Non-Cirrhotic Portal Hypertension: An Update of Diagnosis and Management

Steven Zulkifly, Irsan Hasan***

*Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

**Division of Hepatobiliary, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia/ Dr. Cipto Mangunkusumo General National Hospital, Jakarta

Corresponding author:

Irsan Hasan. Division of Hepatobiliary, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital. Jl. Diponegoro No. 71 Jakarta Indonesia. Phone: +62-21-31900924. Email: irsan_h@yahoo.com

ABSTRACT

Portal hypertension is not the only result of liver cirrhosis. Non-cirrhotic portal hypertension (NCPH) is characterized by elevated portal pressure in the absence of cirrhosis and is often underdiagnosed in daily clinical practice. The clinical manifestations of NCPH are similar to liver cirrhosis. The diagnosis of NCPH is still challenging due to the various underlying etiologies and often require either non-invasive or invasive examination. Laboratory examination, abdominal ultrasound, endoscopic procedure, hepatic venous gradient measurement, and liver biopsy have role in diagnosis of NCPH. The principle management of NCPH is to treat portal hypertension and its complications, such as prophylaxis and acute management of variceal bleeding, anticoagulants, surgery, splenectomy, and liver transplantation.

Keywords: *non-cirrhotic portal hypertension, diagnosis, management*

ABSTRAK

Hipertensi porta tidak hanya disebabkan oleh sirosis hati. Non-cirrhotic portal hypertension (NCPH) ditandai dengan kondisi peningkatan tekanan porta tanpa adanya sirosis dan dan sering sekali terlewati dalam praktik klinis sehari-hari. Manifestasi klinis NCPH hampir mirip dengan sirosis hati. Diagnosis NCPH masih menjadi tantangan tersendiri karena terdapat berbagai etiologi yang mendasari dan tidak jarang memerlukan pemeriksaan penunjang baik non-invasif maupun invasif. Pemeriksaan laboratorium, USG abdomen, endoskopi, pengukuran tekanan vena porta, dan biopsi hati berperan dalam diagnosis NCPH. Prinsip tata laksana NCPH adalah mengatasi hipertensi porta dan komplikasinya, seperti pencegahan dan tata laksana akut pecah varises, pemberian antikoagulan, pembedahan, splenektomi, dan transplantasi hati.

Kata kunci: *non-cirrhotic portal hypertension, diagnosis, tata laksana*

INTRODUCTION

Non-cirrhotic portal hypertension (NCPH) is a relatively rare disease, but has high morbidity and mortality rate. The various etiology of portal hypertension make the diagnosis of NCPH challenging. Almost all cases of portal hypertension are caused by cirrhosis, so that the understanding of clinicians regarding NCPH is limited. Therefore, the aim of this review article is to provide the latest update about NCPH.

DEFINITION AND PREVALANCE

Portal hypertension is defined as a clinical syndrome that characterized by an abnormal elevated portal pressure (the pressure between portal vein and hepatic vein > 5 mmHg). Physiologically, the portal pressure is usually maintained at low level (1–5 mmHg), even though the high blood flow (1 L/minute) in portal system. It indicates the low resistance of the hepatic circulation toward the portal blood flow. In certain liver diseases, the portal pressure can increase to > 5 mmHg due to the alteration of the resistance to portal blood flow. According to the source of etiology, portal hypertension (PH) is classified into pre-hepatic, intra-hepatic, and post-hepatic. Liver cirrhosis is the most common etiology of PH and categorized as intra-hepatic PH. Other common etiologies of intra-hepatic PH include schistosomiasis, sarcoidosis, and sclerosing cholangitis. Pre-hepatic PH is developed when obstruction to portal blood flow occurs before the liver dan post-hepatic PH is found in condition where blockage in portal blood flow is located after the liver. The elevated portal pressure that associated to diseases other than cirrhosis, is defined as non-cirrhotic portal hypertension (NCPH).[1,2]

The prevalence of NCPH is difficult to be estimated due to the many underlying etiologies, various terminologies to describe the similar entity, and lack of epidemiology reports. Portal hypertension that is not associated with cirrhosis and extrahepatic obstruction of portal vein, is first time described as non-cirrhotic portal fibrosis (NCPF). Along with the development of histopathological examination, several terminologies have been developed including hepatoportal sclerosis, idiopathic portal hypertension, and incomplete septal cirrhosis.[3] In 2011, Schouten et al proposed a term idiopathic NCPH to define portal hypertension after exclude all of the etiologies that contributed to elevated portal pressure.[4]

Several studies reported idiopathic NCPH is more common in Asia (developing countries) than Western (developed countries). In Japan, the incidence rate of idiopathic NCPH is estimated 0.75 per 100,000 population in 1985.[5] Reports from several years later found the incidence has declined since 1975, from 33% of all portal hypertension cases to 11 cases per year in 1994.[6] Since there are no national registry of NCPH in India, the epidemiology of NCPH is estimated from personal communication. The incidence of NCPH in India is estimated 23.3% (range 7.9–46.7%) in 1980 and probably declined after 1990.[7] However, in Western countries, the prevalence of idiopathic is only 3–5%.[4,8] The peak age of the incidence of idiopathic NCPH is third and fourth decades of life, with predominance of male or no sex predilection in another study. These characteristics are different to reports from Japan, which the peak age of incidence in second and third decades of life with female ratio to male 3:1. Majority of patients also had low socioeconomic status.[7,9] The reduction of cases in India may be associated with improve sanitation and hygiene and living conditions.[9]

PROGNOSIS

Portal hypertension leads to several complications including esophageal and gastric varices, variceal bleeding, portal hypertensive gastropathy, ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), hepatorenal syndrome (HRS), and development of hepatocellular carcinoma (HCC). The mortality rate in cirrhotic patients with portal hypertension increases as the development of PH, variceal, and variceal bleeding. D'Amico et al in 2014 conducted a study to analyze the prognostic stages of cirrhosis from 25-year follow up study. Five-year mortality rate in compensated cirrhosis without varices, compensated cirrhosis with varices, variceal hemorrhage without other complications, first non-bleeding decompensated event, and any second decompesating event were 1.5%, 10%, 20%, 30%, and 88%, respectively.[10] In contrary to cirrhosis, idiopathic NCPH is reported to have a better prognosis if early diagnosed and promptly treated.[11] Condat et al reported mortality rate in extrahepatic portal vein thrombosis from 136 patients that enrolled between 1983–1998. After follow for a median time of 46 months, the all cause and GI bleeding mortality rate was reported as high as 7% dan 1%, respectively.[12] Spaander et al in 2013 performed retrospective study of 120 patients with non cirrhotic portal vein thrombosis (PVT). The 5-year overall survival (OS) and 10-year OS rate was 90% and 70%, respectively.[13] Schouten et al in 2012 recruited 62 patients with idiopathic non portal cirrhotic hypertension and estimated the 5-years and 10-years OS rate was 78% and 56%, respectively.[14] This emphasize the importance of early recognition and proper management to prevent further complication of idiopathic NCPH.

BRIEF REVIEW OF LIVER VASCULARIZATION

Portal vein is formed by the confluence of three major vein (superior mesenteric vein, inferior mesenteric vein, and splenic vein), draining blood from gastrointestinal tract, pancreas, gallbladder, and spleen. It enters the liver at the hepatic portal and has two main

branches (left and right portal vein). The flow rate in human portal system is approximately 1,000–1,200 mL/minute and comprises 75% of total hepatic blood flow. The elevated pressure in portal vein, regardless of the etiology, develops collateral circulation to deliver portal blood into the systemic veins by the formation of collateral blood flow. The collateral circulation occurs when the portal increases above 10 mmHg. The formation of collateral vessels makes the liver more depend from the hepatic artery. The hepatic artery flow lacks off splanchnic hepatotrophic factors, resulting the shrinkage of liver dan impaired capacity to regenerate. In order to overcome the obstacle in extrahepatic portal venous obstruction, additional collaterals formation will develop as a cavernoma.[15,16]

CLASSIFICATION

As mentioned before, the PH is classified into prehepatic, intrahepatic, posthepatic hypertension. The intrahepatic PH is further divided into three categories presinusoidal (occlusion of portal tract without the involvement of liver parenchyma), sinusoidal (diseases affecting the liver parenchyma), and postsinusoidal (occlusion of central veins). Measurement of the wedged hepatic vein pressure (WHVP) reflects the sinusoidal pressure and helps to differentiate the types of PH. WHVP is normal in prehepatic and presinusoidal PH, but increased in sinusoidal process. There are many conditions that associated with non-cirrhotic PH, as listed in Table 1.[15,17]

Table 1. The classification and etiology of portal hypertension [15,17]

PH classification	Diseases	Imaging findings
Prehepatic PH (Normal FHVP, normal WHVP, normal HVPG, and increased portal pressure)	Extrahepatic portal vein obstruction Portal vein thrombosis (PVT) Splenic vein thrombosis Splanchnic arteriovenous fistula Massive splenomegaly - Infiltrative disease (lymphoma, myeloproliferative disease) - Storage disease (Gaucher's disease)	- Occlusion of splenic / mesenteric and/or portal vein - Normal smooth liver - Splenomegaly Transient elastography - Liver: normal or mild increased (< 10 kPa) - Spleen: increased (> 35 kPa)
Intrahepatic PH		
Presinusoidal PH (Normal FVHP, normal WHVP, normal HVPG, increased portal pressure)	Developmental abnormalities - Adult polycystic disease - Hereditary hemorrhagic disease - Arteriovenous fistulas - Congenital hepatic fibrosis Biliary diseases - Primary biliary cirrhosis - Sclerosing cholangitis - Autoimmune cholangiopathy Neoplastic occlusion of portal vein - Lymphoma - Chronic lymphocytic leukemia - Epitheloid hemangioendothelioma - Epithelial malignancy Granulomatous lesion - Schistosomiasis - Sarcoidosis Noncirrhotic portal fibrosis (NCPF) / idiopathic portal hypertension (IPH)	- Patent portal venous system - Normal or slightly abnormal liver (periportal enhancement) - Splenomegaly Transient elastography - Liver: normal or mild increased (< 10 kPa) - Spleen: > 35 kPa
Sinusoidal PH (Normal FHVP, increased WHVP, increased HVPG)	Liver cirrhosis Sinusoidal fibrosis - Alcoholic hepatitis - Drugs (methotrexate, amiodarone) - Toxins (cooper, vinyl chloride) - Metabolic (NASH, Gaucher's disease) - Inflammatory (viral hepatitis) Sinusoidal collapse - Acute necro-inflammatory Sinusoidal defenestration - Alcoholic liver disease Sinusoidal infiltration - Mastocytosis - Angiogenic myeloid metaplasia - Amyloidosis Sinusoidal compression - Enlarged Kupffer cells (Gaucher disease, leishmaniasis) - Enlarged hepatocytes (alcoholic hepatitis, acute fatty liver of pregnancy)	- Patent portal venous system - Abnormal liver morphology - Splenomegaly Transient elastography - Liver: > 20 kPa - Spleen: > 35 kPa

PH classification	Diseases	Imaging findings
Postsinusioidal PH (If catheterization of hepatic vein could be performed, there will be pressure gradient across the obstruction)	Venocclusive disease - Hepatic irradiation - Drugs (dacarbazine, arabinoside, azathioprine, cyclophosphamide) Phlebosclerosis of hepatic veins - Alcoholic liver disease - Chronic radiation injury - Hypervitaminosis A Primary vascular malignancies - Epitheloid hemangioendothelioma - Angiosarcoma Granulomatous phlebitis - Sarcoidosis - Myocbacterium infection Hepatic vein outflow tract obstruction - Budd-Chiari syndrome	- Occluded hepatic veins - Intrahepatic collaterals - Abnormal liver (right lobe atrophy, caudate lobe hypertrophy) - Marked ascites - Splenomegaly Transient elastography - Liver: increased - Spleen: increased
Posthepatic PH (If catheterization of hepatic vein could be performed, increased FHVP and increased WHVP, normal HVPG)	Inferior vena cava obstruction - Web, tumour, enlarge caudate lobe Constrictive pericarditis Tricuspid regurgitation Severe right sided heart failure Restrictive cardiomyopathy	- Occluded inferior vena cava - Dilatation of hepatic vein - Marked ascites - Splenomegaly Transient elastography - Liver: increased - Spleen: increased

PH: portal hypertension; FHVP: free hepatic vein pressure; WHVP: wedged hepatic vein pressure; HVPG: hepatic vein pressure gradient; NASH: non-alcoholic steatohepatitis; kPa: kilopascal

Table 2. Different in manifestation between cirrhotic and non-cirrhotic portal hypertension[20]

Variable	NCPH/PSVD	Cirrhotic portal hypertension
Age	Children and adults	Adults
Clinical Manifestation		
Gastroesophageal variceal bleeding	First manifestation	Late presentation
Ascites	Uncommon	Common in end-stage
Hepatic encephalopathy	Uncommon	Common in end-stage
Liver failure	Uncommon	Common in end-stage
Diagnostic Features		
Splenomegaly	+++	+
Pancytopenia	+++	+
Liver enzymes	Normal/mild elevated	Usually elevated
HVPG	Normal/mild elevated, high in certain cases	Usually increased

NCPH: non-cirrhotic portal hypertension; PSVD: portosinusoidal vascular disease; HVPG: hepatic venous pressure gradient

The recognition of idiopathic NCPH has been increased in the the past decade, therefore Gottardi et al in 2019 proposed a new term of portosinusoidal vascular disease (PSVD) to overcome the heterogeneity of causes and histopathology findings (hepatoportal sclerosis, obliterative venopathy, nodular regenerative hyperplasia, and incomplete septal cirrhosis) of idiopathic NCPH.[18] PSVD itself is categorized in presinusoidal PH, which characterized by alteration of small branches of portal vein, normal or slightly abnormal liver structure and/or function, and moderate to massive splenomegaly. The exact mechanism of PSVD is still unclear and needs further research. In the Western countries, PSVD and PVT are the most common etiology of NCPH. Infection and prothrombotic states are the most common culprit of PSVD in Eastern and Western countries, respectively.[11,19]

CLINICAL MANIFESTATION

The clinical manifestation of NCPH is often considered similar to portal hypertension in cirrhosis. Table 2 shows different in clinical manifestation between cirrhotic and non-cirrhotic portal hypertension.[20]

NCPH is usually diagnosed in young to middle age patients. The clinical manifestation of NCPH is features of portal hypertension and its complications, without any evidence of liver dysfunction. Left upper quadrant mass (splenomegaly) is found in 26–97% patients of PSVD, with the average size of splenomegaly is 11 cm (moderate to massive). Liver is usually normal or slightly abnormal (enlarged or shrunken). Peripheral stigmata of cirrhosis are absent. Jaundice and HE are uncommon in PSVD, but can be found after bleeding or shunt surgery. Variceal hemorrhage, ascites, and

edema are reported in 32–84%, 10–34%, 4–18%, respectively. Ascites occurs after a bleeding episode and is associated with hypoalbuminemia and prolonged duration of portal hypertension. Thrombosis in splenic vein leads to splenic infarction, resulting recurrence of left upper quadrant abdominal pain. The less frequent thrombosis manifestations are mesenteric vein thrombosis, bowel ischemia, and hemoperitoneum.[17]

DIAGNOSIS

The diagnosis of NCPH is still very challenging until now. However, there are three common pitfalls in diagnosis NCPH. First, NCPH has a very diverse underlying etiology, including rare disease, therefore it does not share common risk factors or similar clinical presentations. Second, the masking effect of portal hypertension manifestation by underlying etiology, particularly in early stages, made the diagnosis of NCPH is more difficult. Last, there are still no reliable noninvasive tests of NCPH. Liver synthetic function test is usually in normal range until reaching the end-stage of diseases.[20]

Laboratory Examination

Approximately 27–87% of NCPH had hematologic abnormalities due to hypersplenism, which anemia is the most common, followed by thrombocytopenia and leucopenia. Anemia microcytic hypochromic is the most frequent abnormalities chronic bleeding, iron deficiency, and hypersplenism. Abnormal liver function test (increased transaminase levels, prolonged prothrombin time, and low albumin level) is seldomly reported in PSVD. Hypoalbuminemia is only found in 16.8% cases. High bilirubin levels is reported in several studies around 8.8–31%. Alkaline phosphatase and gamma-glutamyl transpeptidase are reported increased in patients with extrahepatic portal vein obstruction. The alteration of coagulation system is reported in majority of NCPH cases (80%), including prolonged prothrombin time, reduced fibrinogen, and reduced platelet aggregation.[17]

Radiography Examination

Abdominal doppler ultrasonography (US) is fast, simple, high availability examination, and recommended as the first line radiology investigation in patients with NCPH. Evaluation of size and texture of liver and spleen can help to determine the etiology of PH. The US pattern of PSVD is the thickening of portal vein (> 3 mm) and smooth intrahepatic radicles. The narrowing of intrahepatic second and third portal vein branches (withered tree appearance) could be observed in PSVD. Cavernomatous transformation of portal vein could be seen in extrahepatic portal vein obstruction. Transient elastography (TE) measures the stiffness of liver and spleen and can help to distinguish the source of PH, as mentioned in Table 1. Normal or mild liver stiffness is observed in prehepatic or presinusoidal PH, meanwhile marked elevation of liver stiffness is found in sinusoidal or postsinusoidal PH. Contrast-enhanced computed tomography scan (CT-Scan) shows non-visualization or occlusive thrombosis of portal vein in patients with intrahepatic portal vein abnormalities.[17] Before the diagnosis of PSVD could be made, comprehensive liver imaging should be performed. The aim of this imaging is to determine the presence of radiological abnormalities in PH (splenomegaly and collateral circulation) and evaluate the patency of hepatic veins and portocirculation.[19]

Endoscopy Examination

As many as 80–90% of NCPH had esophageal varices during endoscopy examination. Varices in NCPH is reported to be more severe than liver cirrhosis, which 90% varices in NCPH is large compared to 70% in cirrhosis. Gastroesophageal varices (GOV1 and GOV2) is also more common (31–44% vs. 22%), however portal hypertensive gastropathy (PHG) less common (5.4% vs. 10.9%) than cirrhotic patients. When performed an initial endoscopy and esophageal varices are small, the endoscopist should look for gastric varices or spontaneous shunt. One of collateral circulations that will develop is anorectal varices, which is seen in 63–95% of cases due to selective redistribution to inferior mesenteric vein. However, the bleeding from anorectal varices is rare.[17]

Hemodynamics Measurement

Hepatic vein pressure gradient (HVPG) measurement is the gold standard to detect portal hypertension. It is performed under ultrasound technique with fluoroscopic guidance. It aims to measure portal venous pressure (represented by wedge hepatic vein pressure/WHVP) and systemic venous pressure (represented by free hepatic vein pressure/FHVP). The calculation of HVPG is the pressure gradient between wedged and free hepatic vein pressure. The choice of vascular access location is the right internal jugular vein due to its continuity with the superior vena cava, right

atrium, and inferior vena cava. The vascular sheath is inserted through right internal jugular vein, continued into the IVC, and advanced to right hepatic vein. In this position, the measurement of FHVP could be performed. The measurement of WHVP is obtained through the balloon catheter occlusion.[21,22]

In NCPH, WHVP may be normal or slightly elevated, resulting a normal gradient despite severe portal hypertension has been developed.[21] This limitation of HVPG made this procedure could not be used as reference standard of portal pressure, especially in pre-sinusoidal portal hypertension. To overcome this obstacle, direct measurement of portal pressure is recommended.[23] Zhang et al in 2021 conducted a study to evaluate the consistency measurement between endoscopic ultrasound–portal pressure gradient (EUS-PPG) compared to HVPG. In this procedure, the direct puncture of portal vein was performed and portal pressure could be measured. This study found a 22-G FNA needle is a safe and accurate method to evaluate portal hypertension. EUS-PPG is considered valuable in determining portal pressure in patients with NCPH.[24]

Histopathological Examination

Liver histology examination can help to determine the etiology of NCPH. This procedure is indicated in the diagnosis of PSVD to exclude cirrhosis and other etiologies of NCPH. In order to diagnosis of PSVD, diagnosis of NCPH based on a specimen with minimum size 20 mm with 10 portal spaces.[11] Liver biopsy is not necessary in extrahepatic portal vein obstruction cases.[17] The biopsy specimen should be referred to the expert pathologists to recognize the histological pattern may be associated with primary or secondary disease. There are several histopathological patterns associated with NCPH, as shown in Table 3.[25,26] There are no pathognomonic histology for idiopathic NCPH, however there are several classical signs, including portal/periportal changes (narrowing or sclerosis of portal vein), hepatic lobular lesions (sinusoidal dilatation), incomplete septal cirrhosis, and nodular regenerative hyperplasia.[26]

As mentioned before, idiopathic NCPH only could be diagnosed after ruling out the other etiologies of portal hypertension. In 2011, diagnostic criteria for NCPH have been developed as mentioned in Table 4. All of the criteria must be fulfilled to made the diagnosis of NCPH. Due to the heterogeneity of the disease, European Association for the Vascular Liver Disease (VALDIG) proposed a new terminology of PSVD and its diagnostic criteria, as mentioned in Table 5.[18]

Table 3. Histological pattern in non-cirrhotic portal hypertension[25]

Histopathological patterns	Histological findings	Etiologies
Hepatoportal sclerosis	- Missing portal veins - Herniation of portal veins into sinusoid	- Collagen-vascular disease - Common variable immunodeficiency
Nodule regenerative hyperplasia	- Regenerative nodules lined by atrophic liver cells	- Collagen-vascular disease - Lymphoproliferative disease - Chronic biliary diseases - Common variable immunodeficiency
Portal vein thrombosis	- Missing portal veins - Arterialization of veins	- Hypercoagulable states - Chronic myeloproliferative diseases
Perisinusoidal/ perivenular deposits	- Fibrosis of space of Disse or hepatic vein	- Alcoholic hepatitis - Chronic heart failure - Amyloidosis
Outflow obstruction	- Perivenular hemorrhage or thrombosis	- Rheumatic heart disease - Cor pulmonale - Budd-Chiari syndrome
Sinusoidal dilation	- Congested liver sinus lined by atrophic hepatocytes	- Androgen or oral contraceptives - Sickle cell disease

Table 4. Diagnostic criteria for non-cirrhotic portal hypertension 2011[18]

Clinical criteria	
Signs of portal hypertension (any of the following)	- Splenomegaly or hypersplenism - Gastroesophageal varices - Ascites - Mildly elevated HVPG measurement - Portovenous collaterals
Exclusion of liver cirrhosis based on biopsy	
Exclusion of chronic liver disease etiologies causing cirrhosis or NCPH	- Chronic hepatitis B or C infection - Non-alcoholic steatohepatitis (NASH) - Alcoholic liver diseases - Autoimmune hepatitis - Wilson's disease - Primary biliary cholangitis - Hereditary haemochromatosis
Exclusion of other conditions causing NCPH	- Congenital liver fibrosis - Sarcoidosis - Schistosomiasis
Patent portal hepatic veins based on Doppler USG or CT scan	

HVPG: hepatic venous pressure gradient; NCPH: noncirrhotic portal hypertension; USG: ultrasonography; CT: computerized tomography

Table 5. Diagnostic criteria for PSVD 2019[18]

	Clinical signs of portal hypertension	Histological signs of portal hypertension
Specific	1. Gastroesophageal varices or ectopic varices 2. Portal hypertensive hemorrhage 3. Development of porto-systemic collateral based on imaging	1. Obliterative portal venopathy 2. Nodular regenerative hyperplasia 3. Incomplete septal fibrosis or cirrhosis
Not specific	1. Ascites 2. Platelet count < 150,000 / µL 3. Spleen largest diameter ≥ 13 cm	1. Abnormalities of portal tract (dilatation of arteries, periportal vascular channels) 2. Disturbances of liver architectural (irregular distribution of portal tracts) 3. Sinusoidal dilatation (non-zonal) 4. Mild degree of perisinusoidal fibrosis

Table 6. Diseases and drugs associated to PSVD[11]

Etiology classification	Specific etiology	Specific etiology
Thrombophilia	- Deficiency of protein C, protein S, antithrombin - Antiphospolipid syndrome (APS)	- Factor V Leiden - Prothrombin mutation
Hematologic disorders	- Myeloproliferative neoplasms (MPN) - Spherocytosis - Myleoid metaplasia	- Lymphoproliferative disorders (LPD): Hodgkin, non-Hodgkin, chronic lymphocytic leukemia
Autoimmune diseases	- Rheumatoid arthritis - Systemic lupus erythematosus	- Systemic sclerosis
Gut disease	- Celiac disease	- Inflammatory bowel disease
Immunodeficiency disorder	- Human immunodeficiency virus (HIV) infection	- Primary immunodeficiency
Drug and toxins	- Oxaliplatin - Azathioprine - Cyclophosphamide	- Bleomycin - Chlorambucil - Doxorubicin
Genetic disorders	- Cystic fibrosis - Turner's disease	- Adams-Oliver syndrome

The diagnosis of PSVD must fulfill these two conditions: (1) Liver biopsy ≥ 20 mm shows no signs of cirrhosis; (2) 1 clinical sign specific or 1 histological sign specific for portal hypertension. The alternative criteria diagnostic for PSVD required: (1) No signs of cirrhosis based on liver biopsy ≥ 20 mm; (2) 1 clinical sign non-specific and 1 histological sign non-specific for portal hypertension.[18] According to the definition above, the absence of portal hypertension and presence of PVT do not rule out PSVD. PVT could be co-exist with PSVD and also with viral hepatitis, alcohol consumption, metabolic syndrome. After the diagnosis has been made, clinicians should perform screening for diseases (immunology, prothrombotic or genetic disorders) and drugs. Table 6 comprises the list of diseases and drugs that associated with PSVD.[11]

MANAGEMENT

Gastro-esophageal Varices: Acute Bleeding

The principle management of NCPH is treatment of associated diseases and elevated portal pressure. Variceal hemorrhage is one of the most common complications of NCPH. Baveno VII recommends to perform endoscopic screening for gastro-esophageal varices at the time of diagnosis of PSVD. The use of non-invasive method of variceal screening in cirrhosis patients, such as liver stiffness measurement (LSM) and platelet count, could not be used in PSVD. Management of acute variceal bleeding and prophylaxis, both primary and secondary, are the mainstay treatment of NCPH. Baveno VII also recommended the management similar to portal hypertension in cirrhotic patients.[27]

The initial treatment of acute variceal hemorrhage in NCPH include stabilization of hemodynamic, protection of airway, and use of vasoactive drugs (terlipressin, somatostatin, or octeotride). These therapies will be followed by endoscopic management. In acute esophageal variceal hemorrhage, endoscopic variceal ligation (EVL), or endoscopic sclerotherapy (EST) every three weeks should be performed untuk varices obliteration and followed by nonselective beta-blocker (NSBB) as secondary prophylaxis. For gastroesophageal varices (GOV) type 1 with acute bleeding, the management similar with esophageal varices. In cases of GOV type 2 or isolated gastric varices (IGV) type 1, cyanoacrylate injection is recommended.[28] The indication of trans-jugular intrahepatic portosystemic shunt (TIPS) is esophageal varices bleeding and GOV type 1 or 2 with any of the following condition: Child Pugh (CP) class C < 14 or CP class B > 7 with active bleeding or HVPG > 20 mmHg. TIPS with polytetrafluoroethylene (PTFE)-covered stents should be performed in 72 hours. Balloon-occluded retrograde transvenous obliteration (BRTO) could be considered in GOV type 2 and IGV

type 1.[27] Endoscopic evaluation is recommended after 3 months, then 6 months for 1 year and then yearly.[28]

Gastro-esophageal Varices: Prophylaxis

Primary prophylaxis aims to prevent the variceal hemorrhage in patients with clinically significant portal hypertension (CSPH) by using NSSB. Ferreira et al in 2016 performed a prospective cohort study to determine the natural history and management esophagogastric varices in chronic PVT. As many as 37% of patients with chronic PVT had first portal hypertensive bleeding even though under primary prophylaxis. It also stated that the natural history in noncirrhotic nontumoral PVT is similar to cirrhosis and same management approach is associated with survival rate.[29]

Sarin et al in 2010 conducted a randomized controlled trial to determine the efficacy of EVL and NSBB (propranolol) for secondary prophylaxis in patients with NCPH. As many 51 patients and 50 patients were randomized to EVL (every three weeks) and propranolol (until target resting heart rate 55 beats per minute was achieved or maximal dose 320 mg per day) groups, respectively. After follow-up period of 23 months, the rates of recurrence of variceal hemorrhage were similar between both groups (23.5% in EVL and 18% in propranolol groups). From this research, NSBB was not inferior compared to EVL for secondary prophylaxis variceal bleeding in NCPH.[30] However, Baveno VII in 2022 recommended the combination of NSBB and EVL for secondary prophylaxis, similar to cirrhotic portal hypertension. However, there is limited data on which therapy should be preferred for the prophylaxis in PSVD.[27]

Anticoagulation

The probability of spontaneous resolution of recent PVT in patient without cirrhosis is low, therefore the administration of anticoagulant is mandatory immediately after the diagnosis. Unfractionated heparin (UFH) is not recommended in this situation due to the high risk of heparin-induced thrombocytopenia, except in low glomerular filtration rate (GFR) < 30 mL/minute. Low-molecular weight heparin (LMWH) is suggested to be the first line anticoagulant treatment and switched to vitamin K antagonist when possible. The data of safety of direct oral anticoagulant (DOAC) is still limited. The duration of anticoagulant in recent PVT without cirrhosis is recommended for minimal 6 months and could be continued long term in patients with permanent underlying prothrombotic state. To monitor the effect of anticoagulant, follow up contrast-enhanced CT scan could be ordered 6 months after recent PVT. The measurement of d-dimer is recommended in 1 month after stop the anticoagulant to estimate the risk of recurrence. D-dimer value < 500 ng/mL is associated with low risk of thrombosis recurrence.[27]

If the patients with incomplete resolution of recent PVT at 6 months after therapy, long term anticoagulant is recommended. For patients with past PVT or cavernoma and never received anticoagulation, anticoagulant therapy should be administered with consideration of risk and benefit. In patients with high-risk variceal bleeding, adequate prophylaxis for portal hypertensive bleeding should be started first. The referral to tertiary centers is considered when percutaneous recanalization of portal vein or other vascular interventional procedures is indicated to overcome the refractory complication of PVT. The screening of gastroesophageal varices within 6 months should be performed in all patients who has not been recanalized. If the varix is not found, repeated endoscopy is recommended at 12 months and 2 years thereafter.[27]

The efficacy and safety of anticoagulant in PSVD is still unclear. There are several findings that support the use of anticoagulant in PSVD. First, thickening or obliteration of intrahepatic portal vein is one of the most common histopathological results in PSVD, which could occur due to the previous thrombotic events. Second, PVT is a common complication of PSVD, secondary to blood flow stasis and portal hypertension. Last, several underlying diseases maybe associated with PSVD such as prothrombotic states, MPN, and APS. However, experts recommend anticoagulation in patients with high-risk thrombosis or already developed PVT.[18]

Surgery

Surgery is considered in patients who failed to control the bleeding after endoscopic management. There are two types of surgery: (1) Shunt or bypass surgery; (2) Ablation procedures. Shunt procedure can be performed by using non-physiological or physiological shunts. Non-physiological shunt is performed by making bypass of portal blood into systemic circulation (total or partial shunts). Meanwhile, physiological shunt is performed to still maintain the hepatic portal blood flow and bypassing the level of obstruction by using an autologous graft from superior mesenteric vein to left portal vein. Ablation surgery or devascularization of esophagogastric can be

performed alone or in combination with splenectomy. It is indicated in patients who failed shunts, no shuntable vein is available, and emergency refractory variceal hemorrhage.[17]

Shunt surgery is one of the managements in patients with extrahepatic portal vein obstruction. The absolute indications of this procedures include refractory variceal bleeding, symptomatic hypersplenism (recurrent hemorrhage or infection), thrombocytopenia (< 100,000/mm^3), refractory HE, hepatopulmonary syndrome, and portopulmonary hypertension. This procedure is also indicated in patients with symptomatic splenomegaly (spleen rupture, infarction, limitation of daily living activities), poor quality of life, refractory lower GI bleeding due to anorectral varices, minimal hepatic encephalopathy, and portal biliopathy).[17] The details of surgical intervention in NCPH is described in Table 7.[31]

Splenectomy or Partial Splenic Embolization

In patients with severe hypersplenism (spontaneous hemorrhage episodes, severe transfusion-dependent anemia, and repeated splenic infarcts), splenectomy or partial splenic embolization could be performed. This procedure can increase the platelet count.[18] In animal model, splenectomy has been shown in ameliorating the hyperdynamic circulation and also improving anemia and thrombocytopenia, both in cirrhotic and non-cirrhotic PH.[32]

Liver Transplantation

The data about liver transplantation in patients with NCPH is scarce. Until 2020, only 48 cases of liver transplantation were performed in NCPH, which 38 of them were male. The pathological diagnosis is very diverse, including nodular regenerative hyperplasia, incomplete septal cirrhosis, portal vascular abnormalities, and NCPF. Orthotopic liver transplantation (OLT) and living donor liver transplantation (LDLT) were performed in 35 and 13 patients, respectively. The survival rate after transplantation were favorable, with 33 alive, 5 death, and 10 unknown. Of 5 patients who dead post-transplantation, the duration between procedure and death is 1 month (1 patient), 3 months (1 patient), 4 months (1 patient), and 5 months (2 patients).[33,34] The indication to perform liver transplantation in PSVD is similar with liver cirrhosis.[18] In cirrhotic patients, liver transplantation is indicated in Child Pugh score B/C or model for end-stage liver disease (MELD) score ≥ 15. For patients with MELD score ≤ 14, indication for transplantation is decided on patient-specific basis.[35,36]

Table 7. Details of surgical intervention in NCPH [31]

Procedure	Description of procedure	Indication
Esophagogastric devascularization procedure		
Sugiura technique (most widely known)	- Devascularization of distal esophagus and proximal gastric - Transection and re-anastomosis of esophagus - Splenectomy	Esophageal varices
Hassab technique	- Devascularization of distal esophagus and proximal gastric - Vagotomy and pyloroplasty - Splenectomy	
Mathur technique	- Devascularization of distal esophagus and proximal gastric - Transection and reanastomosis of esophagus - Nissen fundoplication ± splenectomy	
Portoportal shunts		
Rex shunt	Shunting superior mesenteric vein to the left portal system at the recess of Rex	Extrahepatic portal vein obstruction
Portosystemic shunts		
Selective (decompression of variceal-bearing compartment)		- Esophageal varices - Portal gastropathy - Portal biliopathy
Warren's distal splenorenal technique	End-to-side anastomosis of distal splenic vein to left renal vein	
Inokuchi's left gastric venous caval technique	End-to-side anastomosis of left gastric vein vena cava (may require an autologous graft)	
Splenocaval technique	End-to-side anastomosis of distal splenic vein to cava (may require an polytetrafluoroethylene/PTFE graft)	
Partial (incomplete portal system decompression)		
Sarfeh's portocaval	Requires 8 mm interposition PTFE graft	
Nonselective (complete portal system decompression)		
Portocaval	End-to-side or side-to-side anastomosis	
Mesocaval	Side-to-side or with interposition graft	
Mesoatrial	Requires interposition PTFE graft	
Proximal splenorenal	End-to-side anastomosis of proximal splenic vein to left renal vein	

CONCLUSION

The recognition of NCPH has been increased in recent years, even though the incidence is declined based on several reports. Clinicians should seek the underlying etiology in portal hypertension without cirrhosis. The diagnosis of NCPH is still challenging and when the cause is absent, the diagnosis idiopathic NCPH/PSVD could be made. The principle management is related to the portal hypertension and its complications, including prophylaxis and management of acute variceal hemorrhage, anticoagulant, shunt surgery, splenectomy or partial spleen embolization, and liver transplantation.

REFERENCES

1. Bosch J, Berzigotti A. Portal hypertension in cirrhosis. In: Dooley J, Lok A, Garcia-Tsao G, Pinzani M, editors. Sherlock's Diseases of The Liver and Biliary System. 13th ed. United Kingdom: Willey-Blackwell Publishing; 2018. p. 180–208.
2. Gunarathne LS, Rajapaksha H, Shackel N, Angus PW, Herath CB. Cirrhotic portal hypertension: from pathophysiology to novel therapeutics. World J Gastroenterol 2020;26:6111–40.
3. Basu AK, Boyer J, Bhattacharya R, Mallik KC, Sen Gupta KP. Non-cirrhotic portal fibrosis with portal hypertension: a new syndrome. I. Clinical and function studies and results of operations. Indian J Med Res 1967;55:336–50.
4. Schouten JNL, Garcia-Pagan JC, Valla DC, Janssen HLA. Idiopathic noncirrhotic portal hypertension. Hepatology 2011;54:1071–81.
5. Iwata H, Nishikawa A, Tanaka H. National survey on idiopathic portal hypertension. In: Kameda H, editor. 1985 Report of the Research Committee on Aberrant Portal Hemodynamics. Tokyo: Ministry of Health and Welfare; 1986. p. 117–29.
6. Imai F, Kuga K, Komaba M. Interim report on IPH survey. In: Futagawa S, editor. 1992 Report of the Research Committee on Aberrant Portal Hemodynamics. Tokyo: Ministry of health and Welfare; 1993.
7. Kumar S, Ae S, Kumar A, Yogesh AE, Chawla K, Sanjay AE, et al. Noncirrhotic portal fibrosis/idiopathic portal hypertension: APASL recommendations for diagnosis and treatment Members of the APASL Working Party on Portal Hypertension. Hep Intl 2007;1:398–413.
8. Riggio O, Gioia S, Pentassuglio I, Nicoletti V, Valente M, d'Amati G. Idiopathic noncirrhotic portal hypertension: current perspectives. Hepat Med 2016;8:81–8.
9. Lavekar A. A short review of non cirrhotic portal fibrosis. Acta Sci Gastron Disord 2019;2:16–8.
10. D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39:1180–93.
11. Gioia S, Nardelli S, Ridola L, Riggio O. Causes and management of non-cirrhotic portal hypertension. Currr Gastroenterol Rep 2020;22:1–8.
12. Condat B, Pessione F, Hillaire S, Denninger MH, Guillin MC, Poliquin M, et al. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology 2001;120:490–7.
13. Spaander MCW, Hoekstra J, Hansen BE, van Buuren HR, Leebeek FWG, Janssen HLA. 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.
14. Schouten JNL, Nevens F, Hansen B, Laleman W, van den Born M, Komuta M, et al. Idiopathic noncirrhotic portal hypertension is associated with poor survival: Results of a long-term cohort study. Aliment Pharmacol Ther 2012;35:1424–33.
15. Valla DC. Vascular Disorders of the Liver and Extrahepatic Portal Hypertension. In: Dooley J, Lok A, Garcia-Tsao G, Pinzani M, editors. Sherlock's Diseases of The Liver and Biliary System. 13th ed. United Kingdom: Willey-Blackwell Publishing; 2018. p. 209–30.
16. Mathew RP, Venkatesh SK. Liver vascular anatomy: a refresher. Abdom Radiol 2018;43:1886–95.
17. Khanna R, Sarin SK. Non-cirrhotic portal hypertension - diagnosis and management. J Hepatol 2014;60:421–41.
18. 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;4:399–411.
19. Schouten JNL, Verheij J, Seijo S. Idiopathic non-cirrhotic portal hypertension: a review. Orphanet J Rare Dis 2015;10:1–8.
20. Etzion O, Koh C, Heller T. Noncirrhotic portal hypertension: an overview. Clin Liver Dis 2015;6:72–4.
21. Bochnakova T. Hepatic venous pressure gradient. Clin Liver Dis 2021;17:144–8.
22. Philips CA. In pictures: hepatic venous pressure gradient - indications, technique and complications. Int J Anat Radiol Surg 2017;6:1–4.
23. Xu H, Ding H. EUS-guided portal pressure gradient measurement : a promising tool in noncirrhotic portal hypertension. Gastrointest Endosc. 2021;93:286–7.
24. Zhang W, Peng C, Zhang S, Huang S, Shen S, Xu G, et al. EUS-guided portal pressure gradient measurement in patients with acute or subacute portal hypertension. Gastrointest Endosc 2021;93:565–72.
25. Kleiner DE. Noncirrhotic portal hypertension: pathology and nomenclature. Clin Liver Dis 2015;5:123–6.
26. Guido M, Sarcognato S, Sacchi D, Colloredo G. Pathology of idiopathic non-cirrhotic portal hypertension. Virchows Archiv 2018;473:23–31.
27. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII – Renewing consensus in portal hypertension. J Hepatol 2022;76:959–74.
28. Sarin SK, Philips CA, Khanna R. Noncirrhotic portal hypertension: medical and endoscopic management. Clin Liver Dis 2015;6:107–11.
29. Ferreira CN, Seijo S, Plessier A, Silva-Junior G, Turon F, Rautou PE, et al. Natural history and management of esophagogastric varices in chronic noncirrhotic, nontumoral portal vein thrombosis. Hepatology 2016;63:1640–50.
30. Sarin SK, Gupta N, Jha SK, Agrawal A, Mishra SR, Sharma BC, et al. Equal efficacy of endoscopic variceal ligation

and propranolol in preventing variceal bleeding in patients with noncirrhotic portal hypertension. Gastroenterology 2010;139:1238–45.

31. Marti J, Gunasekaran G, Iyer K, Schwartz M. Surgical management of noncirrhotic portal hypertension. Clin Liver Dis 2015;5:112–5.
32. Schwabl P, Seeland BA, Riedl F, Schubert TL, Königshofer P, Brusilovskaya K, et al. Splenectomy ameliorates portal pressure and anemia in animal models of cirrhotic and non-cirrhotic portal hypertension. Adv Med Sci 2022;67:154–62.
33. Krasinskas AM, Eghtesad B, Kamath PS, Demetris AJ, Abraham SC. Liver transplantation for severe intrahepatic noncirrhotic portal hypertension. Liver Transplantation 2005;11:627–34.
34. Kawachi S, Chiba N, Nakagawa M, Kobayashi T, Hikita K, Sano T, et al. Living donor liver transplantation for idiopathic portal hypertension with extrahepatic portal vein stenosis and splenic artery aneurysms: a case report and review of the literature. BMC Surg 2020;20:1–6.
35. Mahmud N. Selection for liver transplantation: indications and evaluation. Curr Hepatol Rep 2020;19:203–12.
36. Graziadei I, Zoller H, Fickert P, Schneeberger S, Finkenstedt A, Peck-Radosavljevic M, et al. Indications for liver transplantation in adults: Recommendations of the Austrian Society for Gastroenterology and Hepatology (ÖGGH) in cooperation with the Austrian Society for Transplantation, Transfusion and Genetics (ATX). Wien Klin Wochenschr 2016;128:679–90.