for Non-malignant PVT

The role of TIPS in PVT patients with and without cirrhosis is discussed separately (Fig. 9.1). Senzolo et al. were one of the earliest to show in a large series that TIPS can be successfully placed in the setting of PVT. However, their study included a heterogeneous population of patients with cirrhosis and non-cirrhosis and those with or without cavernoma. Hence their findings cannot be generalized to all [3].

9.5.1 TIPS Technique

TIPS approach is affected by multiple factors, including the extent of PVT, the expertise of the interventional staff, and the presence of ascites. TIPS can be attempted with a transjugular approach alone (Fig. 9.2a), a combined transjugular

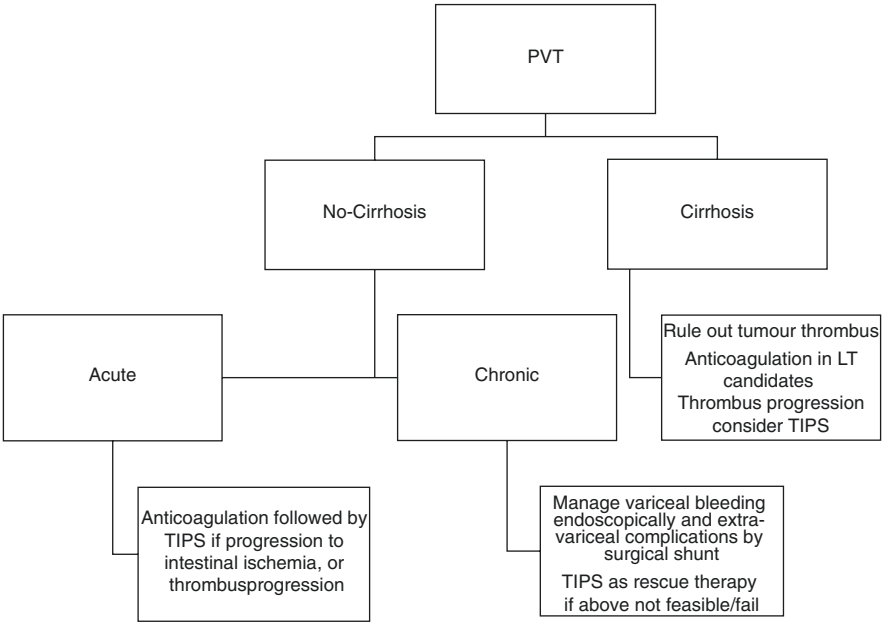

Fig. 9.1 Algorithm for management of PVT and the role of TIPS. *PVT* portal vein thrombosis, *TIPS* transjugular intrahepatic portosystemic shunt, *LT* liver transplantation

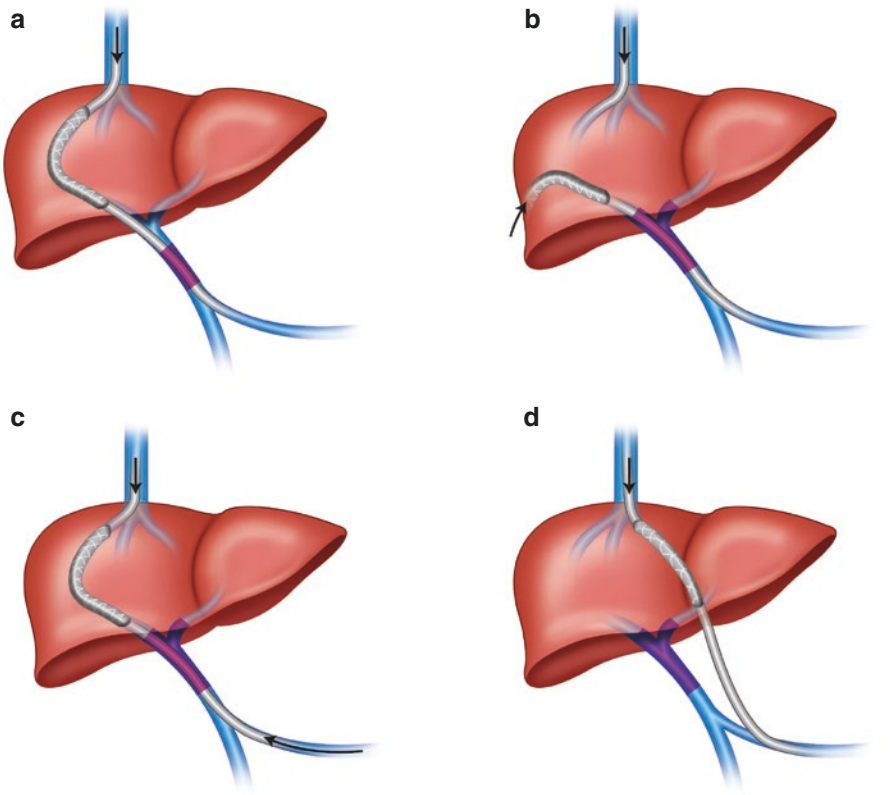

Fig. 9.2 TIPS approach in the setting of portal vein thrombosis (**a**) transjugular, (**b**) combined transhepatic and transjugular, (**c**) combined transsplenic and transjugular, (**d**) placement of TIPS through a large collateral in whom the main portal vein cannot be recanalized

and transhepatic approach (Fig. 9.2b), or a combined transjugular and transsplenic approach (Fig. 9.2c). TIPS can be placed into a recanalized main portal vein or else a dominant collateral vein (Fig. 9.2d). The use of combined transjugular and percutaneous transhepatic/transsplenic approach is recommended if intrahepatic portal vein branches are not visualized or cannot be cannulated via the transjugular approach alone. This combined approach carries a higher risk of bleeding since it involves capsular puncture; hence embolization of the percutaneous tract has been recommended [19].

9.5.2 TIPS for Acute Non-cirrhotic PVT

The standard treatment of acute non-cirrhotic PVT is anticoagulation for at least 6 months; prolonged therapy is recommended in patients with a prothrombotic state [20]. Despite adequate anticoagulation, complete recanalization occurs only in about 40% of these patients. The involvement of SMV or SV and ascites predict the failure of anticoagulation therapy [13]. A subset of patients will progress despite therapeutic anticoagulation. Certain patients with complications like bowel gangrene/perforation usually require surgical thrombectomy, with or without bowel resection. In patients with intestinal ischemia without complications of bowel perforation, transjugular local thrombolysis with or without TIPS placement is a valid therapeutic option. Klinger et al. have described a case series of 17 patients with acute non-cirrhotic and non-malignant PVT, of whom 94% were successfully treated with local therapy in the form of transjugular thrombolysis with or without TIPS placement [21]. TIPS was placed in eight patients; long term patency rates were 88% at the end of 2 years. In this study, 15/17 patients were able to avoid surgery, and none developed sequelae of portal hypertension [21]. A recent prospective study compared the role of interventional therapy (with mechanical and pharmacological thrombolysis), followed by stenting, if required, versus medical therapy. The authors reported that the former therapy was twice as effective in complete recanalization (54% vs. 30%, $p < 0.001$) but with a higher rate of bleeding complication [22]. Prospective randomized controlled trials (RCTs) between therapeutic anticoagulation and transjugular interventional therapy are required to establish the role of these therapies.

9.5.3 TIPS for Chronic Non-cirrhotic PVT

In patients with EHPVO, the recommended therapy for acute variceal bleeding is endoscopic therapy. Surgical shunts are recommended for complications, such as growth failure, symptomatic hypersplenism, portal cavernoma cholangiopathy, and recurrent variceal bleeding, despite endoscopic therapy [14, 23, 24]. Routine anticoagulation is not recommended, and only those with persistent prothrombotic state merit long-term anticoagulation after adequate prophylaxis for variceal bleed [23]. Only a few studies have evaluated the role of TIPS in this setting. Patients with EHPVO, by definition, have the presence of a portal cavernoma, which is a bunch of tortuous vessels with hepatopetal flow replacing the thrombosed main portal vein. The presence of a cavernoma causes technical difficulties in placing TIPS. Qi et al. demonstrated the feasibility and safety of TIPS in non-malignant and non-cirrhotic chronic PVT/EHPVO patients, primarily for recurrent variceal bleed [25]. Successful TIPS placement was possible in 7/20 (35%) of the patients: via a combined transjugular and transhepatic approach in 4, a combined transjugular and transsplenic approach in 2 and a transjugular approach alone in 1. Two patients required placement of TIPS within a collateral vein as the main portal vein could not

be recanalized. Shunt dysfunction occurred in 2/7 (28%) patients, and rebleeding occurred in 1 (14%) patient. None of the patients had post-TIPS encephalopathy; however, one patient had procedure-related bleed due to capsular rupture. As compared to the TIPS failure group, the rebleeding occurred in 14% (vs. 69%) patients in the TIPS success group. However, the difference in mortality was not significant due to the small sample size. In contrast, Fanelli et al., in a small study of 12 patients, reported a success rate of 83% with only one patient having shunt dysfunction and rebleed [26].

The role of TIPS in complications other than variceal bleeding has only been evaluated in one study of 28 children, of whom 17 (60%) underwent successful TIPS placement [27]. Shunt dysfunction occurred in nearly one of third patients, but a significantly higher number of patients in the TIPS success group were free of rebleeding as compared to the TIPS failure group ($p = 0.007$). The improvement in the height-for-age Z score was significantly higher in the TIPS success group as compared to the TIPS failure group ($p = 0.017$).

In view of the low technical success rate and limited availability of expertise, TIPS has a limited role in the management of patients with EHPVO. Surgical shunts, which have universally good results, are the best option. TIPS may have a role in patients not fit for surgery, but this needs to be further explored.

9.5.4 TIPS for Cirrhotic PVT

Baveno VI recommendations for the management of PVT in cirrhosis include regular 6 monthly screening in prospective transplant recipients. Institution of anticoagulation with low molecular weight heparin (LMWH) or oral anticoagulation should be done after screening for varices and appropriate pharmacological or endoscopic prophylaxis, according to the risk of variceal bleeding [23]. The basis of this recommendation in LT candidates is that the presence of advanced PVT increases the surgical complexity and leads to an increase in the rate of graft loss and mortality. Hence the main objective is to prevent thrombus progression and extension [16, 28]. The American Association of Study of Liver Diseases (AASLD) 2009 guidelines for vascular diseases of the liver do not make any recommendations for routine anticoagulation or TIPS for acute or chronic PVT in the setting of cirrhosis [29]. The European Association for the Study of the Liver (EASL) recommendations do not differ much from Baveno VI and recommend anticoagulation for at least 6 months and lifelong extension in those with an extension of the thrombus to SMV and history of intestinal ischemia or LT candidates [20]. The role in patients who are not LT candidates remains to be evaluated. A RCT by Villa et al. has shown that the use of prophylactic anticoagulation (enoxaparin) in Child B and C (B7-C10) can change the natural history of cirrhosis- at the end of 48 and 96 weeks, nearly 16% and 28% developed PVT in control group, respectively, compared with 0% and 8% in the enoxaparin group, with no increased risk of bleeding complications [30]. Patients treated with enoxaparin had lower chances of decompensation and better

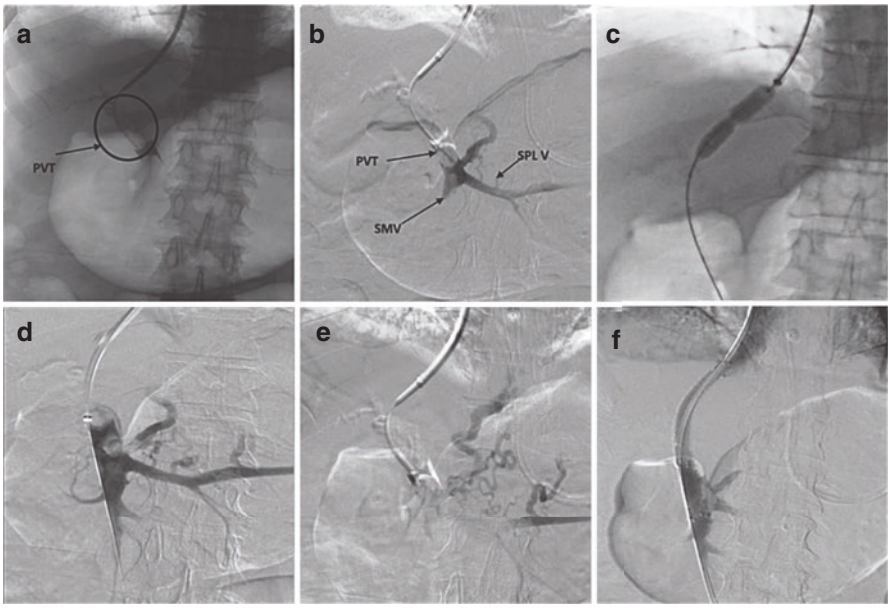

Fig. 9.3 Portogram (**a**) taken after cannulating the right portal vein showed filling defect within the main portal vein, extending till the splenoportal confluence, suggestive of thrombosis (**b**). Prior to TIPS stent placement, intraparenchymal tract was created using 10 mm × 4 cm balloon catheter (**c**). Subsequent portogram showed dilated coronary vein and varices (**d**–**e**). Final angiogram (**f**) after TIPS stent placement showed diversion of portal circulation into IVC with decompression of varices. *PVT* portal vein thrombosis, *SMV* superior mesenteric vein, *SPL V* splenic vein

survival as compared to the control group [30]. The efficacy and safety of anticoagulation with LMWH and vitamin K antagonists (VKAs) has been well established in patients with cirrhosis [31].

TIPS has been shown to be safe and effective in cirrhosis patients with PVT (Fig. 9.3). There is a lack of prospective studies comparing TIPS and anticoagulation. There might be a subgroup of patients who may not benefit from anticoagulation or be unfit for anticoagulation due to a high risk of bleeding. Luca et al. evaluated TIPS placement in 70 non-malignant cirrhotic PVT patients with a procedural success rate of 100%, among whom 57% achieved complete resolution, and 95% maintained long-term patency [32]. On follow up, only 1 in 70 had rebleeding. TIPS dysfunction was significantly higher with use of bare stents as compared to covered stents ($p = 0.0001$). In another study by Han et al., 57 patients with decompensated cirrhosis underwent TIPS primarily for variceal bleed [19]. The technical success rate was 75%, and success was dependent on the presence of cavernoma, degree of thrombosis, the involvement of portal venous branches and SMV extension. Shunt dysfunction occurred in one-fifth patients at the end of 1 year, and hepatic encephalopathy occurred in one-fourth. The rebleeding rates were significantly less in the TIPS success group compared with the TIPS failure group ($p = 0.0004$), while the survival of both groups was similar.

9.5.5 TIPS for Cirrhosis Complications

The use of TIPS in non-transplant population has also been well described. A RCT compared endoscopic band ligation and propranolol with TIPS for secondary prophylaxis of variceal bleeding in patients with cirrhosis and PVT. The authors reported a higher probability of remaining free of variceal bleeding in the TIPS group (78% vs. 43%) with no significant difference in the incidence of hepatic encephalopathy [33]. Subsequently, another trial demonstrated that in patients with cirrhosis and PVT, TIPS within 6 weeks of initial bleeding episode offered an advantage over endoscopic therapy and propranolol in terms of lower rebleeding rates at 1 year (15% vs. 45%) and at 2 years (25% vs. 50%), with no increase in encephalopathy or improvement in survival [34].

9.5.6 TIPS Procedure-Related Complications

TIPS in the setting of PVT, although technically feasible, is not without risk of complications, such as capsular perforation, hematoma, intraperitoneal hemorrhage, damage to the extrahepatic portal vein and biliary injury. Valentin et al., in their meta-analysis of 18 studies of TIPS for PVT patients with underlying liver disease, reported complications to be very rare (<1%), with only 2 cases of liver capsule perforation and hemorrhage leading to death [4]. In contrast, Rodrigues et al., in their meta-analysis of 13 studies, have reported a 10% risk of major complications [5]. Although there is a heterogeneity in complication rate, this can be explained in part by the use of catheter-related thrombolysis, which increased the complication rate to 17.7% vs. 3.3% in the TIPS alone group [5]. The complication rate of TIPS has been reported to be less when the transjugular route alone is used (5.2%), as compared to cases with transhepatic/transsplenic assistance (13.3%) [5]. The meta-analysis from Valentin et al. included studies in which the majority of patients had thrombus localized to the portal vein, and a limited number of patients had SMV or SV extension [4]. As these patients require a more invasive procedure, with more chances of complications, this might also explain the difference in complication rates between the two meta-analyses.

There is no exclusive data on post–TIPS encephalopathy, however, both the meta-analyses report hepatic encephalopathy in close to 25% during follow up.

9.6 Role of Anticoagulants Post-TIPS for PVT

There is limited evidence to support the use of anticoagulants post TIPS for PVT. In the setting of acute non-cirrhotic PVT, Klinger et al. [21] used anticoagulation with LMWH, VKA or directly acting oral anticoagulants (DOAC) for 12 months post-procedure, despite which 3/8 (37.5%) patients had a TIPS thrombosis. In the setting of chronic non-cirrhotic PVT, Qi et al. [25] used VKA, warfarin with target international normalized ratio (INR) of up to 2 for a duration of 6 to 12 months, followed

by lifelong aspirin therapy. They showed shunt dysfunction in 2/7 (28%) patients on follow up. Although anticoagulation has shown to be safe in the setting of cirrhosis, in the study by Han et al. [19] all patients received warfarin for 6–12 months followed by life-long aspirin, and they showed shunt dysfunction rate of 21%. In contrast, in the study by Luca et al. [32], none of the patients received anticoagulation, and the rate of shunt dysfunction with covered stents was 27% at 1 year.

Although LMWH and VKAs have been found to be equally effective in treating PVT, and despite its parenteral administration, LMWH is preferred over VKAs. This is because the use of INR to monitor therapeutic anticoagulation is fallacious in patients with liver disease because of the reduced synthesis of both pro and anticoagulant factors by the liver, and conversely an elevated INR increases the model for end-stage liver disease (MELD) score fallaciously, thus creating problems while listing such patients for liver transplant. In other conditions, such as renal dysfunction, VKAs are preferred over LMWH.

The role of DOACs is being explored in patients with PVT, and new data is emerging. TIPS plays an important role in the management of Budd-Chiari syndrome (BCS) [35]. TIPS is also technically feasible in BCS patients with PVT. Dabigatran has been shown to be as safe and effective in the management of post-TIPS BCS [36]. In a recent systematic review that evaluated the role of DOACs in PVT, they were found to be as effective and safe, with similar risks of major and minor bleeding episodes as traditional VKAs [37]. However, their use is offset by their cost, lack of proven safety in patients with moderate and severe hepatic and renal dysfunction and lack of cost-effective and easily available reversal agents. The issue of recommended duration of anticoagulation with DOACs has not been addressed, and various studies have used it for durations varying from 5 to 13 months [37].

9.7 Limitations of the Existing Data and Future Research

Although TIPS is feasible in the setting of PVT, yet many questions remain unanswered. The role of primary TIPS over anticoagulation alone needs to be explored in a RCT. Most studies have explored the use of TIPS after the failure of anticoagulation. The role of TIPS as compared to surgical shunts in patients with EHPVO in reducing complications, such as variceal bleeding, growth retardation, MHE, and portal cavernoma cholangiopathy, is unclear. Whether doing TIPS for PVT in the setting of cirrhosis changes the natural history of the disease and reduces further decompensation needs to be explored.

9.8 Conclusion

PVT encompasses a broad and heterogenous spectrum of abnormality. The most important distinction is to rule out the presence of underlying cirrhosis and assess the chronicity of the PVT. These subgroups have vastly different etiologies, natural history,

prognosis and treatment implications. The existing treatment recommendations support anticoagulation for a recent PVT, but recommendations for anticoagulation in chronic cases are not very clear. In a subset of patients, anticoagulation is ineffective, and TIPS has a role in further management. TIPS has been shown to effective and safe in PVT with or without cirrhosis, although there are concerns for technical difficulties in patients with chronic PVT and cavernoma. The availability of technical expertise is an important factor that determines the choice of therapy. RCTs evaluating TIPS versus anticoagulation are required to further elucidate the role of TIPS.

References

1. Intagliata NM, Caldwell SH, Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. Gastroenterology. 2019;156(6):1582-1599.e1.
2. Walser EM, NcNees SW, DeLa Pena O, Crow WN, Morgan RA, Soloway R, et al. Portal venous thrombosis: percutaneous therapy and outcome. J Vasc Interv Radiol. 1998;9(1 Pt 1):119–27.
3. Senzolo M, Tibbals J, Cholongitas E, Triantos CK, Burroughs AK, Patch D. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with and without cavernous transformation. Aliment Pharmacol Ther. 2006;23(6):767–75.
4. Valentin N, Korrapati P, Constantino J, Young A, Weisberg I. The role of transjugular intrahepatic portosystemic shunt in the management of portal vein thrombosis: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2018;30(10):1187–93.
5. Rodrigues SG, Sixt S, Abraldes JG, De Gottardi A, Klinger C, Bosch J, et al. Systematic review with meta-analysis: portal vein recanalisation and transjugular intrahepatic portosystemic shunt for portal vein thrombosis. Aliment Pharmacol Ther. 2019;49(1):20–30.
6. Ageno W, Dentali F, Pomero F, Fenoglio L, Squizzato A, Pagani G, et al. Incidence rates and case fatality rates of portal vein thrombosis and Budd-Chiari Syndrome. Thromb Haemost. 2017;117(4):794–800.
7. Ogren M, Bergqvist D, Björck M, Acosta S, Eriksson H, Sternby NH. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. World J Gastroenterol. 2006;12(13):2115–9.
8. Rodríguez-Castro KI, Porte RJ, Nadal E, Germani G, Burra P, Senzolo M. Management of nonneoplastic portal vein thrombosis in the setting of liver transplantation: a systematic review. Transplantation. 2012;94(11):1145–53.
9. Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40(5):736–41.
10. Belli L, Romani F, Sansalone CV, Aseni P, Rondinara G. Portal thrombosis in cirrhotics. A retrospective analysis. Ann Surg. 1986;203(3):286–91.
11. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005;54(5):691–7.
12. Amitrano L, Guardascione MA, Scaglione M, Pezzullo L, Sangiuliano N, Armellino MF, et al. Prognostic factors in noncirrhotic patients with splanchnic vein thromboses. Am J Gastroenterol. 2007;102(11):2464–70.
13. Plessier A, Darwish-Murad S, Hernandez-Guerra M, Consigny Y, Fabris F, Trebicka J, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. Hepatology. 2010;51(1):210–8.
14. Khanna R, Sarin SK. Idiopathic portal hypertension and extrahepatic portal venous obstruction. Hepatol Int. 2018;12(Suppl 1):148–67.

15. Qi X, Guo X, Yoshida EM, Méndez-Sánchez N, De Stefano V, Tacke F, et al. Transient portal vein thrombosis in liver cirrhosis. BMC Med. 2018;16(1):83.
16. Chen H, Turon F, Hernández-Gea V, Fuster J, Garcia-Criado A, Barrufet M, et al. Nontumoral portal vein thrombosis in patients awaiting liver transplantation. Liver Transpl. 2016;22(3):352–65.
17. De Gaetano AM, Lafortune M, Patriquin H, De Franco A, Aubin B, Paradis K. Cavernous transformation of the portal vein: patterns of intrahepatic and splanchnic collateral circulation detected with Doppler sonography. AJR Am J Roentgenol. 1995;165(5):1151–5.
18. Sherman CB, Behr S, Dodge JL, Roberts JP, Yao FY, Mehta N. Distinguishing tumor from bland portal vein thrombus in liver transplant candidates with hepatocellular carcinoma: the A-VENA criteria. Liver Transpl. 2019;25(2):207–16.
19. Han G, Qi X, He C, Yin Z, Wang J, Xia J, et al. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with symptomatic portal hypertension in liver cirrhosis. J Hepatol. 2011;54(1):78–88.
20. European Association for the Study of the Liver. EASL clinical practice guidelines: vascular diseases of the liver. J Hepatol. 2016;64(1):179–202.
21. Klinger C, Riecken B, Schmidt A, De Gottardi A, Meier B, Bosch J, et al. Transjugular local thrombolysis with/without TIPS in patients with acute non-cirrhotic, non-malignant portal vein thrombosis. Dig Liver Dis. 2017;49(12):1345–52.
22. Rössle M, Bettinger D, Trebicka J, Klinger C, Praktiknjo M, Sturm L, et al. A prospective, multicentre study in acute noncirrhotic, nonmalignant portal vein thrombosis: comparison of medical and interventional treatment. Aliment Pharmacol Ther. 2020;52:329–39.
23. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63(3):743–52.
24. Pal S. Current role of surgery in portal hypertension. Indian J Surg. 2012;74(1):55–66.
25. Qi X, Han G, Yin Z, He C, Wang J, Guo W, et al. Transjugular intrahepatic portosystemic shunt for portal cavernoma with symptomatic portal hypertension in non-cirrhotic patients. Dig Dis Sci. 2012;57(4):1072–82.
26. Fanelli F, Angeloni S, Salvatori FM, Marzano C, Boatta E, Merli M, et al. Transjugular intrahepatic portosystemic shunt with expanded-polytetrafuoroethylene-covered stents in noncirrhotic patients with portal cavernoma. Dig Liver Dis. 2011;43(1):78–84.
27. Lv Y, He C, Guo W, Yin Z, Wang J, Zhang B, et al. Transjugular intrahepatic portosystemic shunt for extrahepatic portal venous obstruction in children. J Pediatr Gastroenterol Nutr. 2016;62(2):233–41.
28. Hibi T, Nishida S, Levi DM, Selvaggi G, Tekin A, Fan J, et al. When and why portal vein thrombosis matters in liver transplantation: a critical audit of 174 cases. Ann Surg. 2014;259(4):760–6.
29. DeLeve LD, Valla DC, Garcia-Tsao G, American Association for the Study Liver Diseases. Vascular disorders of the liver. Hepatology. 2009;49(5):1729–64.
30. Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012;143(5):1253–1260.e4.
31. Delgado MG, Seijo S, Yepes I, Achécar L, Catalina MV, García-Criado A, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol. 2012;10(7):776–83.
32. Luca A, Miraglia R, Caruso S, Milazzo M, Sapere C, Maruzzelli L, et al. Short- and long-term effects of the transjugular intrahepatic portosystemic shunt on portal vein thrombosis in patients with cirrhosis. Gut. 2011;60(6):846–52.
33. Luo X, Wang Z, Tsauo J, Zhou B, Zhang H, Li X. Advanced cirrhosis combined with portal vein thrombosis: a randomized trial of TIPS versus endoscopic band ligation plus propranolol for the prevention of recurrent esophageal variceal bleeding. Radiology. 2015;276(1):286–93.

34. Lv Y, Qi X, He C, Wang Z, Yin Z, Niu J, et al. Covered TIPS versus endoscopic band ligation plus propranolol for the prevention of variceal rebleeding in cirrhotic patients with portal vein thrombosis: a randomised controlled trial. Gut. 2018;67(12):2156–68.
35. Shalimar, Gamanagatti SR, Patel AH, Kedia S, Nayak B, Gunjan D, et al. Long-term outcomes of transjugular intrahepatic portosystemic shunt in Indian patients with Budd-Chiari syndrome. Eur J Gastroenterol Hepatol. 2017;29(10):1174–82.
36. Sharma S, Kumar R, Rout G, Gamanagatti SR. Shalimar. Dabigatran as an oral anticoagulant in patients with Budd–Chiari syndrome post-percutaneous endovascular intervention. J Gastroenterol Hepatol. 2020;35(4):654–62.
37. Priyanka P, Kupec JT, Krafft M, Shah NA, Reynolds GJ. Newer oral anticoagulants in the treatment of acute portal vein thrombosis in patients with and without cirrhosis. Int J Hepatol. 2018;2018:8432781.

Liver Transplantation in the Setting of Non-malignant Portal Vein Thrombosis

10

François Durand, Safi Dokmak, Olivier Roux, and Claire Francoz

Abstract

Portal vein thrombosis whose prevalence increases in candidates for liver transplantation remains a challenging issue. In patients with advanced cirrhosis, portal vein thrombosis essentially results from portal hypertension and reduced portal blood flow. Ensuring adequate portal flow to the liver graft is an absolute prerequisite for liver transplantation to be successful. In patients with documented portal vein thrombosis at registration, the objective is to facilitate anatomical portal vein anastomosis with transjugular intrahepatic portosystemic shunt (TIPS) or per-operative thrombectomy, an alternative being jump graft with superior mesenteric vein. In patients with partial portal vein thrombosis, anticoagulation during waiting time should be considered to avoid extension of thrombosis that would preclude anatomical anastomosis. Placement of TIPS is an alternative. There is no evidence that long term anticoagulation is needed after transplantation in patients with anatomical portal vein anastomosis and adequate portal blood flow. Non-anatomical portal anastomoses are an alternative in patients with extensive splanchnic vein thrombosis. The main techniques are renoportal anastomosis using the left renal vein and hemicaval transposition with an anastomosis between the inferior vena cava and the portal vein. However,

F. Durand (✉)
Hepatology & Liver Intensive Care, Hospital Beaujon, Clichy, France

University of Paris, Paris, France
e-mail: francois.durand@bjn.aphp.fr; francois.durand@inserm.fr

S. Dokmak
Hepatobiliary and Pancreatic Surgery, Liver Transplantation, Hospital Beaujon, Clichy, France

O. Roux · C. Francoz
Hepatology & Liver Intensive Care, Hospital Beaujon, Clichy, France

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_10

these non-anatomical techniques are associated with higher morbidity and post-transplant mortality. In addition, non-anatomical procedures do not reverse portal hypertension. Portal vein thrombosis is not a contraindication for living donor liver transplantation. However, since either the right or left portal vein branches are the only available vessels, anastomoses may be technically more complex.

Keywords

Portal vein thrombosis · Portal hypertension · Cirrhosis · Liver transplantation Anticoagulation · TIPS

Abbreviations

CT	Computed tomography
DOAC	Direct acting oral anticoagulant
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
LDLT	Living donor liver transplantation.
MRI	Magnetic resonance imaging
NASH	Non-alcoholic steatohepatitis
PVT	Portal vein thrombosis
TIPS	Transjugular intrahepatic portosystemic shunt
VKA	Vitamin K antagonists

10.1 Introduction

Portal vein thrombosis (PVT) raises particular issues in the setting of transplantation as restoration of both venous and arterial blood flow to the graft are absolute prerequisites for transplantation to be successful. Adequate portal blood flow represents the most important oxygen supply to the graft and, in addition, it reverses portal hypertension. Indeed, increased resistance to portal blood flow, which is a characteristic feature of cirrhosis, rapidly returns to normal after implantation of a liver graft where parenchymal architecture is normal. Restoration of arterial blood flow to the graft is essential to ensure oxygen supply to liver parenchyma and, importantly, to bile ducts since vascularization of bile ducts essentially depends upon arterial blood flow. Indeed, blood supply to bile ducts comes from the hepatic artery and its branches, not (or marginally) the portal vein. Either early or late after liver transplantation, hepatic artery thrombosis/occlusion is typically associated with ischemic cholangiopathy that may rapidly lead to graft loss [1]. Early PVT, which is an uncommon complication in adults, may also result in graft loss due to insufficient blood supply and massive liver ischemia. Late after transplantation, PVT may be apparently well tolerated. However, it leads to recurrence of portal

hypertension and its complications. It may also compromise re-transplantation [2]. End-to-end portal vein anastomosis is the reference in liver transplantation which means that the recipient's portal vein should be patent at the time of transplantation. Alternative surgical techniques can be used to restore portal blood flow to the graft in patients with complete PVT, but these techniques are generally associated with increased morbidity and mortality [3–5]. This chapter will focus on the diagnosis and management of PVT in candidates for transplantation, impact on organ allocation, surgical aspects and impact on outcomes.

10.2 Portal Vein Thrombosis in Candidates for Transplantation

The majority of candidates for liver transplantation are either (i) patients with end stage cirrhosis with complications, such as refractory ascites, encephalopathy, and repeated bacterial infections, or (ii) patients with compensated cirrhosis and small hepatocellular carcinoma (HCC). PVT is mainly observed in the first group of patients with end stage cirrhosis as they have more pronounced portal hypertension.

PVT is not uncommon in candidates for transplantation with advanced cirrhosis, with a prevalence ranging from 5% to 25% according to different series and investigations during workup [2]. However, this prevalence does not seem to be markedly different from that observed in patients with cirrhosis who are not candidates for transplantation [6]. In addition, since in countries where transplantation is performed with deceased donors, the waiting time generally exceeds 6–12 months, a proportion of patients who did not have PVT at evaluation develop thrombosis while on the waiting list (Fig. 10.1a, b). The incidence of new PVT may be 5–10% in long waitlist regions [7]. Even though patients have detailed imaging at evaluation and repeated screening with ultrasound is recommended during waiting time,

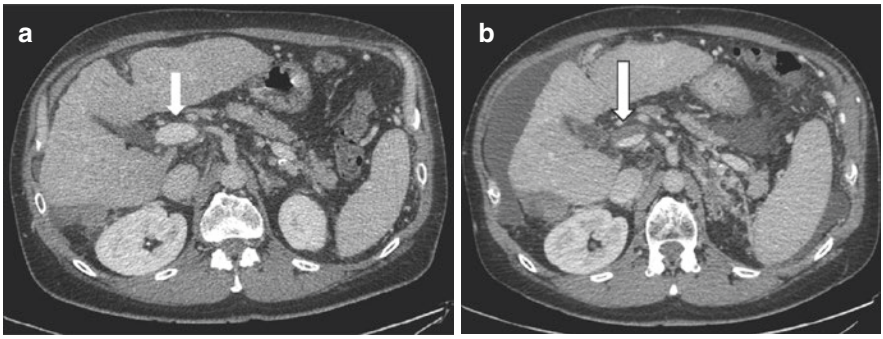

Fig. 10.1 (**a**) Patient with cirrhosis on the waiting list for transplantation with a patent portal vein (arrow) at registration. (**b**) Development of a partial portal vein thrombosis (arrow) during waiting time

several series report relatively high rates of partial PVT discovered at the time of surgery [7, 8].

In patients without cirrhosis, PVT is most often associated with coagulation disorders (either inherited or acquired) or myeloproliferative syndromes [9]. In patients with cirrhosis, by contrast, increased intrahepatic vascular resistance and decreased portal flow seem to be the main factors leading to PVT. Indeed, several studies have shown that the balance of coagulation is generally maintained in patients with decreased coagulation factor and increased INR [10, 11]. Therefore, patients with a major decrease in coagulation factors and low platelet count are not protected against PVT which is typically a complication of end stage cirrhosis. Paradoxically, an inverse correlation exists between platelet count and PVT and patients with low platelet count are at higher risk to develop PVT [7, 12]. Low platelet count which is a consequence of hypersplenism is an indirect marker of the severity of portal hypertension and reduced flow to the portal vein [2]. Reduced portal vein velocity has been identified as a predisposing factor for PVT in cirrhosis [12]. Non-selective β-blockers could also be a predisposing factor for PVT, but more data are needed [13].

It has been shown that some procoagulant factors, including factor V Leiden mutation, are more common in cirrhotic patients with PVT as compared to those without PVT [6, 14]. However, while some coagulation disorders can be clearly identified by genetic tests, other procoagulant disorders may be difficult to identify in cirrhosis due to the non-specific decrease in coagulation factors. A state of chronic systemic inflammatory state which is now well documented in cirrhosis may also contribute to thrombosis although its role needs to be more clearly explored [15]. With the generalization of direct antiviral agents, hepatitis C virus (HCV) infection has markedly decreased as an indication for transplantation. In parallel, non-alcoholic steatohepatitis (NASH) became one of the leading indications for transplantation, at least in North America [16]. Patients with NASH have a hypercoagulable profile and prevalence of PVT in NASH-related cirrhosis seems to be higher than in cirrhosis due to other causes [17]. Therefore, in the future, it can be anticipated that the prevalence of PVT in candidates for transplantation will increase.

A score termed "portal vein thrombosis risk index" has been proposed recently [18]. This score which includes NASH, age, the MELD score, moderate to severe ascites (all associated with an increased risk of PVT) and African American Origin (associated with a decreased risk of PVT) had a relatively modest accuracy to predict incident PVT with an area under curve of 0.70 [18].

Portosinusoidal vascular disease (non-cirrhotic portal hypertension) is an uncommon indication for liver transplantation [19]. However, end stage complications of conditions, such as hepatoportal sclerosis or nodular regenerative hyperplasia, both of which are components of portosinusoidal vascular diseases, can be associated with complications similar to those of end stage cirrhosis (refractory ascites, chronic encephalopathy, etc.) where liver transplantation is the only curative option. PVT is

more common in patients with end stage portosinusoidal vascular diseases than in patients with end stage cirrhosis, even in the absence of documented prothrombotic state [20, 21].

10.3 Diagnosis and Classification of Portal/Splanchnic Vein Thrombosis

The diagnosis of PVT is based on Döppler ultrasound and imaging with infusion of contrast media (computed tomography [CT] scan or magnetic resonance imaging [MRI]) which should be systematically performed during evaluation. MRI does not expose to radiations, but its definition is lower than that of CT scan, especially in patients with large volume ascites [22]. Mesenteric vein may be difficult to explore with ultrasound. In long waitlist regions or countries, it is recommended to perform imaging at a regular interval to detect incident PVT. There is no consensus on the timing of imaging but ultrasound every 3-month while on the waiting list seems a reasonable option [2]. Ultrasound may be repeated at a shorter interval in patients at high risk of developing PVT (small portal vein and/or hepatofugal flow). Any suspicion of PVT on ultrasound should lead to perform CT scan or MRI.

Cruoric PVT should be clearly differentiated from tumor invasion of portal vein branches or the trunk of the portal vein in patients with HCC [23]. Indeed, while transplantation may be considered in patients with PVT, macroscopic tumor invasion is generally considered a definitive contraindication for transplantation due to and especially high risk of early tumor recurrence. Endovascular obstruction adjacent to a tumor, vascular enlargement by the endovascular material, contrast enhancement at the arterial phase within the endovascular material, arterial signal on Döppler ultrasound within the endovascular material and high serum alfa fetoprotein level are characteristic features of tumor invasion [24, 25]. However, a clear distinction may be difficult in patients with infiltrative, ill-defined tumors. In addition, HCC does not exclude cruoric thrombosis.

Splanchnic vein thrombosis can be easily classified according to (i) intraluminal extension of the thrombus (complete occlusion vs. partial thrombosis with persistent blood flow on imaging and (ii) extension of the thrombus (intrahepatic portal vein branches and/or main portal vein and/or superior mesenteric vein and/or splanchnic vein) [2]. Partial thrombosis of the portal vein can coexist with partial or complete thrombosis of superior mesenteric vein for instance (Fig. 10.2). A number of anatomical classifications of PVT have been proposed, the Yerdel classification being a reference [26]. According to this classification, grade 1 corresponds to <50% of light with no or minimal obstruction of the superior mesenteric vein, grade 2 corresponds to >50% including total obstruction of the portal vein, grade 3 corresponds to complete obstruction of the portal and proximal superior mesenteric vein, and grade 4 corresponds to complete obstruction of the portal and superior mesenteric vein.

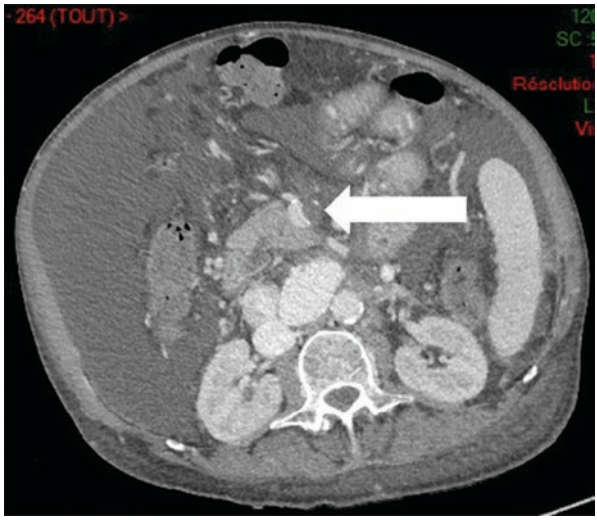

Fig. 10.2 Partial mesenteric vein thrombosis (arrow)

10.4 Impact of Portal Vein Thrombosis on Pre-transplant Mortality: Is Priority Justified?

In most countries, the number of patients who could derive a significant survival benefit from liver transplantation exceeds by far the number of available donors. Therefore, a drastic selection of candidates for transplantation is needed. Different allocation policies can be adopted according to different objectives (equity, justice, and utility). However, during the last two decades, most countries have adopted a "sickest first policy" that prioritizes patients at the highest risk of mortality without transplantation [27–29]. The objective of this sickest first policy is to reduce as much as possible the waiting list mortality, and prioritization is based on the MELD or MELD-Na scores which are robust markers of mortality in patients with cirrhosis [27–29]. Experience shows that allocation based upon MELD or MELD-Na scores does not affect post-transplant outcomes in terms of survival even though the sickest patients experience increased morbidity and longer hospital stay after transplantation.

PVT is a complication of advanced cirrhosis. However, whether PVT is only a marker of disease severity that no longer impacts disease progression at this stage or PVT is a superimposed complication that further contributes to deterioration of liver function and occurrence of additional complications remains a controversial issue.

Contrasting data have been reported. A single-center study based on a large population suggested that occlusive PVT was associated with higher mortality after evaluation and after registration for transplantation, independent of the MELD score [4]. Two series based on the UNOS/OPTN registry suggested that PVT was associated with increased port-transplant mortality but did not affect the waiting list

mortality [3, 30]. A prospective study where cirrhotic patients had screening ultrasound at a regular interval did not show evidence for an association between occurrence of PVT and disease progression [31]. Finally, a recent study also based on the UNOS/OPTN registry and using competing risk analysis showed that patients with cirrhosis and PVT had lower waiting list mortality than patients without PVT [32]. Overall, there is no clear evidence that PVT is associated with increased waiting list mortality independent of other factors predicting outcome. According to the sickest first allocation policy, for a similar MELD or MELD-Na score, there is no obvious justification to give additional priority to patients with PVT. However, it must be noted that in patients receiving vitamin K antagonists (VKA) for PVT, the MELD and MELD-Na scores may be artificially increased, thus overestimating disease severity. Indeed, the MELD score includes INR which increases with the use of VKA. For instance, in a patient not receiving VKA with a bilirubin of 150 μmol/L (8.8 mg/dL), a creatinine of 100 μmol/L (1.1 mg/dL) and an INR of 1.5, the laboratory MELD score is 20. If the same patient with the same baseline laboratory values is placed on VKA with INR increasing up to 2.5, the corresponding MELD score is 26. Similar changes can be observed with the MELD-Na score which also includes INR [29]. Ideally, the MELD score should be calculated before initiation of VKA. However, if the MELD score has to be updated, there are two possible ways to overcome this difficulty. The first way is to use the so-called MELD-XI score which takes into account bilirubin and creatinine, but not INR [33]. The equation is the following: MELD-XI = 5.11 * Ln(bilirubin [mg/dL]) + 11.76 * Ln(creatinine [mg/dL]) + 9.44. Another way is to use factor V instead of INR since its value is not influenced by VKA. A relatively strong but non-linear relation exists between factor V and INR. Therefore, baseline INR (independent of VKA) can be extrapolated from factor V according to the following equation: INR = (factor V [% of normal value]/94.9)$^{-0.81}$ [34]. None of these alternatives to the laboratory MELD score have been extensively validated.

10.5 Management of Portal Vein Thrombosis in Candidates for Transplantation

PVT is a well-documented risk factor for post-transplant morbidity and mortality. In addition, extensive splanchnic vein thrombosis (involving portal vein, splenic vein and superior mesenteric vein) may be a definitive contraindication for liver transplantation. In order of importance, the objectives are (i) to achieve recanalization of portal vein and/or mesenteric vein, (ii) to prevent complete obstruction in patients with non-obstructive thrombosis so that removal of the clot and end-to-end surgical anastomosis can be performed with the portal vein or, alternatively, the superior mesenteric vein, and (iii) to prevent extension of thrombosis in patients with complete obstruction [2].

10.5.1 Anticoagulation

Spontaneous recanalization or improvement is possible in patients with non-occlusive thrombosis. However, the rates of recanalization/improvement are highly variable in different series, ranging from 0% to more than 45% [35–39]. These variations are possibly due to differences in disease severity, diagnostic criteria and imaging protocols. Since portal/mesenteric vein patency is a central issue, treatment of patients on the waiting list is strongly recommended.

Anticoagulation is the first-line option. Several studies have been conducted in candidates for transplantation with encouraging results in those with partial (non-occlusive) thrombosis involving either the portal vein or the mesenteric vein (Table 10.1) [7, 40, 41]. Different protocols have been used with VKA, direct acting oral anticoagulants (DOACs) that inhibit thrombin or FXa and/or low molecular weight heparin (LMWH). Treatment can be initiated with LMWH with a rapid switch to VKA or DOAC [2]. VKA or DOACs can be introduced after "induction" LMWH or the patient can receive oral anticoagulants without initial intravenous/subcutaneous administration. As shown in Table 10.1, recanalization can be

Table 10.1 Anticoagulation in the treatment of portal vein thrombosis in patients with cirrhosis

Author	Year	Patients	Anticoagulation	Recanalization (%)	Extension (%)	Adverse events (%)
Francoz C [7]	2005	19	LMW heparin[a]/ VKA[b]	42	5	0
Senzolo M [41]	2009	26	LMW heparin[a]	50	–	10
Amitrano L [40]	2010	28	LMW heparin[a]	75	7	0
Delgado MG [42]	2012	55	LMW heparin[a]/ VKA[b]	60	0	20
Werner KT [87]	2013	28	VKA[b]	82	0	3
Chung JW [88]	2014	14	VKA[b]	79	0	–
Cui, SB [89]	2015	65	LMW heparin[a]	78	0	15
Chen H [90]	2016	30	VKA[b]	50	10	13
Kwon J [91]	2018	91	LMW heparin[a]	62	4	21
La Mura V [92]	2018	63	VKA[b]	70	0	36
Nagoaki Y [93]	2018	20	Danaproid/ enoxaban	90	5	15
Rodriguez-Castro KI [94]	2019	65	LMW heparin[a]	72	0	5
Hanafy AS [45]	2019	40	Rivaroxaban	85	0	0

[a]LMW heparin denotes low molecular weight heparin
[b]VKA denotes vitamin K antagonists

achieved in 40–85% of cases, a rate which is higher than what can be expected without any anticoagulation [35–39]. A systematic review has shown that 72% in patients on anticoagulation achieved recanalization compared to 42% in patients not receiving treatment [42]. Recanalization is more likely to be achieved in patients with non-occlusive thrombosis. However, in patients with chronic occlusive thrombosis, anticoagulation may prevent extension of thrombosis. For instance, in patients with chronic occlusive PVT, anticoagulation may help preserve mesenteric vein patency which facilitates transplant surgery. Even if patients with cirrhosis have portal hypertension, low platelet count and decreased coagulation factors at baseline, the rate of bleeding complications while receiving anticoagulation is relatively low. Even though there is no evidence that anticoagulation increases the risk of variceal bleeding, it is recommended to check varices and, if present, optimize beta-blockers or initiate a program of elastic band ligation. Importantly, pre-transplant anticoagulation does not seem to have a significant impact on blood loss and duration of transplant surgery [7]. Monitoring VKA in cirrhotic patients with increased INR at baseline is challenging and no consensus exists on targets to be achieved. Anticoagulation induced by VKA can be reversed by administration of fresh frozen plasma pre-operatively.

LMWH has been used in several series with good results in terms of safety and efficacy [43, 44]. The attraction of LMWH is its short half-life. A limitation is the injectable only formulation. In addition, LMWH may be contraindicated in patients with impaired renal function [43].

Experience with DOACs in cirrhosis is still limited. [45–48]. The advantages of DOACs are that there is no need for monitoring and no interference with the MELD score. However, reversibility is a major concern as transplantation with a deceased donor is not an elective surgery that can be planned. However, liver transplantation has been performed successfully in patients receiving dabigatran after administration of the reversal agent idarucizumab pre-operatively [46].

10.5.2 Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS is another option to catheterize the portal vein through transjugular access, perform thrombolysis/mechanical thrombectomy, insert a stent, restore portal flow and then achieve portal vein patency through a low resistance shunt until transplantation (Fig. 10.3a–d). Several case series including selected patients have been reported showing that, in experienced centers, the feasibility was high, ranging from 70% to almost 100% (Table 10.2). The rate of successful insertion of a TIPS in patients with partial or recent PVT is high as there are no technical difficulties in most cases. In the setting of transplantation, a crucial issue is to avoid insertion either too high in the right auricle or too low in the superior mesenteric vein which may represent technical difficulties to complete vascular anastomosis during transplant procedure. Particular attention should be paid to avoid TIPS misplacement [49]. TIPS placement may be technically more difficult in patients with complete

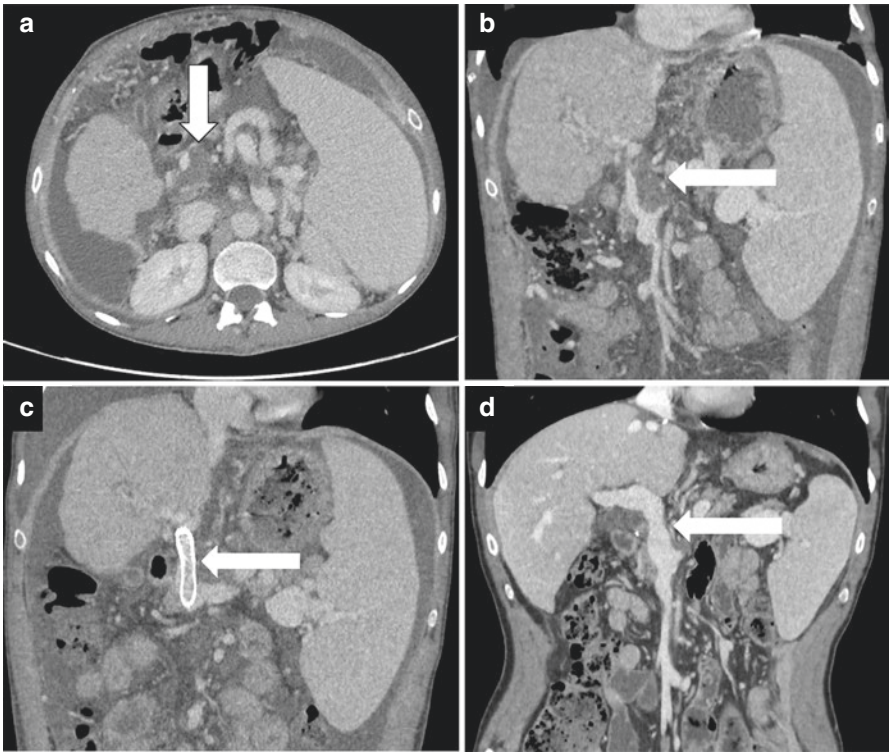

Fig. 10.3 (**a**) Near complete portal vein thrombosis (arrow) in a candidate for transplantation with decompensated cirrhosis. (**b**) Coronal image showing the thrombus with a small patent channel at the periphery of the vessel (coronal image). (**c**) Placement of a covered TIPS to recanalize portal vein while the patient is on the waiting list (coronal image). (**d**) Coronal image performed 1 year after transplantation showing a patent end to end portal vein anastomosis

Table 10.2 TIPS in the treatment of portal vein thrombosis in patients with cirrhosis

Author	Year	Patients	MELD score	Complete thrombosis	Feasibility (%)	Complete recanalization (%)
Bauer J [51]	2006	9	7	6/9	100	89
Han G [57]	2011	57	7	22/57	75	100
Luca A [95]	2011	70	8	24/70	96	60
D'Avola D [96]	2012	15	8	0/15	100	100
Luo X [97]	2015	37	9	13/37	100	65
Rosenqvist K [98]	2016	19	8	15/21	100	74
Wang Z [99]	2016	64	7	37/64	100	78
Lv Y [100]	2017	24	7	8/24	96	91
Thornburg B [101]	2017	61	–	35/61	98	92

chronic PVT with or without cavernoma. However, several series have shown that in selected patients, TIPS placement could be successful in more than 90% of patients [50, 51]. Absence of visibility of intrahepatic portal vein branches on ultrasound is a technical limitation. Successful insertion with trans-splenic or transhepatic puncture has been reported by experienced teams [52, 53]. In general, the rate of dysfunction is lower with covered stents than with bare stents. However, there is no evidence that covered stents are superior in candidates for transplantation [54].

The main limitation of TIPS in the context of transplantation is that the majority of candidates for transplantation have end stage cirrhosis with a high MELD score. In patients with a low MELD score, encephalopathy is an adverse event that occurs in 10–20% of patients [55]. In patients with a MELD score exceeding 18, TIPS is generally contraindicated due to an unacceptable rate of encephalopathy and a risk of further deterioration of cirrhosis [56]. If portal flow is restored, long term patency can be achieved by TIPS without anticoagulation [57, 58]. Therefore, anticoagulation is not recommended in patients with patent TIPS. However, ultrasound screening is strongly recommended at regular intervals. TIPS dysfunction may require revision in a minority of patients. In general, TIPS does not seem to be associated with an increase in mortality and morbidity [59]. However, in a recent series, shunt malposition was observed in 13% of cases [59].

10.6 Transplantation Procedure in Patients with Portal Vein Thrombosis

Different techniques can be used according to the extent of the thrombus and the patency and flow in the portal and mesenteric veins (Table 10.3). When full patency of the portal vein has been achieved before transplantation either with anticoagulation or TIPS, end-to-end portal anastomosis is the reference option. When thrombectomy is impossible in patients with complete PVT, portal blood flow can be restored with the superior mesenteric vein though a jump graft. When complete thrombosis involves both portal and mesenteric veins, non-anatomical anastomosis can be performed between donor portal vein and either the inferior vena cava (caval hemitransposition) or the left renal vein [2].

10.6.1 Partial Portal Vein Thrombosis

In patients with partial PVT, the objective is to perform end-to-end anastomosis and to optimize portal flow in order to ensure adequate blood flow to the graft and to prevent post-transplant re-thrombosis. The clot can be removed during the procedure by eversion thrombectomy or thrombendvenectomy consisting in removal of the clot and the adjacent intimal layer of the vein [60–62]. Whenever possible, the portal vein should be kept open and the clot should be freed and removed while the venous wall is everted (Fig. 10.4). This maneuver should be extended to the splenic and mesenteric veins when needed. If needed, anastomosis should be performed

Table 10.3 Surgical options for liver transplantation in patients with portal vein thrombosis

Extent of thrombosis at the time of transplantation	Surgical option	Anatomical reconstruction	Reversal of portal hypertension after transplantation
Partial portal vein thrombosis	✓ Thrombectomy and end-to-end portal anastomosis	Yes	Yes
Complete portal vein thrombosis	✓ Thrombectomy and end-to-end portal anastomosis ✓ Jump graft between portal vein and SMV[a]	yes No	Yes Yes
Extended thrombosis involving both portal vein and SMV[a]	✓ Reno-portal anastomosis ✓ Cavoportal hemitransposition ✓ Multivisceral transplantation including liver and small bowel (cluster)	No No Yes	No No Yes[b]

[a]SMV denotes superior mesenteric vein
[b]Reversal of portal hypertension may not always be complete

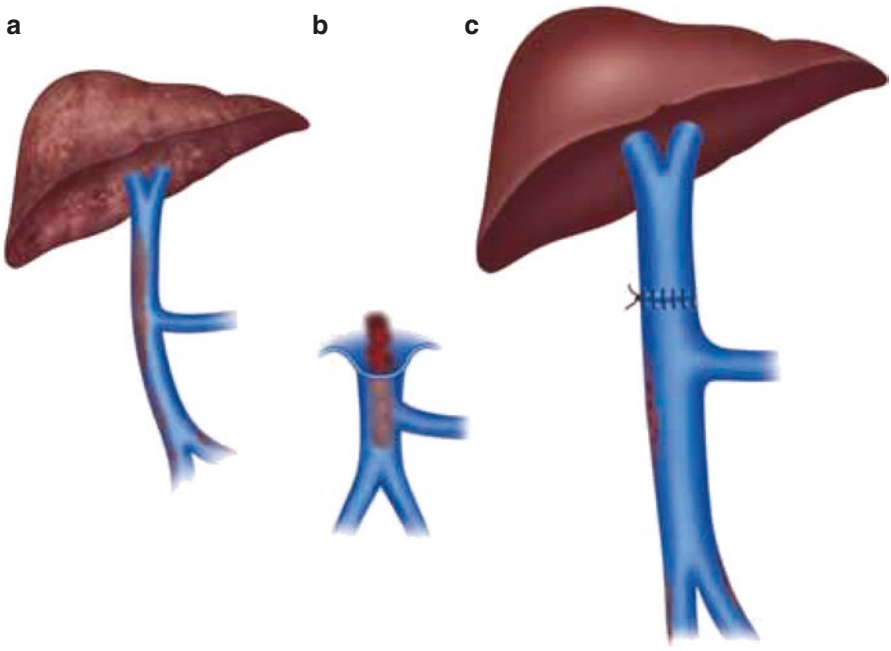

Fig. 10.4 Partial thrombosis of the portal vein in a candidate patient for liver transplantation (**a**). After near complete thrombectomy (**b**), end-to-end anastomosis is performed between both portal veins of the recipient and the liver graft (**c**)

close to the native portal vein to remove as much clot as possible [60]. Removal of the clot is easier in patients with recent thrombosis as compared to those with chronic thrombosis and organized clot. Before completing portal vein anastomosis, portal flow should be checked by removing clamps and flushing portal vein. Interposition of a vascular graft should be avoided as it is a source of post-transplant re-thrombosis [61]. Döppler ultrasound is a useful tool to assess portal blood flow during the transplant procedure. If portal blood flow remains insufficient after completion of end-to-end portal anastomosis, ligation of collateral vessels is an option and portal blood flow after ligation should be checked by Döppler ultrasound perioperatively. Early post-transplant administration of anticoagulation (LMWH in particular) is recommended to avoid re-thrombosis. If post-transplant portal blood is adequate, there is no evidence that long term anticoagulation is needed.

10.6.2 Complete Thrombosis Limited to the Portal Vein

Thrombectomy or thrombendvenectomy followed by end-to-end portal anastomosis may be possible occasionally in patients with recent PVT [8, 60]. However, removing the thrombus may be impossible in patients with chronic thrombosis since the native portal vein only consists in a fibrotic remnant. When it is impossible to restore adequate portal blood flow from the native portal vein, the first-line option is to use the distal portion of the mesenteric vein. An iliac donor vein can be used as a jump graft between donor's portal vein and recipient's mesenteric vein (Fig. 10.5). The jump graft is inserted anterior to the pancreas [63]. And if after anastomoses have been completed, blood flow in the donor's portal vein is not adequate, large porto-systemic shunts should be ligated. Endovascular radiological procedures represent another option to embolize large shunts. Some authors have proposed anastomosis between donor portal vein and collaterals, but these vessels are fragile and anastomosis may be technically difficult (Fig. 10.6) [62]. No large series support this option. Large left gastric vein to portal vein anastomosis has also been reported but clear data on post-transplant outcome are lacking [64, 65].

Portal vein arterialization which consists in creating an anastomosis between the donor's portal vein and an adjacent arterial branch has been proposed to improve post flow [66, 67]. Only small series and case reports have been reported and aneurysmal dilatation of the postal vein following arterialization has been observed late after transplantation [66].

10.6.3 Diffuse Thrombosis of the Portal and Mesenteric Veins

Extensive splanchnic vein thrombosis is a challenge in liver transplantation. The mesenteric vein can no longer be used, and it is impossible to restore a physiological portal flow to the graft. Two non-anatomic alternatives have been proposed and both consist in restoring blood flow through a systemic vein: cavoportal

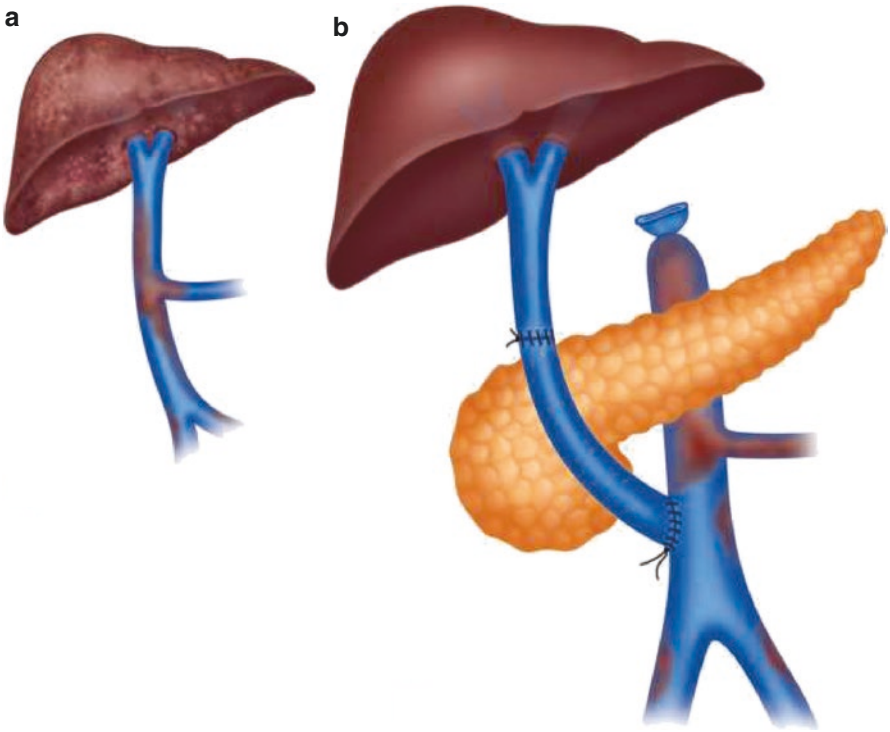

Fig. 10.5 Complete thrombosis of the portal vein and patent superior mesenteric vein in a candidate to liver transplantation (**a**). Failed thrombectomy and the portal flow to the liver graft is achieved with a jump graft on the recipient superior mesenteric vein and passed anterior to the pancreatic gland (**b**)

hemitransposition and anastomosis between donor's portal vein and recipient's left renal vein [68–71].

Cavoportal hemitransposition consists in end-to-end, end-to-side or side-to-end anastomosis between the inferior vena cava and the donor's portal vein (Fig. 10.7) [64, 68, 69]. Calibration of the suprarenal inferior vena cava can be performed to redirect blood flow preferentially to the portal vein. However, this technique may result in inferior vena cava syndrome with edema of the lower limbs and impaired kidney function.

Renoportal anastomosis consists in end-to-end anastomosis between the left renal vein and the donor's portal vein as demonstrated schmatically (Fig. 10.8) and on postoperative CT scan (Fig. 10.9) [64, 68, 71]. Alternatively, interposition of an iliac graft from the donor can be used to complete the anastomosis. In patients who had previous splenorenal shunt, this shunt can be used provided it remains patent and the shunt decompresses the splanchnic venous system [69].

Apart from anastomosis with a previous spleno-renal shunt, none of these non-anatomical techniques reverse portal hypertension. Therefore, patients are at risk of variceal bleeding, bleeding from ectopic varices and other complications of portal

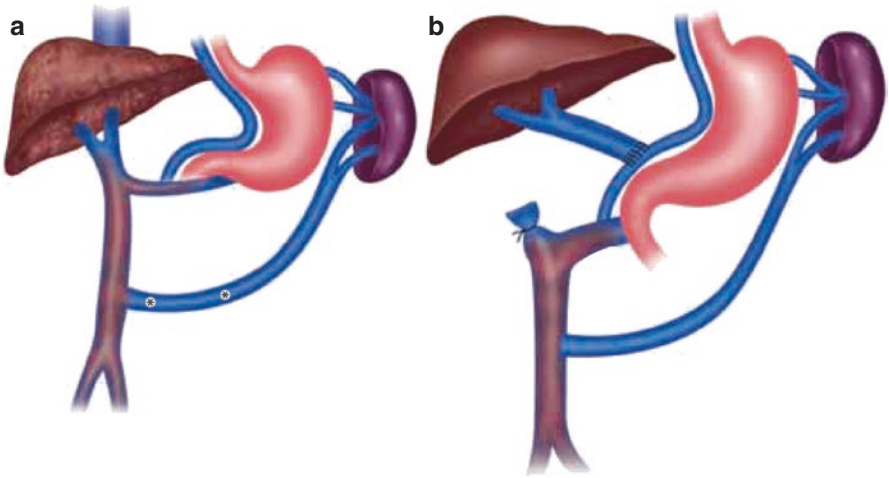

Fig. 10.6 (**a**) Complete thrombosis of the mesentericoportal vein with failed thrombectomy without spleno-renal shunts. Large perigastric varices are developped via mesenterico-colo-splenogastric venous shunts (*). Liver transplantation is performed and the portal anastomosis is done on the perigastric varices (**b**)

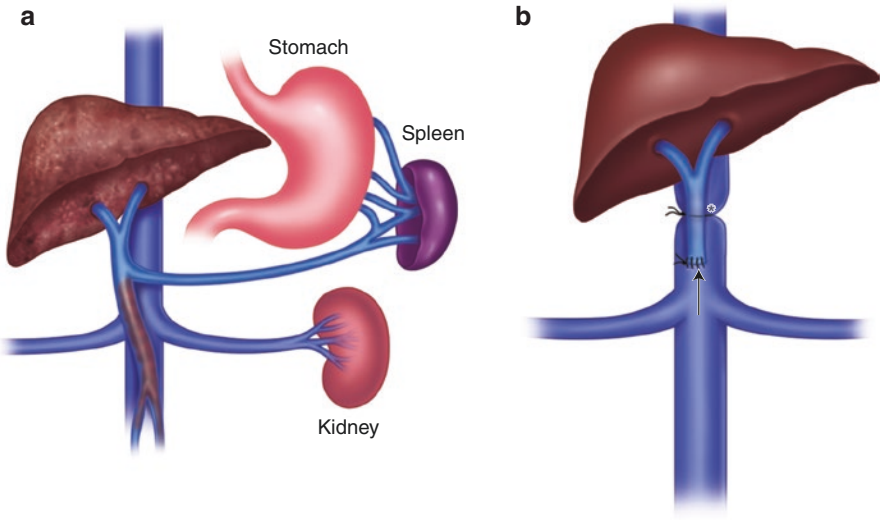

Fig. 10.7 Complete thrombosis of the mesentericoportal vein without large shunts and small bowel transplantation is not planned (**a**). (**b**) Caval hemitransposition is done and the portal anastomosis is performed as end-to-side on the anterior aspect of the recipient vena cava. Suprarenal caval calibration (*) is done to redirect the venous flow into the liver graft

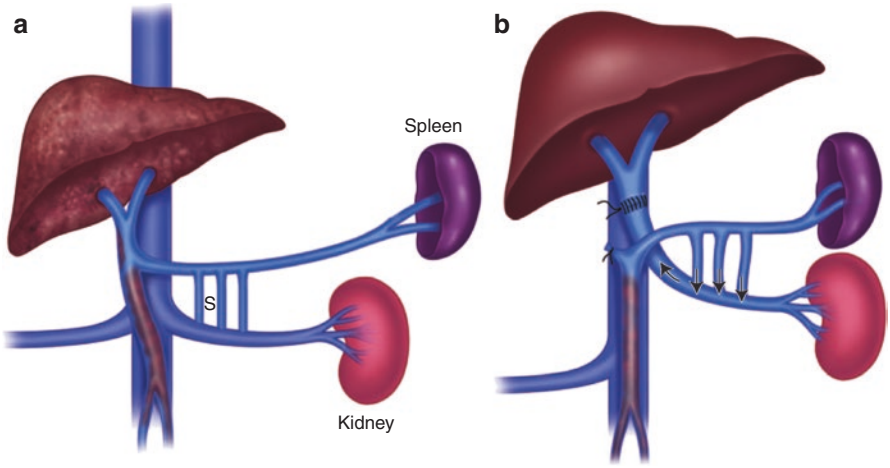

Fig. 10.8 Complete thrombosis of the mesentericoportal vein with large shunts (S) between the splenic and left renal veins (**a**) After failed thrombectomy, the portal flow to the liver graft is achieved with end-to-end reno-portal anastomosis (**b**)

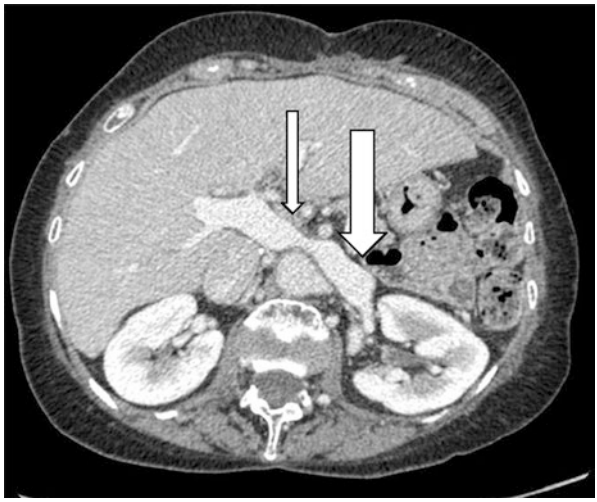

Fig. 10.9 Post operative CT scan showing a renopotal anastomosis between the recipient left renal vein (large arrow) and the graft portal vein (small arrow)

hypertension, such as bacterial translocation and systemic inflammatory response syndrome [2].

The only way to cure, at least in part, portal hypertension is to perform multivisceral transplantation including the liver, small bowel, and pancreas which are transplanted *en bloc* with the corresponding splanchnic vessels. Blood inflow is restored by a single anastomosis between donor's celiac trunk and recipient's infrarenal aorta (Fig. 10.10). Outflow is achieved with an anastomosis between the donor's inferior vena cava and recipient's inferior vena cava [72]. Although this technique

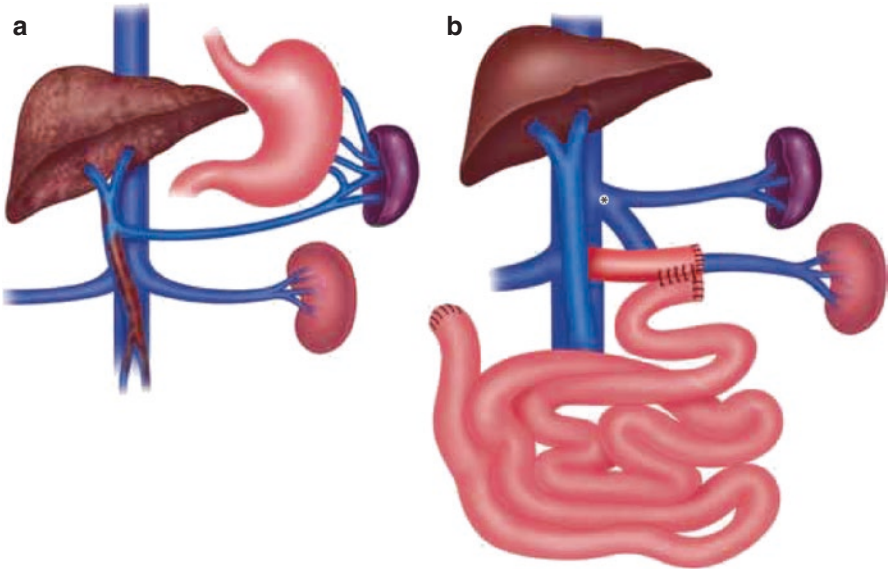

Fig. 10.10 Complete thrombosis of the mesentericoportal vein with severe portal hypertension without spleno-renal shunts (**a**). (**b**) Combined small bowel and liver or multivisceral transplantation is done. When possible, the recipient portal vein is anastomosed definitively on the vena cava (*)

restores anatomical portal flow to the graft and reverses portal hypertension, it has several limitations. This is a complex procedure performed in patients with portal hypertension and numerous collateral vessels. Post-transplant morbidity and mortality are high with a major risk of bacterial infection. Later after transplantation, the rate of rejection of the small bowel is high and potent immunosuppression is needed with subsequent risks of infections and *de novo* malignancies [73].

10.6.4 Portal Vein Thrombosis in the Context of Living Donor Liver Transplantation

Management of PVT in living donor liver transplantation (LDLT) is more complex because the graft only includes the right or the left branch of the portal vein. Most LDLTs in adults are performed with a right graft and the main portal vein is left to the donor. Indeed, minimizing morbidity in the donor is a priority. However, several reports have shown that PVT is not an absolute contraindication for LDLT [74–78]. Most of these reports come from Asian centers. In recipients with partial PVT, eversion and removal of the thrombus is the first-line option as it allows performing end-to-end portal anastomosis. In recipients with complete PVT, extensive thrombectomy is also the first-line option, including in those with thrombosis extending to the superior mesenteric vein [77]. When recanalization of the portal vein is impossible, an iliac or jugular vein should be procured in the recipient to perform reconstruction as described in deceased donor transplantation [75]. Splenectomy as

flow modulation is not recommended as it increases the risk of re-thrombosis after LDLT [79]. In general, LDLT should be considered with more caution in recipients with PVT as surgical technique is more complex and mortality rate is higher [80].

10.7 Impact of Portal Vein Thrombosis on Post-transplant Outcomes

Contrasting results have been reported concerning the impact of PVT on post-transplant outcomes. Several series suggest that post-transplant survival is similar between patients with and without PVT [8, 60, 61]. By contrast, other studies including meta-analysis and studies conducted in large databases suggest that PVT is associated with higher early (3 months to 1 year) mortality rates after transplantation [3, 5, 30, 81]. In particular, patients with NASH and PVT were found to be at higher risk of early mortality as compared to those with NASH and no PVT [81]. In these studies, patients with complete PVT were at higher mortality risk than those with partial PVT [5]. Post-transplant outcome also depends upon the surgical technique. Patients with PVT and end-to-end anastomosis are at lower mortality risk than those with non-anatomical techniques, such as caval hemitranspoition of reno-portal anastomosis [71]. PVT is also a source of post-transplant complications and increased morbidity in liver transplant recipients. Non-anatomical portal anastomoses are associated with variceal bleeding due to persistent portal hypertension, persistent ascites, acute kidney injury and infections [61, 69, 82]. Variceal bleeding should be systematically prevented by beta-blockers and/or endoscopic band ligation. Patients with PVT related to prothrombotic states are at higher risk of post-transplant thrombotic events including pulmonary embolism.

Transplantation benefit is the difference between survival with medical management alone versus liver transplantation. The threshold value of the MELD score that determines transplant benefit in patients with PVT seems slightly higher than in patients without PVT (MELD score of 13 vs. 11, respectively) because post-transplant mortality is higher in those with PVT [3]. However, in almost all North American and European countries, patients with MELD score of 13 do not have a priority for transplantation unless they receive MELD exception points.

10.8 Post-transplant Re-thrombosis: Prevention and Screening

PVT is an uncommon event in adult liver transplantation. Intuitively, patients who had PVT before transplantation may be at higher risk of post-transplant re-thrombosis as a consequence of compromised portal blood flow, partial remnant thrombus in the lumen of the native portal vein, endothelial alterations, complex

non-anatomical anastomoses or underlying prothrombotic state. Early re-thrombosis is generally a cause of graft loss with the need for emergency re-transplantation. Late re-thrombosis, by contrast, does not compromise liver graft function. However, it represents a severe complication with a large spectrum of potential consequences. Importantly, recurrence of extended PVT may compromise re-transplantation [83]. In addition, low portal blood flow after reperfusion may be an independent risk factor for biliary complications [84].

No recommendations exist on anticoagulation in patients who had PVT before transplantation. The approach may differ according to the type of anastomosis (anatomical vs. non-anatomical). The results of previously reported series suggest that long term anticoagulation should not be systematically considered in patients with PVT. Even in the absence of long-term anticoagulation, the incidence of recurrent PVT was lower than 5% [8, 61, 85]. However, a recent study has shown that the rate of re-thrombosis was significantly higher in patients with high grade PVT before transplantation and low portal flow after reperfusion [84]. Practically, portal blood flow and portal vein patency should be screened with ultrasound at regular intervals in patients with PVT prior to transplantation. Even if no threshold values have been established in terms of portal blood flow, long-term anticoagulation is recommended in patients with low portal blood flow after transplantation as well as in patients with complex, non-anatomical anastomosis. VKA remains a reference for long term anticoagulation. DOACs need to be evaluated.

Long-term administration of low dose aspirin after transplantation to prevent hepatic artery thrombosis and other cardiovascular complications is common [86]. There is no evidence that aspirin lowers the rate of PVT after transplantation.

10.9 Conclusions and Perspectives

Despite advances in assessment and selection of candidates of transplantation, refinements in surgical techniques and improvements in perioperative care, PVT remains a challenging issue in liver transplantation. With the growing incidence of NASH, it can be anticipated that the proportion of candidates for transplantation with PVT will be increased. End-to-end portal anastomosis with adequate portal blood flow continues to be the main objective. In any potential candidate for transplantation, risk factors for PVT should be better identified and preventive anticoagulation may be considered in high-risk patients. In patients with PVT, refinements in interventional radiology with trans-splenic approach or minimally invasive techniques to catheterize the superior mesenteric vein could help increase the rate of recanalization. Overall, screening for PVT is a central issue in long waitlist region in order to detect thrombosis at an early stage and to avoid extensive thrombosis of the mesenteric axis.

References

1. Bekker J, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. Am J Transplant. 2009;9(4):746–57. https://doi.org/10.1111/j.1600-6143.2008.02541.x.
2. Francoz C, Valla D, Durand F. Portal vein thrombosis, cirrhosis, and liver transplantation. J Hepatol. 2012;57(1):203–12. https://doi.org/10.1016/j.jhep.2011.12.034.
3. Englesbe MJ, Schaubel DE, Cai S, Guidinger MK, Merion RM. Portal vein thrombosis and liver transplant survival benefit. Liver Transpl. 2010;16(8):999–1005. https://doi.org/10.1002/lt.22105.
4. Englesbe MJ, Kubus J, Muhammad W, Sonnenday CJ, Welling T, Punch JD, et al. Portal vein thrombosis and survival in patients with cirrhosis. Liver Transpl. 2010;16(1):83–90. https://doi.org/10.1002/lt.21941.
5. Zanetto A, Rodriguez-Kastro KI, Germani G, Ferrarese A, Cillo U, Burra P, et al. Mortality in liver transplant recipients with portal vein thrombosis—an updated meta-analysis. Transpl Int. 2018;31(12):1318–29. https://doi.org/10.1111/tri.13353.
6. Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40(5):736–41. https://doi.org/10.1016/j.jhep.2004.01.001.
7. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005;54(5):691–7. https://doi.org/10.1136/gut.2004.042796.
8. Dumortier J, Czyglik O, Poncet G, Blanchet MC, Boucaud C, Henry L, et al. Eversion thrombectomy for portal vein thrombosis during liver transplantation. Am J Transplant. 2002;2(10):934–8. https://doi.org/10.1034/j.1600-6143.2002.21009.x.
9. DeLeve LD, Valla DC, Garcia-Tsao G, American Association for the Study Liver Diseases. Vascular disorders of the liver. Hepatology. 2009;49(5):1729–64. https://doi.org/10.1002/hep.22772.
10. Tsochatzis EA, Senzolo M, Germani G, Gatt A, Burroughs AK. Systematic review: portal vein thrombosis in cirrhosis. Aliment Pharmacol Ther. 2010;31(3):366–74. https://doi.org/10.1111/j.1365-2036.2009.04182.x.
11. Northup PG, Sundaram V, Fallon MB, Reddy KR, Balogun RA, Sanyal AJ, et al. Hypercoagulation and thrombophilia in liver disease. J Thromb Haemost. 2008;6(1):2–9. https://doi.org/10.1111/j.1538-7836.2007.02772.x.
12. Zocco MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, et al. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. J Hepatol. 2009;51(4):682–9. https://doi.org/10.1016/j.jhep.2009.03.013.
13. Nery F, Correia S, Macedo C, Gandara J, Lopes V, Valadares D, et al. Nonselective beta-blockers and the risk of portal vein thrombosis in patients with cirrhosis: results of a prospective longitudinal study. Aliment Pharmacol Ther. 2019;49(5):582–8. https://doi.org/10.1111/apt.15137.
14. Amitrano L, Brancaccio V, Guardascione MA, Margaglione M, Iannaccone L, D'Andrea G, et al. Inherited coagulation disorders in cirrhotic patients with portal vein thrombosis. Hepatology. 2000;31(2):345–8. https://doi.org/10.1002/hep.510310213.
15. Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. Hepatology. 2016;64(4):1249–64. https://doi.org/10.1002/hep.28740.
16. Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148(3):547–55. https://doi.org/10.1053/j.gastro.2014.11.039.

17. Stine JG, Shah NL, Argo CK, Pelletier SJ, Caldwell SH, Northup PG. Increased risk of portal vein thrombosis in patients with cirrhosis due to nonalcoholic steatohepatitis. Liver Transpl. 2015;21(8):1016–21. https://doi.org/10.1002/lt.24134.
18. Gaballa D, Bezinover D, Kadry Z, Eyster E, Wang M, Northup PG, et al. Development of a model to predict portal vein thrombosis in liver transplant candidates: the portal vein thrombosis risk index. Liver Transpl. 2019;25(12):1747–55. https://doi.org/10.1002/lt.25630.
19. De Gottardi A, Rautou PE, Schouten J, Rubbia-Brandt L, Leebeek F, Trebicka J, et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. Lancet Gastroenterol Hepatol. 2019;4(5):399–411. https://doi.org/10.1016/S2468-1253(19)30047-0.
20. Giudicelli H, Rautou PE, Paradis V, Bedossa P, Goria O, Lambert V, et al. Porto-sinusoidal vascular disease. Vascular liver diseases: position papers from the francophone network for vascular liver diseases, the French Association for the Study of the Liver (AFEF), and ERN-rare liver. Clin Res Hepatol Gastroenterol. 2020; https://doi.org/10.1016/j.clinre.2020.03.005.
21. Siramolpiwat S, Seijo S, Miquel R, Berzigotti A, Garcia-Criado A, Darnell A, et al. Idiopathic portal hypertension: natural history and long-term outcome. Hepatology. 2014;59(6):2276–85. https://doi.org/10.1002/hep.26904.
22. Wallner B, Edelman RR, Finn JP, Mattle HP. Bright pleural effusion and ascites on gradient-echo MR images: a potential source of confusion in vascular MR studies. AJR Am J Roentgenol. 1990;155(6):1237–40. https://doi.org/10.2214/ajr.155.6.2122672.
23. Piscaglia F, Gianstefani A, Ravaioli M, Golfieri R, Cappelli A, Giampalma E, et al. Criteria for diagnosing benign portal vein thrombosis in the assessment of patients with cirrhosis and hepatocellular carcinoma for liver transplantation. Liver Transpl. 2010;16(5):658–67. https://doi.org/10.1002/lt.22044.
24. Tublin ME, Dodd GD 3rd, Baron RL. Benign and malignant portal vein thrombosis: differentiation by CT characteristics. AJR Am J Roentgenol. 1997;168(3):719–23. https://doi.org/10.2214/ajr.168.3.9057522.
25. Song ZZ, Huang M, Jiang TA, Zhao QY, Yao L, Mou Y, et al. Diagnosis of portal vein thrombosis discontinued with liver tumors in patients with liver cirrhosis and tumors by contrast-enhanced US: a pilot study. Eur J Radiol. 2010;75(2):185–8. https://doi.org/10.1016/j.ejrad.2009.04.021.
26. Yerdel MA, Gunson B, Mirza D, Karayalcin K, Olliff S, Buckels J, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. Transplantation. 2000;69(9):1873–81. https://doi.org/10.1097/00007890-200005150-00023.
27. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124(1):91–6. https://doi.org/10.1053/gast.2003.50016.
28. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000;31(4):864–71. https://doi.org/10.1053/he.2000.5852.
29. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359(10):1018–26. https://doi.org/10.1056/NEJMoa0801209.
30. Ghabril M, Agarwal S, Lacerda M, Chalasani N, Kwo P, Tector AJ. Portal vein thrombosis is a risk factor for poor early outcomes after liver transplantation: analysis of risk factors and outcomes for portal vein thrombosis in waitlisted patients. Transplantation. 2016;100(1):126–33. https://doi.org/10.1097/TP.0000000000000785.
31. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015;61(2):660–7. https://doi.org/10.1002/hep.27546.
32. Berry K, Taylor J, Liou IW, Ioannou GN. Portal vein thrombosis is not associated with increased mortality among patients with cirrhosis. Clin Gastroenterol Hepatol. 2015;13(3):585–93. https://doi.org/10.1016/j.cgh.2014.10.010.

33. Heuman DM, Mihas AA, Habib A, Gilles HS, Stravitz RT, Sanyal AJ, et al. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. Liver Transpl. 2007;13(1):30–7. https://doi.org/10.1002/lt.20906.
34. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol. 2005;42(Suppl 1):S100–7. https://doi.org/10.1016/j.jhep.2004.11.015.
35. Qi X, Han G, Fan D. Management of portal vein thrombosis in liver cirrhosis. Nat Rev Gastroenterol Hepatol. 2014;11(7):435–46. https://doi.org/10.1038/nrgastro.2014.36.
36. Maruyama H, Okugawa H, Takahashi M, Yokosuka O. De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. Am J Gastroenterol. 2013;108(4):568–74. https://doi.org/10.1038/ajg.2012.452.
37. John BV, Konjeti R, Aggarwal A, Lopez R, Atreja A, Miller C, et al. Impact of untreated portal vein thrombosis on pre and post liver transplant outcomes in cirrhosis. Ann Hepatol. 2013;12(6):952–8.
38. Luca A, Caruso S, Milazzo M, Marrone G, Mamone G, Crino F, et al. Natural course of extrahepatic nonmalignant partial portal vein thrombosis in patients with cirrhosis. Radiology. 2012;265(1):124–32. https://doi.org/10.1148/radiol.12112236.
39. Senzolo M, T MS, Rossetto V, Burra P, Cillo U, Boccagni P, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. Liver Int. 2012;32(6):919–27. https://doi.org/10.1111/j.1478-3231.2012.02785.x.
40. Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, et al. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. J Clin Gastroenterol. 2010;44(6):448–51. https://doi.org/10.1097/MCG.0b013e3181b3ab44.
41. Senzolo M, Sartori MT, Lisman T. Should we give thromboprophylaxis to patients with liver cirrhosis and coagulopathy? HPB (Oxford). 2009;11(6):459–64. https://doi.org/10.1111/j.1477-2574.2009.00079.x.
42. Delgado MG, Seijo S, Yepes I, Achecar L, Catalina MV, Garcia-Criado A, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol. 2012;10(7):776–83. https://doi.org/10.1016/j.cgh.2012.01.012.
43. Northup P, Reutemann B. Management of coagulation and anticoagulation in liver transplantation candidates. Liver Transpl. 2018;24(8):1119–32. https://doi.org/10.1002/lt.25198.
44. Qi X, De Stefano V, Li H, Dai J, Guo X, Fan D. Anticoagulation for the treatment of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Eur J Intern Med. 2015;26(1):23–9. https://doi.org/10.1016/j.ejim.2014.12.002.
45. Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. Vasc Pharmacol. 2019;113:86–91. https://doi.org/10.1016/j.vph.2018.05.002.
46. Intagliata NM, Maitland H, Pellitier S, Caldwell SH. Reversal of direct oral anticoagulants for liver transplantation in cirrhosis: a step forward. Liver Transpl. 2017;23(3):396–7. https://doi.org/10.1002/lt.24708.
47. Hum J, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. Eur J Haematol. 2017;98(4):393–7. https://doi.org/10.1111/ejh.12844.
48. De Gottardi A, Trebicka J, Klinger C, Plessier A, Seijo S, Terziroli B, et al. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. Liver Int. 2017;37(5):694–9. https://doi.org/10.1111/liv.13285.
49. Clavien PA, Selzner M, Tuttle-Newhall JE, Harland RC, Suhocki P. Liver transplantation complicated by misplaced TIPS in the portal vein. Ann Surg. 1998;227(3):440–5. https://doi.org/10.1097/00000658-199803000-00017.
50. Rodrigues SG, Sixt S, Abraldes JG, De Gottardi A, Klinger C, Bosch J, et al. Systematic review with meta-analysis: portal vein recanalisation and transjugular intrahepatic portosystemic shunt for portal vein thrombosis. Aliment Pharmacol Ther. 2019;49(1):20–30. https://doi.org/10.1111/apt.15044.

51. Bauer J, Johnson S, Durham J, Ludkowski M, Trotter J, Bak T, et al. The role of TIPS for portal vein patency in liver transplant patients with portal vein thrombosis. Liver Transpl. 2006;12(10):1544–51. https://doi.org/10.1002/lt.20869.
52. Salem R, Vouche M, Baker T, Herrero JI, Caicedo JC, Fryer J, et al. Pretransplant portal vein recanalization-transjugular intrahepatic portosystemic shunt in patients with complete obliterative portal vein thrombosis. Transplantation. 2015;99(11):2347–55. https://doi.org/10.1097/TP.0000000000000729.
53. Habib A, Desai K, Hickey R, Thornburg B, Vouche M, Vogelzang RL, et al. Portal vein recanalization-transjugularintrahepatic portosystemic shunt using the transsplenic approach to achieve transplant candidacy in patients with chronic portal vein thrombosis. J Vasc Interv Radiol. 2015;26(4):499–506. https://doi.org/10.1016/j.jvir.2014.12.012.
54. Bureau C, Garcia-Pagan JC, Otal P, Pomier-Layrargues G, Chabbert V, Cortez C, et al. Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS: results of a randomized study. Gastroenterology. 2004;126(2):469–75. https://doi.org/10.1053/j.gastro.2003.11.016.
55. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406–60. https://doi.org/10.1016/j.jhep.2018.03.024.
56. Ferral H, Gamboa P, Postoak DW, Albernaz VS, Young CR, Speeg KV, et al. Survival after elective transjugular intrahepatic portosystemic shunt creation: prediction with model for end-stage liver disease score. Radiology. 2004;231(1):231–6. https://doi.org/10.1148/radiol.2311030967.
57. Han G, Qi X, He C, Yin Z, Wang J, Xia J, et al. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with symptomatic portal hypertension in liver cirrhosis. J Hepatol. 2011;54(1):78–88. https://doi.org/10.1016/j.jhep.2010.06.029.
58. Perarnau JM, Baju A, D'Alteroche L, Viguier J, Ayoub J. Feasibility and long-term evolution of TIPS in cirrhotic patients with portal thrombosis. Eur J Gastroenterol Hepatol. 2010;22(9):1093–8. https://doi.org/10.1097/MEG.0b013e328338d995.
59. Matsushima H, Fujiki M, Sasaki K, Cywinski JB, D'Amico G, Uso TD, et al. Can pretransplant TIPS be harmful in liver transplantation? A propensity score matching analysis. Surgery. 2020;168(1):33–9. https://doi.org/10.1016/j.surg.2020.02.017.
60. Molmenti EP, Roodhouse TW, Molmenti H, Jaiswal K, Jung G, Marubashi S, et al. Thrombendvenectomy for organized portal vein thrombosis at the time of liver transplantation. Ann Surg. 2002;235(2):292–6. https://doi.org/10.1097/00000658-200202000-00019.
61. Ravaioli M, Zanello M, Grazi GL, Ercolani G, Cescon M, Del Gaudio M, et al. Portal vein thrombosis and liver transplantation: evolution during 10 years of experience at the University of Bologna. Ann Surg. 2011;253(2):378–84. https://doi.org/10.1097/SLA.0b013e318206818b.
62. Lerut JP, Mazza D, van Leeuw V, Laterre PF, Donataccio M, de Ville de Goyet J, et al. Adult liver transplantation and abnormalities of splanchnic veins: experience in 53 patients. Transpl Int. 1997;10(2):125–32. https://doi.org/10.1007/s001470050025.
63. Figueras J, Torras J, Rafecas A, Fabregat J, Ramos E, Moreno G, et al. Extra-anatomic venous graft for portal vein thrombosis in liver transplantation. Transpl Int. 1997;10(5):407–8. https://doi.org/10.1111/j.1432-2277.1997.tb00940.x.
64. Bhangui P, Lim C, Levesque E, Salloum C, Lahat E, Feray C, et al. Novel classification of non-malignant portal vein thrombosis: a guide to surgical decision-making during liver transplantation. J Hepatol. 2019;71(5):1038–50. https://doi.org/10.1016/j.jhep.2019.08.012.
65. Llado L, Fabregat J, Castellote J, Ramos E, Torras J, Jorba R, et al. Management of portal vein thrombosis in liver transplantation: influence on morbidity and mortality. Clin Transpl. 2007;21(6):716–21. https://doi.org/10.1111/j.1399-0012.2007.00728.x.
66. Bonnet S, Sauvanet A, Bruno O, Sommacale D, Francoz C, Dondero F, et al. Long-term survival after portal vein arterialization for portal vein thrombosis in orthotopic liver transplantation. Gastroenterol Clin Biol. 2010;34(1):23–8. https://doi.org/10.1016/j.gcb.2009.05.013.

67. Charco R, Margarit C, Lopez-Talavera JC, Hidalgo E, Castells L, Allende H, et al. Outcome and hepatic hemodynamics in liver transplant patients with portal vein arterialization. Am J Transplant. 2001;1(2):146–51.
68. Paskonis M, Jurgaitis J, Mehrabi A, Kashfi A, Fonouni H, Strupas K, et al. Surgical strategies for liver transplantation in the case of portal vein thrombosis--current role of cavoportal hemitransposition and renoportal anastomosis. Clin Transpl. 2006;20(5):551–62. https://doi.org/10.1111/j.1399-0012.2006.00560.x.
69. Selvaggi G, Weppler D, Nishida S, Moon J, Levi D, Kato T, et al. Ten-year experience in porto-caval hemitransposition for liver transplantation in the presence of portal vein thrombosis. Am J Transplant. 2007;7(2):454–60. https://doi.org/10.1111/j.1600-6143.2006.01649.x.
70. Gerunda GE, Merenda R, Neri D, Angeli P, Barbazza F, Valmasoni M, et al. Cavoportal hemitransposition: a successful way to overcome the problem of total portosplenomesenteric thrombosis in liver transplantation. Liver Transpl. 2002;8(1):72–5. https://doi.org/10.1053/jlts.2002.30404.
71. D'Amico G, Hassan A, Diago Uso T, Hashmimoto K, Aucejo FN, Fujiki M, et al. Renoportal anastomosis in liver transplantation and its impact on patient outcomes: a systematic literature review. Transpl Int. 2019;32(2):117–27. https://doi.org/10.1111/tri.13368.
72. Vianna R, Giovanardi RO, Fridell JA, Tector AJ. Multivisceral transplantation for diffuse portomesenteric thrombosis in a patient with life-threatening esophagogastroduodenal bleeding. Transplantation. 2005;80(4):534–5. https://doi.org/10.1097/01.tp.0000168344.16547.da.
73. Fujishiro J, Pech TC, Finger TF, Praktinjo M, Stoffels B, Standop J, et al. Influence of immunosuppression on alloresponse, inflammation and contractile function of graft after intestinal transplantation. Am J Transplant. 2010;10(7):1545–55. https://doi.org/10.1111/j.1600-6143.2010.03117.x.
74. Cho JY, Suh KS, Shin WY, Lee HW, Yi NJ, Lee KU. Thrombosis confined to the portal vein is not a contraindication for living donor liver transplantation. World J Surg. 2008;32(8):1731–7. https://doi.org/10.1007/s00268-008-9651-4.
75. Egawa H, Tanaka K, Kasahara M, Takada Y, Oike F, Ogawa K, et al. Single center experience of 39 patients with preoperative portal vein thrombosis among 404 adult living donor liver transplantations. Liver Transpl. 2006;12(10):1512–8. https://doi.org/10.1002/lt.20777.
76. Kadry Z, Selzner N, Handschin A, Mullhaupt B, Renner EL, Clavien PA. Living donor liver transplantation in patients with portal vein thrombosis: a survey and review of technical issues. Transplantation. 2002;74(5):696–701. https://doi.org/10.1097/00007890-200209150-00018.
77. Ikegami T, Yoshizumi T, Tsutsui Y, Harada N, Itoh S, Yoshiya S, et al. Extensive thrombectomy as a legitimate strategy in living donor liver transplantation with advanced portal vein thrombosis. Liver Transpl. 2019;25(12):1768–77. https://doi.org/10.1002/lt.25623.
78. Kuriyama N, Kazuaki G, Hayasaki A, Fujii T, Iizawa Y, Kato H, et al. Surgical procedures of portal vein reconstruction for recipients with portal vein thrombosis in adult-to-adult living donor liver transplantation. Transplant Proc. 2020;52(6):1802–6. https://doi.org/10.1016/j.transproceed.2020.01.155.
79. Linares I, Goldaracena N, Rosales R, Maza L, Kaths M, Kollmann D, et al. Splenectomy as flow modulation strategy and risk factors of de novo portal vein thrombosis in adult-to-adult living donor liver transplantation. Liver Transpl. 2018;24(9):1209–20. https://doi.org/10.1002/lt.25212.
80. Trotter JF. Single-center experience of 39 patients with preoperative portal vein thrombosis among 404 adult living donor liver transplantations. Liver Transpl. 2006;12(10):1455–6. https://doi.org/10.1002/lt.20924.
81. Agbim U, Jiang Y, Kedia SK, Singal AK, Ahmed A, Bhamidimarri KR, et al. Impact of nonmalignant portal vein thrombosis in transplant recipients with nonalcoholic steatohepatitis. Liver Transpl. 2019;25(1):68–78. https://doi.org/10.1002/lt.25322.
82. Azoulay D, Adam R, Castaing D, Muresan S, Essomba A, Vibert E, et al. Liver transplantation with cavoportal or renoportal anastomosis: a solution in cases of diffuse portal thrombosis. Gastroenterol Clin Biol. 2002;26(4):325–30.

83. Lerut J, Tzakis AG, Bron K, Gordon RD, Iwatsuki S, Esquivel CO, et al. Complications of venous reconstruction in human orthotopic liver transplantation. Ann Surg. 1987;205(4):404–14. https://doi.org/10.1097/00000658-198704000-00011.
84. Rizzari MD, Safwan M, Sobolic M, Kitajima T, Collins K, Yoshida A, et al. The impact of portal vein thrombosis on liver transplant outcomes: does grade or flow rate matter? Transplantation. 2020; https://doi.org/10.1097/TP.0000000000003235.
85. Manzanet G, Sanjuan F, Orbis P, Lopez R, Moya A, Juan M, et al. Liver transplantation in patients with portal vein thrombosis. Liver Transpl. 2001;7(2):125–31. https://doi.org/10.1053/jlts.2001.21295.
86. Vivarelli M, La Barba G, Cucchetti A, Lauro A, Del Gaudio M, Ravaioli M, et al. Can antiplatelet prophylaxis reduce the incidence of hepatic artery thrombosis after liver transplantation? Liver Transpl. 2007;13(5):651–4. https://doi.org/10.1002/lt.21028.
87. Werner KT, Sando S, Carey EJ, Vargas HE, Byrne TJ, Douglas DD, et al. Portal vein thrombosis in patients with end stage liver disease awaiting liver transplantation: outcome of anticoagulation. Dig Dis Sci. 2013;58(6):1776–80. https://doi.org/10.1007/s10620-012-2548-y.
88. Chung JW, Kim GH, Lee JH, Ok KS, Jang ES, Jeong SH, et al. Safety, efficacy, and response predictors of anticoagulation for the treatment of nonmalignant portal-vein thrombosis in patients with cirrhosis: a propensity score matching analysis. Clin Mol Hepatol. 2014;20(4):384–91. https://doi.org/10.3350/cmh.2014.20.4.384.
89. Cui SB, Shu RH, Yan SP, Wu H, Chen Y, Wang L, et al. Efficacy and safety of anticoagulation therapy with different doses of enoxaparin for portal vein thrombosis in cirrhotic patients with hepatitis B. Eur J Gastroenterol Hepatol. 2015;27(8):914–9. https://doi.org/10.1097/MEG.0000000000000351.
90. Chen H, Liu L, Qi X, He C, Wu F, Fan D, et al. Efficacy and safety of anticoagulation in more advanced portal vein thrombosis in patients with liver cirrhosis. Eur J Gastroenterol Hepatol. 2016;28(1):82–9. https://doi.org/10.1097/MEG.0000000000000482.
91. Kwon J, Koh Y, Yu SJ, Yoon JH. Low-molecular-weight heparin treatment for portal vein thrombosis in liver cirrhosis: efficacy and the risk of hemorrhagic complications. Thromb Res. 2018;163:71–6. https://doi.org/10.1016/j.thromres.2018.01.032.
92. La Mura V, Braham S, Tosetti G, Branchi F, Bitto N, Moia M, et al. Harmful and beneficial effects of anticoagulants in patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol. 2018;16(7):1146–52.e4. https://doi.org/10.1016/j.cgh.2017.10.016.
93. Nagaoki Y, Aikata H, Daijyo K, Teraoka Y, Shinohara F, Nakamura Y, et al. Efficacy and safety of edoxaban for treatment of portal vein thrombosis following danaparoid sodium in patients with liver cirrhosis. Hepatol Res. 2018;48(1):51–8. https://doi.org/10.1111/hepr.12895.
94. Rodriguez-Castro KI, Vitale A, Fadin M, Shalaby S, Zerbinati P, Sartori MT, et al. A prediction model for successful anticoagulation in cirrhotic portal vein thrombosis. Eur J Gastroenterol Hepatol. 2019;31(1):34–42. https://doi.org/10.1097/MEG.0000000000001237.
95. Luca A, Miraglia R, Caruso S, Milazzo M, Sapere C, Maruzzelli L, et al. Short- and long-term effects of the transjugular intrahepatic portosystemic shunt on portal vein thrombosis in patients with cirrhosis. Gut. 2011;60(6):846–52. https://doi.org/10.1136/gut.2010.228023.
96. D'Avola D, Bilbao JI, Zozaya G, Pardo F, Rotellar F, Inarrairaegui M, et al. Efficacy of transjugular intrahepatic portosystemic shunt to prevent total portal vein thrombosis in cirrhotic patients awaiting for liver transplantation. Transplant Proc. 2012;44(9):2603–5. https://doi.org/10.1016/j.transproceed.2012.09.050.
97. Luo X, Wang Z, Tsauo J, Zhou B, Zhang H, Li X. Advanced cirrhosis combined with portal vein thrombosis: a randomized trial of TIPS versus endoscopic band ligation plus propranolol for the prevention of recurrent esophageal variceal bleeding. Radiology. 2015;276(1):286–93. https://doi.org/10.1148/radiol.15141252.
98. Rosenqvist K, Eriksson LG, Rorsman F, Sangfelt P, Nyman R. Endovascular treatment of acute and chronic portal vein thrombosis in patients with cirrhotic and non-cirrhotic liver. Acta Radiol. 2016;57(5):572–9. https://doi.org/10.1177/0284185115595060.

99. Wang Z, Jiang MS, Zhang HL, Weng NN, Luo XF, Li X, et al. Is post-TIPS anticoagulation therapy necessary in patients with cirrhosis and portal vein thrombosis? A randomized controlled trial. Radiology. 2016;279(3):943–51. https://doi.org/10.1148/radiol.2015150369.
100. Lv Y, Qi X, He C, Wang Z, Yin Z, Niu J, et al. Covered TIPS versus endoscopic band ligation plus propranolol for the prevention of variceal rebleeding in cirrhotic patients with portal vein thrombosis: a randomised controlled trial. Gut. 2018;67(12):2156–68. https://doi.org/10.1136/gutjnl-2017-314634.
101. Thornburg B, Desai K, Hickey R, Hohlastos E, Kulik L, Ganger D, et al. Pretransplantation portal vein recanalization and transjugular intrahepatic portosystemic shunt creation for chronic portal vein thrombosis: final analysis of a 61-patient cohort. J Vasc Interv Radiol. 2017;28(12):1714–21.e2. https://doi.org/10.1016/j.jvir.2017.08.005.

Management of Portal Vein Thrombosis in Liver Cancer

11

Giovanni Battista Levi Sandri

Abstract

Liver cancer can be diagnosed with portal vein thrombosis. Hepatocellular carcinoma is the most frequent primary liver cancer and in 10–40% of new diagnosis of PVT is described. Presence of PVT is associated with a poor prognosis. Different classifications have been proposed to identify potential surgical treatment. Contrariwise to the general recommendation, many centers apply different strategies to treat HCC with PVT. In this chapter, we will analyze the surgical and locoregional options for this patient. The role of downstaging therapy allowing a surgical curative treatment seems to be a more rising option.

Keywords

HCC · ALPPS · Downstaging · TARE · TACE · Locoregional

Portal vein thrombosis (PVT) may occur in primary liver tumor diagnosis. The association of liver tumor with PVT classically portends a poorer prognosis for the patient. The real rate of PVT in liver cancer is unknown. The Liver Cancer Study Group of Japan reported that PVT incidence achieved 62% in autopsy [1]. The most frequent primary liver tumor diagnosed with PVT is hepatocellular carcinoma (HCC) and is observed in 10–40% of HCC patients at diagnosis [2]. PVT is described as one of the three independent factors to predict poor survival for untreated HCC [3]. Once PVT is described, intra and extra-hepatic metastases are often frequent. Patients with HCC and PVT have an expected survival time of

G. B. Levi Sandri (✉)
Division of General Surgery and Liver Transplantation, San Camillo Hospital, Rome, Lazio, Italy
e-mail: glevisandri@scamilloforlanini.rm.it

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_11

2–4 months with the best supportive care. As described in the Barcelona Clinic Liver Cancer (BCLC) staging system for HCC in these management guidelines, HCC with PVT as an advanced stage (C) disease, and systemic therapy with sorafenib is recommended.

Nevertheless, since the early 1980s and 1990s, surgical approaches for treating HCC with PVT have been described, while with inferior survival outcomes than HCC without PVT [4]. However, the technical criteria for surgical treatment of HCC with PVT depend mainly on the degree of tumor extension within the vasculature. Surgical resection of HCC with PVT is considered technically challenging and is increasingly performed in Asian centers in particular [5].

The Liver Cancer Study Group of Japan proposed a macroscopic classification for HCC with PVT in the General Rules for Primary Liver Cancer Clinical and Pathological Study [6]. The PVT was subdivided into five grades named Vp0–Vp4. Vp0 is defined as no tumor thrombus in the portal vein. Vp1 is the presence of a tumor thrombus distal to, but not in, the portal vein's second-order branches. Vp2 is the presence of a tumor thrombus in the second-order branches of the portal vein. Vp3 is a tumor thrombus in the first-order branches of the portal vein. Vp4 is the presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both).

A surgical classification for PVT in HCC patients was proposed in 2007 by Cheng et al. [7]. The author divided the PVT into four types:

1. Tumor thrombus in portal vein segmental or distal branches.
2. Tumor thrombus extending to the right or left portal vein.
3. Tumor thrombus extending to the main portal trunk.
4. Tumor thrombus extending to the main portal trunk and superior mesenteric vein.

The two different classifications are reported in Table 11.1. The corresponding table of Cheng's Classification and Japan's VP classification is reported in Table 11.2 [8].

Table 11.1 Two types of portal vein tumor thrombosis classification: Cheng's classification [8] and Japanese classification [6]

Cheng's classification [8]	
Type I	Tumor thrombus in PV segmental branches or distal
Type II	Tumor thrombus extending to right or left PV
Type III	Tumor thrombus extending to main trunk of PV
Type IV	Tumor thrombus extending to main trunk of PV and to SMV
Japanese classification [6]	
Vp0	No tumor thrombus in the portal venous system
Vp1	Tumor thrombus in third order PV branch or distal
Vp2	Tumor thrombus in second order PV branch
Vp3	Tumor thrombus in first order PV branch
Vp4	Tumor thrombus in main trunk of PV

Table 11.2 Corresponding table of Cheng's Classification and Japan's VP classification [8]

Portal vein	Microscopic PVTT	Segmental branch	Second-order branch	First-order branch	Main trunk	Superior mesenteric vein
Cheng's classification [8]	I_0	I		II	III	IV
Japanese classification [6]		Vp1	Vp2	Vp3	Vp4	

In 2010, Shi et al. [5] classified PVT into four categories for surgical purposes:

1. Tumor thrombi involving only sectoral or segmental portal branches.
2. Involvement of the right/left portal vein.
3. Involvement of the main portal trunk.
4. Involvement of the main portal trunk up to the superior mesenteric vein.

A different survival patient was observed based on the PVT grade. According to the abovementioned classification, surgeons offered a surgical resection with an acceptable survival for patients.

A Japanese nationwide study analyzed 2093 surgical resections of 6474 patients with HCC and PVT between 2000 and 2007 [9]. The authors performed a propensity-matched analysis comparing surgical resection with non-surgical therapy. The surgical resection group was associated with an increased median survival time of 2.9 years, compared with 1.1 years among patients in the non-surgical group. However, the authors found no association for the improved survival in patients with PVT extending into or beyond the main venous bifurcation, representing the aggressive nature of extensive PVT at diagnosis. In the study by Kokudo et al. [9], the survival benefit of resection in the Vp4 patient group was not statistically significant. Moreover, the R2 resection rate was relatively high. The surgical indication for PVT invading the main trunk or contralateral branch remains controversial.

A single nodule of HCC with a diameter lower than 5 cm associated with PVT of a non-major branch will have poor prognosis. In these patients, aggressive treatment, such as hepatic resection or combination therapy, is necessary to increase survival [10].

Zhang and colleagues [11] performed a meta-analysis, including ten studies that compared 2216 resections with 1912 cases treated with TACE or conservative treatment in patients with HCC and PVT. All studies included in the meta-analysis were from Asia. The overall meta-analysis has shown no significantly higher overall survival in the hepatic resection group than in the TACE group (OR: 0.96; 95% CI: 0.44–2.11). The authors described a higher overall survival in patients with peripheral PVT versus patients with the principal PVT when treated with a surgical approach.

An exciting review comparing East and West management of patients with HCC and PVT describes the liver resection difference [12]. For the West experience, the criteria regarding PVT's presence as a contraindication for surgery are more close. In the East expertise, China and Japan recommend surgical resection for patients with segmental PVT. If the portal trunk is involved, resection is considered in China and South Korea. Many differences have been reported in this review, even in the East.

11.1 Surgical Resection

Multiple surgical options are now in the surgeon baggage, including the followings:

- Hepatectomy with en bloc resection of ipsilateral tumor thrombus.
- Resection of tumor and PVT extending to or beyond the main portal vein bifurcation, treated with en bloc vascular resection, repair, and reconstruction.
- Tumor thrombectomy in PVT extending to or beyond the main portal vein bifurcation.

Nowadays, minimally invasive surgery is gaining the main role in the surgical treatment of HCC [13]. In the case of anatomical resection, all segments are resectable. Surgical outcomes are similar between liver resection of unfavorable segments (I, IVa, VII, and VIII) versus anterolateral segments (II, III, IVb, V, and VI) [14]. The limit of size for the minimally invasive resection is now overpassed, and nodules superior to 5 cm are achieved with good results, even major resections [15]. Interestingly, PVT's presence has not been reported as a formal contraindication of the minimally invasive approach.

The future liver remnant (FLR) volume is a critical point in case of major resection. Compared to the conventional two-stage hepatectomy, a new surgical procedure is now used. The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique demonstrates to induce higher hypertrophy of the FLR in a shorter time. The ALPPS procedure increases the chances to achieve a superior R0 resection margin with a low risk of postoperative liver failure.

The first experience of ALPPS for HCC with PVT was published by Vennarecci et al. [16]. The authors achieved good clinical outcomes in a short series [17]. The ALPPS procedure has been used even for a ruptured HCC with PVT grade III as a rescue solution. In this case, the vascular portal control was the first step procedure. A portal vein incision was performed at the bifurcation of the right and left portal veins. A freely floating left part of the thrombus was extracted from the left portal vein to restore the left portal vein. The second ALPPS step was a classic one [18].

A new player in this field is the application of minimally invasive approaches to ALPPS [19]. More recently, the first robotic case has been reported as a safe

procedure [20]. According to the literature, whether to adopt a laparoscopic or robotic approach should be based on the center and surgeon's experience since no significant difference has been demonstrated so far [13]. The important role of minimally invasive procedures for patients requiring significant and complex surgical procedures is decreasing postoperative morbidities.

11.2 Systemic and Locoregional Treatments

According to the BCLC classification, a systemic therapy, such as sorafenib, is recommended in patients with advanced HCC. However, a significant prognostic factor for poorer overall survival in two randomized controlled trials of sorafenib was the vascular invasion in HCC patients [21]. Therefore, locoregional treatments are often used in those patients. For the initially unresectable HCC patients, conversion therapies, such as TACE, PVE, ALPPS, yttrium-90 RE, and sequential TACE and PVE, have been demonstrated to be effective and should be performed [22]. A prospective randomized controlled trial conducted by Wei et al. evaluated the role of neoadjuvant radiation [23]. The patients were randomly assigned into one arm and received neoadjuvant radiation followed by surgery versus a second arm and received surgery alone. The overall survival and disease-free survival rates were significantly higher in the combined group. The results mentioned above should be in favor of a downstaging/bridge therapy for radical surgical treatment.

A repeated conventional transarterial chemoembolization (TACE) has been described to be associated with significant survival benefits in HCC patients with PVT when compared with supportive care [24]. The effectiveness of the combined strategies, TACE plus radiotherapy, has been investigated in a retrospective study [25]. The authors compared two groups: TACE plus RT (n = 203) and TACE plus sorafenib (n = 104). A significantly higher overall progression-free survival rate was observed in the TACE plus RT group compared to the TACE plus sorafenib group (median survival, 6.5 vs. 4.3 months, respectively; p = 0.017).

The safety and efficacy of radioembolization versus sorafenib were analyzed in a systematic review and meta-analysis performed on seventeen studies, including 1321 patients [26]. The analysis concludes in favor of radioembolization, reporting higher overall survival and longer time to progression versus patients treated with sorafenib. Moreover, radiation lobectomy with 90-Yttrium induces comparable increasing volumes in liver lobes while potentially controlling the liver tumor and limiting tumor progression in the untreated lobe [27]. The feasibility of radioembolization as a downstaging therapy even with PVT has been successfully described in a case series [28]. Furthermore, currently, surgical resection could be performed successfully after downstaging treatment as Yttrium-90 even by laparoscopy [29]. As an alternative to ALPPS, a hybrid technique with radiofrequency-assisted liver partition and portal vein ligation with a first laparoscopic radiofrequency step has been proposed for huge HCC with PVT [30].

Stereotactic-body radiotherapy (SBRT) is used more often for HCC with PVT. The highly precise radiotherapy techniques, such as SBRT, can deliver higher doses on more selective targets. A study on 24 patients showed interesting results regarding completed (8.3%) and partial (45.8%) responses. When the tumor thrombus is located in the distal portal vein branch, SBRT followed by TACE could be considered as a practical option [31].

External-beam radiation therapy (EBRT) might be an effective bridging therapy for HCC patients awaiting liver transplantation (LT), which may provide excellent local control with minimal side effects, downsize or stabilize tumors before LT, and achieve an excellent pathological response [32].

In conclusion, PVT is a frequent complication in patients with HCC. The reported experience in the literature suggests resecting patients in selected cases with a minimally invasive approach. Downstaging can be performed before surgery using the preferred center therapy.

References

1. Liver Cancer Study Group of Japan. Primary liver cancer in Japan: clinicopathologic features and results of surgical treatment. Ann Surg. 1990;211:277–87.
2. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol. 2006;12:7561–7.
3. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxi A, Camma C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology. 2010;51:1274–83.
4. Kumada K, Ozawa K, Okamoto R, et al. Hepatic resection for advanced hepatocellular carcinoma with removal of portal vein tumor thrombi. Surgery. 1990;108:821–7.
5. Shi J, Lai EC, Li N, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol. 2010;17:2073–80.
6. Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer, second English edition. Tokyo: Kanehara & Co., Ltd.; 2003.
7. Shuqun C, Mengchao W, Han C, et al. Tumor thrombus types influence the prognosis of hepatocellular carcinoma with the tumor thrombi in the portal vein. Hepato-Gastroenterology. 2007;54(74):499–502.
8. Cheng S, Yang J, Shen F, et al. Multidisciplinary management of hepatocellular carcinoma with portal vein tumor thrombus—Eastern Hepatobiliary Surgical Hospital consensus statement. Oncotarget. 2016;7(26):40816–29. https://doi.org/10.18632/oncotarget.8386.
9. Kokudo T, Hasegawa K, Matsuyama Y, et al. Liver Cancer Study Group of Japan. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol. 2016;65:938–43.
10. Jang TY, Huang CI, Yeh ML, Lin ZY, Chen SC, Chuang WL. The prognosis of bulky hepatocellular carcinoma with nonmajor branch portal vein tumor thrombosis. Medicine (Baltimore). 2019;98(13):e15066. https://doi.org/10.1097/MD.0000000000015066.
11. Zhang ZY, Dong KS, Zhang EL, Zhang LW, Chen XP, Dong HH. Resection might be a meaningful choice for hepatocellular carcinoma with portal vein thrombosis: a systematic review and meta-analysis. Medicine (Baltimore). 2019;98(50):e18362. https://doi.org/10.1097/MD.0000000000018362.
12. Lu J, Zhang XP, Zhong BY, et al. Management of patients with hepatocellular carcinoma and portal vein tumour thrombosis: comparing east and west. Lancet Gastroenterol Hepatol. 2019;4(9):721–30. https://doi.org/10.1016/S2468-1253(19)30178-5.

13. Levi Sandri GB, de Werra E, Mascianà G, et al. Laparoscopic and robotic approach for hepatocellular carcinoma-state of the art. Hepatobiliary Surg Nutr. 2016;5(6):478–84. https://doi.org/10.21037/hbsn.2016.05.05.
14. Levi Sandri GB, Ettorre GM, Aldrighetti L, et al. Laparoscopic liver resection of hepatocellular carcinoma located in unfavorable segments: a propensity score-matched analysis from the I Go MILS (Italian Group of Minimally Invasive Liver Surgery) Registry. Surg Endosc. 2019;33(5):1451–8. https://doi.org/10.1007/s00464-018-6426-3.
15. Levi Sandri GB, Spoletini G, Vennarecci G, Francone E, Abu Hilal M, Ettorre GM. Laparoscopic liver resection for large HCC: short- and long-term outcomes in relation to tumor size. Surg Endosc. 2018;32(12):4772–9. https://doi.org/10.1007/s00464-018-6225-x.
16. Vennarecci G, Laurenzi A, Santoro R, Colasanti M, Lepiane P, Ettorre GM. The ALPPS procedure: a surgical option for hepatocellular carcinoma with major vascular invasion. World J Surg. 2014;38(6):1498–503.
17. Vennarecci G, Ferraro D, Tudisco A, et al. The ALPPS procedure: hepatocellular carcinoma as a main indication. An Italian single-center experience. Updat Surg. 2019;71(1):67–75. https://doi.org/10.1007/s13304-018-0596-3.
18. Levi Sandri GB, Vennarecci G, Lepiane P, Ettorre GM. Associating liver partition and portal vein ligation for bleeding hepatocellular carcinoma in HBV cirrhosis: a safety strategy. Transl Gastroenterol Hepatol. 2017;2:20. https://doi.org/10.21037/tgh.2017.03.08.
19. Melandro F, Giovanardi F, Hassan R, et al. Minimally invasive approach in the setting of ALPPS procedure: a systematic review of the literature. J Gastrointest Surg. 2019;23(9):1917–24.
20. Di Benedetto F, Assirati G, Magistri P. Full robotic ALPPS for HCC with intrahepatic portal vein thrombosis. Int J Med Robot. 2020;16(2):e2087. https://doi.org/10.1002/rcs.2087.
21. Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. J Hepatol. 2017;67:999–1008.
22. Zhang ZF, Luo YJ, Lu Q, Dai SX, Sha WH. Conversion therapy and suitable timing for subsequent salvage surgery for initially unresectable hepatocellular carcinoma: what is new? World J Clin Cases. 2018;6(9):259–73. https://doi.org/10.12998/wjcc.v6.i9.259.
23. Wei X, Jiang Y, Zhang X, et al. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a randomized, open-label, multicenter controlled study. J Clin Oncol. 2019;37:2141–51.
24. Kim KM, Kim JH, Park IS, Ko GY, Yoon HK, Sung KB, Lim YS, Lee HC, Chung YH, Lee YS, et al. Reappraisal of repeated transarterial chemoembolization in the treatment of hepatocellular carcinoma with portal vein invasion. J Gastroenterol Hepatol. 2009;24:806–14.
25. Chu HH, Kim JH, Shim JH, Yoon SM, Kim PH, Alrashidi I. Chemoembolization plus radiotherapy versus chemoembolization plus sorafenib for the treatment of hepatocellular carcinoma invading the portal vein: a propensity score matching analysis. Cancers (Basel). 2020;12(5):1116. https://doi.org/10.3390/cancers12051116.
26. Kim PH, Choi SH, Kim JH, Park SH. Comparison of radioembolization and sorafenib for the treatment of hepatocellular carcinoma with portal vein tumor thrombosis: a systematic review and meta-analysis of safety and efficacy. Korean J Radiol. 2019;20(3):385–98. https://doi.org/10.3348/kjr.2018.0496.
27. Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol. 2013;59(5):1029–36. https://doi.org/10.1016/j.jhep.2013.06.015.
28. Tabone M, Calvo A, Russolillo N, Langella S, Carbonatto P, Lo Tesoriere R, Richetta E, Pellerito R, Ferrero A. Downstaging unresectable hepatocellular carcinoma by radioembolization using 90-yttrium resin microspheres: a single center experience. J Gastrointest Oncol. 2020;11(1):84–90. https://doi.org/10.21037/jgo.2019.06.01.
29. Rotellar F, Zozaya G, Martí-Cruchaga P, Pardo F. Laparoscopic right hepatectomy after radioembolization using yttrium-90 resin microspheres. Surg Oncol. 2017;26(1):71–2. https://doi.org/10.1016/j.suronc.2016.12.004.

30. Tang K, Zhang B, Dong L, Wang L, Jin Y, Tang Z. Successful treatment of a huge hepatic carcinoma with right portal vein thrombosis: a case report. Medicine (Baltimore). 2020;99(17):e19636. https://doi.org/10.1097/MD.0000000000019636.
31. Choi HS, Kang KM, Jeong BK, Jeong H, Lee YH, Ha IB, Song JH. Effectiveness of stereotactic body radiotherapy for portal vein tumor thrombosis in patients with hepatocellular carcinoma and underlying chronic liver disease. Asia Pac J Clin Oncol. 2020 Aug 5. https://doi.org/10.1111/ajco.13361.
32. Han B, Li C, Meng H, Gomes Romeiro F, Mancuso A, Zhou Z, Levi Sandri GB, Xu Y, Han T, Han L, Shao L, Qi X. Efficacy and safety of external-beam radiation therapy for hepatocellular carcinoma: An overview of current evidence according to the different target population. Biosci Trends. 2019 Mar 14;13(1):10-22. https://doi.org/10.5582/bst.2018.01261.

Future Directions

12

Marcello Bianchini and Erica Villa

Abstract

Portal vein thrombosis (PVT) is a well-known complication of liver diseases; however, still much has to be done to improve the knowledge and treatment of this condition. Relevant methodological flaws have led to controversial results and many questions remain unanswered. Prospective, controlled quality studies are strongly required to advance in this field. PVT development prediction using scores, biomarkers or viscoelastic tests are promising emerging topics but a research planning on data collection and validation strategy should be defined. Direct oral anti-coagulants (DOACs) seem to be safe and effective in the treatment of PVT, but prospective randomized controlled data are lacking as well as indication about length of therapy and stopping rules. Future lines of research should focus not only on avoidance of thrombosis but also on exploring the extended role of anticoagulation as anti-inflammatory and antifibrotic intervention.

Keywords

Portal vein thrombosis · Future directions · Perspectives · Natural history Antithrombotic treatment · Anticoagulation · Thrombosis prophylaxis

M. Bianchini · E. Villa (✉)
Division of Gastroenterology, Università di Modena e Reggio Emilia, AOU di Modena, Modena, Italy
e-mail: bianchini.marcello@aou.mo.it; erica.villa@unimore.it

X. Qi, W. Xie (eds.), *Portal Vein Thrombosis*,
https://doi.org/10.1007/978-981-33-6538-4_12

Abbreviations

DOAC	Direct oral anti-coagulants
HCC	Hepatocellular carcinoma
LMWH	Low molecular weight heparin
LT	Liver transplantation
PVT	Portal vein thrombosis
TIPS	Transjugular intrahepatic portosystemic shunt
US	UltraSonography
VTE	Venous thrombo-embolism

Balfour and Steward described the first case of portal vein thrombosis (PVT) in 1869, regarding a patient with splenomegaly, varices and ascites [1]. Interest in this complication began to grow in the 50s [2, 3] and was progressively increased in parallel with the improvement of the imaging techniques [4, 5] and the availability of treatment options.

Currently, more than 5000 papers on PVT are traceable in PubMed and more than 50,000 in Google Scholar. Despite this considerable amount of literature, robust, large, prospective, controlled data are lacking. The majority of the published studies, especially but not exclusively on the treatment strategies, consists in retrospective uncontrolled case series. These relevant methodological flaws are not surprising as they reflect the old-fashioned view of PVT as a condition independent from the general progression of the underlying cirrhosis (which is the associated condition in a large majority of cases) and therefore not contextualized in the overall clinical picture of chronic liver disease. The studies on natural history are a fair example. Of about 200 papers retrieved, the majority are reviews. Only few [6–12] present original data. Some of the studies highlight the clinical impact of PVT on progression of liver disease; others, including a large-scale study [10], state that PVT has no impact on mortality or on liver transplantation (LT). Only three are prospective series, one on a small cohort with incomplete PVT aiming at evaluating impact on natural history in relation with regression or progression of PVT [7]. The other two exploit the data of the control arms of two interventional studies to give insight on PVT natural history [13, 14]. One study indicates a 10.7% cumulative incidence at 5 years of PVT in Child-Pugh A patients [13] while the other, in Child-Pugh B-C patients, reports a 27.7% incidence at 2 years [14]. What is evident from these studies is that PVT is a clear-cut marker of progressive chronic liver disease, but it is not in itself a causal factor for it. An international web based clinical registry will likely provide standardized, prospective data and help defining the course of this disease [15].

The substantial methodological issues of the studies published so far cast their shadow also on the future studies to come on some of the most relevant topics in the field that should be addressed, e.g., identification of subjects at risk of developing PVT, prophylaxis, treatment, and role of the last generation anticoagulant drugs [16].

12.1 Risk Factors for PVT

Identification of subjects at risk of PVT remains a critical issue. It is apparent that PVT is a marker of progressed chronic liver disease rather than a determinant of its progression [17]. It can be inferred therefore that in patients with cirrhosis there can be an overlap between PVT risk and that for other complications, as for example hepatocellular carcinoma (HCC). Data from a large French database suggest that a 6-month timeframe is both adequate for HCC and PVT screening [14].

Evaluation of portal flow reduction has been suggested as a predictor for risk of PVT [17, 18]. The methodological limitations of these studies (e.g., low number of PVT patients and retrospective nature of the studies) suggest caution. The main drawback, however, is likely represented by the technical difficulties of reliably measuring portal blood flow. This suggests that it would be useful to substantiate these data with more sophisticated techniques, like, for example, phase contrast magnetic resonance [19].

Several other studies explored different techniques and scores to predict PVT development in order to better focus surveillance, especially in the subset of LT candidates. Search for a single biomarker has not produced consistent results; therefore, different groups have tried a combination of variables in order to improve prediction. The PVT index [20] and the disseminated intravascular coagulation score [21] are examples of this effort. Regrettably, all the scores proposed present a good negative but a weak positive predictive power for PVT development. Recently, attention has been drawn on coagulation and viscoelastic assays as short-term predictors for thrombosis [22]. The studies published so far show that these tests are able to predict on the short-term (i.e., in the peri-transplant period) PVT risk. It remains to be defined whether they could be adapted to long-term surveillance and to guide anticoagulation treatment. MicroRNAs have been used up to now mainly to enhance the identification of established thrombotic conditions, mostly on a tumoral background [23, 24]. However, the increased sensitivity of microRNA detection could be exploited in order to evaluate thrombophilic conditions in cirrhosis. An interesting approach involves new informatics technologies, which have been used to predict PVT risk in patients with acute pancreatitis (radical basis function (RBF) artificial neural networks model) [25] or the identification of acute symptomatic PVT (using a support vector machine (SVM) classifier coupled with a least absolute shrinkage and selection operator) [26]. These methodologies could be helpful for analyzing large retrospective and/or prospective databases to identify variables useful to design prospective studies in the chronic setting.

12.2 PVT Treatment and Prophylaxis

On the treatment side, there is quite an agreement on the therapeutic role of anticoagulation for established PVT [27–29]. There are, however, several unresolved issues, e.g., length of the treatment [30] and stopping rules for it, all depending on the retrospective and uncontrolled nature of the studies available. The definition of

"provoked" or "unprovoked" PVT, assimilated to that of venous thrombo-embolism (VTE), could grossly steer the treatment length decision, but prospective data are lacking [31]. To further complicate the issue, several studies report a small proportion of patients who achieve a spontaneous resolution of PVT [32]. Unfortunately, we do not have yet a biomarker able to predict which patient will be able to spontaneously recanalize PVT.

The same issues of the studies performed with traditional anticoagulants are being reproduced with the new direct oral anti-coagulants (DOACs) [33]. The initial ban on their use in patients with liver diseases has prevented the exploration of their efficacy and safety in a controlled manner. Therefore, most published studies are retrospective case series collected exploiting treatment of patients with cirrhosis for diverse conditions, most often atrial fibrillation [34, 35]. The only prospective randomized controlled trial published enrolled 80 patients with chronic HCV infection but not clearly defined as having cirrhosis. The study compared rivaroxaban with warfarin [36]. Rivaroxaban was safer and more effective than warfarin in obtaining PVT recanalization.

Apart from pharmacological treatments, other non-pharmacological interventions (transjugular intrahepatic portosystemic shunt [TIPS], thrombectomy, surgery, LT) have been proposed for PVT therapy [37]. For none of them, a competitive advantage was found in comparison with pharmacological treatment [38]. Comparative studies are scant and scarcely informative. The scenario is even worse in the field of PVT prophylaxis. Only a single prospective randomized study is available, which showed a distinctive advantage in the anticoagulated group not only for PVT prevention but also in term of rate of decompensation and mortality [13]. Unfortunately, a confirmatory study was prematurely stopped due to insufficient enrollment (Childbenox study—ClinicalTrials.gov Identifier: NCT02271295).

12.3 Conclusion

On the whole, what is really lacking are well-designed prospective studies without selection bias that could be able to answer few clear-cut questions. As the Enoxaparin study [13] indicates, prevention of PVT has a much broader meaning than simple avoidance of thrombosis. Heparins interact with pro-inflammatory and procoagulant factors and is able to prevent coagulopathy related to inflammation during sepsis [39]. Long-term enoxaparin was associated with significant IL-6 decrease and improvement of intestinal mucosal permeability, with decrease of circulating bacterial DNA and decreased inflammation [13]. In addition, anticoagulation is able to reduce hepatic resistance and portal pressure [40] and improve liver fibrosis [41].

The complex interaction between coagulation, inflammation and fibrosis, which clinically ends up in PVT, clearly indicates that the events behind PVT occurrence are extremely complicated and are pathogenetically linked with the occurrence and the progression of liver disease [42]. Future studies should therefore follow the line of analyzing the course of events linking occurrence of PVT and progression of chronic liver disease in the attempt of preventing them both.

References

1. Balfour GW, Steward GT. Case of enlarged spleen complicated with ascites, both depending upon varicose dilatation and thrombosis of the portal vein. Edin Med J. 1869;14(7):589–98.
2. McKittrick JB, Vikery AL. Thrombosis of portal vein and branches of superior mesenteric vein. N Engl J Med. 1949;241(3):130–2. https://doi.org/10.1056/NEJM194907212410308.
3. Clinical pathological conferences of Northwestern University Medical School. Primary splenic vein thrombosis with complication. Q Bull Northwest Univ Med Sch. 1952;26(3):245–9.
4. Nebesar RA, Pollard JJ. Portal venography by selective arterial catheterization. Am J Roentgenol Radium Therapy, Nucl Med. 1966;97:477–87. https://doi.org/10.2214/ajr.97.2.477.
5. Vujic I, Rogers CI, LeVeen HH. Computed tomographic detection of portal vein thrombosis. Radiology. 1980;135(3):697–8. https://doi.org/10.1148/radiology.135.3.7384457.
6. Luca A, Caruso S, Milazzo M, Marrone G, Mamone G, Crinò F, Maruzzelli L, Miraglia R, Floridia G, Vizzini G. Natural course of extrahepatic nonmalignant partial portal vein thrombosis in patients with cirrhosis. Radiology. 2012;265(1):124–32. https://doi.org/10.1148/radiol.12112236.
7. Girleanu I, Stanciu C, Cojocariu C, Boiculese L, Singeap AM, Trifan A. Natural course of nonmalignant partial portal vein thrombosis in cirrhotic patients. Saudi J Gastroenterol. 2014;20(5):288–92. https://doi.org/10.4103/1319-3767.141687.
8. Acuna-Villaorduna A, Tran V, Gonzalez-Lugo JD, Azimi-Nekoo E, Billett HH. Natural history and clinical outcomes in patients with portal vein thrombosis by etiology: a retrospective cohort study. Thromb Res. 2019;174:137–40. https://doi.org/10.1016/j.thromres.2018.12.019.
9. Maruyama H, Okugawa H, Takahashi M, Yokosuka O. De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. Am J Gastroenterol. 2013;108(4):568–74. https://doi.org/10.1038/ajg.2012.452.
10. Berry K, Taylor J, Liou IW, Ioannou GN. Portal vein thrombosis is not associated with increased mortality among patients with cirrhosis. Clin Gastroenterol Hepatol. 2015;13:585–93. https://doi.org/10.1016/j.cgh.2014.10.010.
11. Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, Grandone E, Balzano A. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol. 2004;40(5):736–41. https://doi.org/10.1016/j.jhep.2004.01.001.
12. Søgaard KK, Darvalics B, Horváth-Puhó E, Sørensen HT. Survival after splanchnic vein thrombosis: a 20-year nationwide cohort study. Thromb Res. 2016;141:1–7. https://doi.org/10.1016/j.thromres.2016.02.024.
13. Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, Tata C, Zecchini R, Gitto S, Petta S, Lei B, Bernabucci V, Vukotic R, De Maria N, Schepis F, Karampatou A, Caporali C, Simoni L, Del Buono M, Zambotto B, Turola E, Fornaciari G, Schianchi S, Ferrari A, Valla D. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012;143:1253–60. https://doi.org/10.1053/j.gastro.2012.07.018.
14. Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, Plessier A, Roulot D, Chaffaut C, Bourcier V, Trinchet JC, Valla DC, Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology. 2015;61:660–7. https://doi.org/10.1002/hep.27546.
15. Violi F, Corazza GR, Caldwell SH, Perticone F, Gatta A, Angelico M, Farcomeni A, Masotti M, Napoleone L, Vestri A, Raparelli V, Basili S, PRO-LIVER Collaborators. Portal vein thrombosis relevance on liver cirrhosis: Italian Venous Thrombotic Events Registry. Intern Emerg Med. 2016;11:1059–66. https://doi.org/10.1007/s11739-016-1416-8.
16. Leonardi F, Maria N, Villa E. Anticoagulation in cirrhosis: a new paradigm? Clin Mol Hepatol. 2017;23:13–21. https://doi.org/10.3350/cmh.2016.0110.

17. Zocco MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, Riccardi L, Lancellotti S, Santoliquido A, Flore R, Pompili M, Rapaccini GL, Tondi P, Gasbarrini GB, Landolfi R, Gasbarrini A. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. J Hepatol. 2009;51(4):682–9. https://doi.org/10.1016/j.jhep.2009.03.013.
18. Stine JG, Wang J, Shah PM, Argo CK, Intagliata N, Uflacker A, Caldwell SH, Northup PG. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: a matched case-control study. Liver Int. 2018;38:94–101. https://doi.org/10.1111/liv.13500.
19. Cakmak O, Elmas N, Tamsel S, Demirpolat G, Sever A, Altunel E, Killi R. Role of contrast-enhanced 3D magnetic resonance portography in evaluating portal venous system compared with color Doppler ultrasonography. Abdom Imaging. 2008;33:65–71. https://doi.org/10.1007/s00261-007-9229-x.
20. Gaballa D, Bezinover D, Kadri Z, Eyster E, Wang M, Northup PG, Stine JG. Development of a model to predict portal vein thrombosis in liver transplant candidates: the portal vein thrombosis risk index. Liver Transpl. 2019;25:1747–55. https://doi.org/10.1002/lt.25630.
21. Cui SB, Fu Z, Feng Y, Xie XY, Ma X, Liu T, Wang L, Wu H, Zhu Q. The disseminated intravascular coagulation score is a novel predictor for portal vein thrombosis in cirrhotic patients with hepatitis B. Thromb Res. 2018;161:7–11. https://doi.org/10.1016/j.thromres.2017.11.010.
22. Kamel Y, Hassanin A, Ahmed AR, Gad E, Afifi M, Khalil M, Görlinger K, Yassen K. Perioperative thromboelastometry for adult living donor liver transplant recipients with a tendency to hypercoagulability: a prospective observational cohort study. Transfus Med Hemother. 2018;45:404–12. https://doi.org/10.1159/000489605.
23. Xi Q, Zhang HX, Whang Z, Liu ZY, Xie QF, Hu K, Zang Z, Mu GY, Ma LY, Jiang J, Cui YM. The predictive value of circulating microRNAs for venous thromboembolism diagnosis: a systematic review and diagnostic meta-analysis. Thromb Res. 2019;181:127–34. https://doi.org/10.1016/j.thromres.2019.07.024.
24. Liu S, Guo W, Shi J, Li N, Yu X, Xue J, Fu X, Chu K, Lu C, Zhao J, Xie D, Wu M, Cheng S, Liu S. MicroRNA-135a contributes to the development of portal vein tumor thrombus by promoting metastasis in hepatocellular carcinoma. J Hepatol. 2012;56:389–96. https://doi.org/10.1016/j.jhep.2011.08.008.
25. Fei Y, Hu J, Gao K, Tu J, Wang W, Quin Li W. Risk prediction for portal vein thrombosis in acute pancreatitis using radial basis function. Ann Vasc Surg. 2018;47:78–84. https://doi.org/10.1016/j.avsg.2017.09.004.
26. Liu K, Chen J, Zhang K, Wang S, Li X. A diagnostic prediction model of acute symptomatic portal vein thrombosis. Ann Vasc Surg. 2019;61:394–9. https://doi.org/10.1016/j.avsg.2019.04.037.
27. Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. Gastroenterology. 2017;153:480–7. https://doi.org/10.1053/j.gastro.2017.04.042.
28. Intagliata N, Cladwell SH, Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. Gastroenterology. 2019;156(6):1582–99. https://doi.org/10.1053/j.gastro.2019.01.265.
29. O'Leary J, Greenberg CS, Patton HM, Caldwell SH. AGA clinical practice update: coagulation in cirrhosis. Gastroenterology. 2019;157(1):34–43. https://doi.org/10.1053/j.gastro.2019.03.070.
30. Bergère M, Erard-Poinsot D, Boillot O, Valette PJ, Guillaud O, Chambon-Augoyard C, Dumortier J. Portal vein thrombosis and liver cirrhosis: long-term anticoagulation is effective and safe. Clin Res Hepatol Gastroenterol. 2019;43:395–402. https://doi.org/10.1016/j.clinre.2018.11.011.
31. Valeriani E, Riva N, Di Nisio M, Ageno W. Splanchnic vein thrombosis: current perspectives. Vasc Health Risk Manag. 2019;15:449–61. https://doi.org/10.2147/VHRM.S197732.
32. John BV, Konjeti R, Aggarwal A, Lopez R, Atreja A, Miller C, Zein NN, Carey WD. Impact of untreated portal vein thrombosis on pre and post liver transplant outcomes in cirrhosis. Ann Hepatol. 2013;12:952–8.

33. Mannucci PM, Tripodi A. Direct oral anticoagulants and cirrhosis: more evidence still needed for efficacy and safety in portal vein thrombosis. Vasc Pharmacol. 2019;113:92–3. https://doi.org/10.1016/j.vph.2018.06.005.
34. Intagliata NM, Henry ZH, Maitland H, Shah NL, Argo CK, Northup PG, Caldwell SH. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci. 2016;61:1721–7. https://doi.org/10.1007/s10620-015-4012-2.
35. De Gottardi A, Trebicka J, Klinger C, Plessier A, Seijo S, Terziroli B, Magenta L, Semela D, Buscarini E, Langlet P, Görtzen J, Puente A, Müllhaupt B, Navascuès C, Nery F, Deltenre P, Turon F, Engelmann C, Arya R, Caca K, Peck-Radosavljevic M, Leebeek FWG, Valla D, Garcia-Pagan JC, Investigators VALDIG. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. Liver Int. 2017;37:694–9. https://doi.org/10.1111/liv.13285.
36. Hanafy AS, Abd-Elsalam A, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. Vasc Pharmacol. 2019;113:86–91. https://doi.org/10.1016/j.vph.2018.05.002.
37. Senzolo M, Patch D, Miotto D, Ferronato C, Cholongitas E, Burroughs AK. Interventional treatment should be incorporated in the algorithm for the management of patients with portal vein thrombosis. Hepatology. 2008;48:1352–3. https://doi.org/10.1002/hep.22503.
38. Stine JG, Northup PG. Management of non-tumoral portal vein thrombosis in patients with cirrhosis. Dig Dis Sci. 2019;64:619–26. https://doi.org/10.1007/s10620-018-5427-3.
39. Poterucha TJ, Libby P, Goldhaber SZ. More than an anticoagulant: do heparins have direct anti-inflammatory effects? Thromb Haemost. 2017;117:437–44. https://doi.org/10.1160/TH16-08-0620.
40. Cerini F, Vilaseca M, Lafoz E, García-Irigoyen O, García-Calderó H, Tripathi DM, Avila M, Reverter JC, Bosch J, Gracia-Sancho J, García-Pagán JC. Enoxaparin reduces hepatic vascular resistance and portal pressure in cirrhotic rats. J Hepatol. 2016;64:834–42. https://doi.org/10.1016/j.jhep.2015.12.003.
41. Lee KC, Hsu WF, Hsieh YC, Chan CC, Yang YY, Huang YH, Hou MC, Lin HC. Dabigatran reduces liver fibrosis in thioacetamide-injured rats. Dig Dis Sci. 2019;64:102–12. https://doi.org/10.1007/s10620-018-5311-1.
42. Turco L, Schepis F, Villa E. The role of anticoagulation in treating portal hypertension. Curr Hepatol Rep. 2018;17(3):200–8. https://doi.org/10.1007/s11901-018-0406-x.