Idiopathic Portal Hypertension: A Misnomer

Dominique-Charles Valla

DHU UNITY, Service d'Hépatologie; CRI, UMR1149,
Inserm and Université Paris Diderot, Hôpital Beaujon, Clichy, France

Keck School of Medicine, USC

November 19, 2015

Idiopathic Portal Hypertension: A Misnomer

Dominique-Charles Valla

Nothing to disclose

Case 1

- 34-yr old female, bleeding GE varices
- Crohn's disease in remission
- 15 yrs of azathioprine therapy +/- Infliximab
- Platelets 90 G/L. Mild elevation in liver enzymes. Normal bilirubin and INR
- MDCT: smooth dysmorphic liver, enlarged spleen, portosystemic collaterals, patent hepatic & portal veins
- No evidence for alcohol misuse, metabolic syndrome, viral hepatitis or autoimmune disease

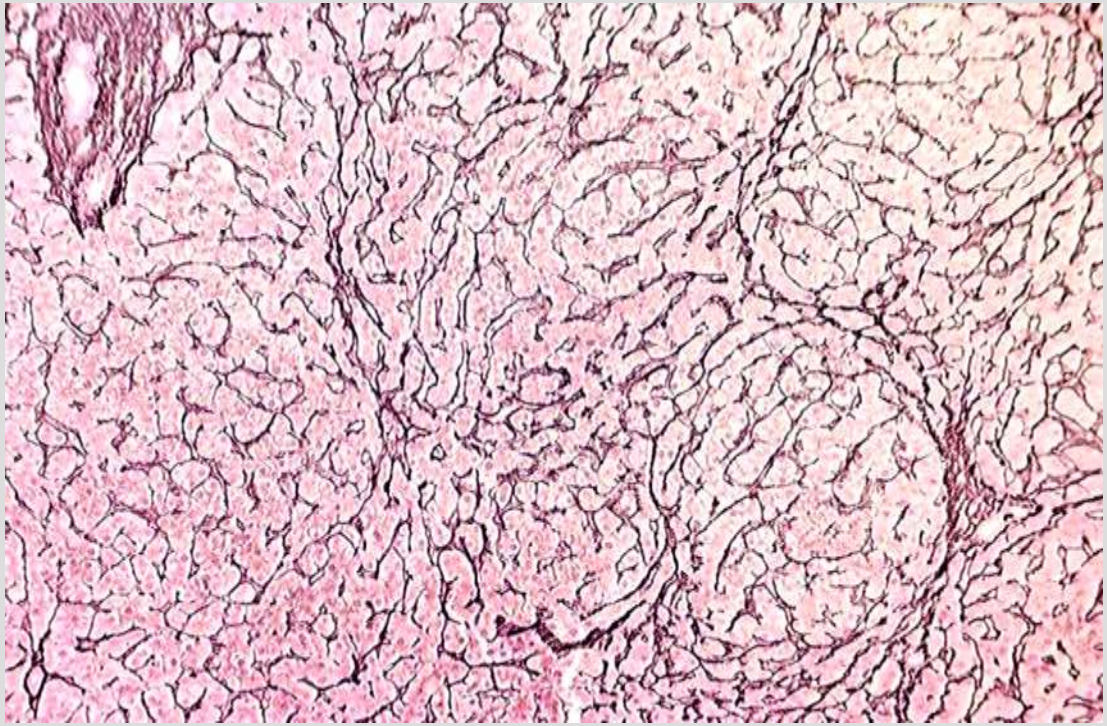
Case 1

Transjugular transvenous liver biopsy

HVPG 8 mmHg

No cirrhosis

Nodular regenerative hyperplasia



Case 2

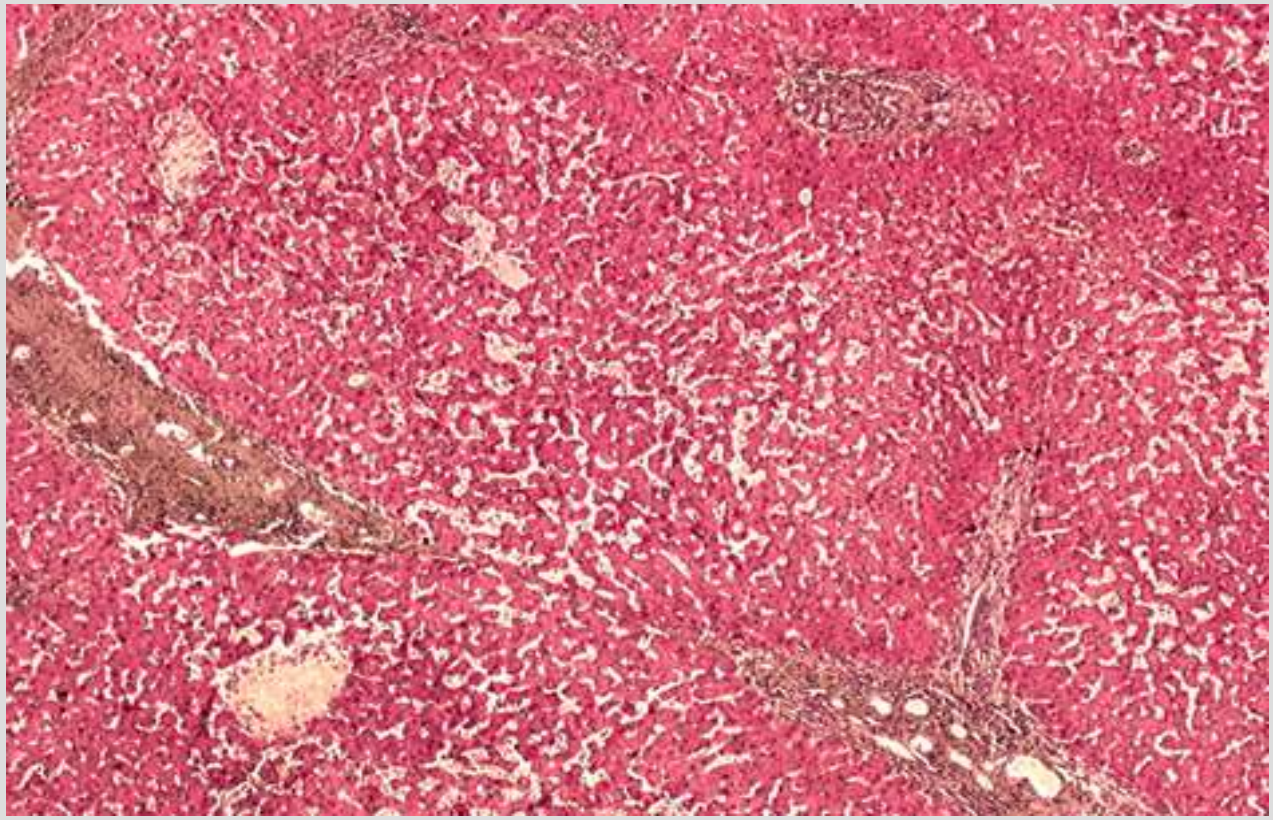
- 42-yr old male, enlarged spleen (routine exam)
- Platelets 245 G/L. Mildly elevated liver enzymes. Bilirubin 1.5 mg/dL, INR 1.25
- Doppler-US: smooth dysmorphic liver, markedly enlarged spleen (22 cm), portosystemic collaterals, patent hepatic & portal veins
- No evidence for alcohol misuse, metabolic syndrome, viral hepatitis or autoimmune disease
- V617F-JAK2 in peripheral WBC

Case 2

Transcapsular liver biopsy

No cirrhosis

- Obliterative portal venopathy
- Hepatoportal sclerosis
- Noncirrhotic portal fibrosis



Idiopathic Portal Hypertension

Definition

- Portal hypertension
- No other cause for portal hypertension
- Absence of cirrhosis and causes for cirrhosis

Schouten Hepatology 2011. Plessier, J Hepatol 2012.
Khanna and Sarin J Hepatol 2014

Well-Characterized Causes for PHT

- Extrahepatic portal vein obstruction
- Budd-Chiari syndrome (including small hepatic veins)
- SOS/VOD
- Congenital hepatic fibrosis
- Schistosomiasis
- Cirrhosis and conditions causing cirrhosis

Schouten Hepatology 2011. Plessier, J Hepatol 2012.
Khanna and Sarin J Hepatol 2014

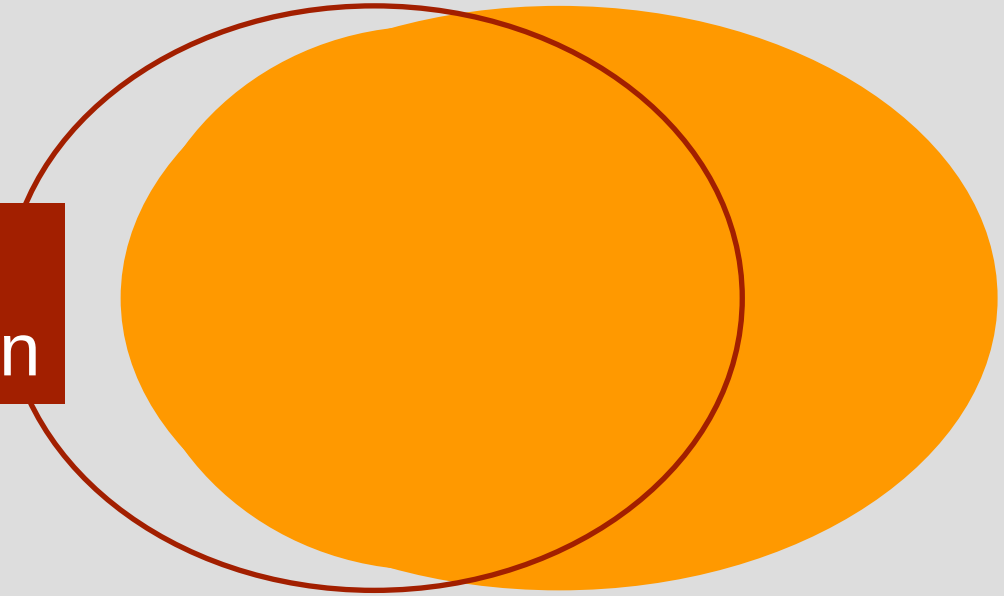
Idiopathic Portal Hypertension

- Hepatoportal sclerosis (Mikkelsen, 1966)
- Incomplete septal cirrhosis (Popper, 1966)
- Idiopathic portal hypertension (Boyer, 1967)
- Non-cirrhotic portal fibrosis (Boyer, 1967)
- Obliterative portal venopathy (Nayak, Iber 1969)
- ‘Non cirrhotic intrahepatic portal hypertension’ (Sherlock 1969)

IPH and related entities

Pathology

- Obliterative portal venopathy
- Hepatoportal sclerosis
- Noncirrhotic portal fibrosis
- Nodular regenerative hyperplasia



Misnomer #1 :
No portal hypertension

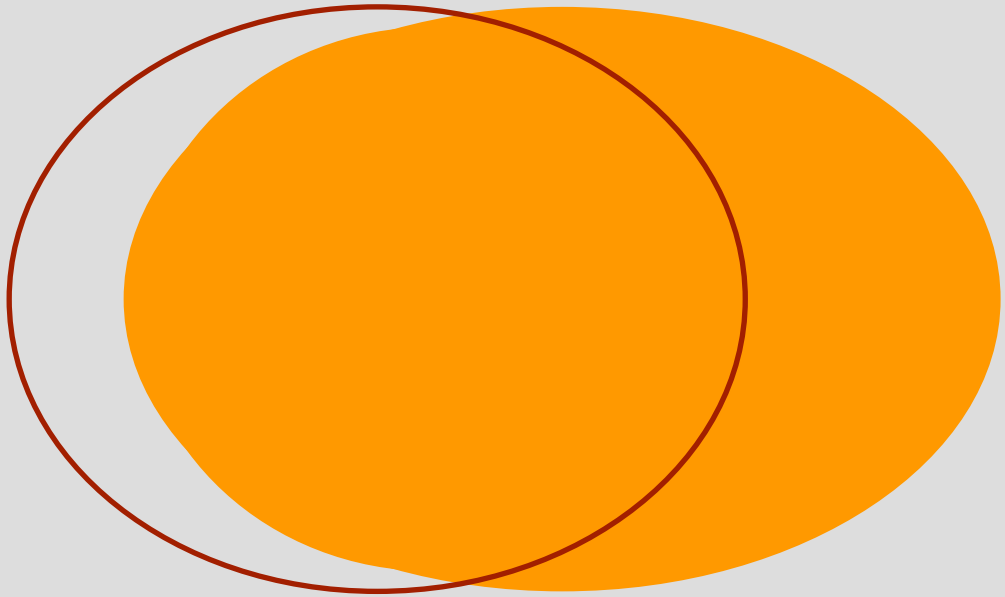
Clinics &
Pathology

Idiopathic portal hypertension
Noncirrhotic intrahepatic portal hypertension

IPH and related entities

Pathology

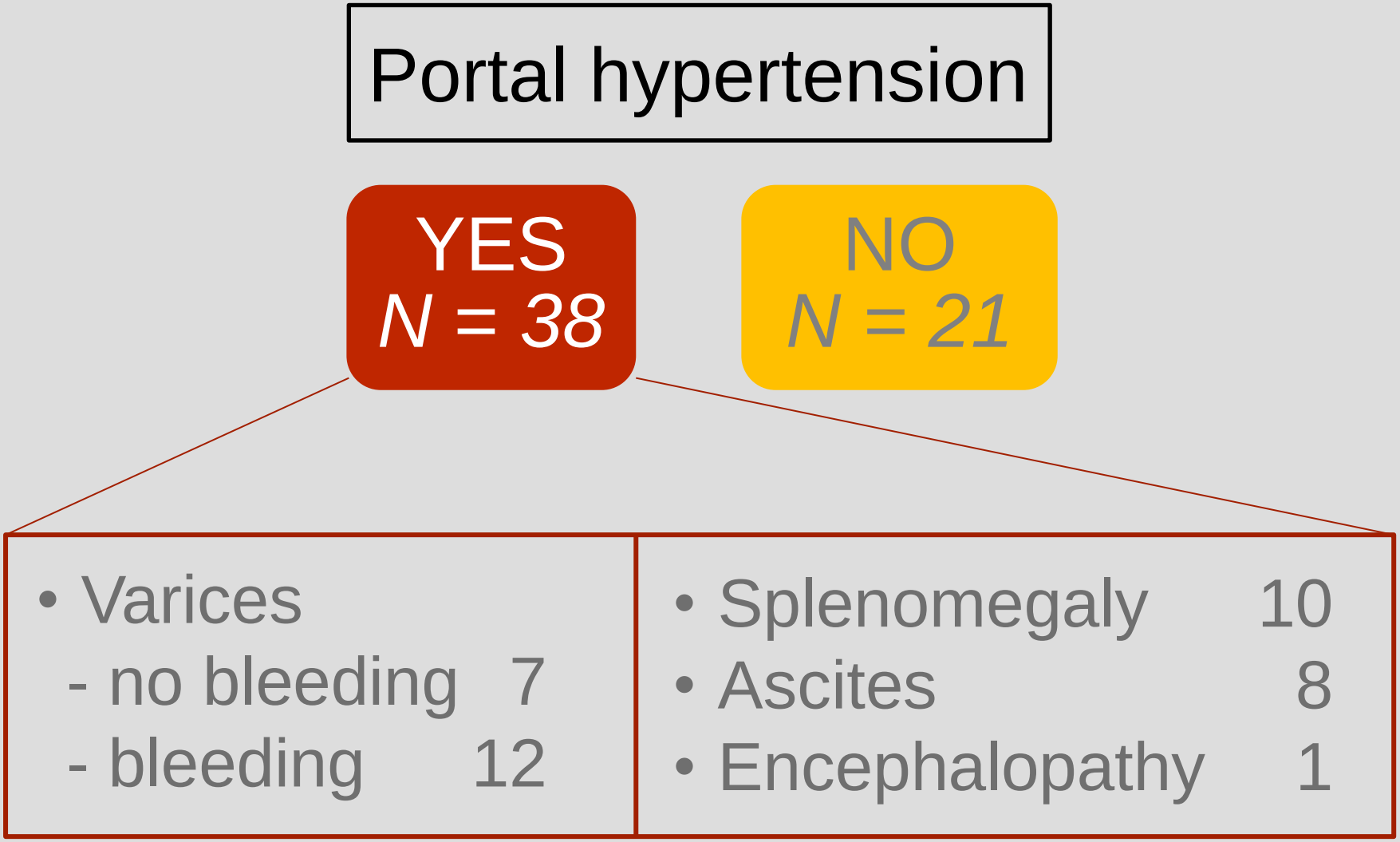
- Obliterative portal venopathy
- Hepatoportal sclerosis



Clinics & Pathology

Idiopathic portal hypertension
Noncirrhotic intrahepatic portal hypertension

Obliterative Portal Venopathy (*N = 59*)



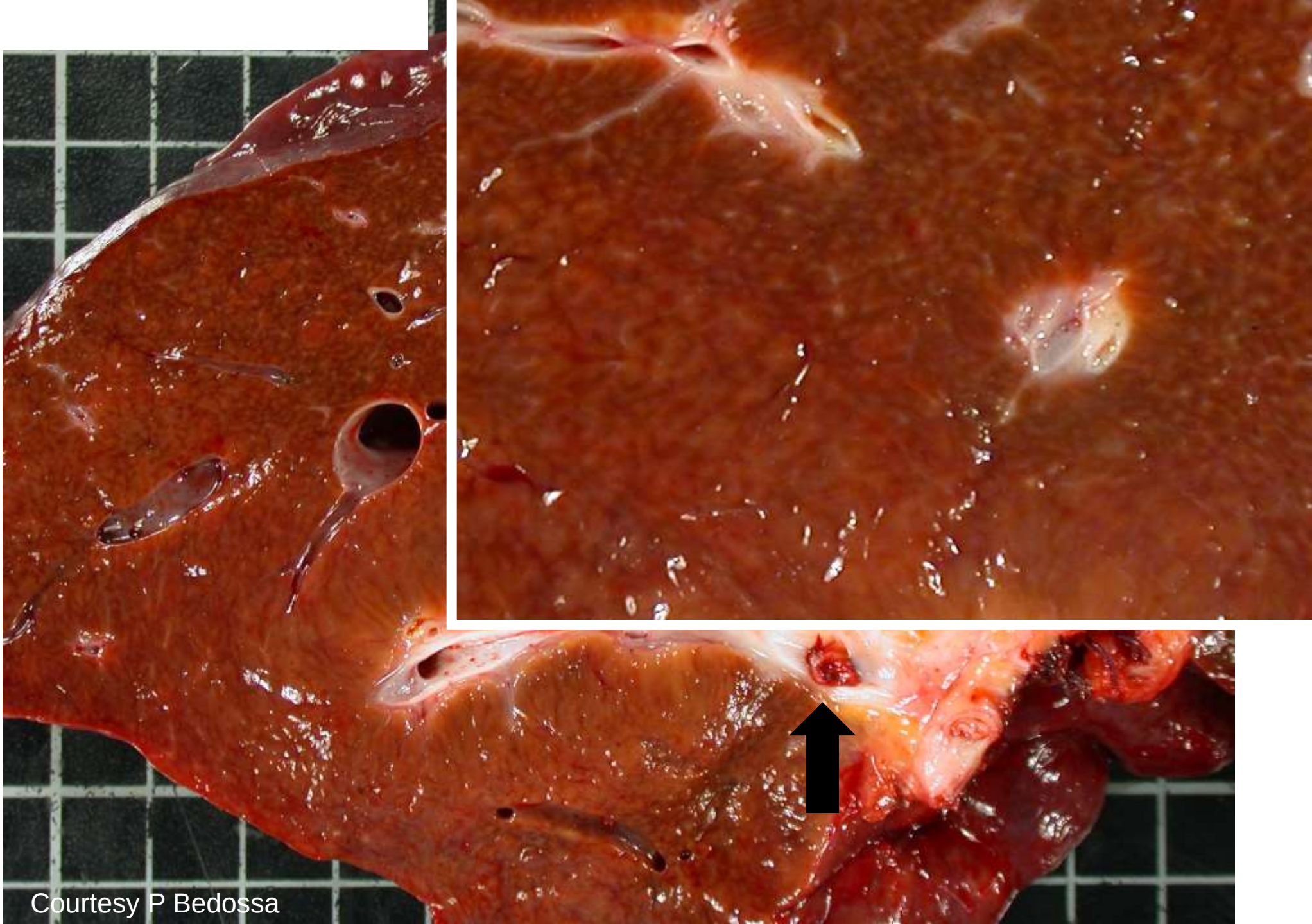
Cazals-Hatem. J Hepatol 2011

Idiopathic Portal Hypertension

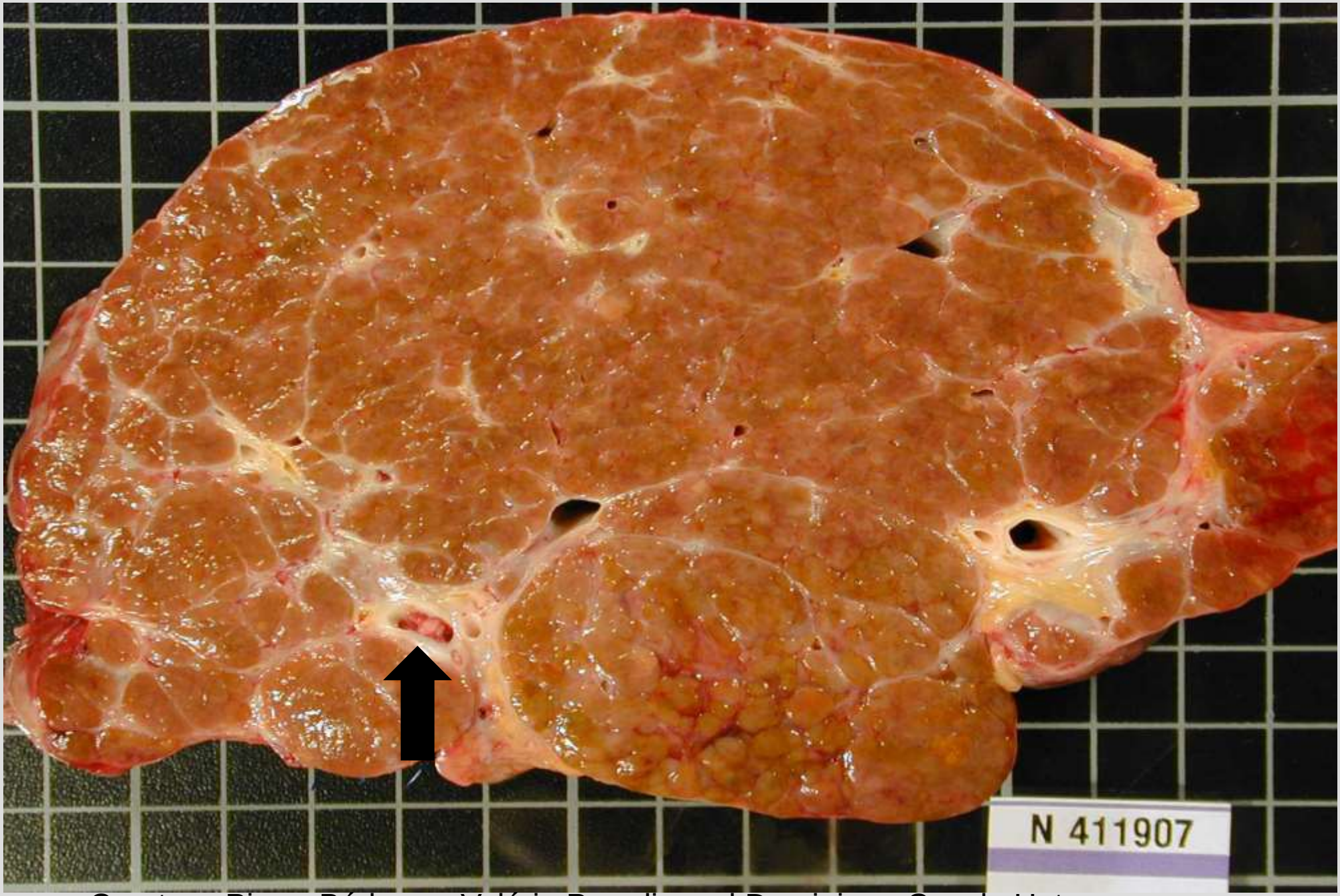
Definition

- Portal hypertension
- No other cause for portal hypertension
- Absence of cirrhosis and causes for cirrhosis

Schouten Hepatology 2011. Plessier, J Hepatol 2012.
Khanna and Sarin J Hepatol 2014



Courtesy P Bedossa



Courtesy Pierre Bédossa, Valérie Paradis and Dominique Cazals-Hatem

Obliterative Portal Venopathy (*N = 59*)

Portal hypertension

YES *38*

NO *21*

Extrahepatic portal vein thrombosis

NO *31*

YES *7*

33%

YES *6*

NO *15*

29%

Cazals-Hatem. J Hepatol 2011

Idiopathic Portal Hypertension

Definition

- Portal hypertension
- No other cause for portal hypertension
- Absence of cirrhosis and causes for cirrhosis

Schouten Hepatology 2011. Plessier, J Hepatol 2012.
Khanna and Sarin J Hepatol 2014

Obliterative Portal Venopathy in Explants

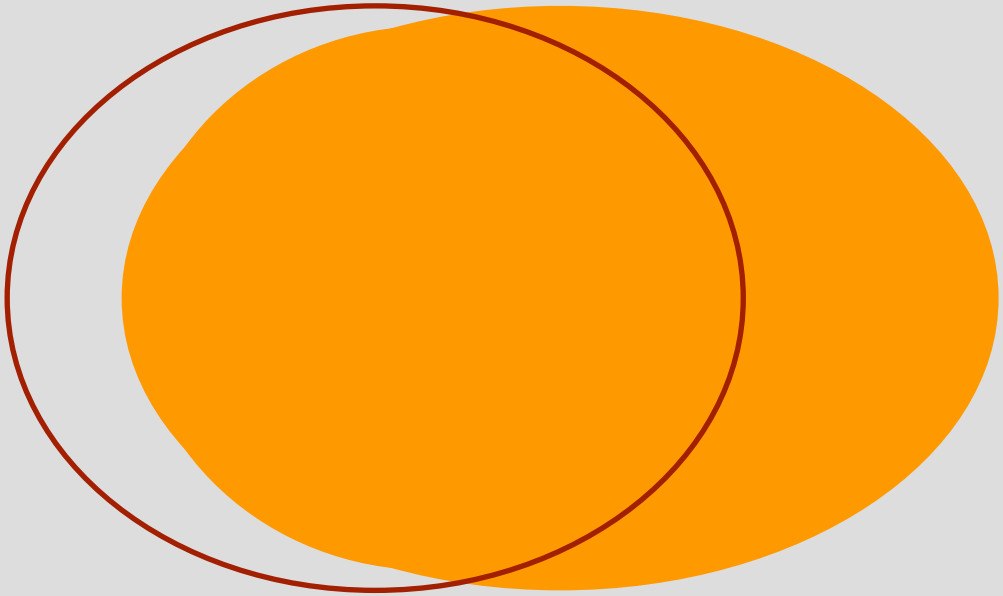
Pretransplant diagnosis	N = 21
Cryptogenic cirrhosis	10
Autoimmune cirrhosis	3
Drug-induced cirrhosis	3
Alcoholic cirrhosis	2
Viral hepatitis related cirrhosis	2
Genetic hemochromatosis	1

Adapted from Krasinskas, Liver transplant 2005 and Isabel Fiel, Am J Pathol 2007

IPH and related entities

Pathology

- Obliterative portal venopathy
- ~~Hepatoportal sclerosis~~
- ~~Noncirrhotic portal fibrosis~~
- Nodular regenerative hyperplasia



Clinics & Pathology

Idiopathic portal hypertension
Noncirrhotic intrahepatic portal hypertension

Idiopathic Portal Hypertension

- Definition and description
- Associated systemic disease
- Diagnosis
- Therapy and Outcome

Sytemic Disease Associated with IPH

1st Author	Selection	N	%
Cazals-Hatem	OPV	59	49 %
Siramolpiwat	IPH	69	43 %
Schouten	IPH	62	58 %

Cazals-Hatem, J Hepatol 2011. Schouten, APT 2012.
Siramolpiwat, Hepatology 2014

Sytemic Disease Associated with IPH

1st Author	Selection	N	%
Cazals			%
Siramolpiwat	IPH	69	43 %
Schouten	IPH	62	58 %

Misnomer #2:
Not idiopathic in 50% of patients !

Cazals-Hatem, J Hepatol 2011. Schouten, APT 2012.
Siramolpiwat, Hepatology 2014

Sytemic Disease Associated with IPH

Prothrombotic cond.	Myeloproliferative neoplasia, APS
Blood diseases	Lymphoproliferative neoplasia, Sickle cell disease
Disordered immunity	Immune deficiency syndromes Autoimmune disorders
Drug exposure	Purine analogs
Congenital defects	Turner S., Adams-Ollivier S., etc.
None of the above	Familial and sporadic cases

Cazals-Hatem, J Hepatol 2011. Schouten, APT 2012.
Siramolpiwat, Hepatology 2014. Semela, Clin Liver Dis 2015

Azathioprine, Crohn's disease and NRH

Thiopurine-naive patients (433 operated patients)

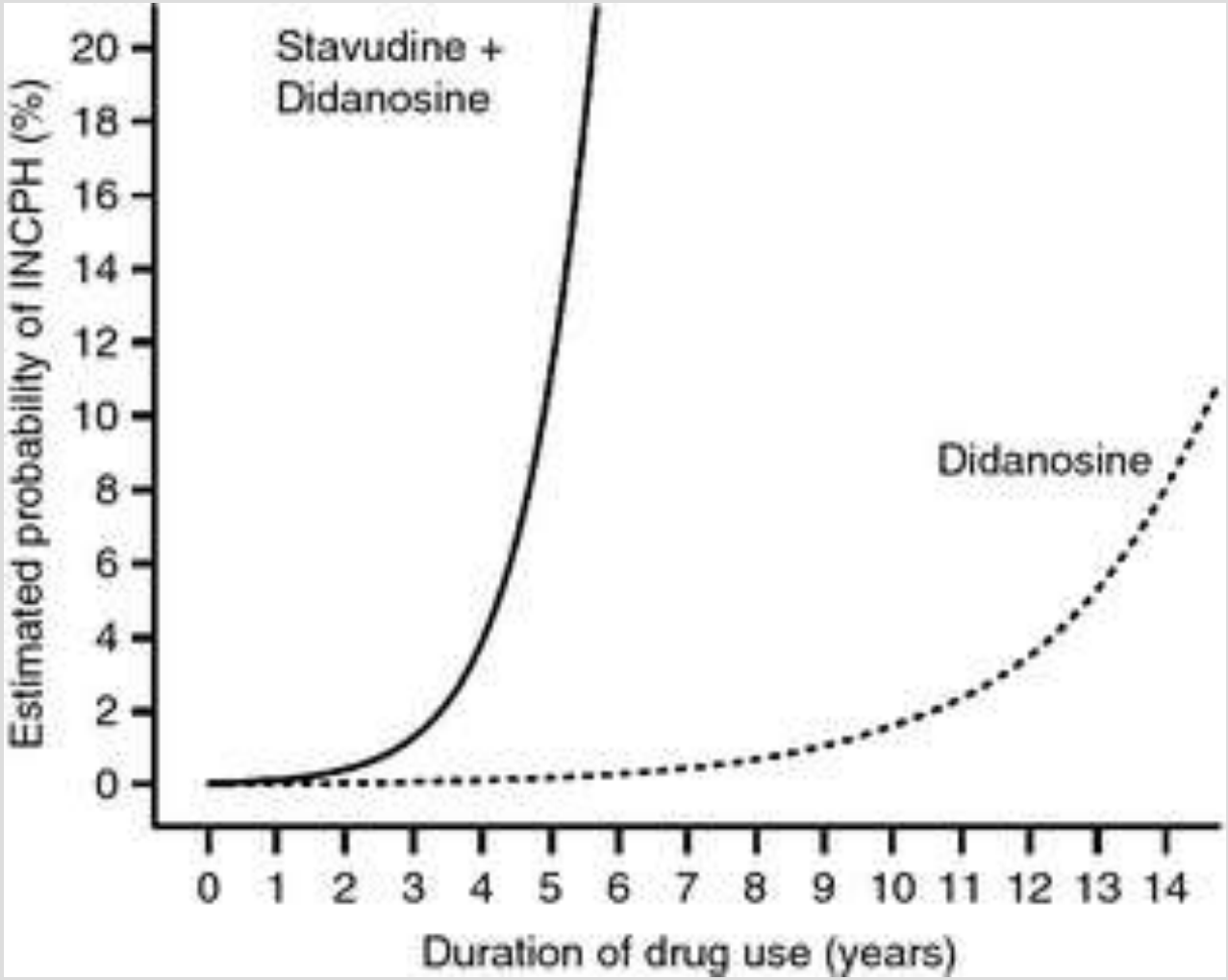
Estimated prevalence 6%

Thiopurine-treated patients (1888 consecutive patients)

10-yr cumulative incidence 1.28±0.45%

De Boer, Scand J Gastroenterol 2008. Seksik, IBD 2011

Didanosine, HIV infection and IPH



Schouten, APT 2012

Idiopathic Portal Hypertension

- Definition
- Associated conditions
- Diagnosis
- Therapy and Outcome

Idiopathic Portal Hypertension Demographics

- Mean age: 38-46
- Male/Female: 2/1
- Familial cases: about 10%

Cazals-Hatem, J Hepatol 2011. Verheij, Histopathology 2013. Siramolpiwat Hepatology 2014

Laboratory features of IPH

	IPH
Platelets (10^3/μL)	106 (27–454)
Albumin (g/l)	38 (20–52)
Bilirubin (μmol/L)	17 (5–100)
INR	1.1 (1.0–1.4)

Verheij, Histopathology 2013

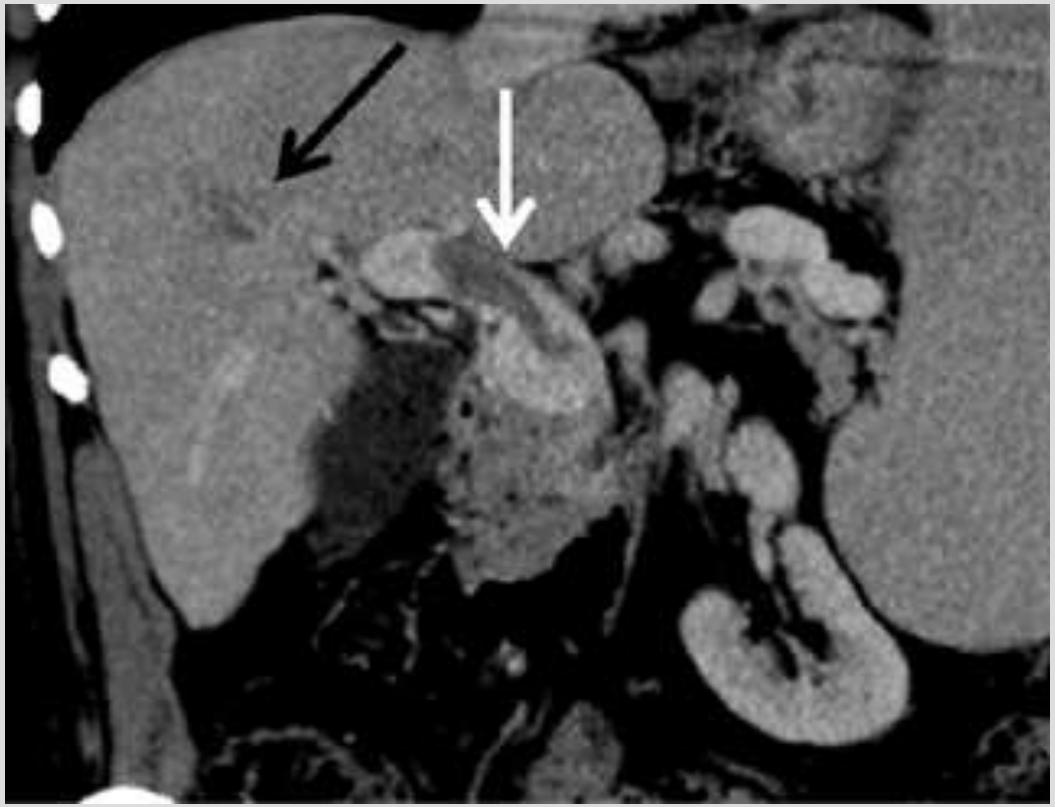
Transaminases and alkaline phosphatase variably increased

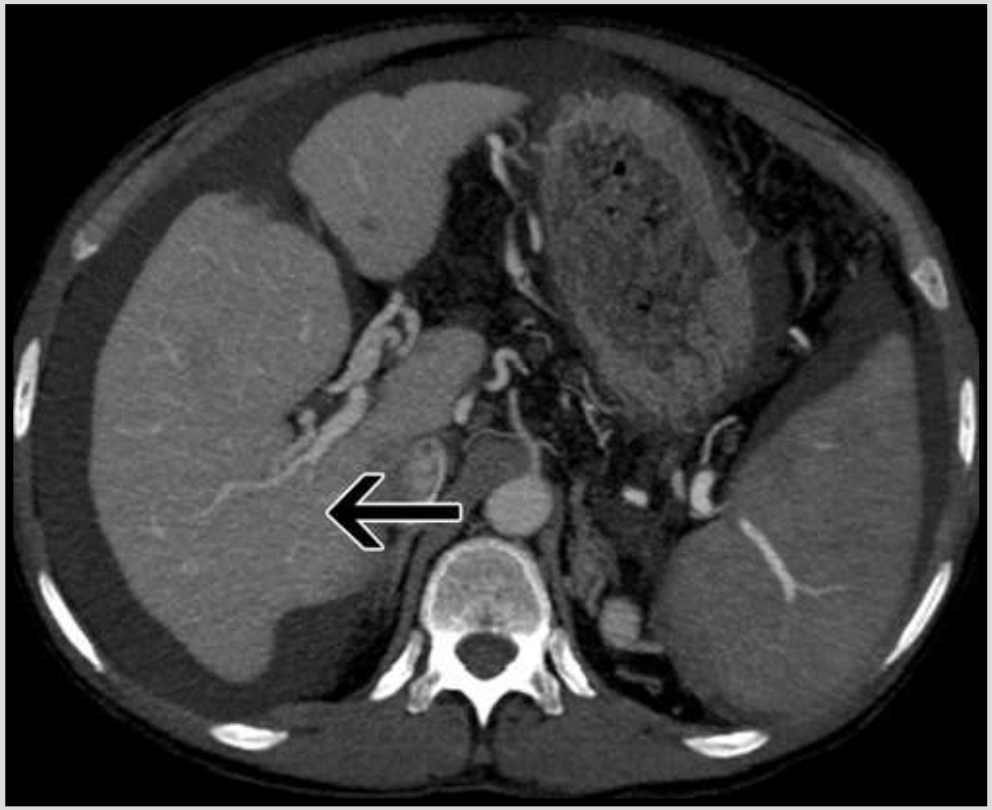
Imaging with MDCT or MR

	IPH (n=42)	Cirrhosis (n=42)
Nodular liver surface	17%	88%
Enlarged I and atrophic IV	24%	64%
EHPVT	43%	12%
Abnormal IH portal veins	58%	2%

Glatard, Radiology 2012. Khrisnan, AJR 2012

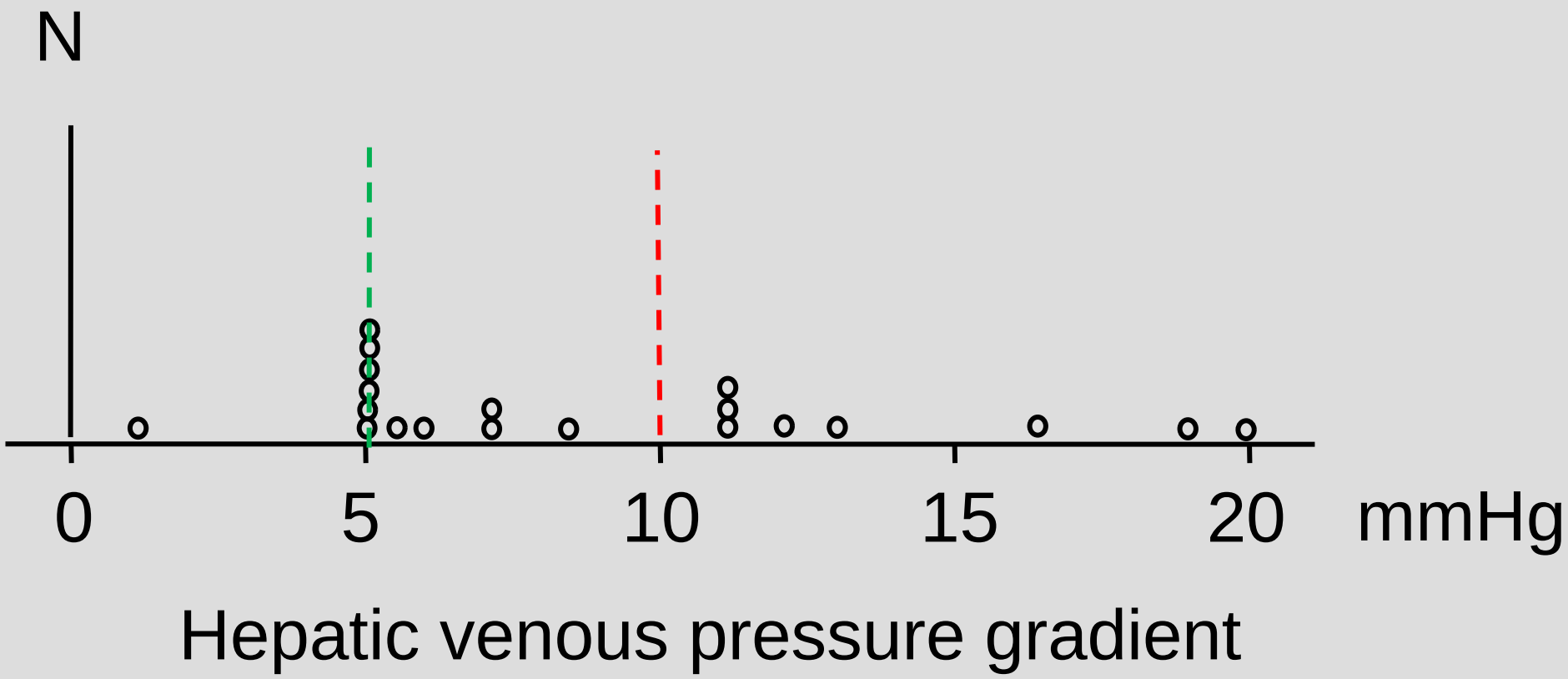
Imaging of Idiopathic Portal Hypertension





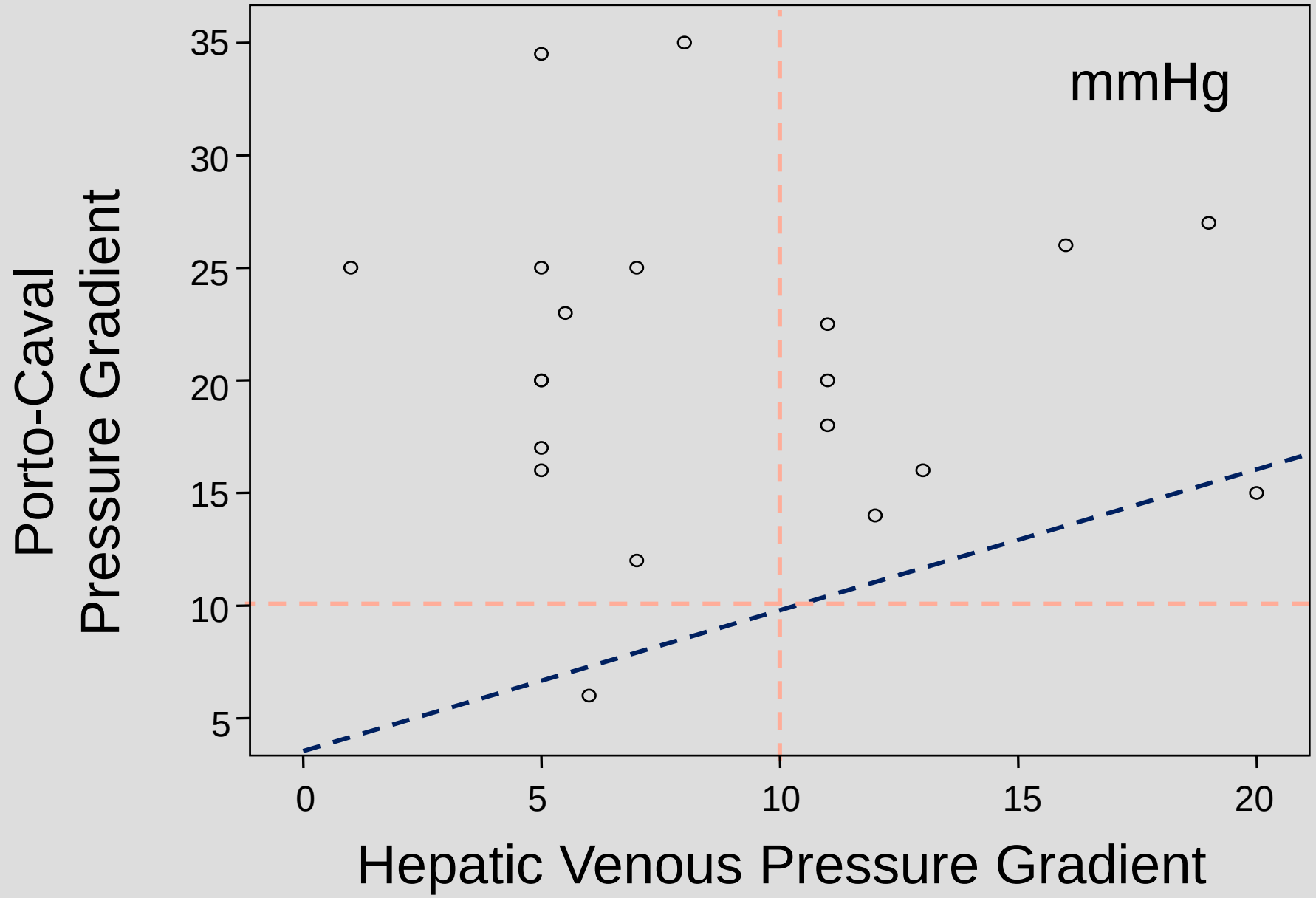
Glatard. Radiology 2012

Idiopathic Portal Hypertension – HVPG



Bissonnette et al. EASL 2015; Sarin Gut 1987

Idiopathic Portal Hypertension - Hemodynamics

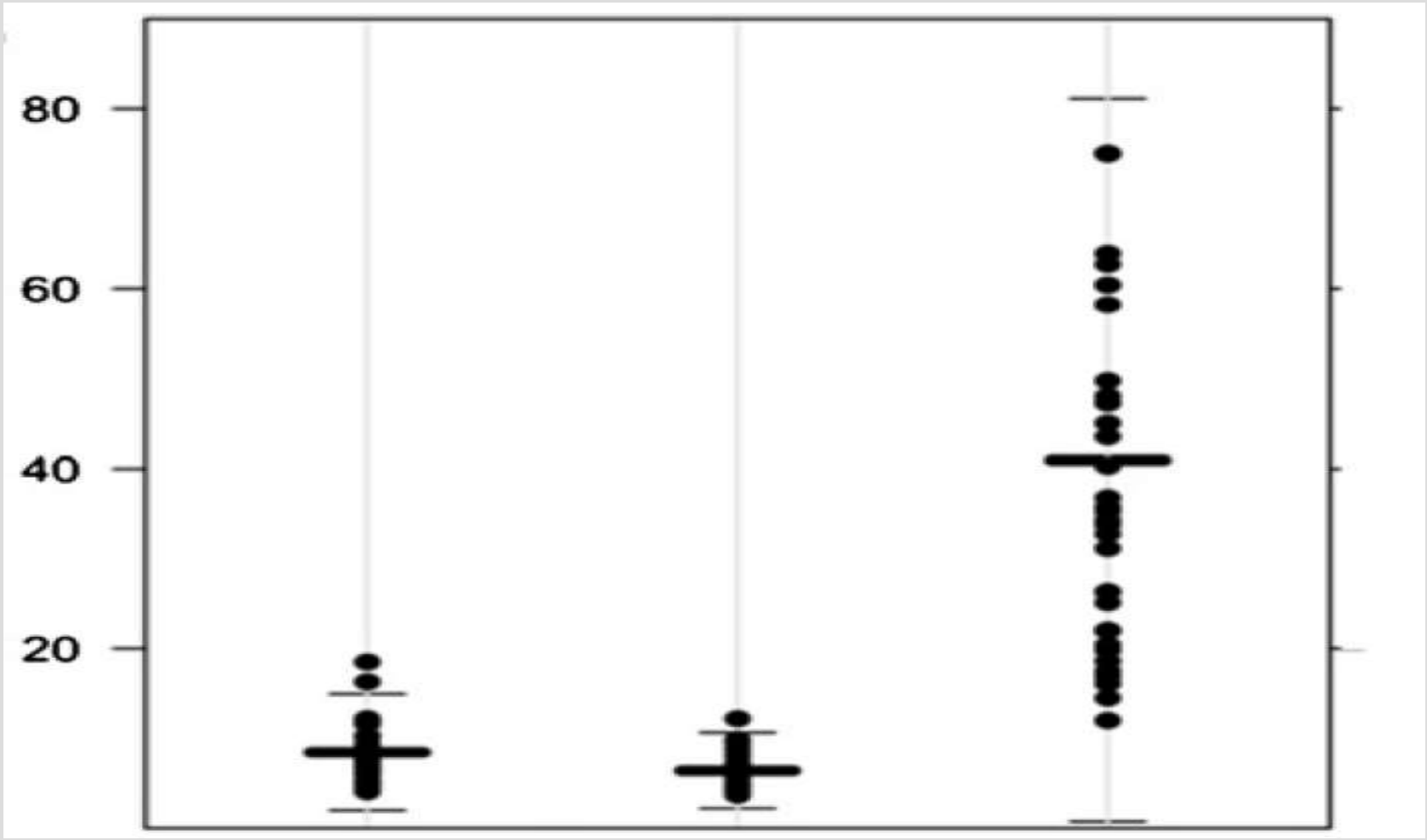


Bissonnette et al. EASL-ILC 2015 Submitted

Liver Stiffness

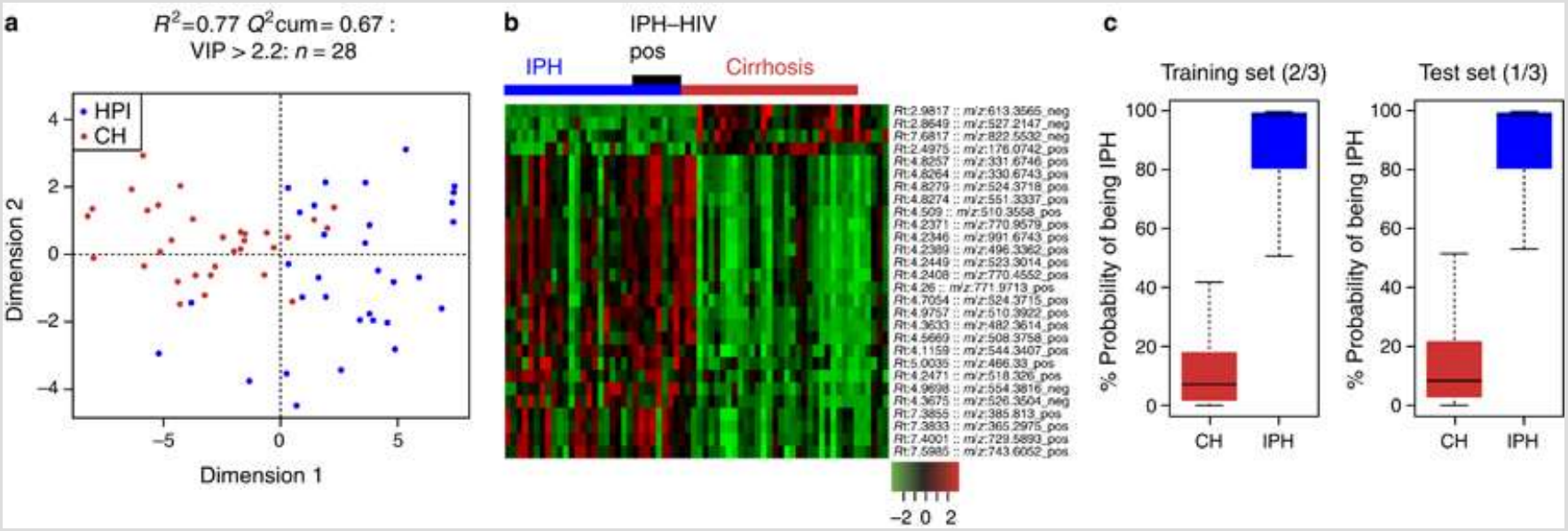
kPa

Fibroscan

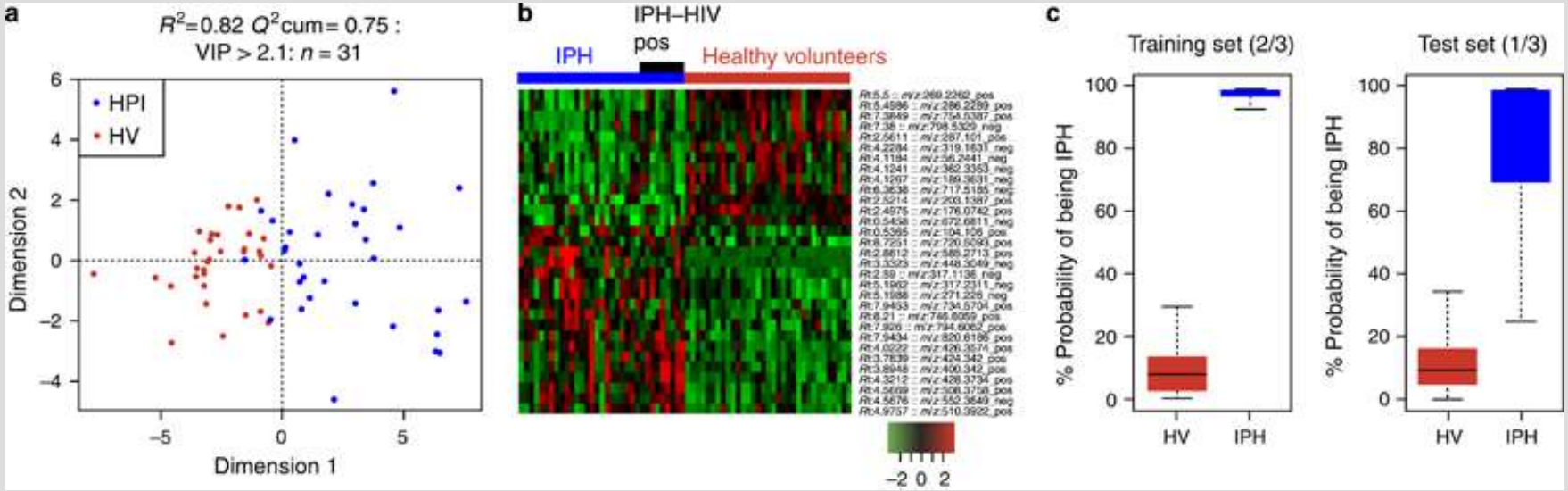


Seijo, Dig Liv Dis 2012

Idiopathic Portal Hypertension *vs* Cirrhosis



Idiopathic Portal Hypertension *vs* Healthy Hontrols

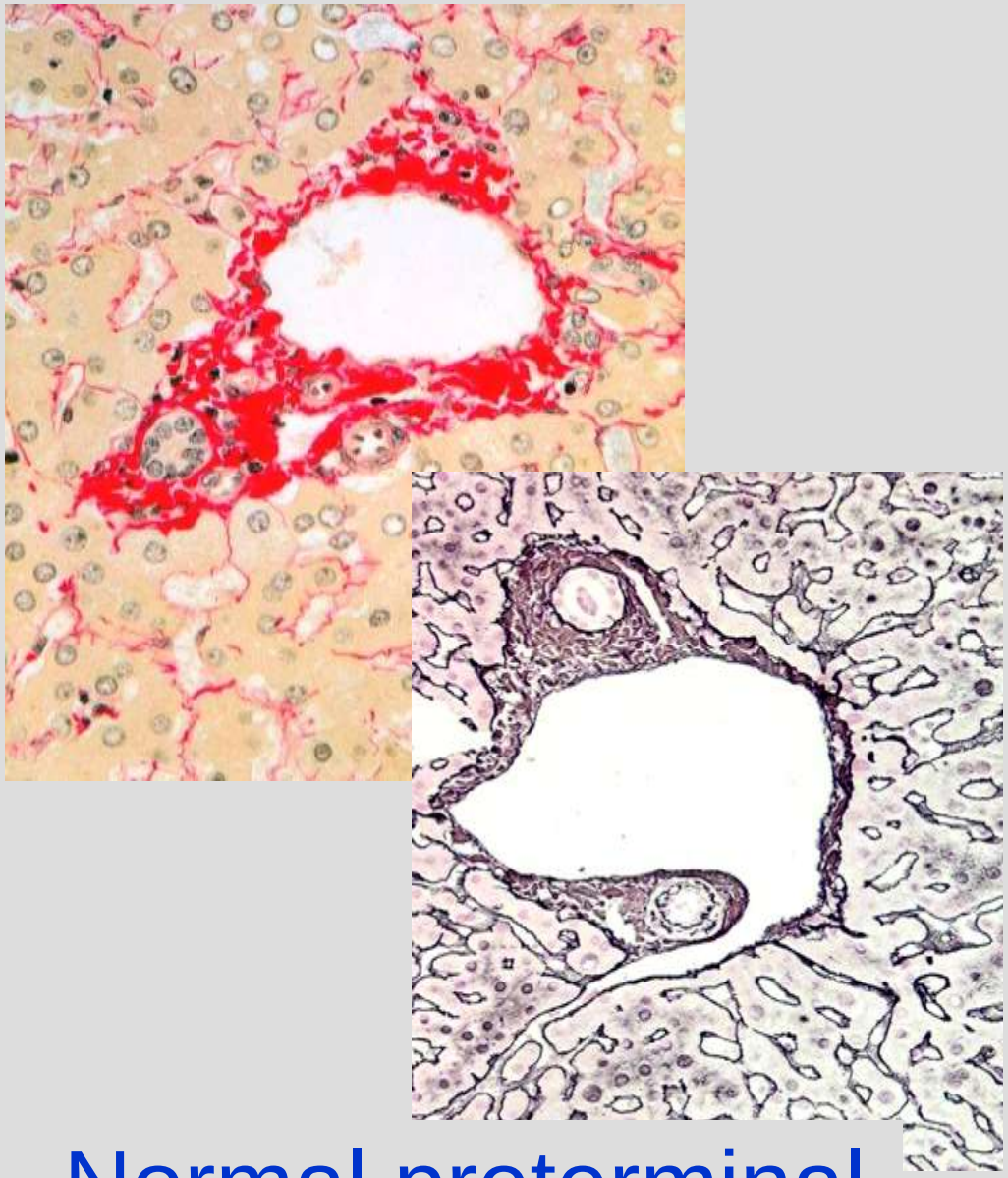


Seijo. Am J Gastroenterol 2013

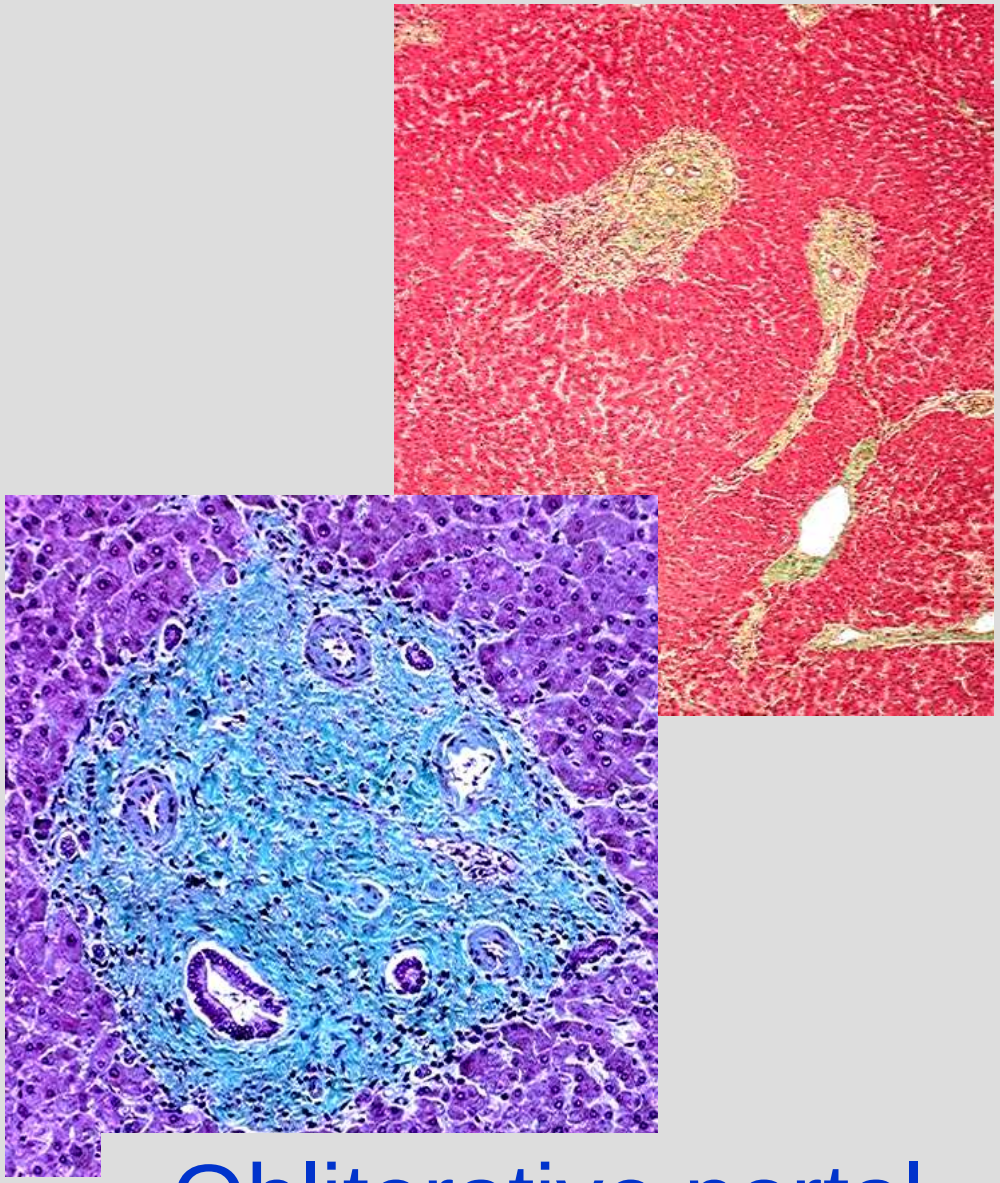
IPH - Diagnosis

- Non invasive diagnosis still not possible
- High degree of suspicion
  - no cause for parenchymal liver disease
  - no or mild liver dysfunction
  - associated conditions
- Biomarkers ?
- Specific findings at liver biopsy ?

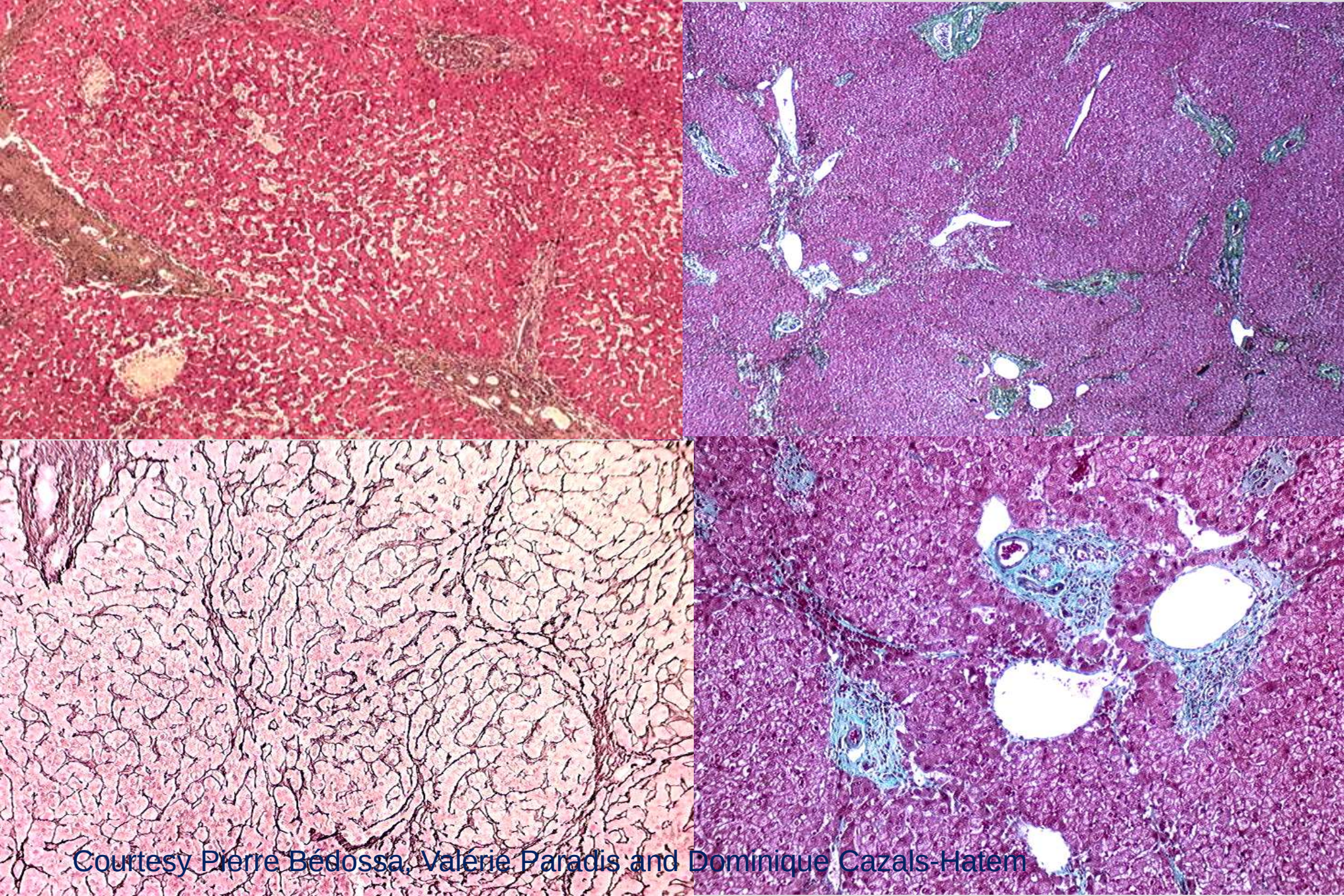
Hillaire et al. Gut 2002, Chang, Am J Gastro 2009
Seijo, Dig Dis Sci 2012, Seijo, Am J Gastroenterol 2013



Normal preterminal portal venules



Obliterative portal venopathy



Courtesy Pierre Bédossa, Valérie Paradis and Dominique Cazals-Hatem

Obliterative Portal Venopathy

Abnormal portal veins in > 2/3 of portal tracts

100% of patients
50% of needle specimens
Median of 3 LBx needed for diagnosis

Identification of cases through pathology files

1987-2007; 59 Patients; 89 Liver specimens
(> 1cm, > 6 portal tracts); length 13.3 mm

Cazals-Hatem. J Hepatol 2011

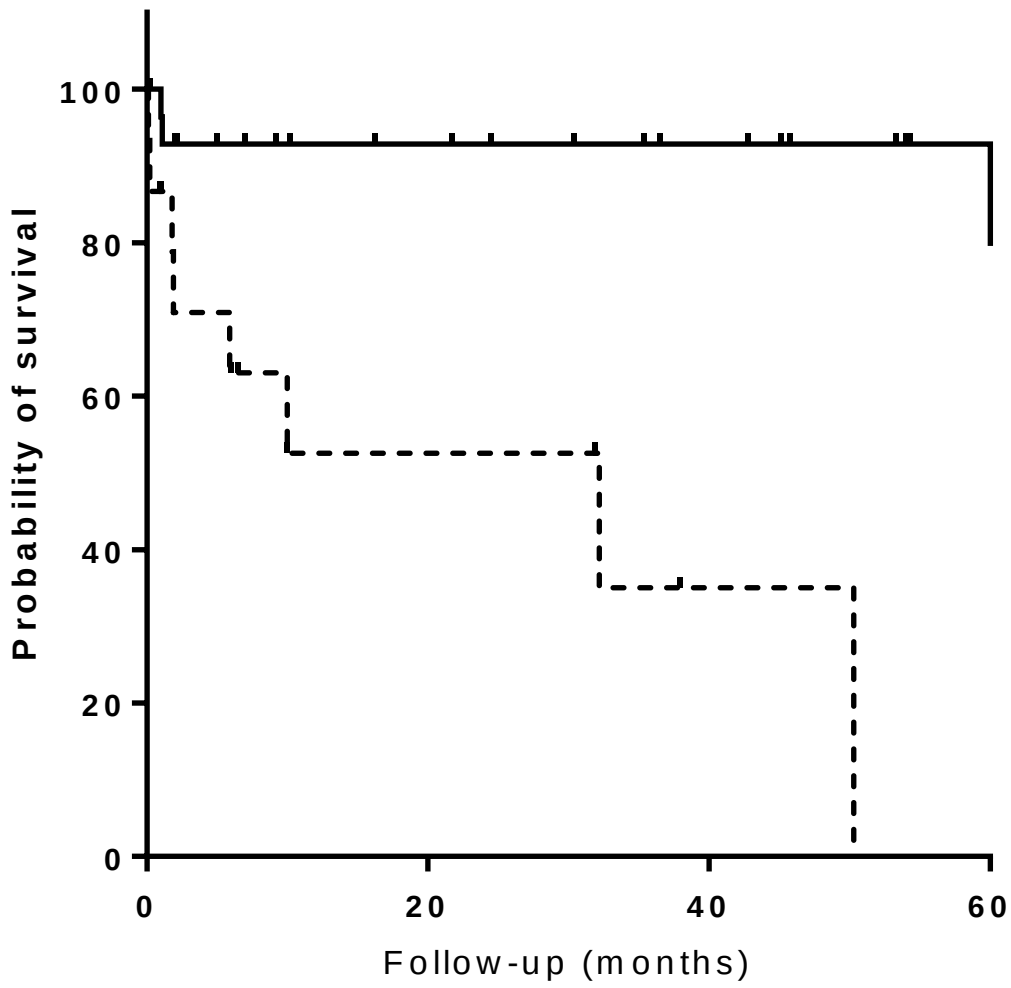
Idiopathic Portal Hypertension

- Definition
- Associated conditions
- Diagnosis
- Therapy and Outcome

Treatment proposed for IPH

- For portal hypertension
  - NSBB and endoscopic ligation
  - TIPS
- For end stage liver disease
  - Liver transplantation
- For portal vein thrombosis
  - Anticoagulation therapy

TIPS for IPH



Total	42
Refractory ascites	16
Recurrent bleeds	25
Exs. enteropathy	1

Bissonnette et al. EASL-ILC 2015. Submited

Treatment proposed for IPH

- For portal hypertension
  - NSBB and endoscopic ligation
  - TIPS
- For end stage liver disease
  - Liver transplantation
- For portal vein thrombosis
  - Anticoagulation therapy

Obliterative portal venopathy

Outcome in 59 patients

Follow-up – *yr*	8.6 ± 7.8
Extrahepatic PVT	13/46 (28%)
Progression/development of PHT	27 (46%)
Liver transplantation	9 (15%)
Death	5 (8%)

Cazals-Hatem. J Hepatol 2011

Mortality/Liver transplantation in Patients with IPH

Reference	Kingham 1981	Hillaire, 2002	Cazals-H, 2011	Schouten, 2012	Siramolpiwat, 2014
Country	UK	FR	FR	BE & NL	SP
N	59	28	59	62	69
Follow-up	5-yr	7.6 yr	8.6 yr	7.5 yr	6.7 yr
Mortality/LTx	10%	14%	19%	44%	13%

IPH: A mysterious syndrome

- An entity characterized by various alterations in intrahepatic portal veins and/or sinusoids, with or without clinically significant portal hypertension.
- Associated systemic conditions are common, varied and peculiar. Their link with liver alterations is not understood yet.
- Likely under-recognized. High degree of suspicion needed in patients with « cryptogenic liver disease »
- High risk of extrahepatic PVT. Relatively good medium term outcome.

IPH: A mysterious syndrome

- Is anticoagulation beneficial ?
- Will systems biology help identify discrete components?
- Can a specific disorder of the endothelium of intra-hepatic portal vein and/or sinusoids be implicated ?
- Does this disorder play a role as a comorbid factor in other chronic liver disease ?

Histopathological Features of IPH (Nedle biopsy)

Histopathological feature	Verheij	Cazals
Portal phlebosclerosis	95	96
Paraportal shunt vessels	89	38
Increased vascular channels in portal tracts	71	-
Portal vein dilatation	34	-
Thin incomplete septa	10	38
Nodular regeneration	56	70
Sinusoidal dilatation	94	41
Perisinusoidal fibrosis	97	57
Central perivenular fibrosis	65	-

Results are %

Verheij, Histopathology 2013 (n = 70). Cazals, J Hepatol 2011 (n = 82)

Laboratory features of IPH and PVT

	IPH	PVT	*P*
Platelets (10^6/mm^3)	106 (27–454)	237 (10–593)	0.01
Albumin (g/l)	38 (20–52)	38 (28–45)	0.41
Bilirubin (IM)	17 (5–100)	24 (10–66)	0.24
INR	1.1 (1.0–1.4)	1.0 (1.0–1.3)	0.28

Verheij, Histopathology 2013

Transaminases and alkaline phosphatase variably increased

Prevalence of IPH in Europe

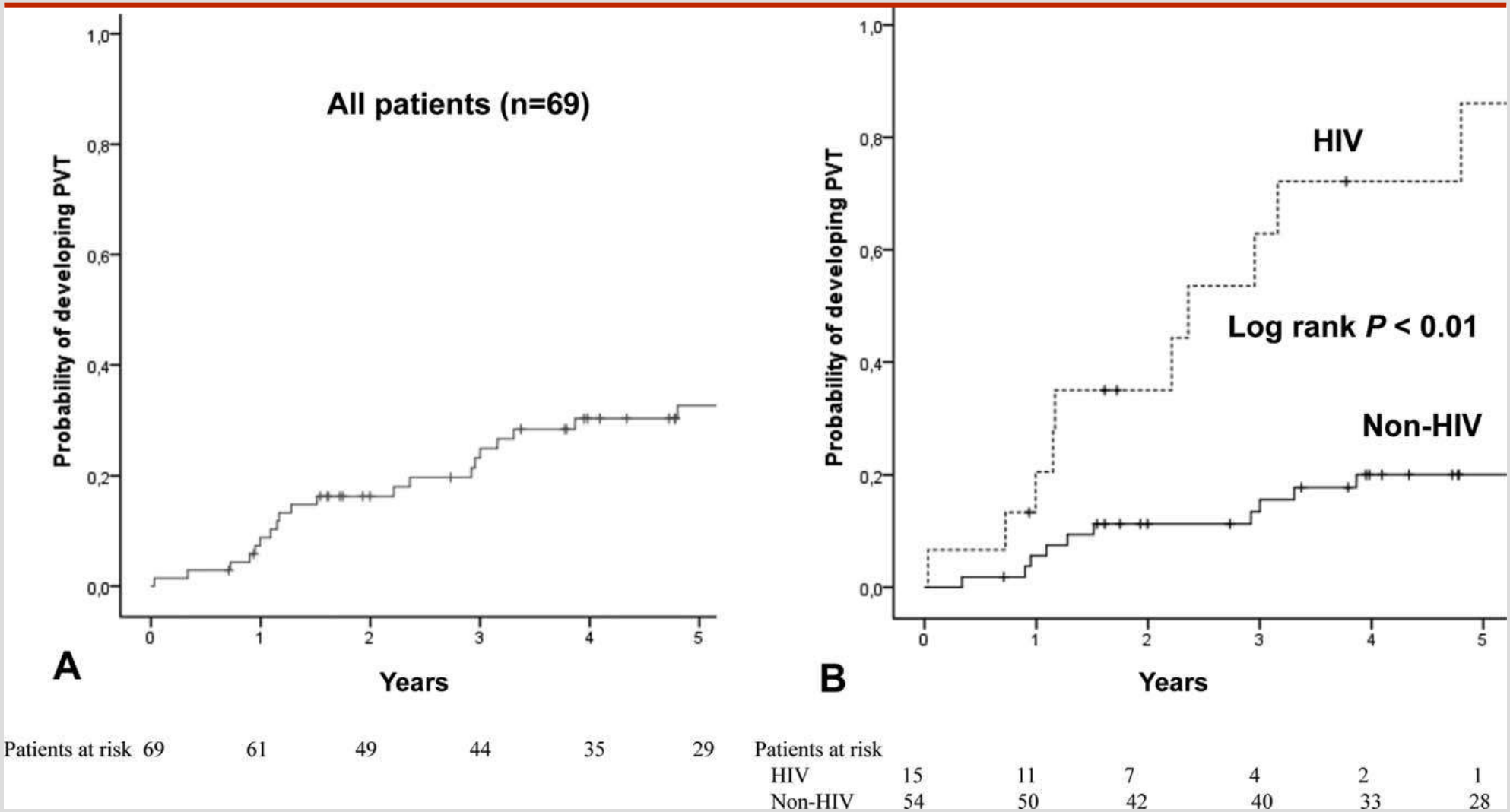
Reference	Kingham, 1981	Hillaire, 2002	Cazals-H, 2011	Schouten, 2012	Siramolpiwat 2014
N.	59	28	76	62	85
Country	UK	FR	FR	BE & NL	Catalonia
Period	1949-1979	1994-1998	1987-2007	1992-2010	1995-2012
Estimated prevalence (p.10^6)	1.1	0.5	1.2	2.4	13.7
Comments		Underestimated ?			Overestimated ?

Pathology of IPH

9 Explanted Livers	
Liver weight (g) *Mean (range)*	837 (610-1640)
Dysmorphic liver	6 (67%)
Obliterated large portal veins	6 (67%)
Hepatic venopathy	2 (22%)

Cazals-Hatem, J Hepatol 2011

Risk of PVT in IPH



Siramolpiwat, Hepatology 2014

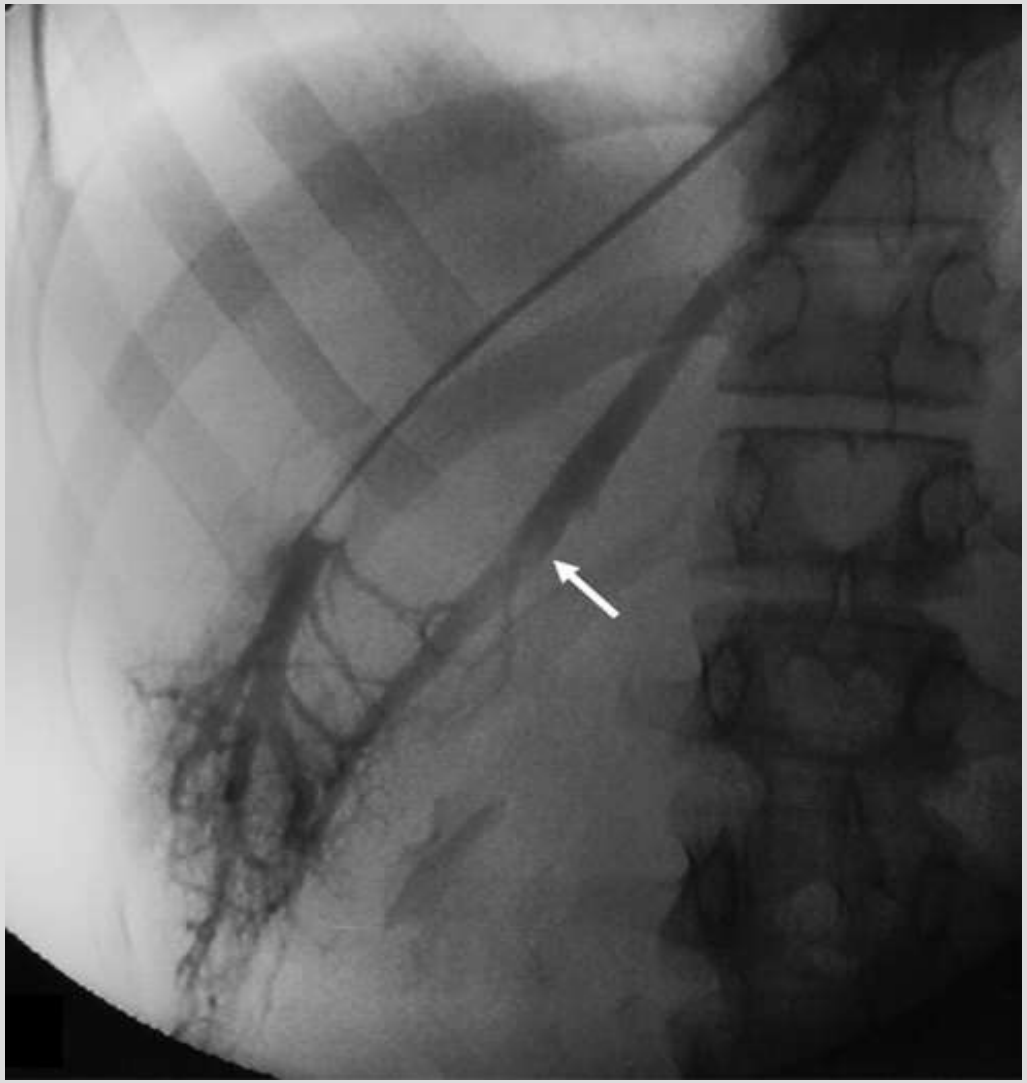
Outcome of Obliterative Portal Venopathy

	Prothrombotic Disorders 18 (30)	Immune- mediated disorders 10 (17)	Other patients 31 (53)
OUTCOME			
Follow-up (Years)	5 ± 5.8	13 ± 7	9 ± 8
Extrahepatic Portal Vein Thrombo	4/8 (50)	3/9 (33)	6/29 (21)
Deterioration/occurrence of PHT	6 (33)	6 (60)	15 (48)
Liver Transplantation	0	1 (10)	8 (26)
Death	0	2 (20)	3 (10)
TREATMENT			
Anticoagulant (AC)	13 (72)	5 (50)	10 (33)
Delay diagnosis/ AC therapy (Yea	0.7	4.6	3.6

Cazals-Hatem, J Hepatol 2011

HVPG and Veno-Venous Collaterals

- 50% of patients
- Prevent pressure measurements in 30%



Seijo, Dig Liv Dis 2012

Conditions Associated with IPH

29 (49%)

Immune mediated disorders	**11**
Rheumatoid arthritis	3
Common variable immunodeficiency	1
Wegener disease	1
Sharp syndrome	1
Others	5
Prothrombotic condition	**18**
Myeloproliferative disease (MPD)	10
Factor II mutation	3
Protein S deficiency	3
Protein C deficiency	3
C677T MTHFR homozygous	2

Cazals-Hatem, J Hepatol 2011

Conditions Associated with IPH

36 (58%)

Azathioprine treatment	8	(13)
Haematological disorders	8	(13)
Malignancies	4	(7)
Myeloproliferative disorders	3	(5)
Idiopatic thrombocytopenic purpura	1	(2)
Chronic HIV infection	5	(8)
Immunological disorders	5	(8)
Genetic disorders	4	(7)
Arsenicum treatment	4	(7)
Chemo 7 years before diagnosis	1	(1)
Crohn’s disease (Azathioprine naive)	1	(2)

Conditions Associated with IPH

30 (43%)

HIV infection	15 (22%)
Immunological disorders	7 (10%)

Common variable immunodeficiency, Graves' disease, POEMS, Rheumatoid arthritis, SLE, systemic sclerosis with pulmonary hypertension, unclassified

Hematological disorders	6 (9%)

Aplastic anemia (2), Hodgkin's lymphoma, marginal B cell lymphoma, idiopathic thrombocytopenic purpura, multiple myeloma

Prothrombotic disorders (evaluated in 60 patients)	5 (8%)

Prothrombin gene mutation (2), antiphospholipid syndrome, factor V Leiden mutation, protein S deficiency

Obliterative portal venopathy (*N = 59*)

Portal hypertension

YES *38*

NO *21*

Extrahepatic portal vein thrombosis

NO *31*

YES *7*

YES *6*

NO *15*

Cavernoma	7
Acute PVT	6

Cazals-Hatem. J Hepatol 2011

Idiopathic portal hypertension
Genetic component

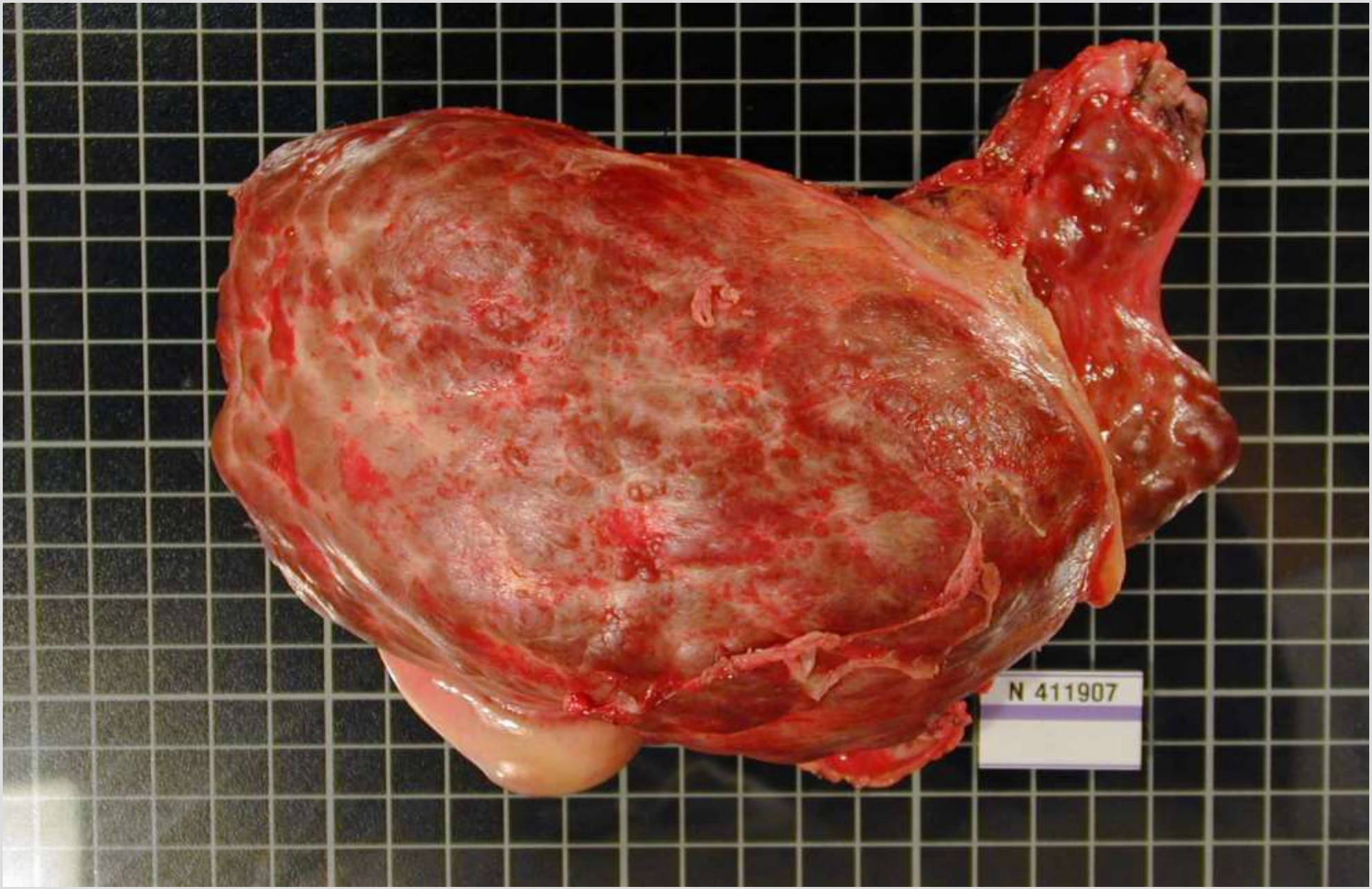
Congenital defect	Familial cases
Turner syndrome Adams-Oliver syndrome Telomerase complex mutations	Nodular regenerative hyperplasia Incomplete septal cirrhosis Idiopathic portal hypertension

Schouten Hepatology 2011. Plessier J Hepatol 2012. Franchi-Abella J Pediatr 2014

Histopathological Features of IPH

HISTOLOGICAL LESIONS	BIOPSY SPECIMEN N = 82 (%) Mean Size°= 13.7mm [5-30]	EXPLANTED LIVERS N = 9 (%) Mean Weight= 837g [610-1,640]
Obliteration of portal venules	79* (96)	9 (100)
Nodular regenerative hyperplasia	57 (70)	9 (100)
Perisinusoidal fibrosis	47 (57)	9 (100)
Sinusoidal dilatation	34 (41)	6 (67)
Aberrant vessels	31 (38)	5 (55)
Extensive portal fibrosis ¤ (>F1)	25 (30)	8 (89)
Dysmorphic liver		6 (67)
Obliterated large portal veins		6 (67)
Hepatic venopathy		2 (22)

Cazals-Hatem, J Hepatol 2011



Courtesy Pierre Bédossa, Valérie Paradis and Dominique Cazals-Hatem