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GUIDELINES

Non-cirrhotic portal fibrosis/idiopathic portal hypertension: APASL recommendations for diagnosis and management

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Abstract

Since the Asian Pacific Association for the Study of the Liver (APASL) published guidelines on non-cirrhotic portal fibrosis/idiopathic portal hypertension in 2007, there has been a surge in new information, especially with the introduction of the term porto-sinusoidal vascular disorder (PSVD). Non-cirrhotic intra-hepatic causes of portal hypertension include disorders with a clearly identifiable etiology, such as schistosomiasis, as well as disorders with an unclear etiology such as non-cirrhotic portal fibrosis (NCPF), also termed idiopathic portal hypertension (IPH). This entity is being increasingly recognized as being associated with systemic disease and drug therapy, especially cancer therapy. An international working group with extensive expertise in portal hypertension was assigned with formulating consensus guidelines to clarify the definition, diagnosis, histological features, natural history, and management of NCPF/IPH, especially in the context of PSVD. The guidelines were prepared based on evidence from existing published literature. Whenever there was paucity of evidence, expert opinion was included after detailed deliberation. The goal of this manuscript, therefore, is to enhance the current understanding and help create global consensus on the issues surrounding NCPF/IPH.

Keywords Non-cirrhotic portal hypertension · Porto-sinusoidal vascular disease · Idiopathic non-cirrhotic portal hypertension · NCPF · INCPH · NCPH · Obliterative portal venopathy · Portal hypertension · Variceal bleed · Incomplete septal cirrhosis · Nodular regenerative hyperplasia · APASL consensus

Abbreviations

ANA	Antinuclear antibody
APASL	Asian Pacific Association for the Study of the Liver
APS	Antiphospholipid syndrome
ARFI	Acoustic radiation force impulse
ASMA	Anti smooth muscle antibody
AST	Aspartate transaminase
ALT	Alanine transaminase
BRTO	Balloon occluded retrograde transvenous obliteration
CARTO	Coil-assisted retrograde transvenous obliteration
CD	Crohn's disease
CVID	Common variable immunodeficiency
EHPVO	Extra hepatic portal vein obstruction
EUS	Endoscopic ultrasound
EVL	Endoscopic variceal ligation
GRADE	Grading of recommendations, assessment, development, and evaluations
HIV	Human immunodeficiency virus
HAART	Highly active anti retroviral therapy
HE	Hepatic encephalopathy
HLA DR3	Major histocompatibility complex, class II, DR beta 3
HVPG	Hepatic venous pressure gradient
IL6	Interleukin 6
IHP	Intrahepatic pressure

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ISP	Intrasplenic pressure
INCPH	Idiopathic non cirrhotic portal hypertension
IPH	Idiopathic portal hypertension
LSM	Liver stiffness measurement
LT	Liver transplant
MHE	Minimal hepatic encephalopathy
NCPH	Non-cirrhotic portal hypertension
NCPF	Non-cirrhotic portal fibrosis
NRH	Nodular regenerative hyperplasia
NSBB	Non-selective beta-blockers
OPV	Obliterative portal venopathy
PARTO	Plug-assisted retrograde transvenous obliteration
PB	Portal biliopathy
PHTN	Portal hypertension
PSAE	Partial splenic artery embolisation
PSVD	Porto sinusoidal vascular disorder
PVT	Portal vein thrombosis
SOS	Sinusoidal obstruction syndrome
SSM	Splenic stiffness
SWE	Shear wave elastography
TIPS	Transjugular intrahepatic portosystemic shunt
TNF	Tumor necrosis factor
TRG	Telomere-related genes
UC	Ulcerative colitis
VCAM	Vascular cell adhesion molecule
VOD	Veno-occlusive disease

Introduction

The term 'Portal Hypertension' was coined by Gilbert and Carnot in 1902 [1]. Cirrhosis is the most common cause of portal hypertension, though patients may present with features of portal hypertension such as splenomegaly, variceal bleeding, and ascites in the absence of cirrhosis. These patients typically are found to have one the following entities (Fig. 1): (i) extrahepatic splanchnic venous thrombosis (portal vein or splenic vein thrombosis), (ii) intrahepatic disorders in which a definitive cause of portal hypertension can be identified—such as schistosomiasis and sinusoidal obstruction syndrome (iii), and intrahepatic disorders in which there is no clear cause of portal hypertension identifiable. The latter group was generally labeled as having non-cirrhotic portal fibrosis (NCPF)/idiopathic portal hypertension (IPH) [2].

European experts have recently proposed the term 'Porto-sinusoidal vascular disorder' (PSVD), as a broader clinico-pathological entity to define essentially the same condition but also including patients without portal hypertension or having competing etiologies. [3]. An update of the 2007 NCPF/IPH APASL guidelines was required to clear the confusion in terminology and incorporate the advances in the understanding of this disease [4]. To present a broader perspective, experts from outside Asia were also included.

The Asian Pacific Association for the Study of the liver (APASL) set up a working group in 2023 with a mandate

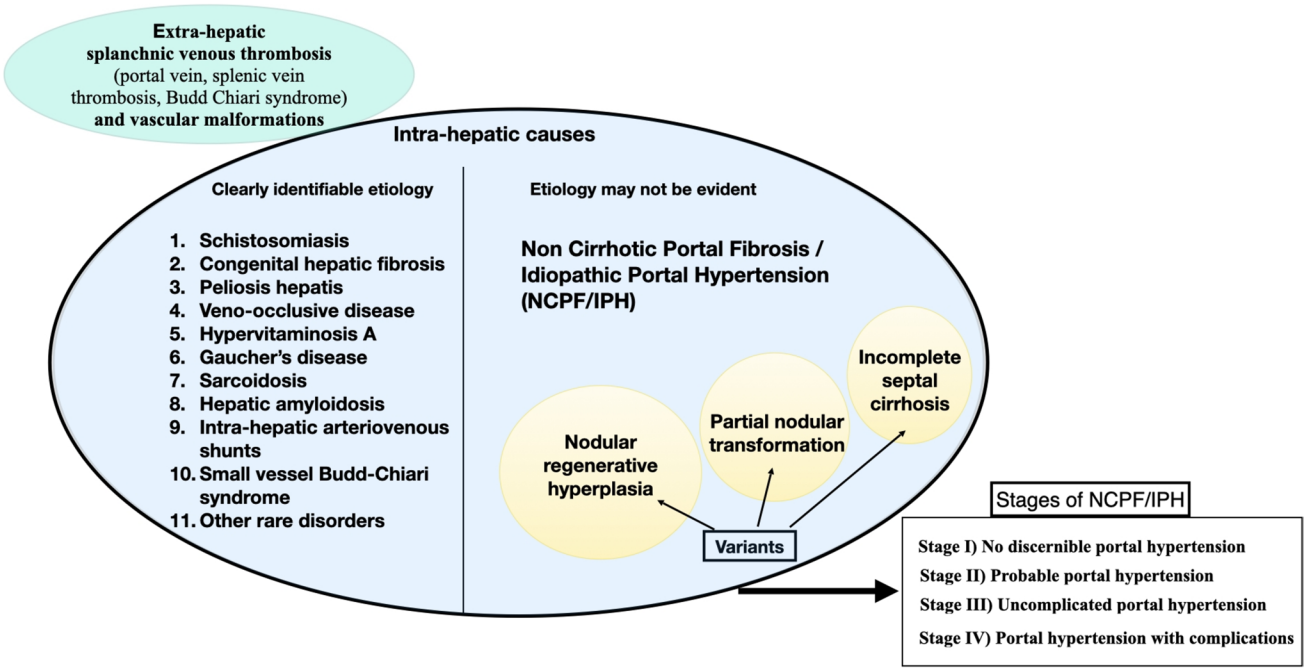

Fig. 1 Causes of portal hypertension other than cirrhosis

to review the current knowledge, relevance of the term NCPF/IPH, and if so, to develop an updated consensus on aspects of portal hypertension seen in the absence of cirrhosis. Specific disorders such as schistosomiasis and extrahepatic portal vein thrombosis leading to non-cirrhotic portal hypertension were not discussed. The international working group included expert hepatologists, pathologists, radiologists, hepatobiliary surgeons, and basic scientists worldwide. Experts were asked to critically analyze different aspects of NCPF/IPH, and develop consensus statements. Experts were divided into seven groups, and each group was assigned one section according to their area of expertise to prepare a preliminary draft of the consensus statements. The process was as follows: review of published literature; survey of current diagnostic and management approaches; and discussion on controversial issues. These statements were circulated to the entire body of experts for review. The Delphi system of agreement was followed, and the statements were modified until at least 80% agreement was achieved, or the statement was dropped. The recommendations were ranked using the GRADE system after assessing the level of existing evidence (Table 1) [5]. Additionally, the quality of evidence and strength of recommendations were summarized (Table 2).

Definition and nomenclature

A significant challenge in this area is unifying the highly varied criteria and nomenclature that have been used to characterize the entity of portal hypertension of unclear etiology in the absence of cirrhosis. A timeline of nomenclature is provided in Table 3 [3, 7–14]. The consensus panel agreed that NCPF/IPH encompasses a group of hepatic vascular diseases with varied etiologies and histopathologic features, and characterized by intrahepatic vascular lesions and evidence of portal hypertension in the absence of histological evidence of cirrhosis. Noncirrhotic portal fibrosis (NCPF)/idiopathic portal hypertension (IPH) is still the preferred term in most of Asia. [6, 7]. For the purposes of this review, NCPF and IPH are used interchangeably, though minor differences in the epidemiology, clinical features, risk factors, and probable pathogenesis between NCPF and IPH have been noted in publications [6, 13–19]. NCPF typically presents in males during their third-to-fourth decade of life, while IPH is seen commonly in women in their fifth decade. Splenomegaly is a common feature in both entities, seen in a significant majority of patients (74–97%), whereas, variceal bleeding is more common in NCPF (65–72%) as compared to IPH (35%). Association with autoimmune conditions is more common in IPH than NCPF.

The term NCPF/IPH covers terminologies used throughout Asia. In Europe, what is termed NCPF/IPH in this document was designated as idiopathic non-cirrhotic portal hypertension (INCPH) [7, 20]. Other terminologies used and based on histopathologic findings include hepatoportal sclerosis [9], obliterative portal venopathy (OPV) [11], and nodular regenerative hyperplasia (NRH) [8]; these latter terminologies do not necessarily indicate that the patient has portal hypertension [21]. The presence of NCPF without portal hypertension was postulated over 3 decades ago and termed as 'pre-NCPF' or' early NCPF' [14]. This fact has relevance as it allows inclusion of patients in a continuum of disease—with the described histological changes—before they develop portal hypertension.

Recently, porto-sinusoidal vascular disease (PSVD) was proposed as an entity, encompassing previously described disorders including NCPF/IPH, but primarily based on histological features, and without the requirement of portal hypertension [3]. Histological diagnostic criteria for PSVD include 'specific' as well as 'non-specific' features. Specific histologic features include obliterative portal venopathy (thickening of vessel wall, occlusion of the lumen, and vanishing of portal veins), nodular regenerative hyperplasia, and incomplete septal fibrosis/ cirrhosis. Non-specific histologic features include portal tract abnormalities (multiplication, dilation of arteries, peri-portal vascular channels, and aberrant vessels); architectural disturbance: irregular distribution of the portal tracts and central veins, non-zonal sinusoidal dilation, and mild peri-sinusoidal fibrosis.

Table 1 Grading of evidence and recommendations (adapted from the GRADE system) [5]

High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
	Grading of recommendation	
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed important patient outcomes, and cost	1
Conditional recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	2

Table 2 Summary of recommendations for diagnosis and management of non-cirrhotic portal fibrosis/idiopathic portal hypertension (NCPF/IPH)

Sr. no.	Recommendations (quality of evidence, strength of recommendation)
1	NCPF/IPH is a condition of varied etiology typically manifesting as portal hypertension in the absence of extrahepatic portal venous obstruction or specific known causes of cirrhosis or schistosomiasis, and is characterized by narrowing/loss of small and medium branches of the portal vein that result in the development of portal hypertension. (A,1)
2	All the histological features of PSVD with very few exceptions are well described in NCPF/IPH, and thus, it is recommended that NCPF/IPH terminology be used in preference to PSVD. (B,1)
3	Patients with NCPF/IPH should be evaluated for exposure to drugs and toxins, and may be evaluated for underlying immunological, genetic and thrombophilic disorders. (B,2)
4	A. In the presence of portal hypertension, NCPF/IPH can be diagnosed in an adequate-sized needle biopsy of the liver with adequate number of portal tracts (ideally 20 mm and 10 in number) by identification of obliterative portal venopathy, nodular regenerative hyperplasia, and incomplete septal fibrosis. All features may not be seen in the same biopsy specimen. (A,1) B. Histological diagnosis of NCPF/IPH requires the absence of i) regenerative nodules, ii) features of possible or definite cirrhosis, and iii) other specific etiologies such as schistosomiasis. (A,1) C. In the absence of overt portal hypertension, a diagnosis of early NCPF/IPH can be suggested by the presence of risk factors and specific histological features like obliterative portal venopathy, nodular regenerative hyperplasia, and incomplete septal fibrosis described above (B,2) OR non-specific histological features such as portal tract abnormalities (multiplication, dilation of arteries, peri-portal vascular channels, and aberrant vessels); architectural disturbance: irregular distribution of the portal tracts and central veins, non-zonal sinusoidal dilation, and mild peri-sinusoidal fibrosis (C,2)
5	A. HVPG is normal or minimally elevated in patients with NCPF. (A,1) B. A pressure gradient may exist between the spleen and the liver (intrasplenic pressure – intrahepatic interstitial pressure [IHP]) and between the IHP and the wedged hepatic venous pressure (WHVP) (IHP – WHVP). (A,1)
6	A. In patients with portal hypertension, using transient elastography or MR elastography (MRE) a diagnosis of NCPF/IPH is suggested by the presence of the following features: 1. LSM is lower in patients with NCPF/IPH than in patients with cirrhosis. (C,2) 2. Spleen stiffness is markedly elevated in patients with NCPF/IPH. (A,1) 3. A higher splenic stiffness to liver stiffness ratio increases the accuracy of diagnosis of NCPF. (B,2) B. More data are needed for role of SWE/ARFI in diagnosis of NCPF/IPH
7	NCPF/IPH should be suspected in the following situations: a) Unexplained splenomegaly (B,1) b) Variceal hemorrhage without any evidence of hepatocellular decompensation. (B,1) c) Portal hypertension in the absence of cirrhosis/hepatocellular dysfunction. (A,1) d) Unexplained chronic elevation in liver biochemistry. (B,1)
8	A. Hypersplenism in the presence of NCPF/IPH can be diagnosed in the presence of the following: (i) monolineage or multilineage peripheral cytopenias; (ii) hypercellular or normocellular bone marrow, and, (iii) splenomegaly. (A,1) B. Symptomatic hypersplenism is diagnosed by the presence of thrombocytopenia and non-portal hypertension spontaneous bleeding episodes including gum bleeding, epistaxis, or menorrhagia in the absence of obvious causes. (C,1)
9	A. Patients with NCPF/IPH have a better long-term prognosis as compared to patients with compensated cirrhosis. (B,1) B. Mortality from acute variceal hemorrhage in patients with NCPF/IPH is lower than in patients with acute variceal hemorrhage in cirrhosis probably because liver function is typically better preserved in patients with NCPF/IPH than in those with cirrhosis. (B,1)
10	A. The prevalence of gastroesophageal variceal hemorrhage in patients with NCPF/IPH is high. (B,1) B. A small proportion of adults with NCPF/IPH may develop ascites, especially after a variceal bleed. (B,1)
11	Overt hepatic encephalopathy in NCPF/IPH is rare, but minimal encephalopathy may be present in up to one-third of patients, especially in the presence of large spontaneous portosystemic shunts. (B,1)
12	Only a small proportion of children and adults with NCPF/IPH experience a poor clinical outcome due to uncontrolled bleeding or progressive liver failure. (C,2)
13	The natural history of patients with NCPF/IPH may be divided into 4 stages (C,1) I. No clinical or radiological evidence of portal hypertension (the disease is suggested by pathological evidence of hepatic vascular abnormalities alone) II. Probable portal hypertension III. Portal hypertension without complications and IV. Portal hypertension with complications
14	Other factors related to progression of disease in NCPF/IPH include age at diagnosis, and underlying associated chronic immuno-inflammatory, genetic, or malignancy-related disorders. (C,2)
15	Portal vein thrombosis may develop in patients with NCPF/IPH and may be associated with a poorer outcome. NCPF/IPH patients should be serially monitored for development of portal vein thrombosis. (C,2)
16	Patients with NCPF/IPH should undergo upper gastrointestinal endoscopy as surveillance for the presence of esophageal/gastric varices (C,1)

Table 2 (continued)

Sr. no.	Recommendations (quality of evidence, strength of recommendation)
17	Prevention of variceal bleeding should be a priority in the management of NCPF/IPH, because the absence of bleeding is associated with better long-term outcomes (C,2)
18	Pre-primary prophylaxis is not currently recommended for patients with NCPF/IPH given the absence of data supporting its use. (C,2)
19	Endoscopic variceal ligation is recommended as primary prophylaxis against esophageal variceal bleeding in patients with NCPF/IPH who have large varices. Non-selective beta-blocker therapy is an acceptable alternative in these patients, though it should be recognized that monitoring the response to therapy using HVPG may be inaccurate. (C,1)
20	No recommendations can be made at the present time regarding primary prophylaxis to prevent gastric variceal bleeding
21	Neither portosystemic shunt surgery nor transjugular intrahepatic portosystemic shunt (TIPS) is recommended as primary prophylaxis against variceal bleeding in patients with NCPF/IPH. (C,1)
22	A. General measures for control of acute variceal hemorrhage are similar to those for patients with cirrhosis.(C,2) B. Vasoactive drugs should be combined with endoscopic therapy for the control of acute variceal bleeding and initiated preferably at least 30 min before endoscopy. (A,1) C. Endoscopic variceal ligation (EVL) is the preferred endoscopic modality used to obliterate esophageal varices in NCPF/IPH patients with esophageal variceal hemorrhage. (B,2) D. Prophylactic antibiotics are recommended based on the current guidelines for cirrhosis, although data on this for NCPF/IPH patients are lacking. (C,2) E. Transjugular intrahepatic portosystemic shunt (TIPS) may be used a salvage therapy when a combination of endoscopic and pharmacological treatment have failed to control the variceal bleeding. The role of early TIPS in NCPF/IPH requires further study. (C,2)
23	For secondary prophylaxis of esophageal variceal bleeding, non-selective beta-blockers in combination with EVL are recommended. (C,1)
24	Transjugular intrahepatic portosystemic shunt (TIPS) may be considered when there is recurrence of variceal bleeding despite a combination of endoscopic and pharmacological therapy, but data are limited. (C,2)
25	Balloon occluded retrograde transvenous obliteration (BRTO)/plug-assisted retrograde transvenous obliteration (PARTO) or coil-assisted retrograde transvenous obliteration (CARTO) may be effective in secondary prevention of gastric variceal bleeding, and are best used in the presence of a gastrorenal shunt.(B,1)
26	A. Partial splenic artery embolization may be considered for patients with symptomatic hypersplenism. (B,1) B. Shunt surgery may be considered in patients with symptomatic hypersplenism who have also bled from varices– recognizing that there is a risk of developing HE and other long-term complications (portopulmonary hypertension, glomerulopathy, etc.) following surgery. (B,2) C. Splenectomy without portosystemic shunt surgery should be avoided. (C.2)
27	Liver transplantation is not usually required for patients with NCPF/IPH, but may be offered to those patients with liver failure or refractory portal hypertensive complications. (A,1)

Table 3 Nomenclature timeline [3, 7–14]

Name	Author	Year
1. NRH (nodular regenerative hyperplasia)	Steiner PE [8]	1959
1. Hepatoportal sclerosis	Mikkelsen WP et al. [9]	1965
1. IPH (Idiopathic portal hypertension)	Boyer JL et al. [10]	1967
1. OPV (Obliterative portal venopathy)	Nayak NC et al. [11]	1969
1. NCPF (non-cirrhotic portal fibrosis)	Ramalingaswamy V et al. (ICMR) [12]	1969
1. IPH (Idiopathic portal hypertension)	Kobayashi Y et al. (committee on IPH, Japan) [13]	1976
1. Pre/early NCPF	Sarin SK [14]	1989
1. INCPH (idiopathic non-cirrhotic portal hypertension)	Schouten JN [7]	2011
1. PSVD (porto-sinusoidal vascular disorder)	De Gottardi et al. [3]	2022

The APASL expert group comprehensively examined the published literature around PSVD and agreed unanimously that PSVD is not a novel entity. Other than for trivial differences, all of the risk factors, histology, and clinical features of PSVD are well described as part of NCPF/IPH guidelines of APASL published in 2007 (Table 4) [3, 4, 7, 14, 21]. One of the key reasons proposed by proponents of the PSVD nomenclature was that there are patients without portal hypertension who have liver histology compatible with the diagnosis. However, this largely indicates an earlier stage of

Table 4 Comparison of APASL 2007 guidelines on NCPF/IPH with the proposal for PSVD [3, 4, 7, 14, 21]

Feature	Similarities/differences	NCPF/IPH	PSVD
Is presence of Portal Hypertension (PHT) necessary for diagnosis?	Difference	Yes However, the concept of 'pre-NCPF' or 'early NCPF' exists since 1989 for the early stages of the NCPF/IPH	No Histology alone is sufficient even in absence of PHT
Associated risk factors	Similarities	Infections Autoimmune disorders Prothrombotic disorders Chronic exposure to toxins Prolonged treatment with drugs Genetic disorders	
	Difference	Blood diseases are not mentioned Portal vein thrombosis (if present prior to NCPF/IPH) excluded	Blood diseases are added Presence of portal vein thrombosis is not an exclusion for PSVD
Histological features	Similarities	Absence of cirrhosis in an adequate-sized liver biopsy Nodular regenerative hyperplasia Incomplete septal cirrhosis Obliterative portal venopathy Portal tract vascular abnormalities Dilatation of sinusoids and peri-portal vessels Focal nodular hyperplasia	
	Differences	Fibrous expansion of portal tracts Rounded or streaky fibrosis	Mild peri-sinusoidal fibrosis
Whether concomitant etiologies preclude the diagnosis?	Difference	Yes	No
Risk of portal vein thrombosis	Similarities	More frequent than in patients with liver cirrhosis Development of portal vein thrombosis associated with poor prognosis	

the disease rather than a novel disease entity. An identical situation where patients had histological features of NCPF/IPH in the absence of portal hypertension was proposed over three and-a-half decade ago and was termed as "pre-NCPF" or "early NCPF" [3, 14]. The only difference is that in PSVD, the fibrosis pattern described is peri-cellular, a pattern that has not been described in NCPF/IPH [3]. Based on these facts, the APASL expert group retained the term NCPF/IPH and integrated recent advancements in understanding the disease. The experts also acknowledged the presence of a subgroup of patients with features of NCPF/IPH but without portal hypertension, particularly in the presence of nodular regenerative hyperplasia (NRH).

Histopathologic features of NCPF/IPH

Narrowing down a histological diagnosis of NCPF may pose challenges due to the heterogeneous distribution and severity of the lesions. Various histologic features have been described, depending on whether liver specimens are obtained at autopsy, or by wedge biopsy or needle-liver biopsy. This is important, because histological features present on wedge biopsy may not all be visible on needle biopsy.

Macroscopic examination (autopsy/explant): liver on gross examination may appear normal, enlarged, or shrunken. Fibrous thickening of the capsule with subcapsular septations, sclerosis of intrahepatic portal vein branches, and approximation of portal tracts to the surface may be seen [6, 22, 23]. The surface appears nodular in NRH, closely resembling cirrhosis. NRH presents a more granular surface with less pronounced elevations and nodules smaller than 2 mm, which appear paler compared to the surrounding parenchyma [24]. Superficial biopsies/wedge biopsies may be mistakenly reported as cirrhosis, especially when taken from livers with surface nodularity. Histological features noted in autopsies include increased portal collagenous connective tissue and sclerosis and obliteration of small branches of portal veins in most cases. Intimal fibrosis and elastosis, leading to subendothelial thickening and compromised lumen, may cause thickening of the veins which occasionally resemble arteries. Recanalized thrombi may be seen. Mild inflammation, regenerative nodules, aberrant vasculature, and recanalized thrombi are occasional histologic findings in autopsy biopsies [24]. Hepatic vein may show sclerosis or small branches may show slight dilatation.

Microscopic features (Fig. 2)*:* It is important to emphasize that all the histological features considered characteristic

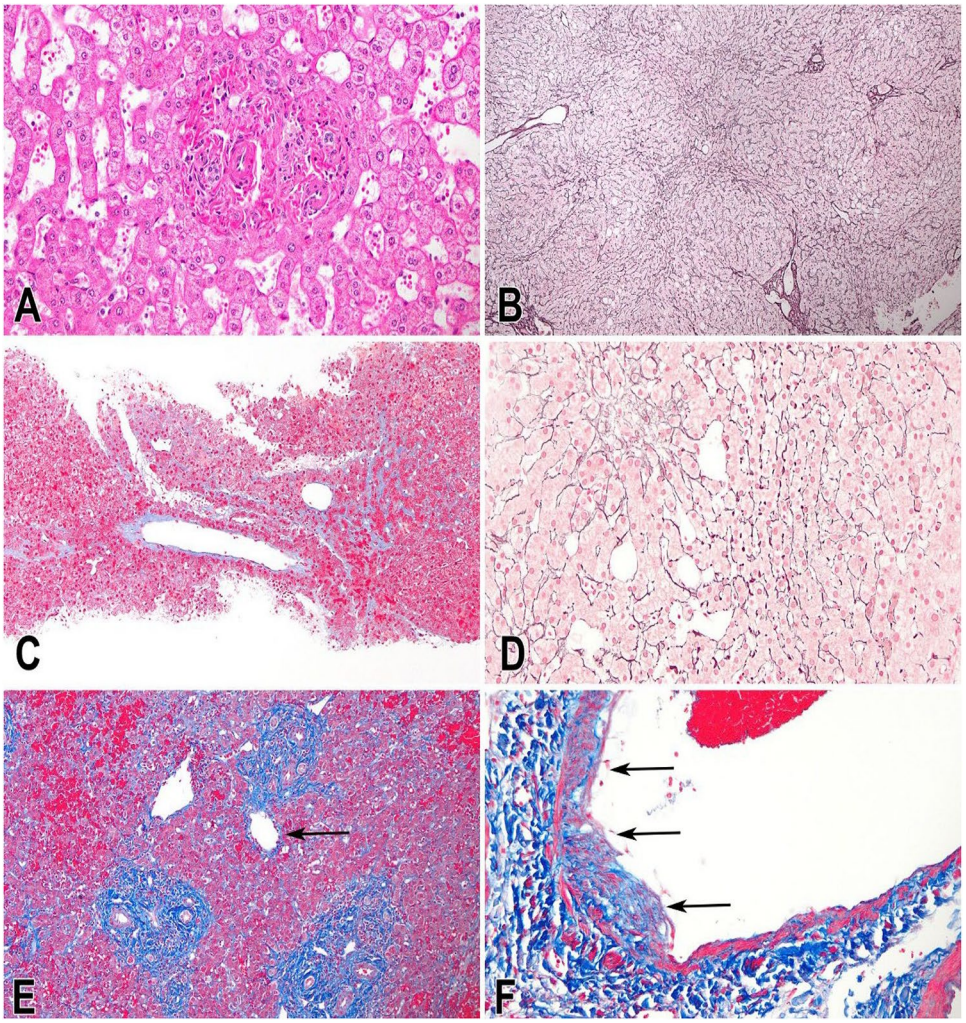

Fig. 2 Pathological changes seen in non-cirrhotic portal hypertension. **A** Small rounded portal area lacking a distinct portal vein. The surrounding sinuses are dilated. (H & E, 200×). **B** Nodular regenerative hyperplasia with nodules of wide hepatocyte plates alternating with narrowed, atrophic hepatocyte plates. (Reticulin, 40×). **C** Perisinusoidal fibrosis in an area of hepatocyte atrophy around a large central vein (Masson, 100×). **D** Multiple small central vein profiles in the region between two regenerative nodules (Reticulin, 200×). **E** Three small portal areas clustered abnormally together. One portal area shows a portal vein displaced to the edge of the portal area (arrow). (Masson, 100×). **F** Large portal vein with early phlebosclerotic changes (arrows). (Masson, 200×)

of PSVD (nodular regenerative hyperplasia, obliterative portal venopathy/portal vein stenosis, and incomplete septal fibrosis/cirrhosis) have been well described with NCPF/IPH.

Historically, different terminologies have been used to describe the histological features of NCPF/IPH (Table 3). The term “obliterative portal venopathy” was coined by Nayak and Ramalingaswamy in 1969 based on biopsy specimens from autopsy, exhibiting increased portal collagenous tissue and sclerosis along with obliteration of small portal vein branches [11]. Mikkelsen used the term "hepatoportal sclerosis" to describe intimal sclerosis and thickening of intrahepatic and extrahepatic portal vein branches in patients with non-cirrhotic portal hypertension [9]. OPV is also now termed as portal vein stenosis [25]. Collagen deposition in the space of Disse has been observed by electron microscopy [26]. Induction of elastin expression in portal veins has been identified in NCPF [27].

The collagen and elastin deposition in IPH may be a result of increased connective tissue growth factor expression and decreased MMP-9 expression in portal tracts [28]. Sato Y and group suggested the role of endothelial dysfunction and endothelial–mesenchymal transition [29]. Endothelial–mesenchymal transition (EMT) is a phenomenon whereby vascular endothelial cells acquire myofibroblastic features characterized by an ability to express mesenchymal cell products that are related to tissue fibrogenesis. EMT has been shown to be associated with development OPV.

Other findings seen in NCPF/IPH include scarring of terminal portal tracts, obliteration/disappearance of portal vein radicles, aberrant portal tract vessels, portal vein dilatation with herniation into the surrounding hepatic parenchyma, capillary and necro inflammatory bridging between portal tracts and terminal hepatic veins, isolated mega- sinusoids, and slender, curved fibrous septa. The lobular architecture is usually preserved with minimal hepatocyte injury [22, 23, 30–32]. These findings, however, may be inconspicuous or absent on needle biopsy specimens. Also, the entire spectrum of portal vascular changes may not be present in all patients with NCPF/IPH, and portal venous structures may not always be obliterated, with a narrowed but still visible

lumen. In the light of these findings, the term "phlebosclerosis" is more appropriate; and defined as a portal venous structure (predominantly small and medium branches) with a reduced or completely sclerosed lumen. Notably, a study of biopsy specimens from patients with NCPF described the following specific features: phlebosclerosis, portal tract fibrosis, portal tract remnants, and septal fibrosis, with phlebosclerosis being the most common identifiable abnormality seen in two-thirds of specimens [32]. Non-specific features included sinusoidal and portal vein dilatation, para-portal shunt vessels, and increased vascular channels in portal tracts and lobular parenchyma, observed in approximately 45% of patients. It has been postulated that these aberrant vessels represent development of intrahepatic collateral vessels to compensate for the portal circulatory disturbance caused by obliteration of terminal portal vein branches [33, 34]. Histology is normal in 13% of patients. Histological features of NCPF/IPH are summarized in Table 5 and representative images are provided in Figs. 3, 4, 5.

Incomplete septal cirrhosis and nodular regenerative hyperplasia are reported in patients with NCPF/IPH [35]. They can be considered as special histological variants of NCPF/IPH (Fig. 1). Histologic features of incomplete septal cirrhosis comprise thin incomplete septa, abnormal spacing between draining veins and portal tracts, parenchymal hyperplasia, crowding of reticulin fibers, and nodularity. These features may represent disease regression and have also been observed in cirrhosis [36]. NRH, a histological feature common to NCPF/IPH and PSVD, was first defined by Steiner in 1959 as a condition characterized by diffuse benign transformation of the hepatic parenchyma into small regenerative nodules distributed evenly throughout the liver with minimal or no fibrosis in the peri-sinusoidal or peri-portal areas [8]. Nodules typically measure 1–3 mm, with hepatocytes arranged in plates more than one cell thick plates. These cells may exhibit enlargement and hypertrophic nuclei (Fig. 4). In the internodular areas, hepatocytes are small, atrophic, and compressed into thin, parallel plates. This compression, best visualized with a reticulin stain, may be accompanied by sinusoidal dilation and slit-like central veins [37]. Wanless proposed histologic criteria and classification for NRH in 1990 [24] which included the presence of hepatocellular nodules < 3 mm in diameter that were not surrounded by fibrosis (nodules graded 0–3 + based on the extent of nodularity noted through all fields of the biopsy), and the presence of fibrous septa (graded 0–3). Biopsy specimens that met the criteria of 3 + nodularity and 0–1 fibrous septa were classified as nodular regenerative hyperplasia.

Histological features of NRH can be seen in multiple conditions including various systemic diseases and after exposure to certain drugs [38–42]. NRH is not always associated with portal hypertension and the clinical significance in the absence of portal hypertension is incompletely understood. However, when NRH is identified in the absence of clear clinical evidence of portal hypertension, these patients

Table 5 Histological features of NCPF/IPH

Feature	Description
Specific histological features [11, 30, 31]	
Phlebosclerosis (also called as obliterative portal venopathy/OPV)	Portal vein branch (predominantly small and medium PV branches) with a reduced or completely sclerosed lumen
Incomplete septal fibrosis*	Thin incomplete septae that do not connect vascular structures (portal areas and/or central veins
Nodular regenerative hyperplasia (NRH)	Diffuse benign nodular transformation of the hepatic parenchyma with minimal or no fibrosis in the peri-sinusoidal or peri-portal areas Nodules (1–3 mm size with hepatocytes arranged in plates more than one cell thick) are separated by hepatocytes which are small, atrophic, and compressed into thin, parallel plates (internodular areas) highlighted by reticulin stain
Additional histological features that may be seen in NCPF/IPH [22–26]	
Para-portal shunt vessels	Enlarged thin-walled vessels located outside but in close contact with portal tracts
PV dilatation	PV:HA diameter > 3:1
Increased vascularity of portal tract	Small thin-walled vascular spaces located within the portal tracts
Aberrant portal tract vasculature	Aberrant thin-walled vessels herniating from the portal tract into the para-portal area, sometimes into the lobules where they can give a pseudoangiomatous appearance; prominent hepatic artery; arterial multiplication
Architectural disturbance	Irregular distribution of the portal tracts and central veins
Sinusoidal dilatation	Non-zonal sinusoidal enlargement
Mild peri-sinusoidal fibrosis	May be seen on connective tissue stains or more often with electron microscopy
Peri-venular fibrosis	

*May also be seen in conditions associated with chronic hepatitis like Hepatitis B & C etch as well as in regressed cirrhosis

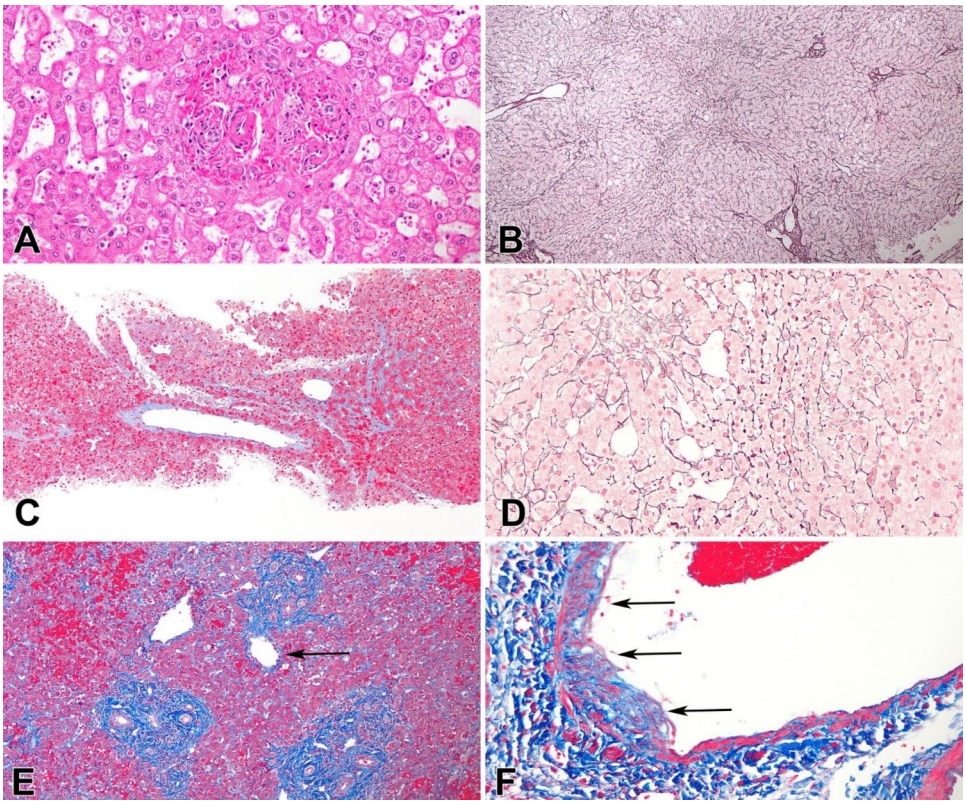

Fig. 3 Characteristics of phlebosclerosis (obliterative portal venopathy). **A** Portal vein too small for the portal area in a case of severe combined immunodeficiency. (H&E, 400×). **B** MIssing portal vein in nodular regenerative hyperplasia (H&E, 200×). C, D. Missing portal veins in Deficiency of Adenosine Deaminase 2. (**C** H&E, 200×. **D** Masson, 200×). **E** Missing portal vein in prolidase deficiency (H&E, 400×). Large portal vein showing narrowing of lumen. The original extent of lumen is demarcated by the thin layer of smooth muscle (arrows). (Masson, 200×)

should be characterized and may be considered as having NCPF/IPH and a follow-up is warranted.

Nakanuma [43] proposed staging of IPH with a combination of hepatic parenchymal atrophy and portal venous thrombosis. Stage I is non-atrophic liver without subcapsular parenchymal atrophy, stage II is non-atrophic liver with subcapsular parenchymal atrophy, stage III is atrophic liver with subcapsular parenchymal atrophy, and stage IV is portal venous occlusive thrombosis. The authors postulated that progression occurs from stages I to IV, with stage IV occurring late in disease course. However, it is important to note that this staging system is designed for the gross description of the liver on pathology, typically in explant or autopsy settings, but the clinical counterpart of each stage is unclear.

Risk factors

The etiology of NCPF/IPH continues to evolve. Several studies have identified risk factors but definite causal association remains to be determined. Approximately 70% patients of NCPF/IPH have at least one identifiable risk factor [44] and one-third of the patients have multiple risk factors (Table 6). The predominant etiologic factors vary from region to region, with infections probably playing a major role in developing countries and systemic diseases and drugs contributing in other countries.

Infections

Bacterial infection from the gut with repeated septic embolization of the portal circulation has been hypothesised as a possible risk factor for the development of NCPF/IPH [45–47]. Thrombin along with other endogenous factors such as cytokines and activated coagulation factors released in response to bacterial infections may lead to stellate cell activation and development of portal fibrosis [48]. A higher prevalence of NCPF/IPH in developing countries and the decline in prevalence with improved standards of hygiene support this potential pathogenic mechanism [49]. Repetitive in vivo thrombotic events may also be associated with development of NCPF/IPH as shown by Klein et al. in their rat models of NCPH using microspheres for portal vein embolization [50].

HIV appears to have direct cytopathic effect on sinusoidal endothelial cells causing a range of pathologic abnormalities (i.e., sinusoidal dilatation) that are present in NCPF/IPH [51]. With highly active anti-retroviral therapy (HAART), the lifespan of HIV-infected patients has increased, leading to growing recognition of NCPF/IPH in this patient cohort, even in the absence of detectable HIV infection.

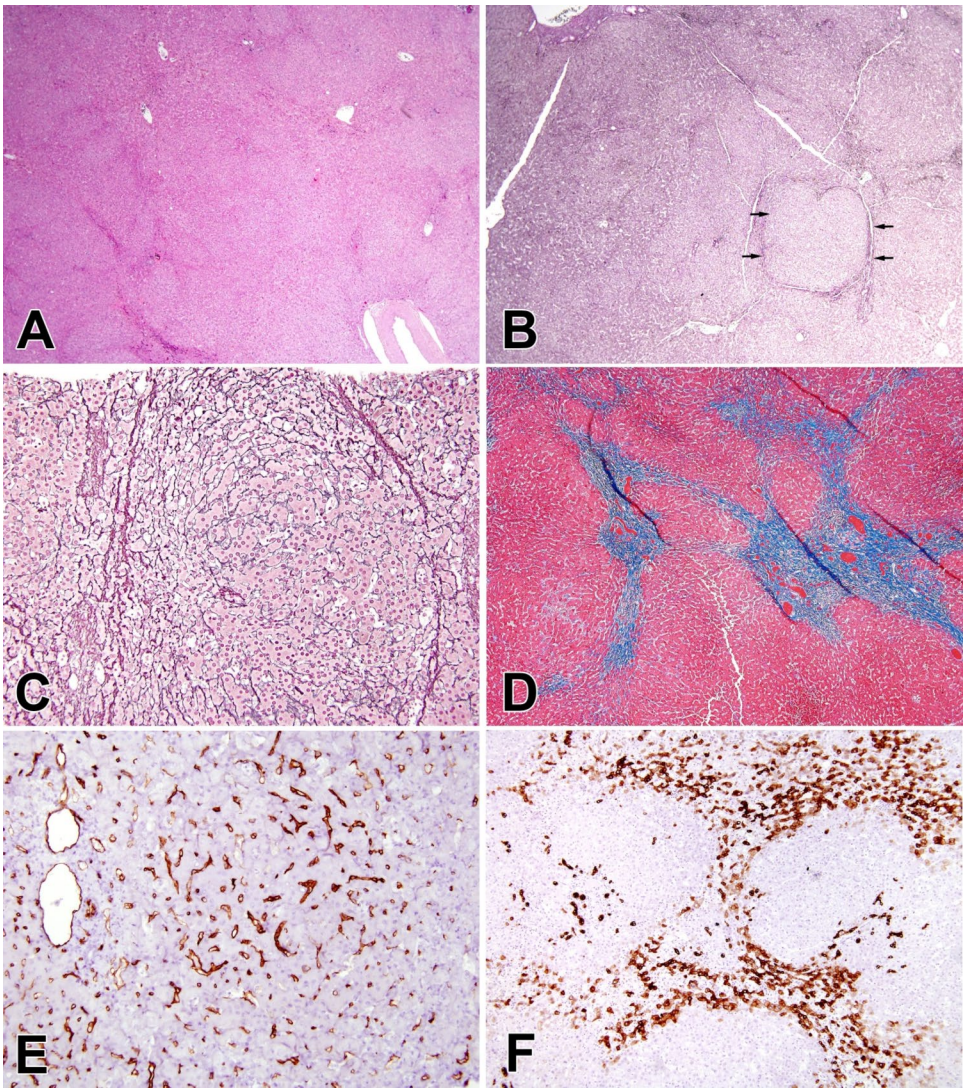

Fig. 4 Characteristics of nodular regenerative hyperplasia. **A** At low magnification there is vague nodularity with congestion around the edges of nodules (H&E, 40×). **B** Nodules are better seen on a reticulin stain (prominent nodule indicated by arrows), where closely spaced sinusoidal collagen in atrophic areas will be darker than the center of the nodules, where the liver cell plates are wide. (Reticulin, 40×). **C** In needle biopsies, an alternating pattern of wide and narrow liver cell plates is seen on the reticulin stain. (Reticulin, 200×). **D** Incomplete septal cirrhosis may develop in nodular regenerative hyperplasia by loss of atrophic hepatocytes with replacement by fibrosis. (Masson, 40×). Diagnosis may be aided using immunohistochemistry. **E** Sinusoidal endothelial cells may express CD34 abnormally in zones 2 and 3 as sinusoids become capillarized. (anti-CD34, 200×). **F** Atrophic hepatocytes may express keratin 7, outlining the regenerative nodules. (anti-keratin 7, 100×)

Drug exposure

There is increasing recognition of NCPF/IPH in Western countries, which may be attributable to increased exposure to chemotherapeutic drugs, HAART, and other drugs. Of particular interest is the association of oxaliplatin with OPV and NRH, and histological features of NCPF/IPH. Other histological features of NCPF/IPH have been reported in patients treated with oxaliplatin, including para-portal shunts and sinusoidal dilatation [52]. Oxaliplatin induced sinusoidal damage with resultant chronic hypoxia and obliteration of capillaries may predispose to development of NRH [53, 54]. Advanced age and higher cumulative HAART exposure is also related to NCPF/IPH. In a Dutch study, clinically overt portal hypertension was found to be present in around 0.09% in HIV patients [55]. This study also identified long-term exposure of didanosine or short-term combination treatment of didanosine with stavudine or tenofovir to be a definite risk factor for NCPF [OR 2]. Didanosine has been strongly implicated as causative factor in NCPF/IPH in many studies [56–58]. Other drugs implicated are azathioprine [59], 6-thioguanine [60], bleomycin, busulfan, and cyclophosphamide [61–63].

It is important to recognize that most of the publications linking specific drugs to NCPF/IPH are case reports or small retrospective studies. Further, only a small proportion of patients who are exposed to these chemotherapeutic drugs develop NCPF/IPH and a much larger cohort may have histologic features without any clinical evidence of portal hypertension. Hence, long-term follow-up of patients with isolated histologic features of NCPF/IPH without portal hypertension is needed. Also, oxaliplatin is known to cause sinusoidal endothelial injury, extravasation of RBCs into the space of Disse, and peri-sinusoidal fibrosis [53].

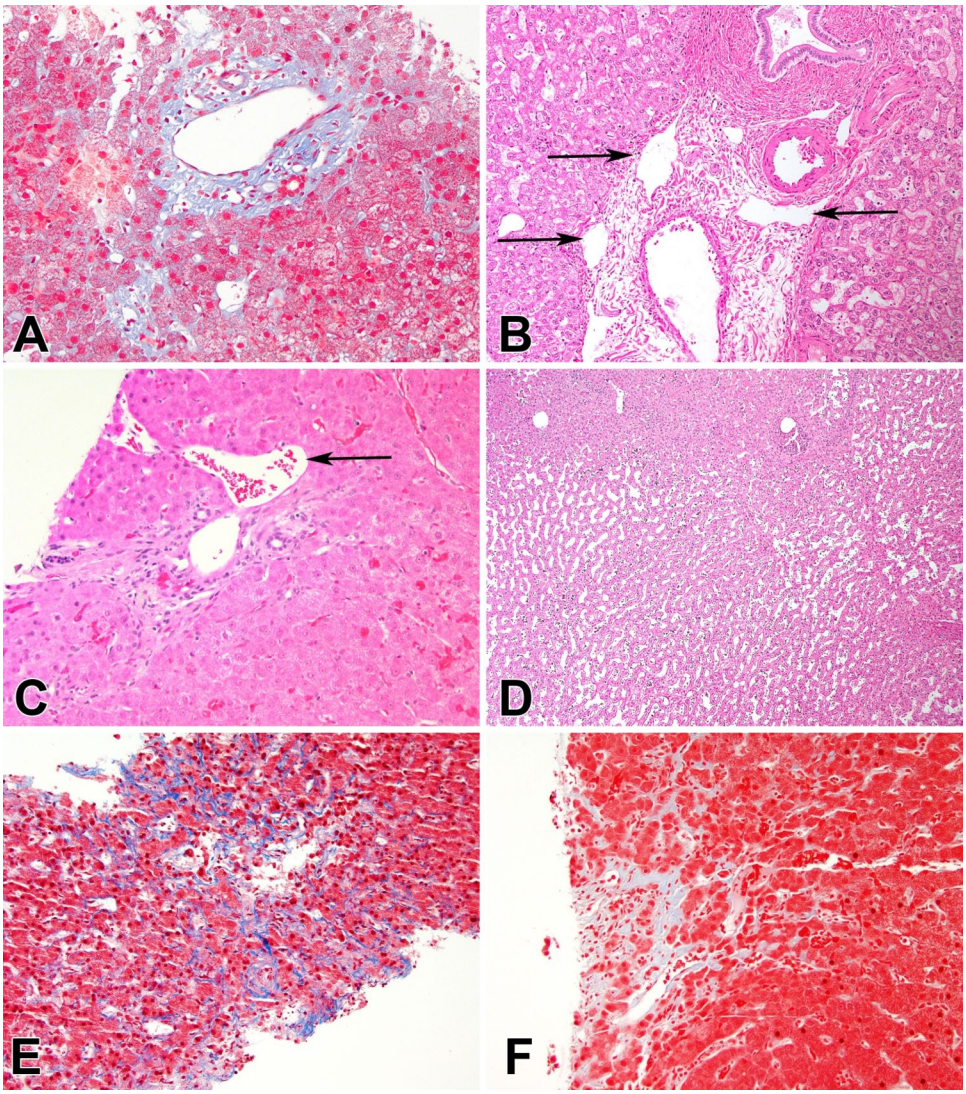

Fig. 5 Additional histological findings that may be seen in NCPF/IPH. A variety of less specific histological findings can be identified in biopsies of patients with NCPF/IPH. **A** Dilation of the portal vein is noted when the diameter of the portal vein is more than three times the diameter of the hepatic artery (Masson, 200×). **B** Multiple thin-walled vessels (arrows) may be seen in addition to the hepatic artery and portal vein (H&E, 100×). **C** The portal vein may show a direct connection to hepatic sinusoids (arrow) (H&E, 200×). **D** Sinusoidal dilation may be irregularly distributed due to irregular loss of portal veins (H&E, 40×). **E** Delicate sinusoidal fibrosis is often seen in areas of hepatocyte atrophy in nodular regenerative hyperplasia (Masson, 200×). **F** Peri-venular fibrosis may be present and associated with thicker peri-sinusoidal fibrosis (Masson, 200×)

Toxins

In India, arsenic exposure in drinking water has been reported to be associated with portal fibrosis [64–66]. Similar studies from the West have reported that arsenic preparations for psoriasis in the form of Fowler's solution may be associated with portal fibrosis [67]. In patients with liver dysfunction and chronic arsenic ingestion, liver histology is notable for peri-portal fibrosis and multiple vascular channels in the expanded portal zones [68, 69]. High hepatic oxidative stress and IL-6/TNF-alpha levels seen with chronic arsenic ingestion probably cause immune-mediated endothelial damage and development of NCPF [70, 71]. A study from East India included 248 patients with evidence of chronic arsenic toxicity caused by contaminated drinking water [72] of whom 69 patients underwent liver biopsy for evaluation of abnormal liver tests. NCPF was present in 91% of these biopsies, although arsenic levels were not elevated in all liver specimens. Other environmental toxins implicated in NCPF/IPH include vinyl chloride and copper sulfate (vineyard sprayers).

Inherited and acquired thrombophilia

Much research has been done in thrombophilia since publication of the last guidelines. Mural thrombi and obliteration of portal vein radicles on histology hint towards an underlying prothrombotic state. Patients with NCPF/IPH consistently have histologic evidence of thrombosis of medium/large sized portal vein branches, and portal vein thrombosis (PVT) is found in around 40% of these patients [73, 76].

Nakanuma et al. in their histopathologic review of NCPH reported fresh and organizing thrombi, recanalization of thrombi, and intimal thickening in nearly all the specimens examined [74].

Table 6 Risk factors associated with NCPF/IPH [39–94]

1. Genetic	Telomere disorders (mutations in TERT and TERC) Developmental disorders (NOTCH1 and CTC1) Turner's syndrome HLA-DR3 positive Familial obliterative portal venopathy (FOPV) gene mutations Adams–Olivier syndrome
2. Drug-induced vascular injuries (DIVI)*	Azathioprine Methotrexate Oxaliplatin Didanosine Stavudine 6-Thioguanine
3. Immune disorders	Progressive systemic sclerosis Systemic lupus erythematosus Rheumatoid arthritis Felty's syndrome Celiac disease** Mixed connective tissue disease Crohn's disease Human Immunodeficiency Virus Disease* Others: Common variable immunodeficiency syndrome, hyper IgM syndrome, X-Linked Agammaglobulinemia
4. Thrombophilic disorders*/hematological diseases	Protein C deficiency Myeloproliferative neoplasms Factor V Leiden mutations Anti-phospholipid antibody Others (prothrombin gene mutation, MTHFR mutations) Complement factor gene mutation** ADAMTS13 deficiency**
5. Infections & herbs and toxin-induced injuries (HTIIs)	Xenobiotics Arsenic** Vinyl chloride Pyrrolizidine alkaloids Recurrent/chronic low-grade abdominal infections** Tropical Sprue**

*More common in Europe

**More common in Asia–Pacific region

Identification of a strong association between NCPF, PVT, and thrombophilia suggests that NCPF and EHPVO may be part of a spectrum of liver diseases associated with thrombophilia [75]. Approximately 30% of patients have one or more underlying prothrombotic condition in NCPF/IPH [21, 44, 73, 76], with antiphospholipid syndrome (APS) the most frequent prothrombotic condition reported.

Hematological disease

Acquired autoimmune protein S deficiency and secondary thrombophilia, which may be linked to NCPF/IPH and portal hypertension, have been reported in HIV patients [77]. NCPF/IPH has also been reported as a long-term complication of bone marrow transplant [57, 78, 79]. Other conditions associated with NCPF/IPH include hematologic disorders such as myeloproliferative disease and multiple myeloma [80].

Rheumatological/immunologic disorders

Immunological disorders are identified in approximately 10% of patients with NCPF/IPH, particularly in Western countries [44, 55, 81–83]. Systemic sclerosis, systemic lupus erythematosus, multiple sclerosis, autoimmune thyroiditis, inflammatory bowel diseases (UC/CD), and celiac disease which may be associated with acquired thrombophilia are some of the immune-mediated disorders seen to be associated with NCPF/IPH. Elevation of IgA anti-cardiolipin antibody has been observed in celiac disease, which may be a predisposing factor [84]. These observations have been made on a background of immunologic abnormalities documented in the previous studies such as with decreased total peripheral T lymphocytes and suppressor/cytotoxic (T8) subtype with an increased CD4:CD8 ratio, increased VCAM1, increased soluble TNF-receptor I and II [85–87]. Histologic changes of NCPF/IPH specially NRH, have also

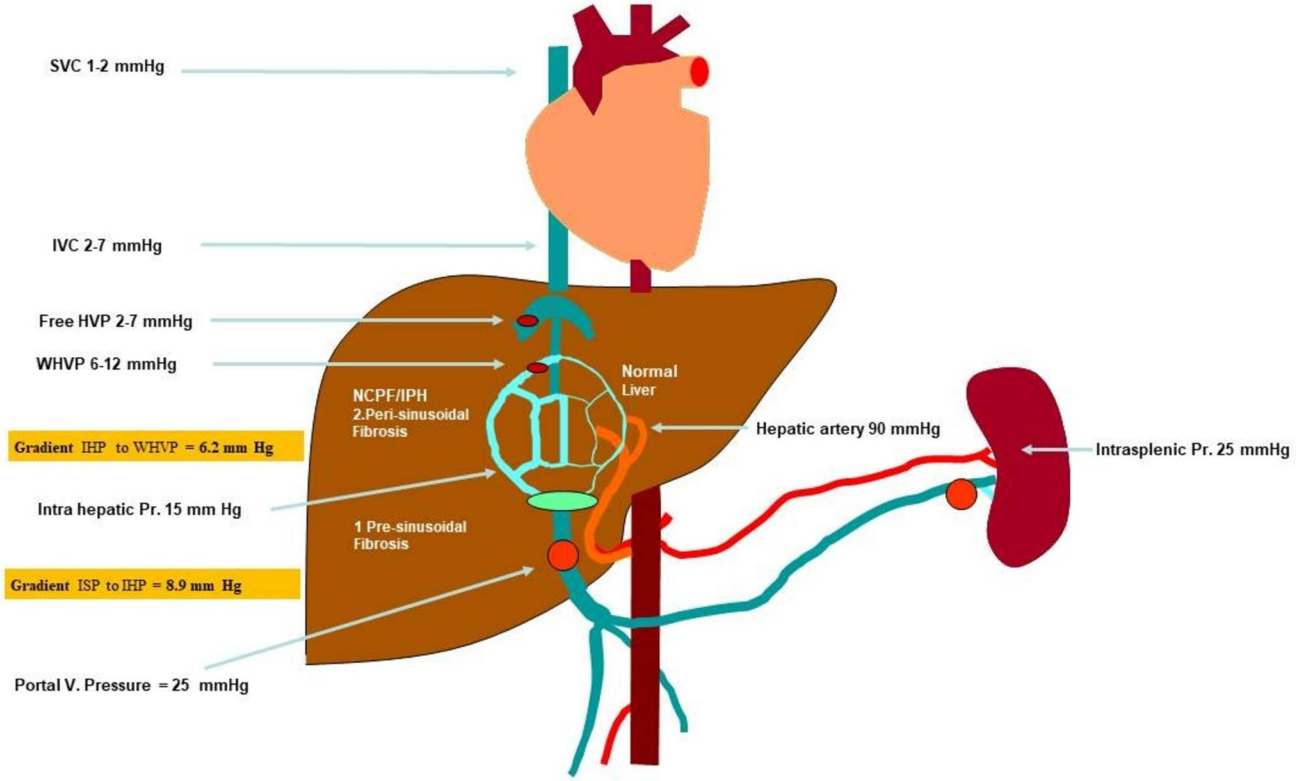

Fig. 6 Hemodynamics in NCPF/IPH. The figure shows two sites of resistance and gradient in NCPF/IPH patients; at presinusoidal level (between intrasplenic and intrahepatic region) and peri-sinusoidal level (between intrahepatic and wedge hepatic region). It shows that intrasplenic pressure reflects true portal pressure, but HVPG is significantly lower than the portal pressure

been observed in patients with immune dysfunction disorders such as common variable immunodeficiency (CVID), X-linked agammaglobulinemia, and chronic granulomatous disease [88–90]. The prevalence of NRH in CVID ranges from 9 to 79% [91], with postulated mechanisms including lymphocytic infiltration of the liver, lymphocyte-mediated cytotoxicity causing sinusoidal endothelial damage, and altered portal blood flow leading to vascular injury [92]. X-linked agammaglobulinemia (XLA) is also associated with NRH. In a study of 21 patients with XLA, eight patients underwent liver biopsy, of whom 6 were found to have NRH (National Institutes of Health XLA cohort) [93]. An Italian study identified potential pathophysiologic processes causing NCPF in patients with primary immunoglobulin deficiencies [94]. The authors postulated that repeated infections, inflammation, splenomegaly, increased blood venous flow, and lymphocyte abnormalities in these patients contributed to liver damage leading to non-cirrhotic portal hypertension.

Genetic/hereditary disorders

Familial aggregation of NCPH and HLA-DR3 positivity [95] suggest a genetic predisposition to the development of portal fibrosis in response to environmental stimuli. Many studies have reported clustering of cases in families, particularly children [96, 97]. An Australian case series reported an autosomal dominant inheritance pattern in NCPH [98]; however, the pathologic gene(s) could not be identified. The association between NRH and short telomere syndrome is well recognized [99, 100]. Telomere-related gene (TRG) mutations have emerged as a significant genetic alteration closely associated with NCPF/IPH [101, 102]. A recent French study revealed that 48% of patients with TRG mutations exhibited histologic features of NCPF/IPH [101]. The authors not only studied the prevalence of liver diseases in patients with TRG mutations but also compared it with a control population and showed a significantly increased risk of liver diseases associated with these mutations (OR 12.0). NCPF was found to be more common than advanced fibrosis/cirrhosis (42% and 15% respectively). Exosome sequencing and further molecular analysis may identify predisposing genetic mutations.

Consensus statements

Statement 1

NCPF/IPH is a condition of varied etiology typically manifesting as portal hypertension in the absence of extrahepatic portal venous obstruction or specific known causes of cirrhosis or schistosomiasis, and is characterized by narrowing/loss of small and medium branches of the portal vein that result in the development of portal hypertension. (A,1).

Statement 2

All the histological features of PSVD with very few exceptions are well described in NCPF/IPH, and thus, it is recommended that NCPF/IPH terminology be used in preference to PSVD. (B,1).

Statement 3

Patients with NCPF/IPH should be evaluated for exposure to drugs and toxins, and may be evaluated for underlying immunological, genetic, and thrombophilic disorders. (B,2).

Diagnosis

In the previous guideline, NCPF/IPH was defined as a condition occurring in the presence of portal hypertensive features such as esophageal varices or splenomegaly with a normal or near normal HVPG and the absence of mesenteric thrombosis or histological evidence of cirrhosis [4]. However, many studies have highlighted the presence of histopathologic features like NCPF in the absence of portal hypertension. For example, features of obliterative portal venopathy and nodular regenerative hyperplasia (NRH) in the absence of portal hypertension were described as early as in 1980s more frequently in elderly (>60 years) as compared to younger patients [24, 103].

In a study of 482 liver biopsies obtained from patients with unexplained non-cirrhotic chronic liver disease without portal hypertension, approximately 19.5% were found to have evidence of OPV [81]. The histological features in these biopsies were like the features seen in liver biopsies obtained from 20 patients with NCPF/IPH. Moreover, liver biochemistry, autoimmune markers, and thrombophilic conditions were comparable between these two groups. The patients without portal hypertension were probably part of the same disease spectrum, but at an earlier stage of disease.

NCPF/IPH as a disease continuum: We recommend conceptualizing NCPF/IPH similar to other chronic liver diseases where the development of portal hypertension represents a late stage of the disease. Currently, there is no established method to predict which individuals will ultimately develop clinically significant portal hypertension (CSPH). Hence, it is proposed to include patients with evidence of vascular lesions in small- and medium-sized portal vein branches even in the absence of overt portal hypertension among the NCPF/IPH category.

Statement 4

A. In the presence of portal hypertension, NCPF/IPH can be diagnosed in an adequate-sized needle biopsy of the liver with adequate number of portal tracts (ideally 20 mm and 10 in number) by identification of obliterative portal venopathy, nodular regenerative hyperplasia, and incomplete septal fibrosis. All features may not be seen in the same biopsy specimen. (A,1)
B. Histological diagnosis of NCPF/IPH requires the absence of (i) regenerative nodules, (ii) features of possible or definite cirrhosis, and (iii) other specific etiologies such as schistosomiasis. (A,1)
C. In the absence of overt portal hypertension, a diagnosis of early NCPF/IPH can be suggested by the presence of risk factors and histological features like obliterative portal venopathy, nodular regenerative hyperplasia, and incomplete septal fibrosis (B,2) OR non-specific histological features such as portal tract abnormalities (multiplication, dilation of arteries, peri-portal vascular channels, and aberrant vessels); architectural disturbance: irregular distribution of the portal tracts and central veins, non-zonal sinusoidal dilation and mild peri-sinusoidal fibrosis (C,2)

Hemodynamics in NCPF/IPH

In NCPF/IPH, unlike in cirrhosis, mean intrasplenic (ISP) and intravariceal pressures were found to be elevated as compared to wedged hepatic venous pressure (WHVP) and intrahepatic interstitial pressure (IHP) [104]. Two discrete pressure gradients between ISP and IHP (8.9 ± 6.5 mmHg) and another between IHP and WHVP (6.2 ± 5.6 mmHg) have been observed, suggesting 2 sites of resistance in these cases: presinusoidal and peri-sinusoidal (see Fig. 6). The intravariceal pressure is similar irrespective of the site of resistance. Importantly, the patients included in the study had a patent spleno-portal venous axis. In recently published two letters to editor, the authors found that endoscopic ultrasound guided portal pressure measurement was more useful than HVPG in two and nine patients, respectively, with NCPF/IPH [105, 106].

Recent studies have shown that in NCPF/IPH, HVPG is normal or slightly elevated with a median value of

approximately 8 mmHg (range 5–20 mmHg) [107]. Further studies are needed to evaluate the site and the humoral factors that increase portal pressure in the absence of structural abnormalities. Of note is that portal and splenic venous blood flow increase in NCPF/IPH and may contribute to a rise in HVPG over time. There is need for studies of serial HVPG measurement in patients with NCPF to see if the portal hemodynamics alters over time and influences the disease course.

Statement 5

A. HVPG is normal or minimally elevated in patients with NCPF. (A,1)
B. A pressure gradient may exist between the spleen and the liver (intrasplenic pressure–intrahepatic interstitial pressure [IHP]) and between the IHP and the wedged hepatic venous pressure (WHVP) (IHP–WHVP).

Role of non-invasive tests

In patients with NCPF/IPH, ultrasound examination with Doppler and cross-sectional abdominal imaging (CT, MRI scans) show splenomegaly and portosystemic collaterals without significant ascites. The splanchnic and hepatic veins are patent; the portal vein may be dilated but the intrahepatic branches may be pruned peripherally. Liver and spleen stiffness measurements may provide valuable evidence as to the presence of NCPF/IPH. In NCPF, spleen stiffness measurement (SSM) is typically higher than liver stiffness measurement (LSM) which is normal or mildly elevated. MR elastography may also be helpful diagnostically. On MR elastography (MRE), the normal liver stiffness is ≤ 2.9 kPa, and cirrhosis is diagnosed when the liver stiffness is ≥ 5 kPa [108]. The normal splenic stiffness is < 3.6 kPa; in the presence of esophageal varices in patients with cirrhosis the spleen stiffness is > 10.5 kPa [109]. Measuring both SSM and LSM in patients with portal hypertension can help distinguish cirrhosis as a cause of portal hypertension from noncirrhotic causes of portal hypertension. MRE based LSM < 4.7 kPa and an SSM/LSM cutoff of > 1.23 yielded a 97.6% sensitivity, 100% specificity, and an AUROC of 0.99 for diagnosis of NCPF/IPH, with only rare cases of NCPH classified as cirrhosis [110, 111]. Small studies have shown that on acoustic radiation force impulse (ARFI) elastography, an ultrasound technique, values of spleen-liver stiffness > 1.7 are strongly suggestive of NCP/IPHF, and values < 1.7 are indicative of cirrhosis [112]. A recent study from India showed that an SSM/LSM ratio cut-off of 3.67 predicted NCPF in pediatric and adolescent patients with excellent sensitivity and specificity (99% and 95.9%) [113].

Statement 6

A. In patients with portal hypertension, using transient elastography or MR elastography (MRE), a diagnosis of NCPF/IPH is suggested by the presence of the following features:
A LSM is lower in patients with NCPF/IPH than in patients with cirrhosis. (C,2)
B Spleen stiffness is markedly elevated in patients with NCPF/IPH.
C A higher splenic stiffness to liver stiffness ratio increases the accuracy of diagnosis of NCPF. (B,2)
B. More data are needed for role of SWE/ARFI in diagnosis of NCPF/IPH.

When to clinically suspect NCPF/IPH

The clinical scenarios where NCPF/IPH should be suspected include the following: (i) patients with portal hypertension in the absence of clinical evidence of cirrhosis/hepatic parenchymal dysfunction and (ii) unexplained splenomegaly, and (iii) patients with unexplained chronic abnormalities in routine hematological tests, liver tests, or imaging findings. Isolated abnormal liver tests may be found in some patients with OPV without portal hypertension [21, 44, 81]. Liver enzymes including AST/ALT/ALP and GGT are minimally to moderately elevated and liver synthetic function is typically normal (normal bilirubin and albumin values). Since some patients who present with abnormal liver tests subsequently develop portal hypertension on follow-up, it has been suggested that NCPF/IPH should be considered in patients with abnormal liver tests even in the absence of portal hypertension. Long-term follow-up studies are needed to establish natural history of unexplained elevated liver tests and the risk of developing NCPF/IPH. PVT in patients with NCPF/IPH is not uncommon and serial imaging, hemodynamic study, and liver histology should be considered.

Clinical presentations of NCPF/IPH

The typical clinical presentation of NCPF is with acute variceal hemorrhage associated with splenomegaly, anemia, and pancytopenia. Splenomegaly disproportionate to the degree of hepatic dysfunction is more often seen in NCPF/IPH and extrahepatic portal venous thrombosis than in other liver diseases that cause portal hypertension. Heaviness and

feeling of a mass in the left upper quadrant are common. Severe left upper quadrant pain is uncommon, and may be due to development of spontaneous splenic infarction and peri-splenitis[114]. Ascites, jaundice, and hepatic encephalopathy are rare but may occur in association with an episode of variceal hemorrhage. In early stages, before the onset of portal hypertension, the patient may remain asymptomatic (stages 1 and 2).

Statement 7

NCPF/IPH should be suspected in the following situations:

a) Unexplained splenomegaly. (B,1)
b) Variceal hemorrhage without any evidence of hepatocellular decompensation. (B,1)
c) Portal hypertension in the absence of cirrhosis/hepatocellular dysfunction. (A,1)
d) Unexplained chronic elevation in liver biochemistry. (B,1)

Hypersplenism in NCPF/IPH

In 1955, Damshek proposed the following diagnostic criteria for hypersplenism: (i) monolineage or mutilineage peripheral cytopenias; (ii) compensatory hyperplasia of bone marrow; (iii) splenomegaly; and (iv) correction of cytopenias after splenectomy [115]. Hypersplenism in patients with portal hypertension represents increased pooling and/or destruction of the formed elements of blood (platelets, red blood cells, and white blood cells) by the enlarged spleen. Hypersplenism is present in 27–87% patients with NCPF, with anemia being the commonest abnormality followed by thrombocytopenia and leucopenia [75].

Symptomatic hypersplenism was defined by consensus as hypersplenism leading to spontaneous non-portal hypertension bleeding episodes (such as epistaxis, gum bleed, or menorrhagia) in the absence of obvious causes. It was debated whether to include severe anemia requiring blood transfusions in this definition. However, a consensus could not be reached amongst the experts, because the reasons for the anemia could be multi-factorial and were therefore not included. Symptomatic hypersplenism is more commonly seen in older patients, with larger spleen and higher portal pressure and is associated with a higher likelihood of triple cell lines defect [116].

Symptomatic hypersplenism results in poor quality of life and may warrant intervention. Although hypersplenism is often considered to be an important complication in NCPF/IPH patients, its management is difficult; splenectomy alone in patients with IPH may be associated with severe infections and thromboembolic complications [117] and should be avoided.

Statement 8

A. Hypersplenism in the presence of NCPF/IPH can be diagnosed in the presence of the following: (i) monolineage or multilineage peripheral cytopenias; (ii) hypercellular or normocellular bone marrow, and, (iii) splenomegaly. (A,1)
B. Symptomatic hypersplenism is diagnosed by the presence of thrombocytopenia and non-portal hypertensive spontaneous bleeding episodes including gum bleeding, epistaxis or menorrhagia in the absence of apparent causes. (C,1)

Natural history of NCPF/IPH

The natural history of NCPF/IPH is unclear, but was thought previously to be largely benign. However, recent data suggest that the course may be insidiously progressive and punctuated by decompensating events over the long term [118, 119]. Patients typically experience repeated portal hypertension-related complications, in particular well-tolerated episodes of variceal bleeding. Other features include splenomegaly presenting as left upper quadrant abdominal discomfort, anemia, leukopenia, and/or thrombocytopenia. Nearly 70% of patients with NCPF/IPH have large varices at diagnosis, and one-third have variceal bleeding as the index presentation [76]. Uncommon clinical features of NCPF/IPH include peri-splenitis/splenic infarction, bowel ischemia, hemobilia, and hemoperitoneum. However, many patients may be asymptomatic. The actuarial probability of developing small varices in those without varices is estimated to be 10%, 20%, and 69% at 1, 2, and 5 years, respectively [70]. The frequency of variceal bleeding increases with age; interestingly, it has been reported that there is a median of one bleeding episode before recognition of the underlying disease [15, 16, 119]. Ascites as the first sign of portal hypertension is rare and usually occurs following variceal bleeding; ascites occurring in the absence of variceal bleeding is associated with poor long-term outcome [80]. A recent meta-analysis of data from patients with NCPF/IPH revealed that minimal HE or overt HE was present in 33% and 1% of patients, respectively [120]. Jaundice is rare (< 2%). Hepatopulmonary syndrome is seen in around 10% of patients [121], and hepatocellular carcinoma develops in those with concomitant risk factors such as chronic viral hepatitis [122]. A small, single-center long-term follow-up study over 30 years reported a 5-year survival of 90% and a 30-year survival of 55% [123]. A few European multicentric studies have shown a transplant-free survival of 80–90% at 10yrs

[20, 21, 76]. Presence of concomitant serious comorbidities and ascites are factors associated with poor outcomes.

An Italian multicentric study provides intriguing insight into the natural history and clinical features of PSVD in pediatric patients. Authors identified two distinct clinical phenotypes of pediatric patients diagnosed as PSVD on histology—characterized by portal hypertension or chronic elevation of transaminases without portal hypertension. [124]. Histologic differences between the two groups were subtle, with OPV and hypervascularity of portal tracts being more commonly seen in portal hypertension group. A proportion of patients with portal hypertension at the time of diagnosis developed portal hypertension-related complications and 19% required liver transplant at median 7 year follow-up, while none of these complications were seen in the second group.

In children with NCPF/IPH, the endoscopic eradication of esophageal varices is associated with a good prognosis, [125, 126], although up to one-third of patients have a recurrence of esophageal varices. A small proportion of patients have uncontrolled bleeding or progressive liver failure leading to death or requiring liver transplantation. In adults with NCPF/IPH, the 10-year survival after eradicating esophagogastric varices or after shunt surgery has been reported to be nearly 100% and 80%, respectively [114]. In 20–33% of cases, the liver may undergo progressive parenchymal atrophy with subsequent hepatic decompensation, and such patients may need liver transplantation [126, 127]. In a study from India, NCPF/IPH constituted approximately 5% of the subset of patients with "cryptogenic cirrhosis "considered eligible for liver transplantation," [128]. Another study of native explant livers demonstrated obliterative changes in portal vein branches and portal fibrosis consistent with NCPF/IPH in all cases misclassified as cryptogenic cirrhosis [129].

In patients with NCPF/IPH, a European study identified a concomitant severe underlying disorder, such as an immunological disease or malignancy, as a poor prognostic factor [80]. Further, development of complicated (hepatopulmonary syndrome) or recurrent (bleeding, ascites, or HE) portal hypertension events was associated with the need for liver transplantation in small series [11, 130]. Nonetheless, it is notable that only 13% of patients with NCPF/IPH die from end-stage liver-related disease(s) [21, 80]. Progression to end-stage liver disease and risk of death appears to be related to ascites, advanced age, and underlying conditions associated with NCPF/IPH [80].

Based on the available evidence, we propose that the natural history of NCPF/IPH be divided into four stages as follows, based on the presence or absence of portal hypertension and its complications.

Stage I) No discernible portal hypertension, and characterized by normal spleen size, no clinical evidence of portal hypertension, normal HVPG; the diagnosis is made on liver histopathology.

Stage II) Probable portal hypertension, characterized by increased splenic stiffness but absence of varices on endoscopy, or other complications of portal hypertension.

Stage III) Uncomplicated portal hypertension, characterized by increased splenic stiffness and presence of portosystemic collaterals on imaging or presence of varices on endoscopy, but absence of variceal bleed, hepatic encephalopathy, or portal vein thrombosis.

Stage IV) Portal hypertension with complications, characterized by the presence of variceal bleeding, ascites, symptomatic hypersplenism, hepatic encephalopathy, or portal vein thrombosis AND parenchymal extinction.

Patients can present in any stage and progress from one stage to another. Each stage is likely to be associated with significantly different outcomes; prognosis also depends upon concurrent conditions associated with NCPF/IPH. At the current time, it is unclear whether regression of the disease takes place.

Statement 9

A. Patients with NCPF/IPH have a better long-term prognosis as compared to patients with compensated cirrhosis. (B,1)
B. Mortality from acute variceal hemorrhage in patients with NCPF/IPH is lower than in patients with acute variceal hemorrhage in cirrhosis probably because liver function is typically better preserved in patients with NCPF/IPH than in those with cirrhosis. (B,1)

Statement 10

A. The prevalence of gastroesophageal variceal hemorrhage in patients with NCPF/IPH is high. (B,1)
B. A small proportion of adults with NCPF/IPH may develop ascites, especially after a variceal bleed. (B,1)

Statement 11

Overt hepatic encephalopathy in NCPF/IPH is rare, but minimal encephalopathy may be present in up to one-third of patients, especially in the presence of large spontaneous portosystemic shunts. (B,1)).

Statement 12

Only a small proportion of children and adults with NCPF/IPH experience a poor clinical outcome due to uncontrolled bleeding or progressive liver failure. (C,2).

Statement 13

The natural history of patients with NCPF/IPH may be divided into 4 stages. (C,1)

I. No discernible clinical or radiological evidence of portal hypertension (the disease is suggested by pathological evidence of hepatic vascular abnormalities alone).
II. Probable portal hypertension
III. Portal hypertension without complications, and
IV. Portal hypertension with complications.

Statement 14

Other factors related to progression of disease in NCPF/IPH include age at diagnosis, and underlying associated chronic immuno-inflammatory, genetic, or malignancy-related disorders. (C,2).

Portal vein thrombosis in patients with NCPF/IPH

Hypercoagulable states have been identified in 8–50% of patients with IPH. In this context, a higher prevalence of portal vein thrombosis (PVT) has been reported in IPH compared to NCPF. Portal vein thrombosis was reported in nearly 13 to 46% of cases of IPH with the annual probability of developing PVT in IPH being 9% [76]. The risk factors identified with development of PVT in NCPF/IPH are presence of prothrombotic disorders, concomitant HIV infection, and variceal bleeding at diagnosis [55, 76, 131]. Acute PVT in NCPF/IPH may be asymptomatic, associated with non-specific symptoms, or can present with acute variceal bleeding and ascites, and is associated with worse outcomes [132].

Statement 15

Portal vein thrombosis may develop in patients with NCPF/IPH and may be associated with an unfavorable outcome. NCPF/IPH patients should be serially monitored for development of PVT. (C,2).

Concomitant liver diseases in NCPF/IPH

The frequencies of hepatitis B (HBV) and C (HCV) infections in patients with NCPF are comparable to that in the general population but may be higher in patients who have received blood products [15]. One study of patients with NCPF/IPH, found a higher prevalence of HBV than general population [133]. There are also reports of patients with chronic HCV infection with clinically significant symptomatic portal hypertension in the absence of cirrhosis. The natural history of NCPF/IPH with concurrent or superadded HBV and HCV infection has not been well described. Needless to add, such patients should be carefully monitored for development of chronic liver disease. A few reports have suggested an association between IPH and the development of hepatocellular carcinoma [123].

Variceal screening

Non-invasive tests to detect portal hypertension or esophageal varices in patients NCPF/IPH have not been well studied. Therefore, patients diagnosed with NCPF/IPH undergo upper endoscopy for variceal screening. Several studies have shown the utility of splenic stiffness in cirrhosis to in identifying patients at high risk of variceal bleeding [134, 135], but these findings cannot yet be extrapolated to patients with NCPF/IPH.

Primary prophylaxis for esophageal variceal bleeding

The natural history of esophageal varices in NCPF/IPH is poorly understood. There are also no studies in patients with NCPF/IPH with long-term endoscopic follow-up for the development and progression of esophageal varices. Regression of varices seen in patients with cirrhosis following treatment of underlying etiology resulting in decrease in liver fibrosis [135] has not been studied in NCPF/IPH. EVL and beta-blockers are commonly used therapy for primary prophylaxis of esophageal varices in cirrhosis [136]. However, there are no randomized-controlled trials on primary prophylaxis in NCPF/IPH.

One study suggested efficacy of both EVL alone and EVL combined with propranolol for primary prophylaxis of variceal hemorrhage in NCPF/IPH, but the sample size was too small to draw meaningful conclusions [137]. In patients with varices on endoscopy, EVL is the preferred mode of therapy, since the hemodynamic response to beta-blockers in patients with NCPF/IPH cannot be reliably monitored, though HVPG is typically near normal. To accurately

assess the efficacy of beta-blocker therapy, measurements of splenic pulp pressure or direct portal pressure are required, but are seldom carried out in practice.

Porto-systemic shunt surgery for primary prophylaxis should not be performed in patients with NCPF/IPH. A study from India of 45 patients with NCPF/IPH [138], including 41 of whom were treated with a prophylactic proximal splenorenal shunt, 2 with splenectomy, and 2 with devascularization—showed no operative mortality. Over a follow-up period of 49 months, three patients bled and two late deaths unrelated to surgery occurred. However, there was delayed morbidity in 47%, including seven patients who developed partial splenic thrombosis; four with glomerulonephritis; two with pulmonary AV fistulae; and five with ascites requiring diuretics. Thus, while shunt surgery itself was considered safe, there was substantial delayed morbidity. Patients with gastric varices (of greater than 2 cm in diameter) may be treated with N-butyl-cyanoacrylate injection or EUS-guided coiling or balloon-occluded retrograde transvenous obliteration (BRTO) or plug-assisted retrograde transvenous obliteration (PARTO) if a splenorenal shunt is present.

Statement 16

Patients with NCPF/IPH should undergo upper gastrointestinal endoscopy as surveillance for the presence of esophageal/gastric varices. (C,1)

Statement 17

Prevention of variceal bleeding should be a priority in managing NCPF/IPH, because the absence of bleeding is associated with better long-term outcomes. (C,2).

Statement 18: pre-primary prophylaxis of variceal bleeding

Pre-primary prophylaxis is not currently recommended for patients with NCPF/IPH given the absence of data supporting its use. (C,2)

Statement 19

Endoscopic variceal ligation is recommended as primary prophylaxis against esophageal variceal bleeding in patients with NCPF/IPH who have large varices. Non-selective beta-blocker therapy is an acceptable alternative in these patients, though it should be recognized that monitoring the response to therapy using HVPG may be inaccurate. (C,1).

Statement 20

No recommendations can be made at present regarding primary prophylaxis to prevent gastric variceal bleeding.

Statement 21

Neither portosystemic shunt surgery nor transjugular intrahepatic portosystemic shunt (TIPS) is recommended as primary prophylaxis against variceal bleeding in patients with NCPF/IPH. (C,1).

Acute variceal hemorrhage management

Acute variceal hemorrhage is a common complication in NCPF/IPH. Despite the advances in management of variceal hemorrhage, there remains a significant rebleeding and mortality risk [139]. Although data on the treatment of acute variceal hemorrhage in NCPF/IPH are limited, management principles and techniques are the similar to patients with cirrhosis and variceal bleeding.

Initial steps in the management of acute variceal hemorrhage include assessing the severity of bleeding and appropriate volume resuscitation. Over-aggressive volume therapy can aggravate bleeding and increase the risk of rebleeding due to increased intravascular volume resulting in increased portal pressure and may also cause complications such as pulmonary edema and ascites. A restrictive approach to blood transfusion is generally advised to maintain hemoglobin levels in the 7-8 g/dl range [140]. Platelets (usually for platelets below 50,000/mm^3) and fresh-frozen plasma transfusion have often been used to correct coagulopathy; however, they can cause fluid overload and rebound portal hypertension and typically do not adequately correct coagulopathy [141]. Thromboelastography (TEG)-guided correction could potentially guide optimal blood product transfusion strategy in portal hypertension-related bleeding. TEG-guided transfusion strategy is associated with reduced blood product transfusion without compromising hemostasis in patients with cirrhosis [142].

Vasoactive drugs, such as somatostatin, octreotide, or terlipressin, should be started early and should be combined with endoscopic therapy. However, great care is warranted when terlipressin is used, because terlipressin has been associated with the development of pulmonary complications, especially when used in combination with albumin [143]. Endoscopic variceal therapy appears to be more effective with lower rebleeding rate when combined with vasoactive drugs versus endoscopy alone [144]. Currently, short-term antibiotic prophylaxis is recommended in the management of gastrointestinal bleeding in patients

with cirrhosis as it reduces bacterial infections, variceal rebleeding, and mortality [145–147]. Bacterial infections in variceal bleeding are far more common in cirrhotics (35–66%) than in non-cirrhotic cases (5–7%) [148]. Of note is that antibiotic prophylaxis in gastrointestinal bleeding in the setting of NCPF/IPH has not been adequately studied, but it is still recommended. In patients with gastric variceal bleeding, initial endoscopic hemostasis should be achieved using N-butyl-cyanoacrylate or EUS-guided coil embolization.

Statement 22: acute variceal bleed management

A. General measures for control of acute variceal hemorrhage are similar to those for patients with cirrhosis. (C,2)
B. Vasoactive drugs should be combined with endoscopic therapy for the control of acute variceal bleeding and initiated preferably at least 30 min before endoscopy. (A,1)
C. EVL is the preferred endoscopic modality used to obliterate esophageal varices in NCPF/IPH patients with esophageal variceal hemorrhage. (B,2)
D. Prophylactic antibiotics are recommended based on the current guidelines for cirrhosis, although data on this for NCPF/IPH patients are lacking. (C,2)
E. Transjugular intrahepatic portosystemic shunt may be used a salvage therapy when a combination of endoscopic and pharmacological treatment have failed to control the variceal bleeding. The role of early TIPS in NCPF/IPH requires further study. (C,2)

Secondary prophylaxis

There are no trials to inform the optimal secondary prophylaxis regimen in patients with NCPF/IPH with acute variceal bleeding. In the absence of such trials, endoscopic variceal ligation may be repeated every 2–3 weeks until varices are completely eradicated. NSBB should be initiated for secondary prophylaxis and continued after obliteration of esophageal varices. In a pivotal study by Sarin et al., NSBB alone was found to be non-inferior to repeated EVL and variceal eradication strategy for secondary prophylaxis of variceal bleeding in patients with NCPF [149].

Secondary prophylaxis for gastric variceal hemorrhage should be based on the endoscopic appearance of varices, underlying vascular anatomy, co-morbid conditions, and local expertise. BRTO, PARTO, or coil-assisted retrograde transvenous obliteration (CARTO) are optimal endovascular therapy in the presence of gastro-renal shunts and should be performed if local expertise is available. Cross-sectional imaging should be performed to determine vascular anatomy and evaluate for the presence of portosystemic shunts and gastrorenal shunts [150]. Unlike cirrhosis, there is paucity of data on use of TIPS in patients with NCPF/IPH, but TIPS may be considered in patients with refractory or recurrent esophageal or gastric variceal bleeds, despite optimal endoscopic, radiological, and pharmacological therapy.

Statement 23

For secondary prophylaxis of esophageal variceal bleeding, non-selective beta-blockers in combination with EVL are recommended. (C,1)

Statement 24

TIPS may be considered when there is recurrence of variceal bleeding despite a combination of endoscopic and pharmacological therapy, but data are limited. (C,2).

Statement 25

Balloon occluded retrograde transvenous obliteration (BRTO)/plug-assisted retrograde transvenous obliteration (PARTO) or coil-assisted retrograde transvenous obliteration (CARTO) may be effective in secondary prevention of gastric variceal bleeding and are best used in the presence of a gastrorenal shunt. (B,1).

Management of hypersplenism

Hypersplenism is a common complication of portal hypertension in patients with NCPF, but treatment is rarely required, unless patient develops symptomatic hypersplenism. Splenectomy was considered the treatment of choice for symptomatic hypersplenism, but partial splenic artery embolization (PSAE) is an alternative treatment modality to splenectomy for managing hypersplenism with similar efficacy in improving blood counts and fewer complications [151]. In addition, PSAE has several advantages over splenectomy including faster recovery and lack of a need of blood transfusion. It involves selective occlusion of splenic artery branches resulting in partial devascularisation of spleen while preserving its essential functions including protection against infection [152, 153]. In PSAE, minor complications such as post embolization syndrome occur frequently [154]. However, major complications such as splenic abscess can occur, though infrequent, and can result in mortality. Therefore, PSAE may be considered carefully, and only in the management of symptomatic hypersplenism.

Data on hypersplenism resolution following shunt surgery in NCPF is limited, but encouraging. In NCPF, following

shunt surgery, splenic size and splenic pulp pressure may reduce [155], although there is a risk of MHE, glomerulonephritis, pulmonary arteriovenous fistula, and ascites [138]. The surgery also reduces the risk of variceal bleeds. Though portosystemic surgical shunts reduce variceal bleeding, they are a less-than-ideal treatment option for symptomatic hypersplenism.

Splenectomy alone should be avoided due to the risk of postoperative infections, particularly overwhelming infections which occur in 3–5%, characterized by bacteremia and sepsis, with mortality reaching up to 50% [156]. In addition, splenectomy in the setting of portal hypertension is associated with a significant risk of portal vein thrombosis.

Statement 26:- management of hypersplenism

a) Partial splenic artery embolization should be considered for patients with symptomatic hypersplenism. (B,1)
b) Shunt surgery may be considered in patients with symptomatic hypersplenism who have also bled from varices—recognizing that there is a risk of developing HE and other long-term complications (portopulmonary hypertension, glomerulopathy, etc.) following surgery. (B,2)
c) Splenectomy without portosystemic shunt surgery should be avoided. (C,2)

Liver transplantation

NCPF/IPH can progress to more advanced liver disease with liver failure that may become an indication for liver transplantation (LT) [128–130, 157]. An earlier study has shown that NCPF /IPH constitutes 5% of subset of end-stage liver considered eligible for LT, presenting mostly as "cryptogenic cirrhosis" [128]. Chronic liver disease of other etiologies also supervene on pre-existent NCPF/IPH and can present as end-stage liver disease. Indications for LT in patients with NCPF/IPH include complications such as end-stage liver disease and refractory HE. In a recent multicenter European study among 79 cases patients of with NCPF/IPH who underwent liver transplantation, it was shown that (1) persistence of a severe associated underlying co-morbid condition, (2) elevated bilirubin level pre-transplantation, or (3) serum creatinine > 100 μmol/L adversely impacted outcome [158]. Refractory ascites, hepatic encephalopathy, and hepatopulmonary syndrome were found to be the most frequent indications for LT. Post-transplant recurrence, though rare, has also been documented [158]. More studies are needed to identify patients who are at risk of developing recurrence and optimal treatment strategy for prevention and management of recurrence.

NRH, a histological variant of NCPF/IPH, can develop after liver transplant as well. A study by Chen et al. [159] showed that 49 of 3711 (1.3%) adult patients who underwent LT developed NRH on follow-up. The mean time from LT to diagnosis of NRH was 79.5 months and risk factors postulated were history of autoimmune conditions, azathioprine, and chemotherapy.

Statement 27: liver transplantation

Liver transplantation is not usually required for patients with NCPF/IPH, but may be offered to those patients with liver failure or refractory portal hypertensive complications. (A1).

Future implications and directions

1. The natural history of early stages of NCPF/IPH needs to be studied and predictors of progression identified. This will help to identify patients with high risk of progressing to develop portal hypertension in future and thereby providing an opportunity to intervene early.
2. The choice of non-invasive tests during the early stages of NCPF for following up these patients as well as the time interval and duration of follow-up will have to be determined with prospective studies.
3. Time of initiation and choice of beta-blockers for effective prevention of portal hypertension-related complications are ambiguous at present and prospective studies with objective evaluation of treatment response will answer these queries in future.
4. There is a need for regional liver associations to come together to clear the confusion regarding the terminologies and work together for the progress of science and benefit of the patients.
5. There is a need to identify therapeutic targets for preventing progression of diseases and potentially reverse the fibrosis and portal hypertension in NCPF/IPH.
6. The role and timing of anticoagulation in management of NCPF/IPH, if any, needs to be determined

Summary

An international group of experts, in collaboration with APASL, prepared these guidelines to provide clarity and direction with regards to the nomenclature, etiology, pathology, diagnosis, natural history, and management of NCPF/IPH. It is apparent that the current nomenclature for this group of diseases is confusing; however, it is proposed to continue to use the term NCPF/IPH. Importantly, PSVD appears to be the same disease as NCPF/IPH with only

minimal differences, and thus, the use of this terminology further complicates the field. The pathogenesis and evolution of NCPF/IPH is becoming better understood. While the clinical features of NCPF/IPH are relatively distinct and should lead to a high index of suspicion of NCPF/IPH; reaching a definitive diagnosis requires considerable expertise, often including the involvement of an expert hepatologist and/or liver pathologist and in some cases, experts in portal hemodynamic studies. Most patients with NCPF/IPH present with features of portal hypertension which is characteristically more severe than evidenced by the degree of hepatic parenchymal disease. The natural history of stage 3 and 4 of NCPF/IPH has been well studied. The typical initial clinical presentation is with variceal bleeding as a sole clue to the possible presence of liver disease, or a splenomegaly. A small proportion of patients may present without any clinical features of PHT. The natural history of stage 1 and 2 of NCPF/IPH prior to the development of evident portal hypertension is now getting a lot of attention and the data are likely to be available in the near future. Portal vein thrombosis and ascites (not related to variceal bleeding) in patients with NCPF/IPH are associated with an unfavorable prognosis. Currently, treatment should be focused on management of portal hypertension and its complications. Liver transplantation is needed in only a small minority of patients who develop refractory complications of portal hypertension. Future studies should aim to understand the pathophysiology (especially mechanistic studies) and natural history of early NCPF/IPH. Indeed, proper recognition and acceptance of the term and improved understanding of the mechanisms underlying NCPF/IPH may lead to novel targeted therapies and expand the horizon of portal hypertension.

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Declarations

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