Liver specificities in myelofibrosis and impact on transplantation procedure

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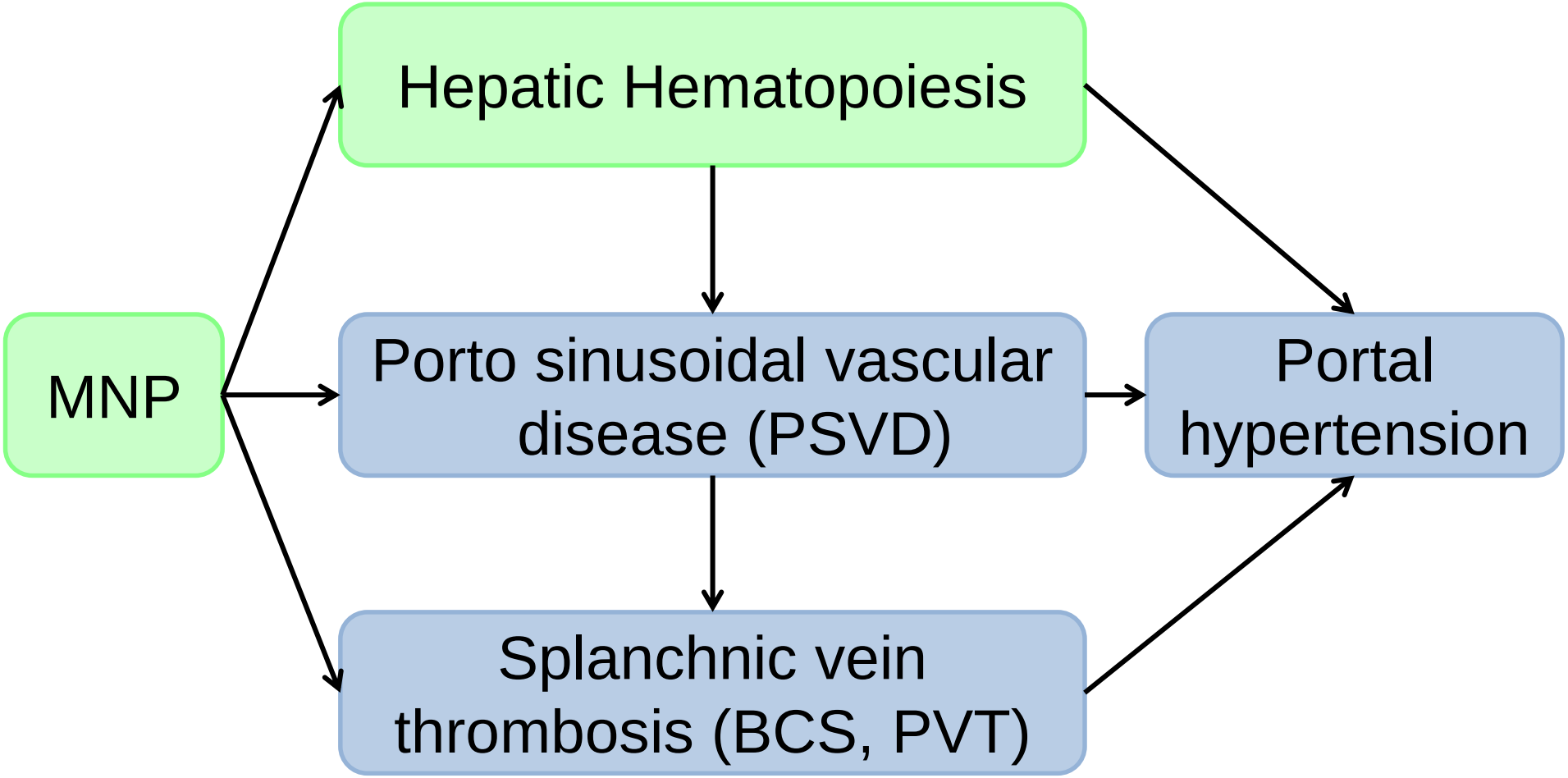
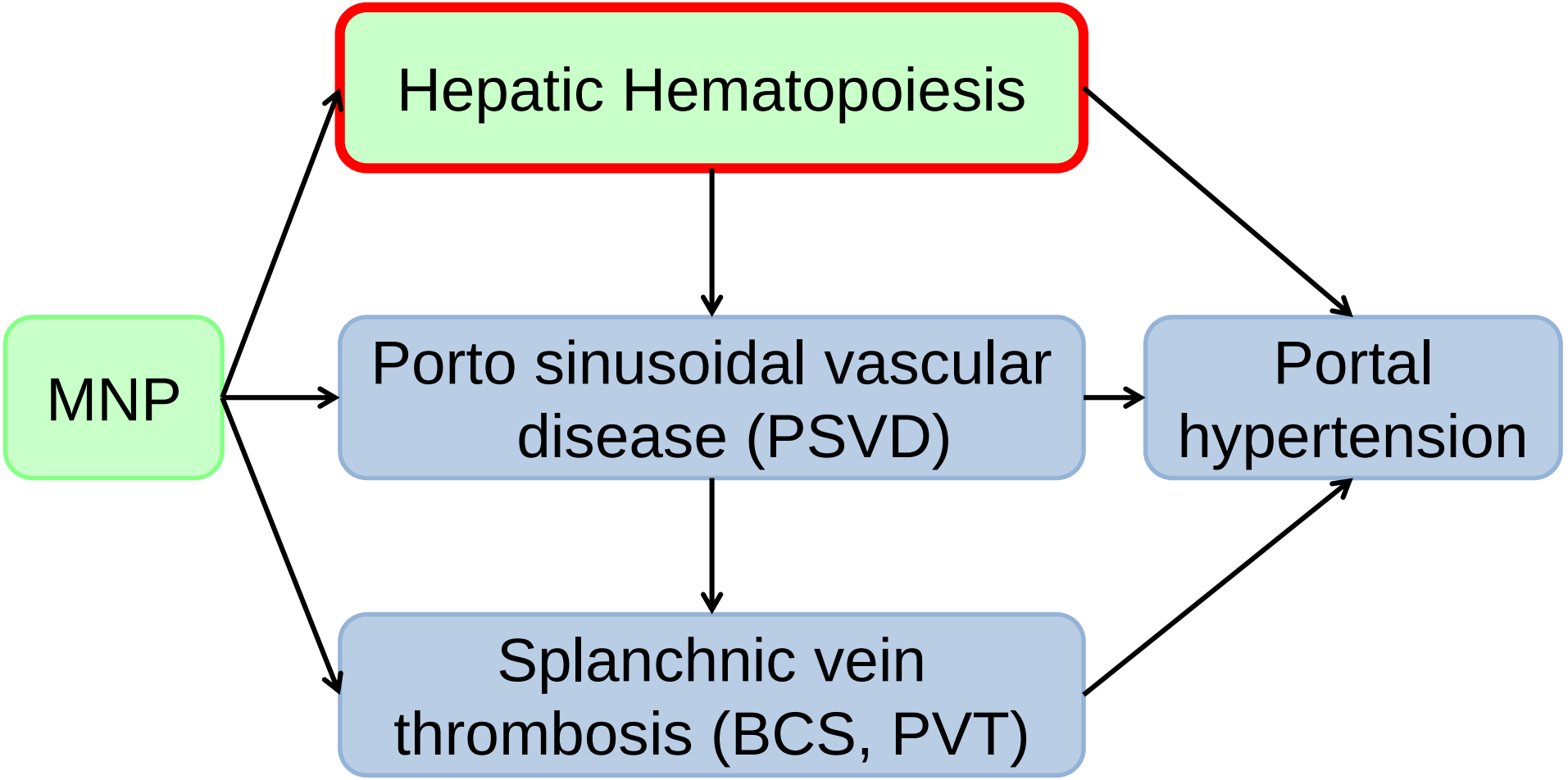

Hepatic Hematopoiesis
MNP
Porto sinusoidal vascular disease (PSVD)
Portal hypertension
Splanchnic vein thrombosis (BCS, PVT)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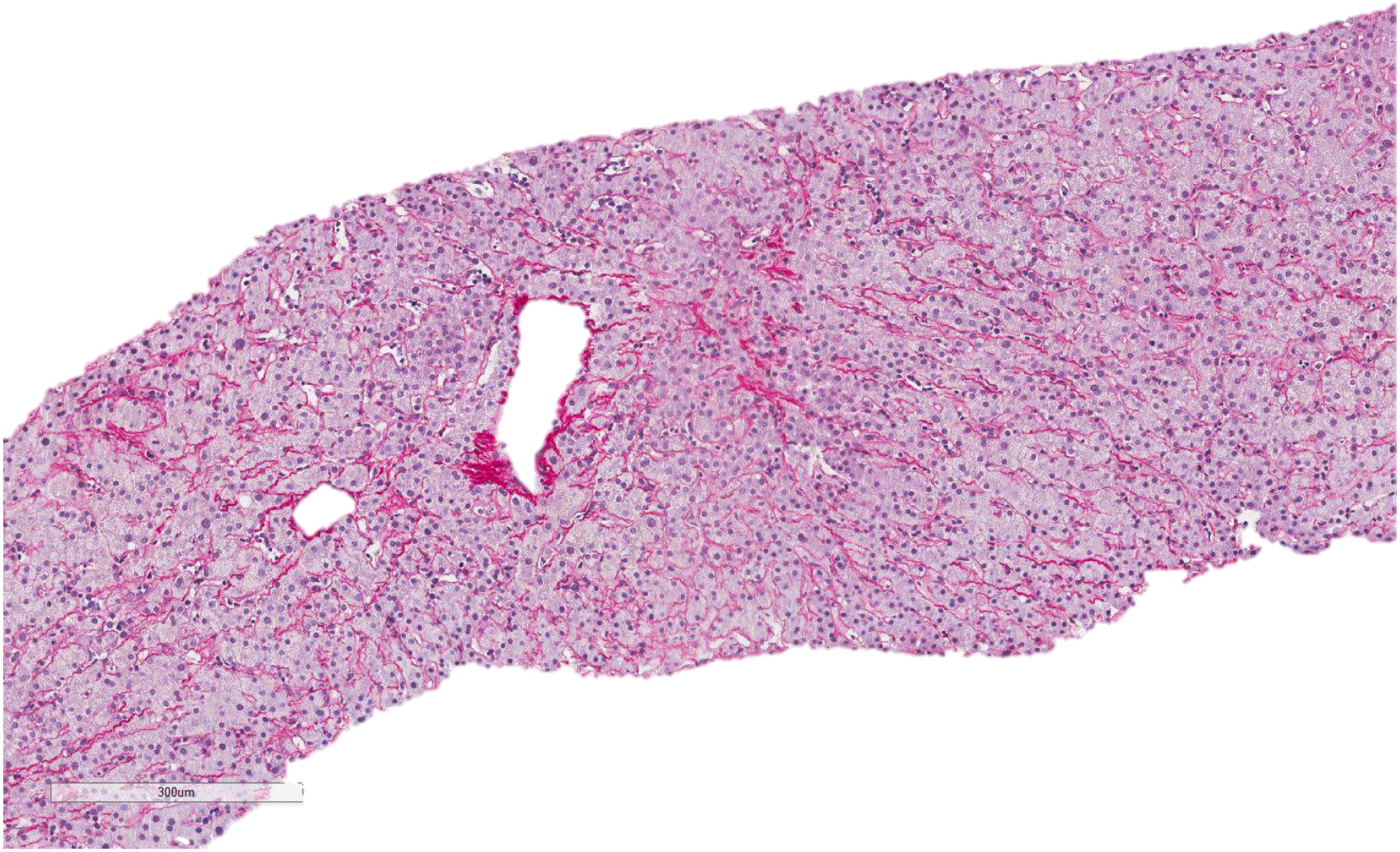
Case of a 65 yr-old male

- 1996: essential thrombocythemia and myelofibrosis
- Treatment: interferon, anagrelide
- Work up before transplantation:
  - ALK 3N, GGT 7N, PT 100%, normal serum bilirubin, splenomegaly, no ascites
  - Negative work up for chronic liver disease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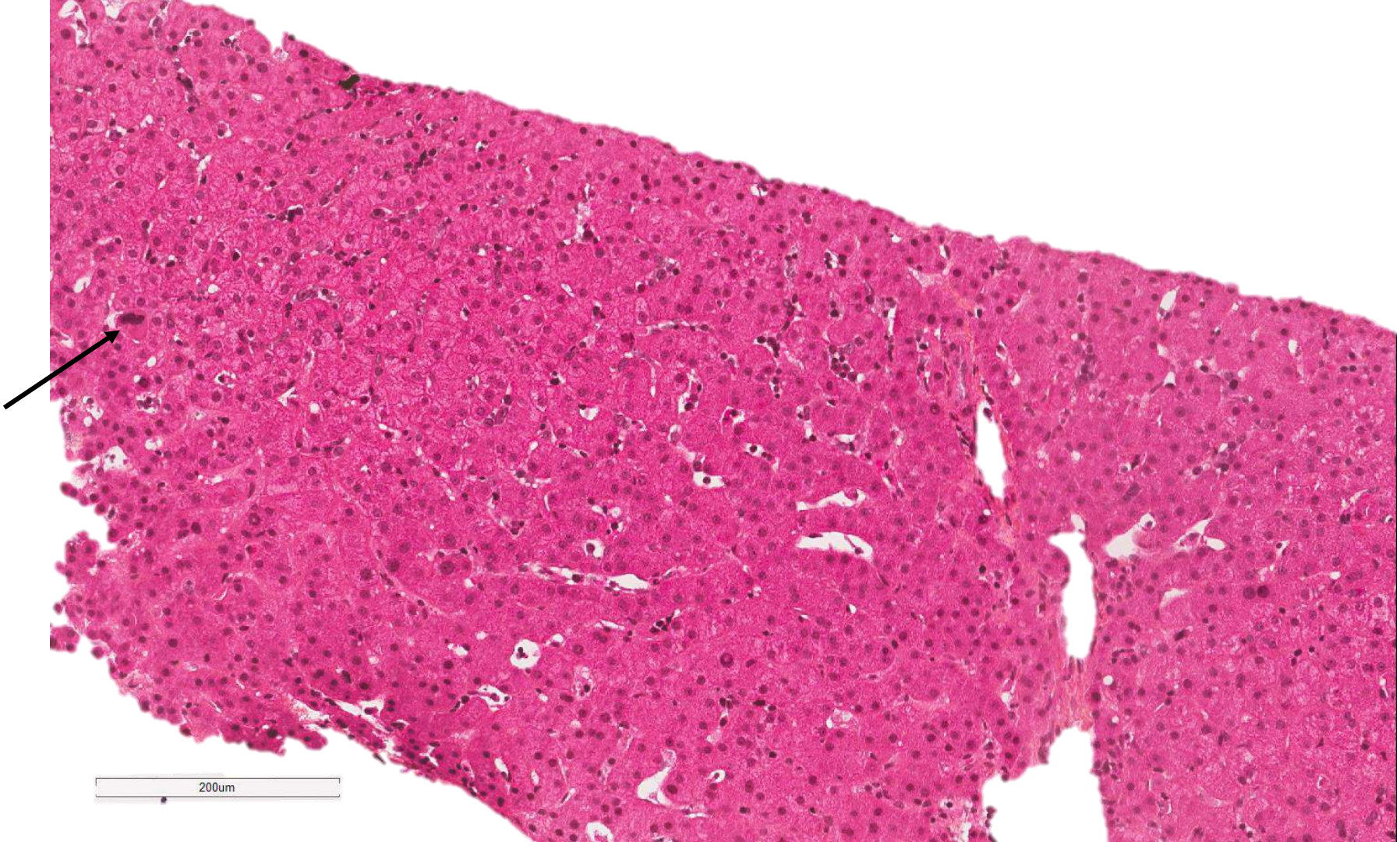
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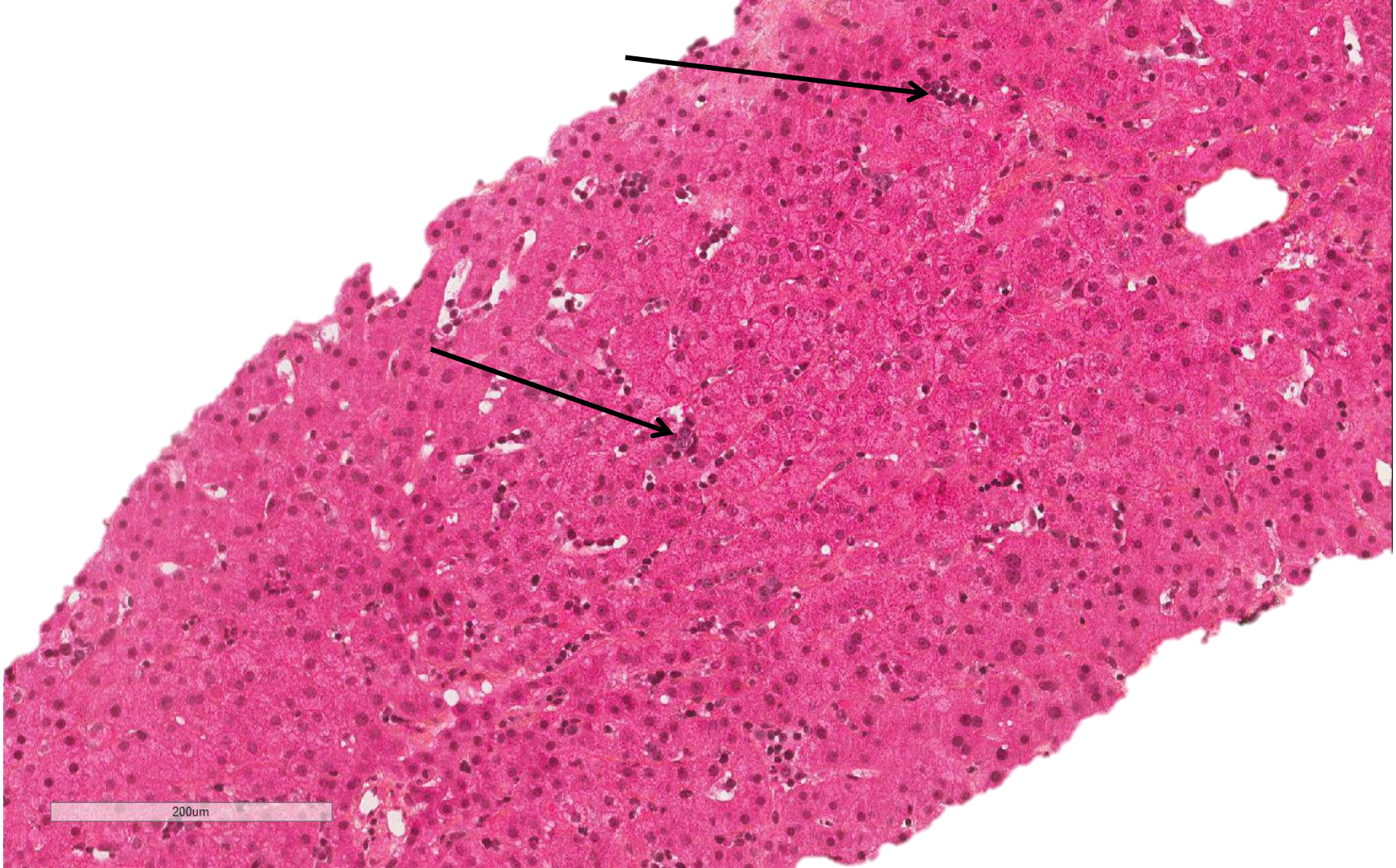
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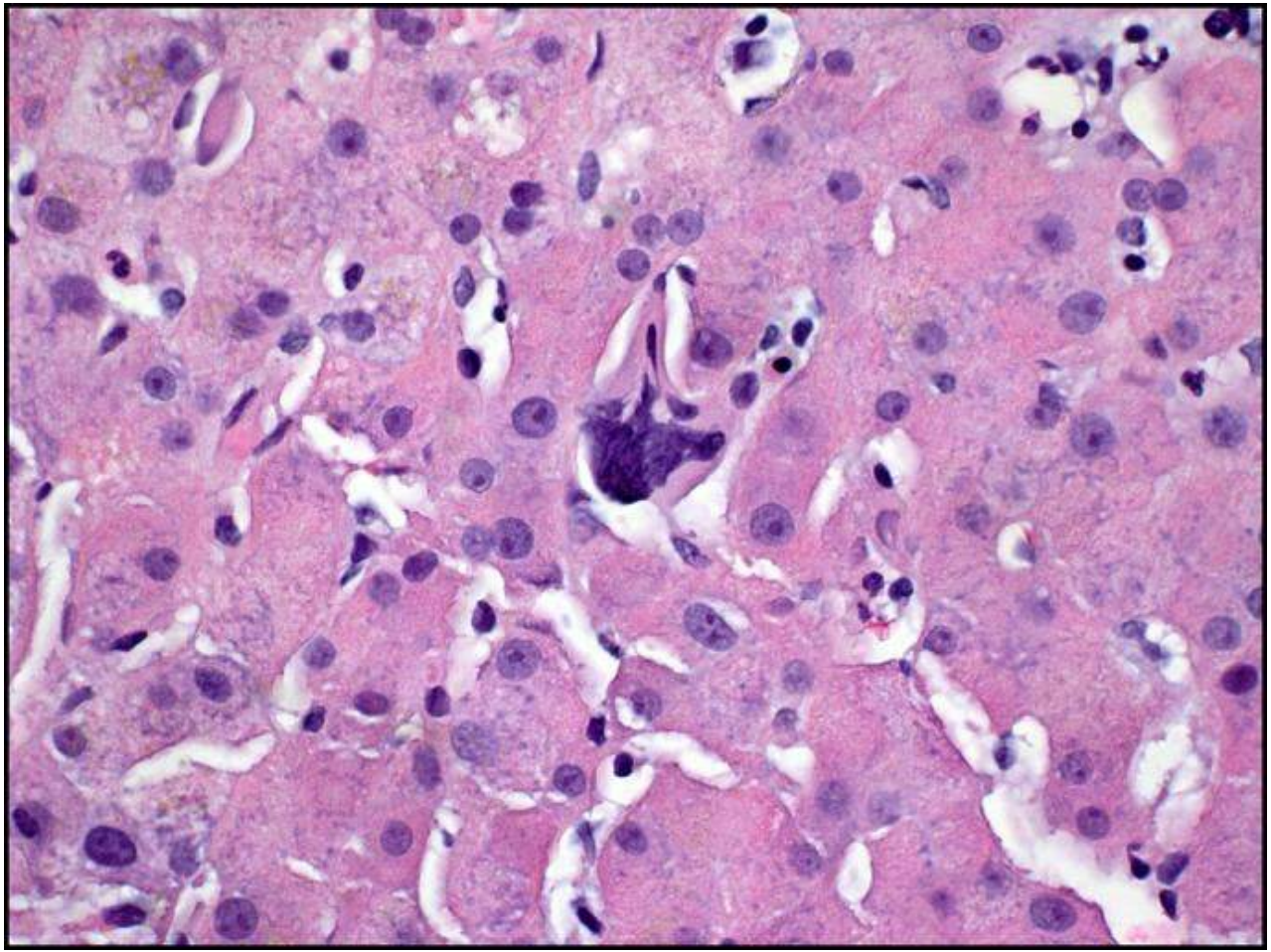
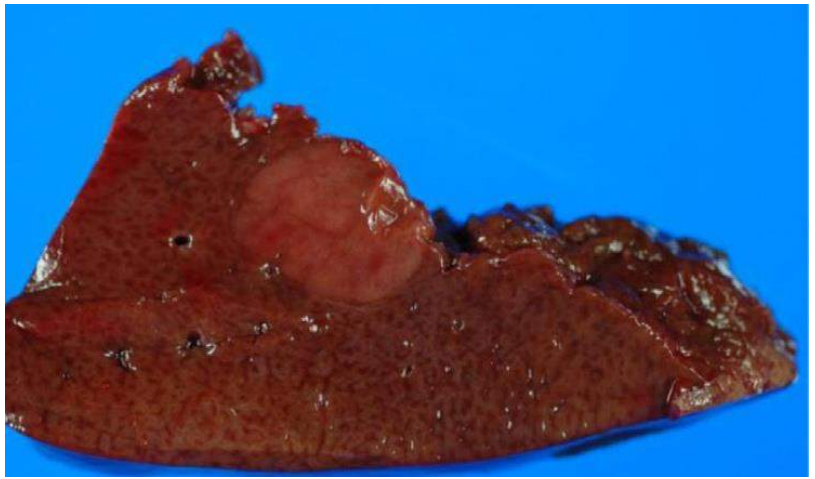


Extramedullar hematopoiesis

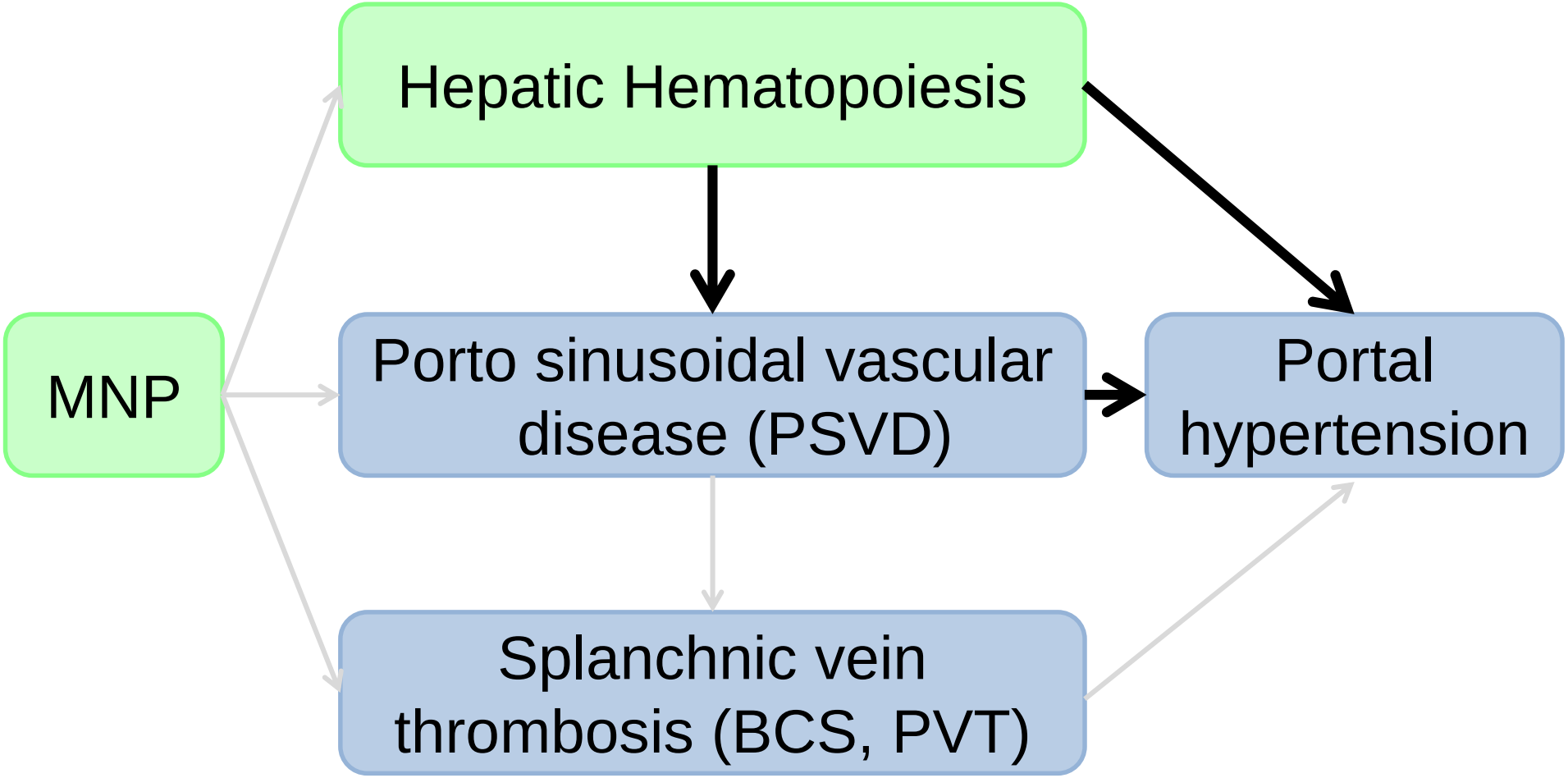
- ✓ Myelofibrosis can lead to extramedullary hematopoiesis
- ✓ Generally found in liver, spleen and lymph nodes
- ✓ Occurs as a compensatory response by hyperplastic hematopoietic tissue in bone marrow infiltration
- ✓ Diagnosis is made on biopsy
- ✓ Liver hematopoiesis: very scare literature

Liver manifestations

- ✓ Asymptomatic, mild liver tests abnormalities (GGT, ALK)
- ✓ Mass mimicking a neoplasm or fatty lesions



Zhang, Dig Liver Dis. 2020; Gupta AJR 2004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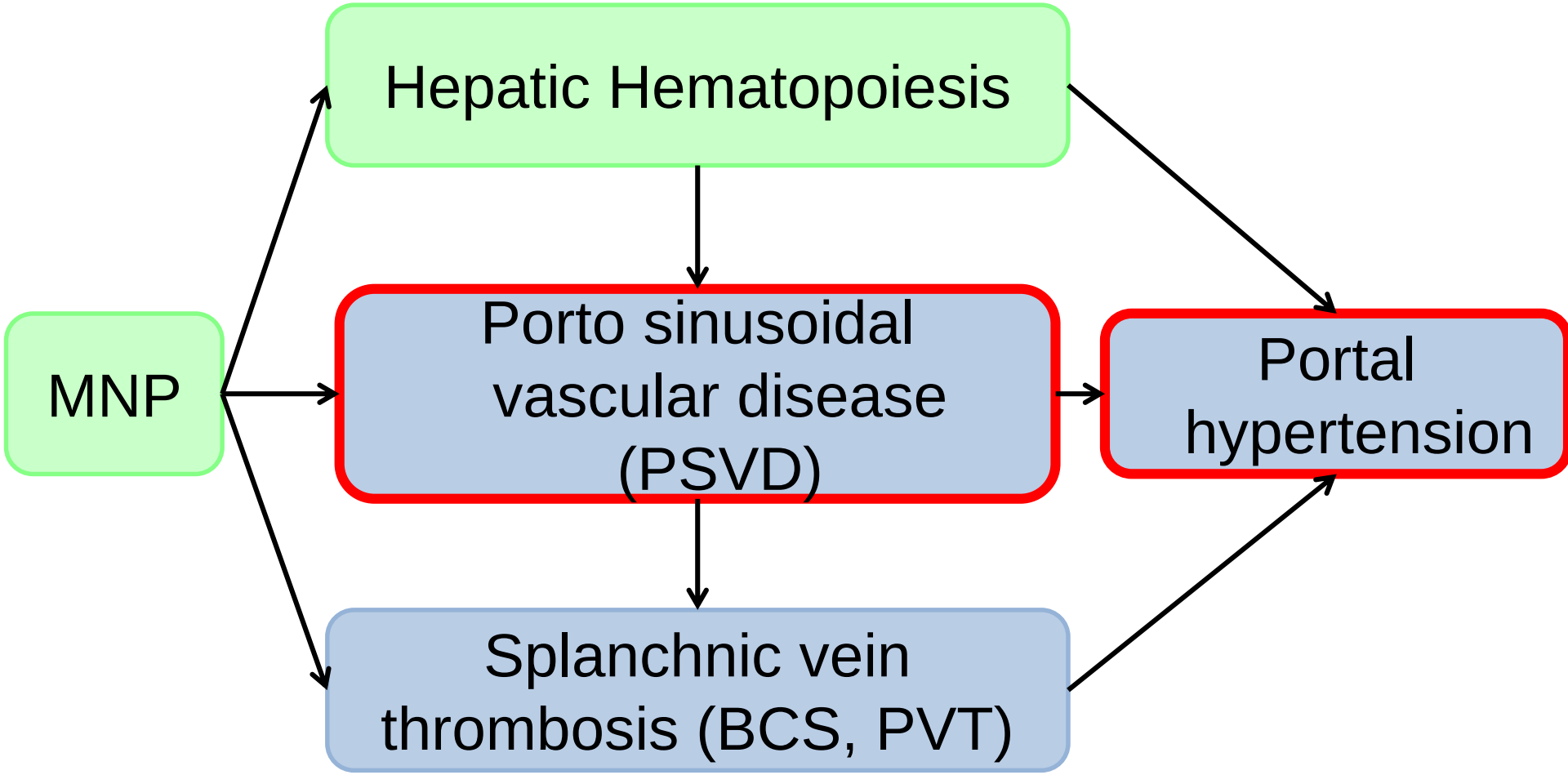
Liver manifestations

- ✓ Asymptomatic, mild liver tests abnormalities (GGT, ALK)
- ✓ Mass mimicking a neoplasm or fatty lesions
- ✓ Portal hypertension? Sinusoids obstuction? PSVD association? (Beaujon experience)

Treatment

- ✓Hepatologist point of view:
  - ✓Hematologic treatment optimisation
  - ✓Bone marrow transplantation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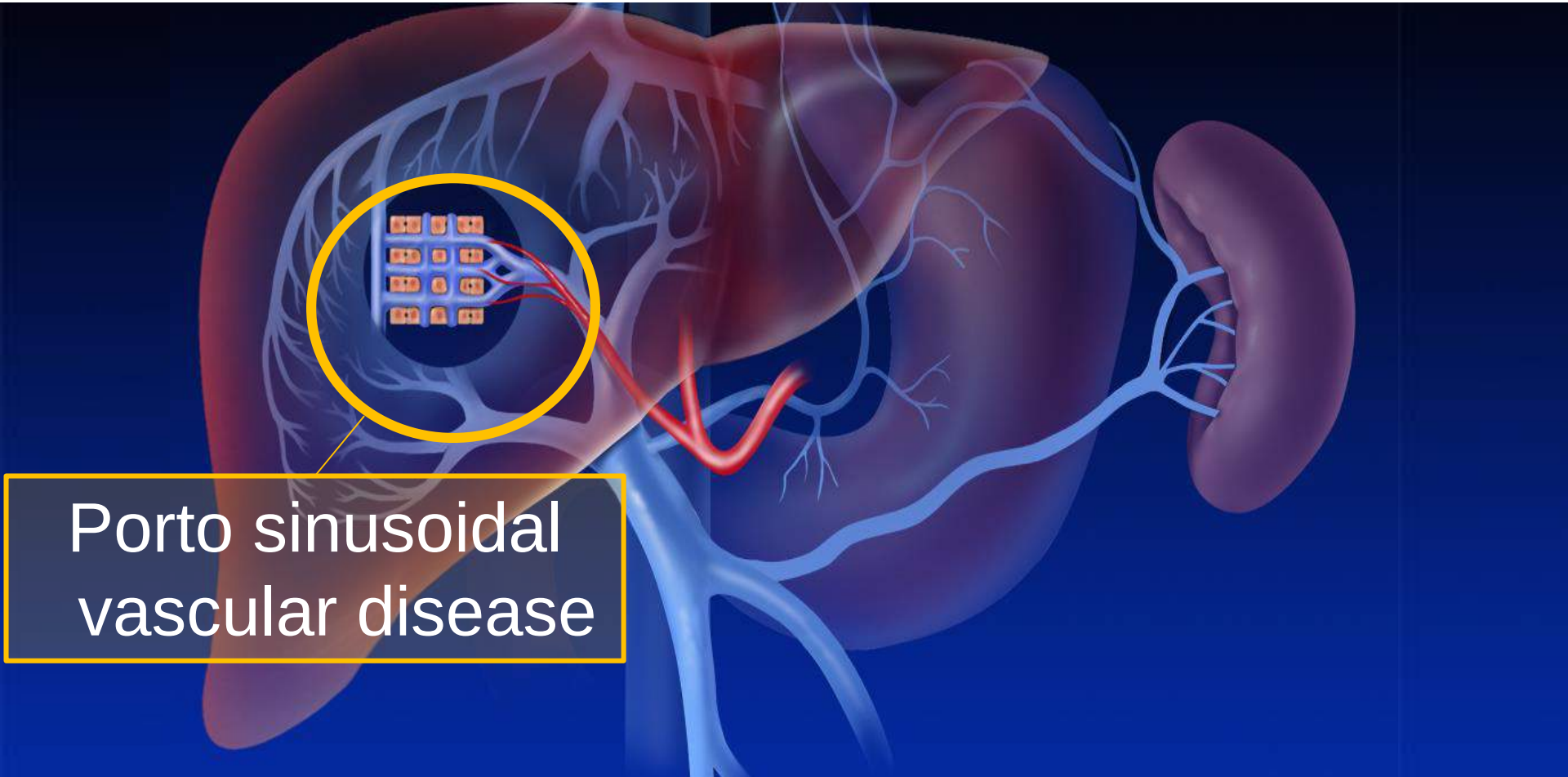
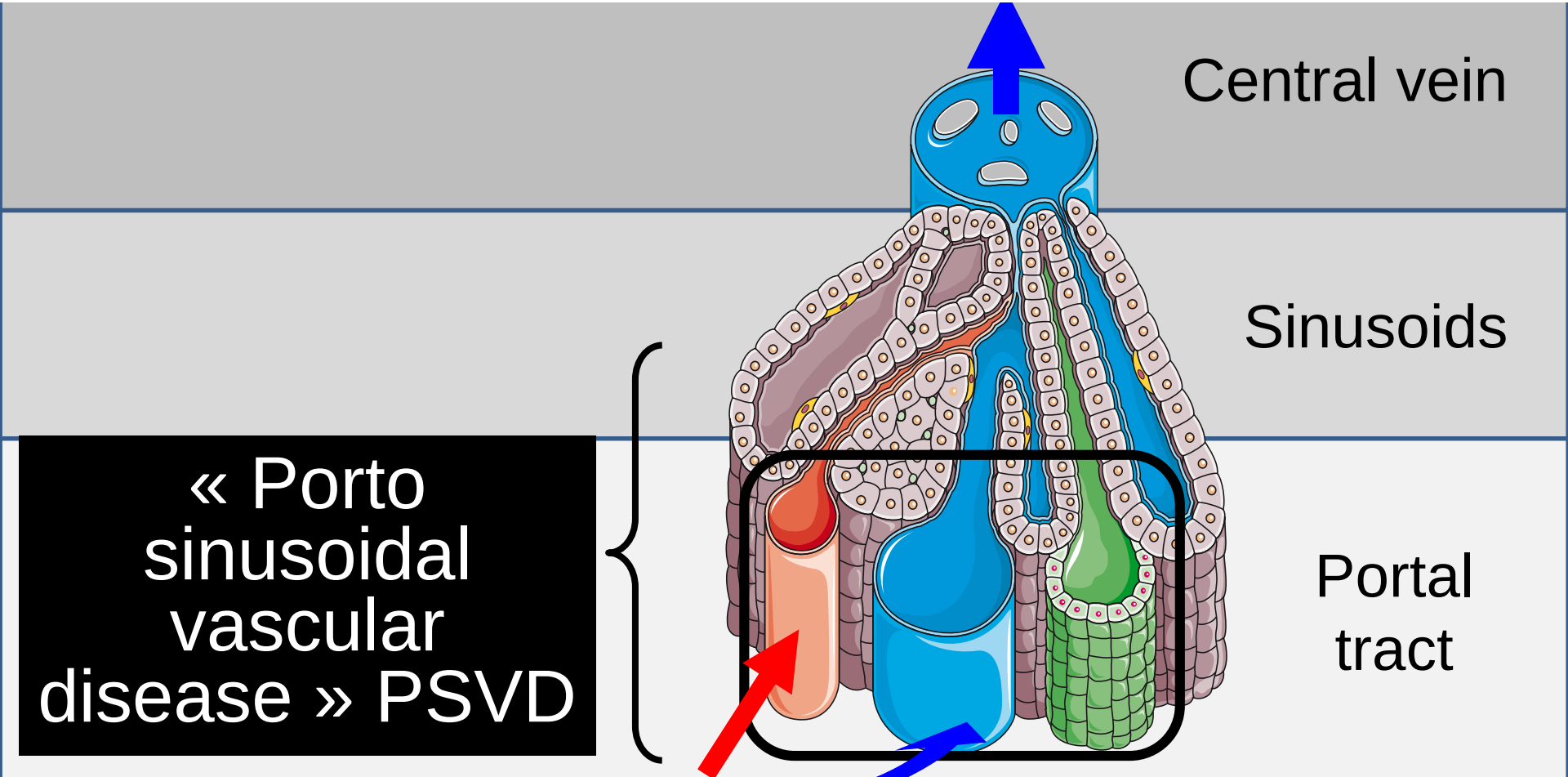
Small hepatic vein disease



Porto sinusoidal vascular disease



PSVD: Manifestations

Age (year)	40 - 50
Liver tests abnormalities	90 %
Portal hypertension/complications	**70%/50%**
Portal vein thrombosis	30 - 50%
PT < 50%	**15%**
Low liver stiffness (<14 kPa)	**90%**

Cazals-Hatem, J Hepatol 2010; Mallet, Aids 2007; Guido, Liv Int 2016 ; Barge, Liv Int 2016

PSVD : Definition

Liver biopsy
> 20 mm
without
cirrhosis

+

1 sign specific for portal hypertension *or* 1 histological specific lesion for PSVD

OR

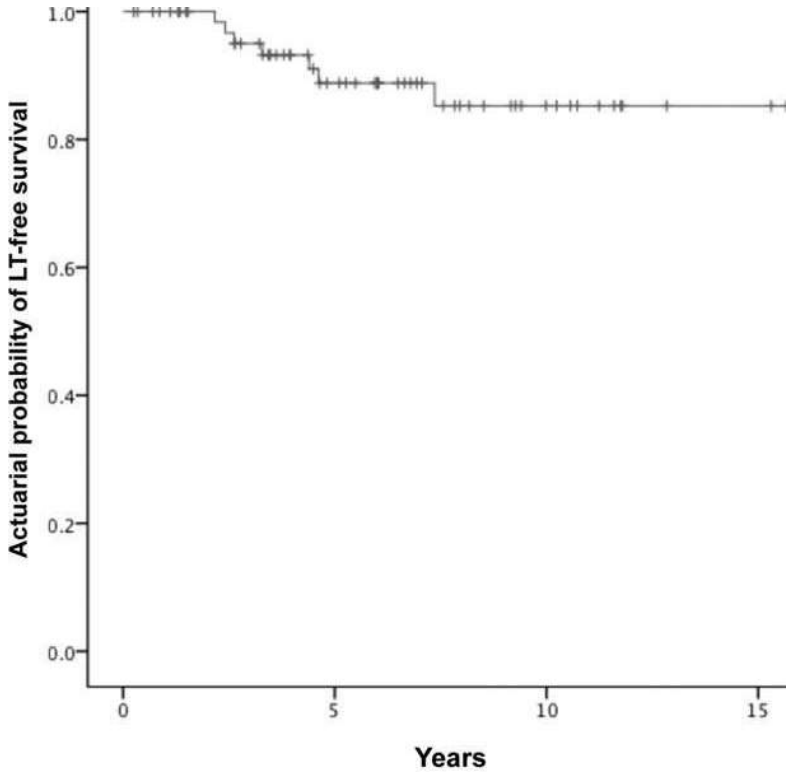
Liver biopsy
> 20 mm
without
cirrhosis

+

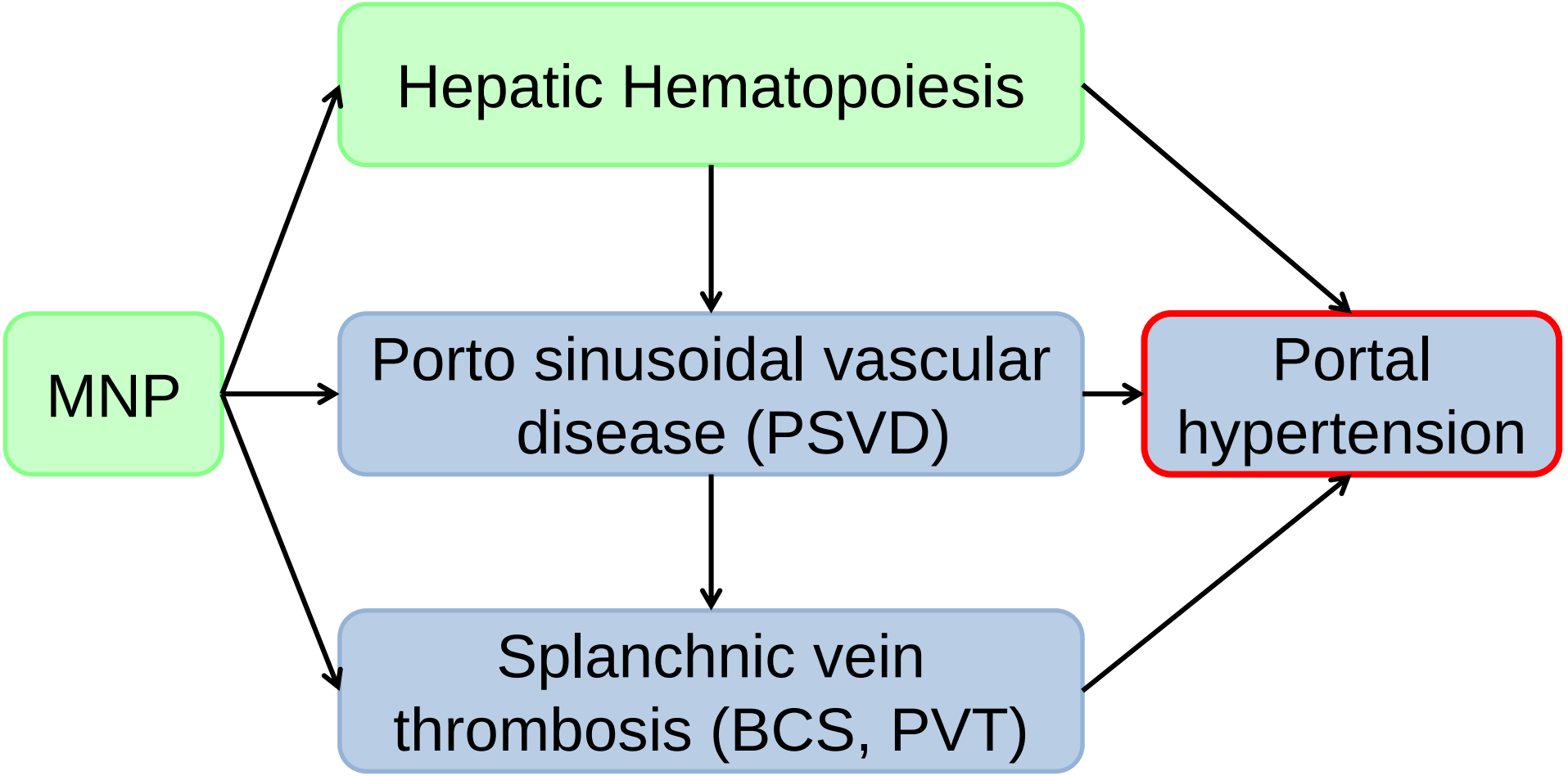
1 sign not specific for portal hypertension *and* 1 histological lesion not specific for PSVD

De Gottardi *et al,* Lancet Gastro Hepat 2019

Prognosis



Siramolpiwat Hepatology 2014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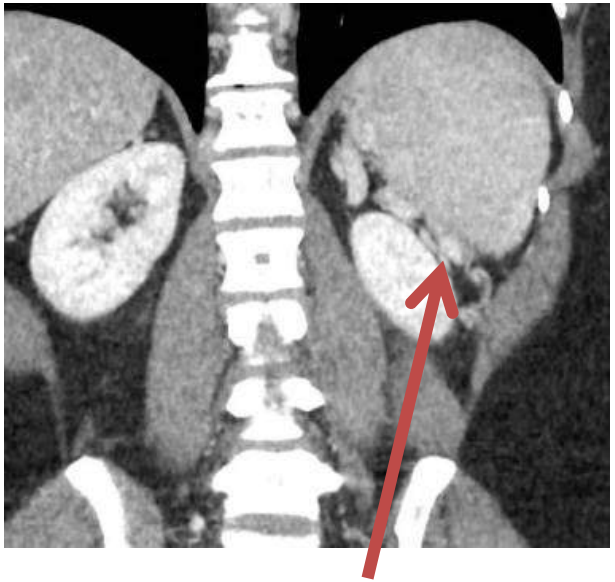
Portal hypertension

- ✓ Specific signs
- ✓ Non specific signs

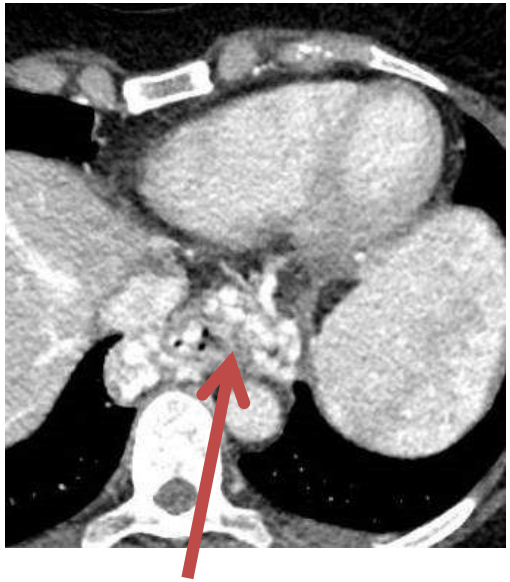
Portal hypertension

✓Specific signs: portosystemic collaterals

Gastric



Splenorenal



Paraoesophageal

Portal hypertension

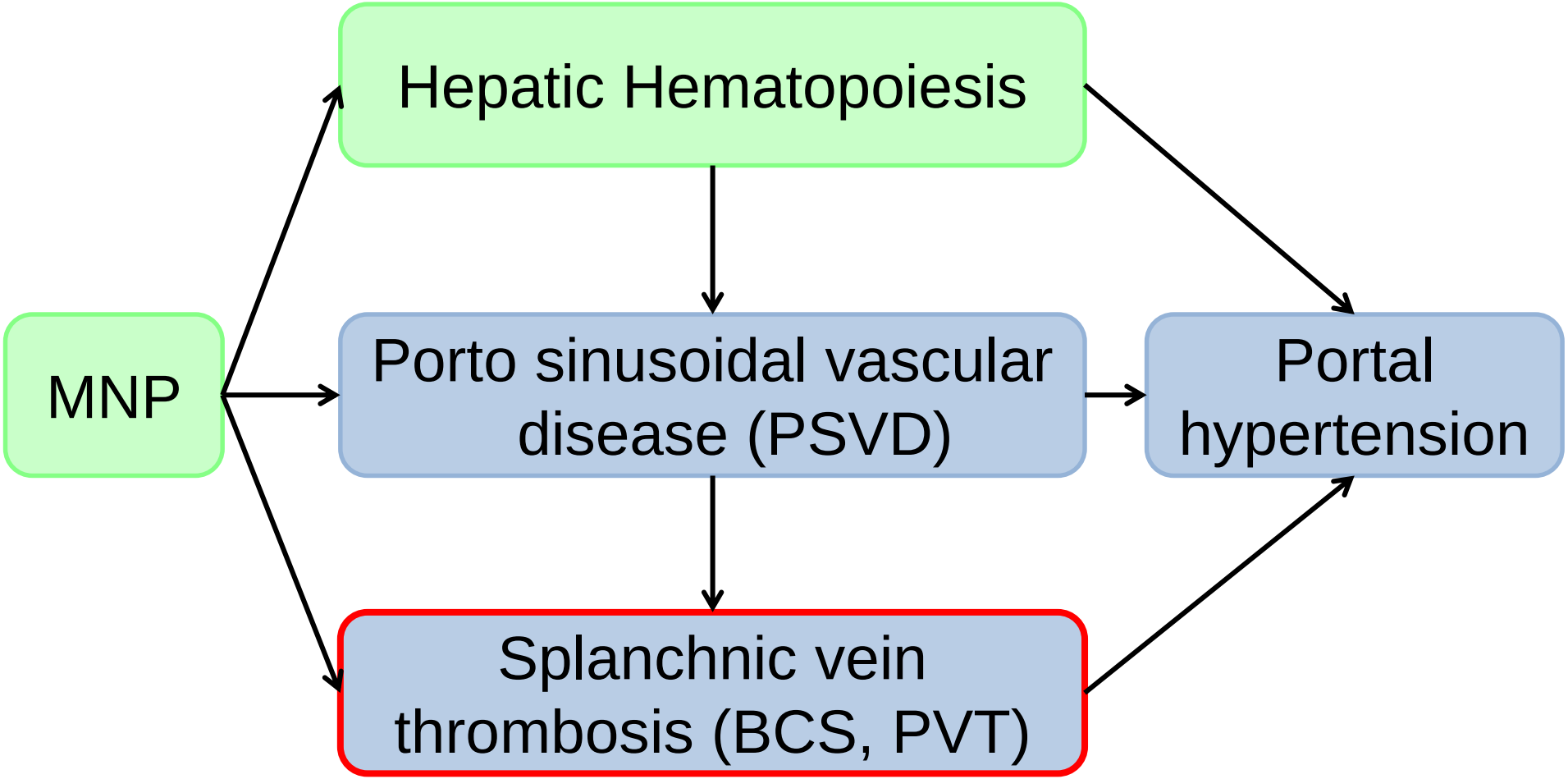
- ✓Specific signs: eosophageal or gastric varices

Small Large

Portal hypertension

- ✓ Specific signs

- ✓ Non specific signs: ascites , thrombocytopenia (<150 G/L), splenomegaly (> 13cm)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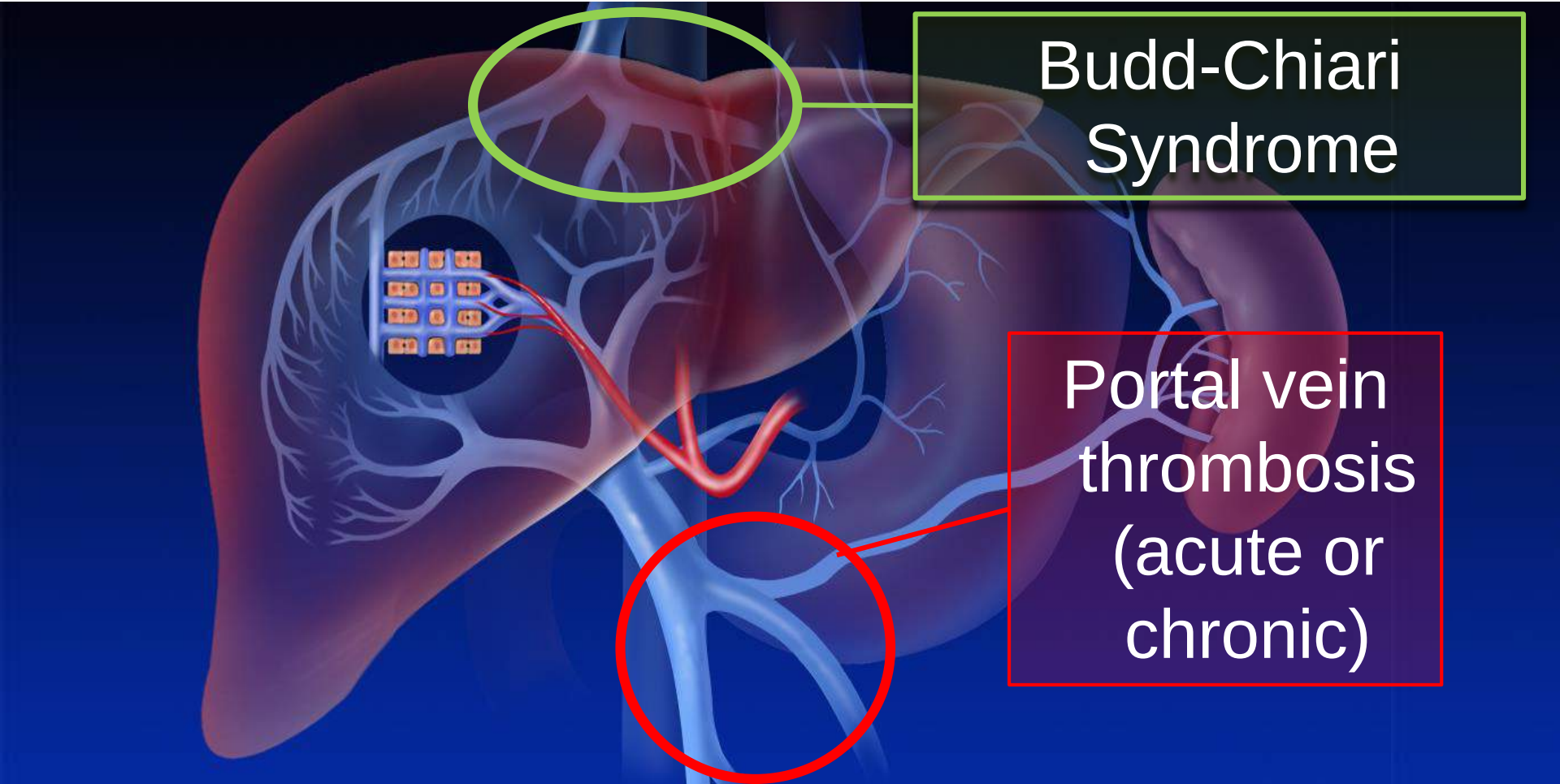
Splanchnic vein thrombosis (SVT)



Incidence of splanchnic vein thrombosis

	General population	MPN
Budd-Chiari (/10^5)	0.1	1200
Portal vein thrombosis (/10^5)	4	6100

V Hernandez-Gea, J Hepatol 2019

MNP and Vascular liver disease are associated

	BCS	PVT	PSVD
Myeloproliferative Neoplasm	49%	30 %	8%
APLS	25%	10%	1%
FV or FII Leiden	15%	16%	7%
Other systemic	25%	5%	38%

Murad, Ann Intern Med 2009; Plessier, Hepatology 2010; Siramolpiwat Hepatology 2014

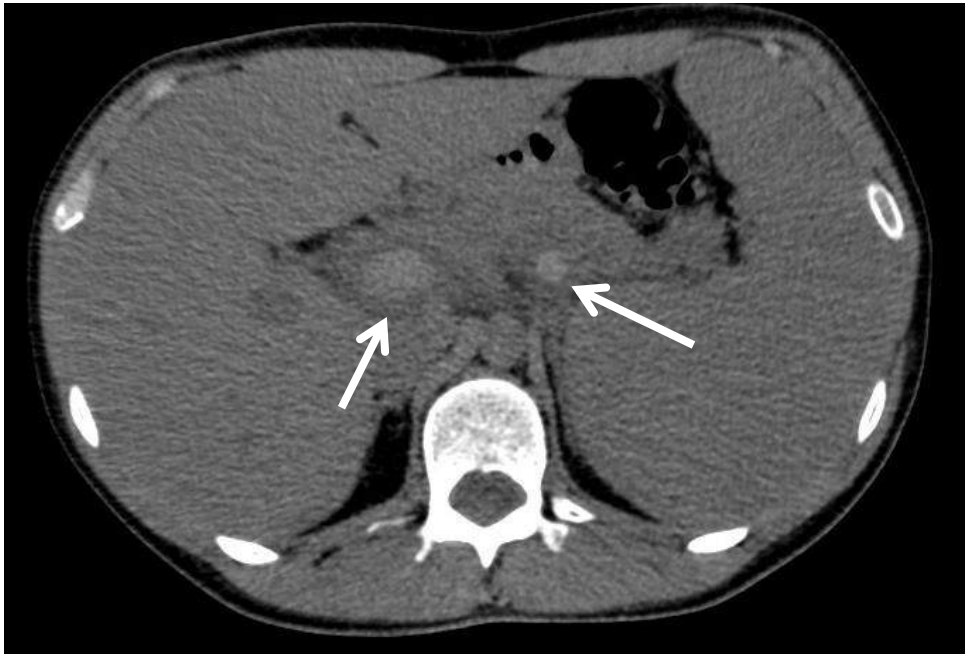
Risk Factors for Splanchnic thrombosis

	BCS	PVT	PSVD
At least one	84%	67%	20%
Multiple	46%	18%	-
Local factor	5%	21%	-

Murad, Ann Intern Med 2009; Plessier, Hepatology 2010; Siramolpiwat Hepatology 2014

Acute PVT: Diagnosis

No enhancement



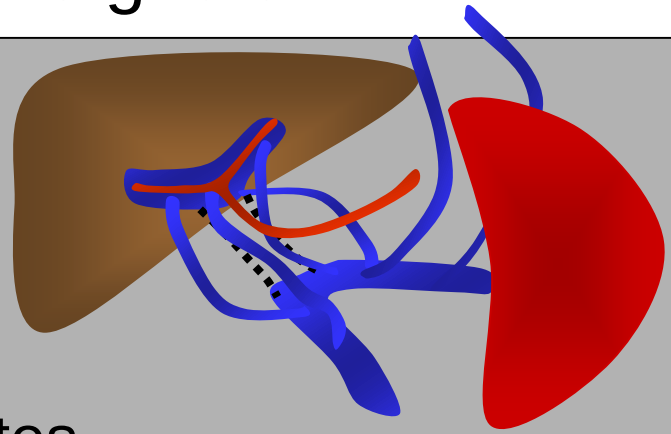
Portal phase

No collaterals

Chronic PVT: Diagnosis

Collaterals

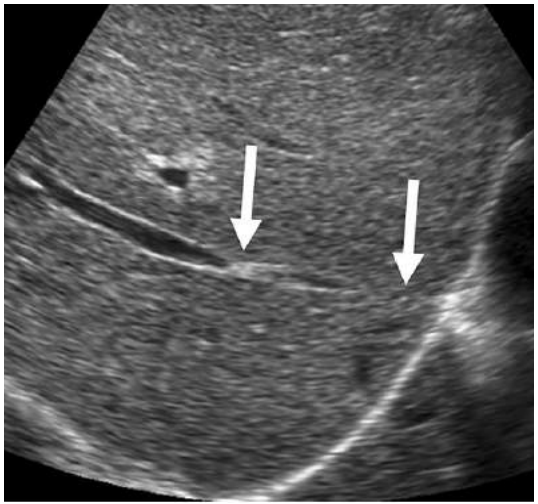
Signs of PHT

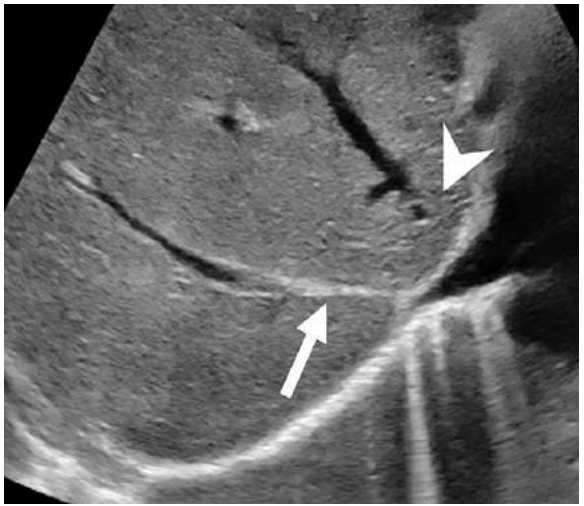


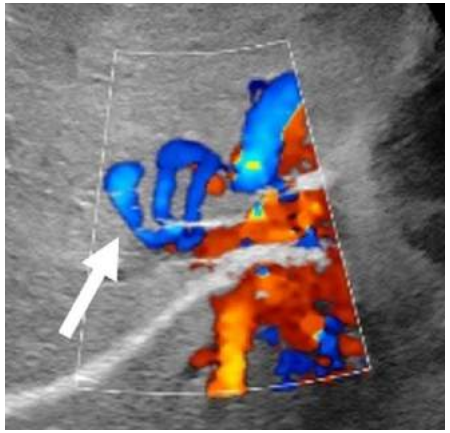
Ascites
Esophageal / Gastric varices
Splenomegaly
Hepatic encephalopathy

Plessier, J Hepatol 2012. Plessier, Hepatology 2009

Budd Chiari Syndrome: Diagnosis

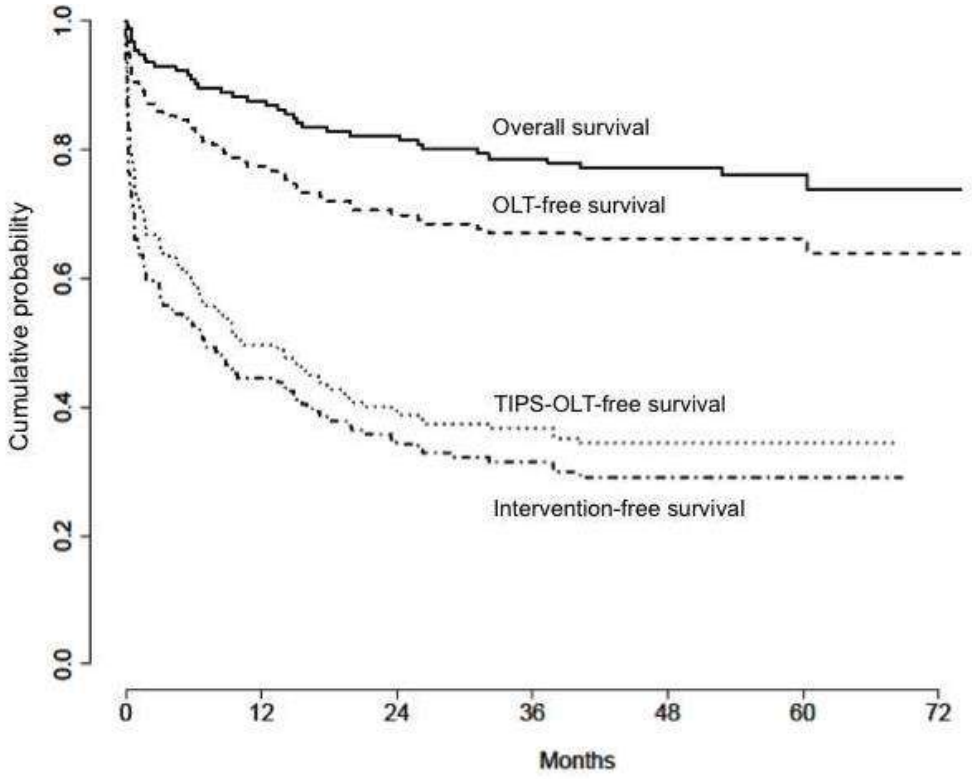






- ✓Absent flow
- ✓Occlusion : cord like segment (chronic) or thrombosis (acute)
- ✓Intrahepatic collaterals

Treatment / Prognosis



Anticoagulation therapy

Angioplasty TIPS

Liver transplantation (OLT)

Seijo, Hepatology 2013. Baveno 2015

Prognosis in the context of MNP

- ✓SVT and PV or ET:
  - ✓3705 PV/ET, 118 with SVT
  - ✓ increased risk of
    - ✓death (HR 2.47, 95% CI 1.5-4.01, $p < 0.001$)
    - ✓venous thrombosis (IRR 3.4, 95%CI 2.1-5.5, $p < 0.001$)
    - ✓major bleeding (IRR 3.6, 95%CI 2.3-5.5, $p < 0.001$)
    - ✓second cancer (IRR 2.37, 95%CI 1.4-4.1, $p = 0.002$)
  - ✓SVT was not associated with lower risk of MF

Alvarez-Larrán, Ann Hematol 2020

Prognosis in the context of MNP

- ✓PV and ET patients presenting with SVT have shorter survival (5-year reduction) than patients without SVT of the same age and sex.

- ✓SVT and myelofibrosis:
  - ✓same conclusion?
  - ✓no data

Alvarez-Larrán, Ann Hematol 2020

Myelofibrosis, SVT and Ruxolitinib

- ✓ Phase 2 study : safety and efficacy of Ruxolitinib in patients with MNP and splanchnic thrombosis
- ✓ 12 MF, 5 PV, 4 ET
- ✓ 18 PVT, 2 BCS, 1 PVT and BCS
- ✓ Results :
  - ✓ Toxicities similar to those in patients without SVT
  - ✓ At W24 : ≥35% reduction in spleen volume = 29%
  - ✓ At W72 : maintained their response = 62%

Pieri Am J Hematol 2017

Conclusion

- ✓ Myeloproliferative neoplasm are prothrombotic conditions strongly associated with splanchnic vein thrombosis and portosinusoidal disease.
- ✓ The occurrence of liver hematopoiesis should make consider an optimization of the hematologic treatment.
- ✓ Because of portal hypertension and their complications, hepatic hematopoiesis and vascular liver disease need to be diagnosed and treated before a bone marrow transplantation.
- ✓ Ruxolitinib appears safe and effective in patients with MF and SVT

Reference centre for vascular liver diseases

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