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# Current and Future Management of PSC

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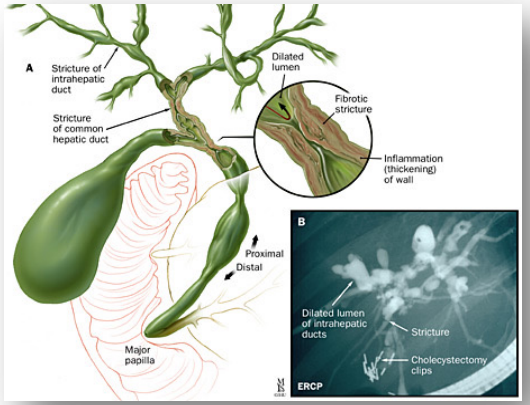
# Disclosures

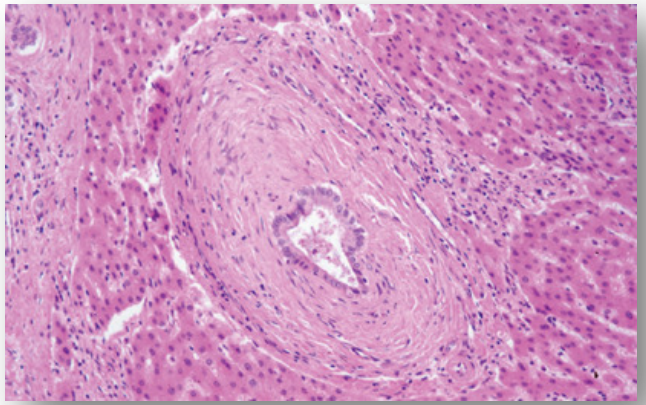
- Advisor for Cymabay Therapeutics, GSK Pharmaceuticals, Invea Therapeutics, Ipsen Bioscience
- Grants from Boston Scientific, Calliditas Therapeutics, ChemoMab, COUR Pharmaceuticals, Cymabay Therapeutics, Gilead Sciences, GSK Pharmaceuticals, Hanmi Pharmaceuticals, Intercept Pharmaceuticals, Ipsen Bioscience, Mirum Pharmaceuticals, Novo Nordisk, Pliant Therapeutics, Viking Therapeutics

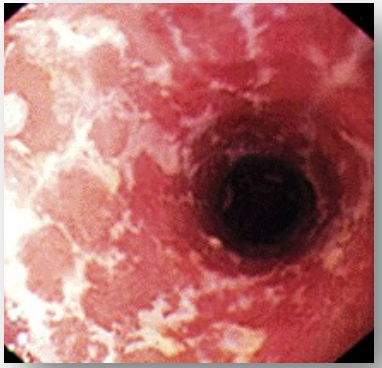
# Outline

- Introduction and Definitions
- Diagnosis
- Natural History and Prognosis
- Management
  - Medical Management
  - Cancer Surveillance
  - Liver Transplantation

# Primary Sclerosing Cholangitis (PSC)





- Inflammatory/fibrotic disease of the large bile ducts
- Associated with colitis
- Male predominance
- Affects wide age range

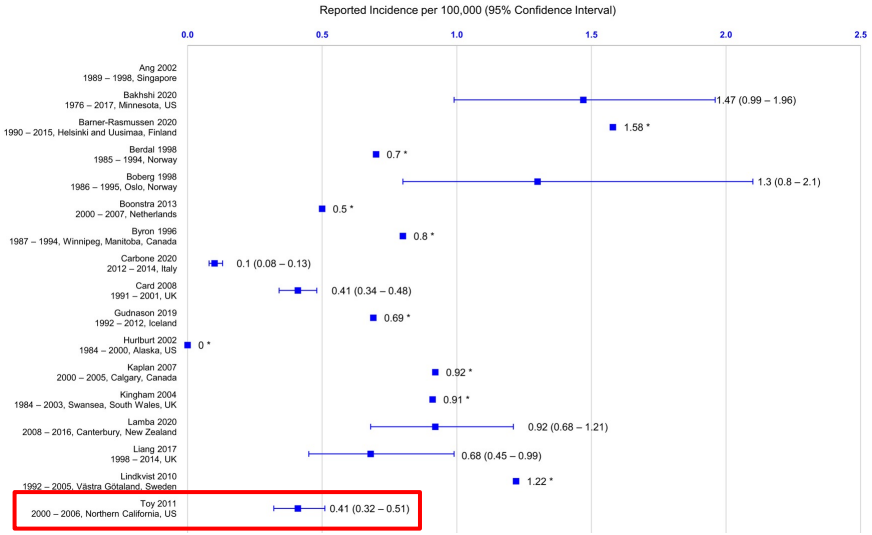
# Definitions of Strictures

- Dominant (*Structural*)
  Stricture on ERCP with a diameter of ≤1.5 mm in the common bile duct or of ≤ 1 mm in the hepatic duct
- High-grade (*Structural*)
  Stricture on MRI with cholangiopancreatography with >75% reduction in the common bile duct or hepatic ducts
- Relevant (*Functional*)
  Any biliary stricture of the common bile duct or hepatic ducts associated with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis
  EASL requires it also to be of "high-grade"

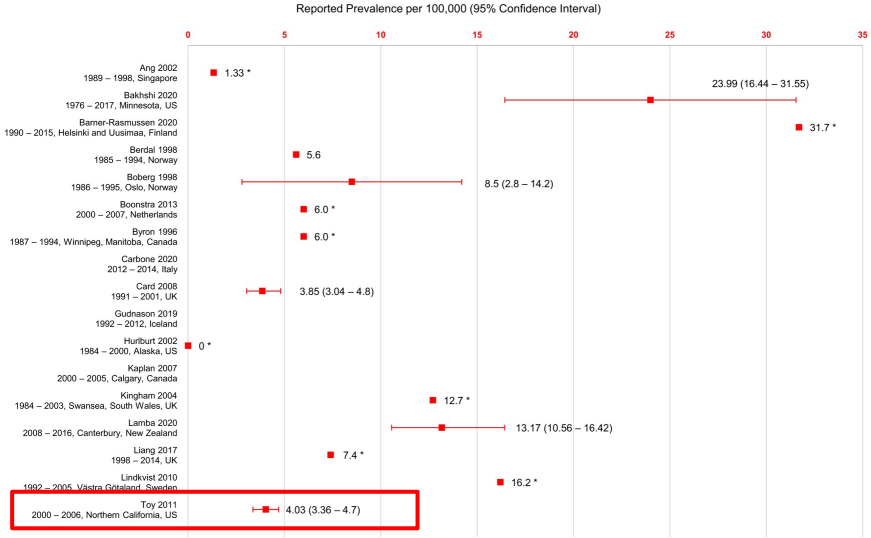
*Hepatology*. 2023;77(2):659-702.

# PSC Epidemiology

Incidence 1–1.5 cases per 100,000 person-years




Prevalence 6–16 cases per 100,000




*Clin Gastroenterol Hepatol*. 2022;20(8):1687-1700.

# PSC Variants

- Large duct PSC
  - Also known as PSC
- Small duct PSC
  - Characterized by typical cholestatic and histological features of PSC
  - Normal bile ducts on cholangiography
  - In absence of IBD, consider other rare causes such as *ABCB4* (PFIC) mutations
- PSC/AIH Overlap
  - Features of PSC
  - Clinical, biochemical, and histological features of AIH

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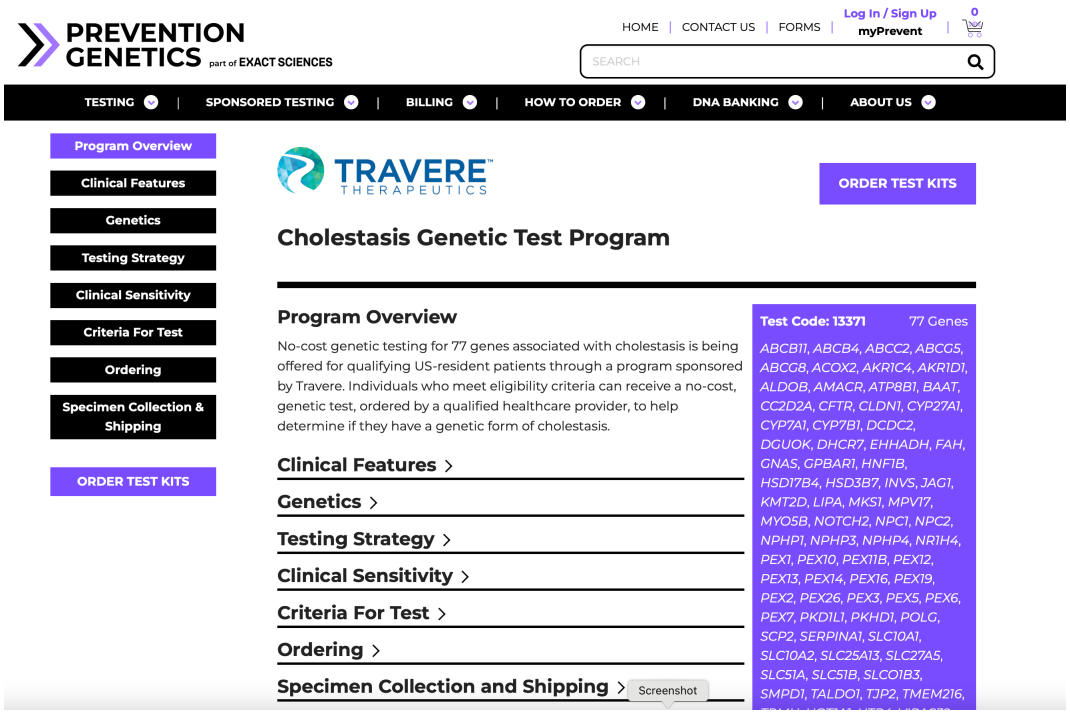

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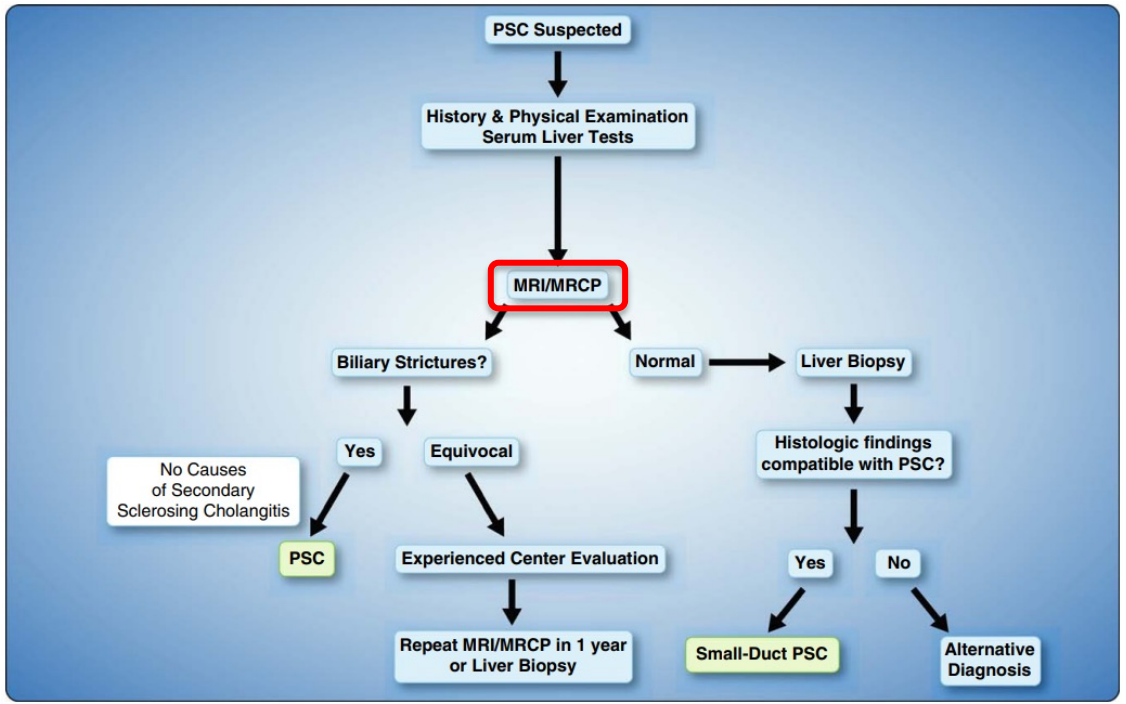
*Hepatology*. 2023;77(2):659-702.

# Presentation

- ~50% are asymptomatic at presentation[1]
- Common symptoms include fatigue, abdominal pain, fever, and pruritus
- 75% have elevated alkaline phosphatase (25% do not)[2]
  - Elevated ALT common
  - >5 x ULN suggest AIH overlap
- Autoantibodies including ANA, ASMA, and p-ANCA are common
  - Non-specific
  - No prognostic value

[1]*Gut*. 1996;38:610–5; [2]*Gastroenterology*. 2016;151(4):660-9.

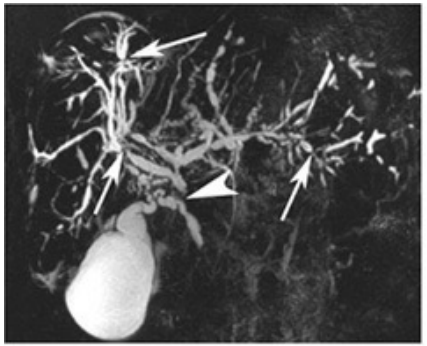
# Diagnosis – ERCP Never, Biopsy Rarely




*Hepatology*. 2023;77(2):659-702.

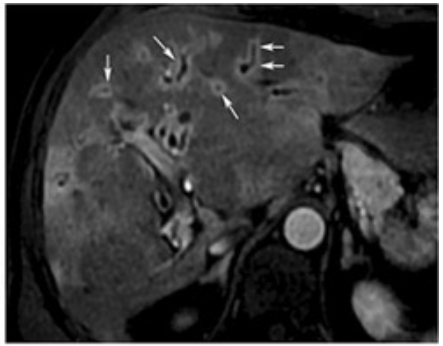
# MRI Features of PSC

Strictures of intrahepatic biliary ducts

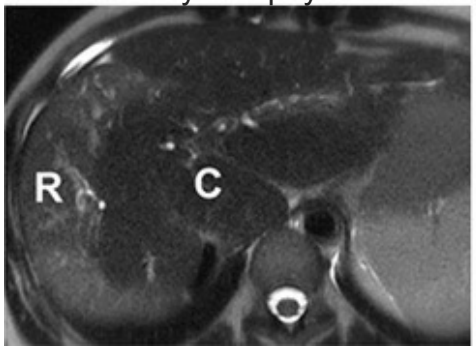


"High grade" stricture of common hepatic duct

Biliary wall thickening
Mural contrast enhancement

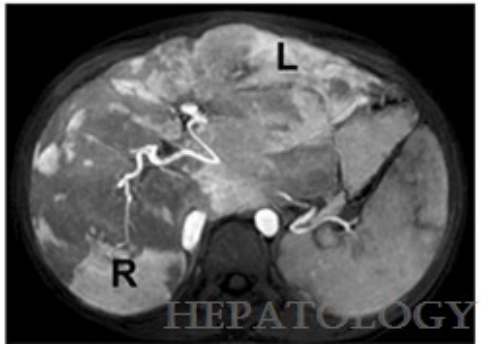


Dysmorphy




- Enlargement of the caudate lobe
- Atrophy with high signal intensity of the right liver lobe

Contrast enhancement heterogeneity

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# Secondary Sclerosing Cholangitis

**Infectious**

- HIV-related cholangiopathy
- Recurrent pyogenic cholangitis
- Parasitic cholangiopathy
- ***COVID-19***

**Ischemic**

- Critically ill patients
- Hereditary hemorrhagic telangiectasis
- Intra-arterial chemotherapy
- Hepatic artery thrombosis

**Malignant**

- Cholangiocarcinoma
- Diffuse intrahepatic metastasis
- Langerhans cell histiocytosis
- Lymphoma

**Autoimmune**

- Eosinophilic cholangitis
- Hepatic inflammatory pseudotumor
- ***IgG4-associated cholangitis***
- Mast cell cholangiopathy
- Sarcoidosis

**Anatomic**

- Choledocholithiasis
- Intrahepatic lithiasis
- Cystic fibrosis liver disease

**Surgical biliary trauma**

- Anastomotic stricture
- Portal hypertensive biliopathy
- Recurrent pancreatitis
- Sickle cell cholangiopathy
- Choledochal cyst

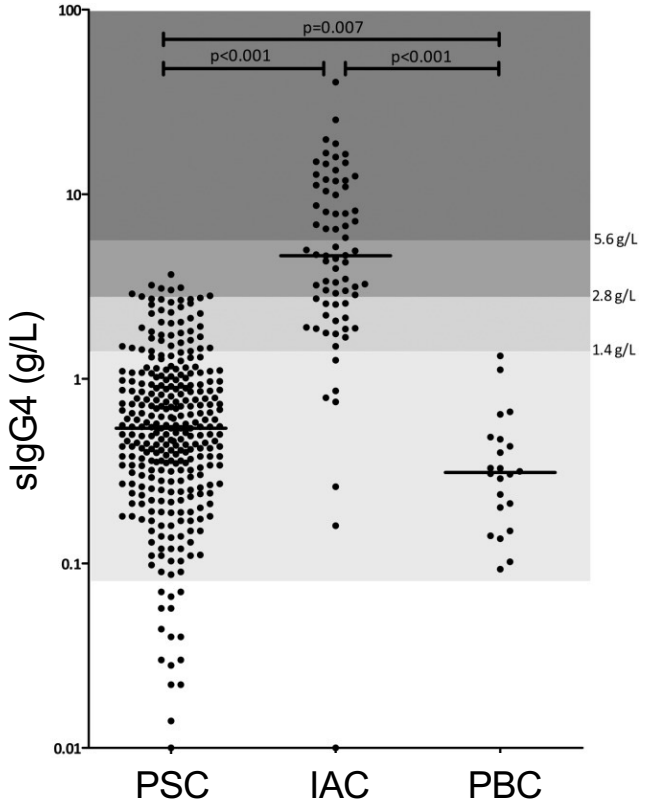
**Drug-induced**

- ***Immunotherapy with checkpoint inhibitors***

*Hepatology*. 2023;77(2):659-702.

# PSC versus IgG4-Associated Cholangitis

- Cholangiograms can look similar
- 5-15% of PSC patients have elevated IgG4
- IgG4-AC is clinically distinct
  - Older men
  - <10% have IBD
  - Frequently have other organ involvement
  - Serum IgG4 > 2.8 g/L
  - Stromiform fibrosis on biopsy
  - Steroid Responsive




Boonstra K et al. *Hepatology.* 2014;59:1954-63.

# PSC Histology

Typical histologic features of PSC

- Periductal fibrosis and fibro-obliterative duct lesions

Compatible features

- Bile duct loss
- Ductular reaction/proliferation
- Biliary pattern of interface activity
- Chronic cholestatic changes in periportal hepatocytes

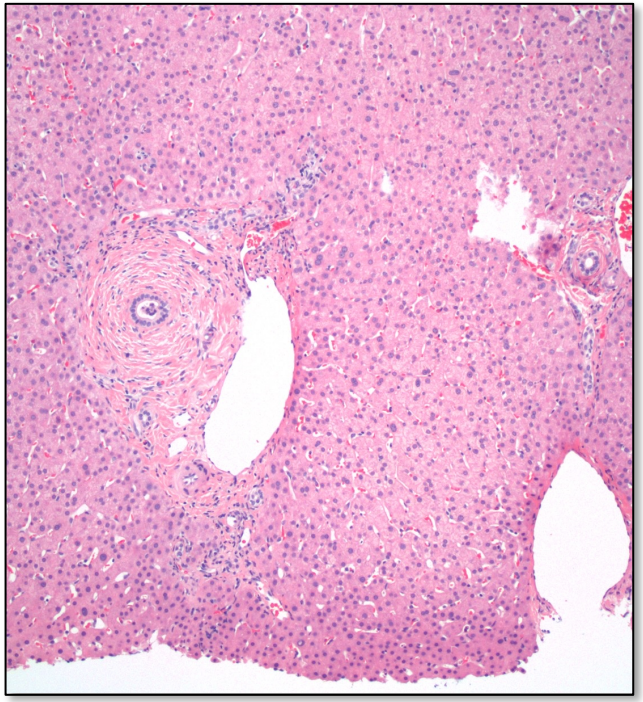


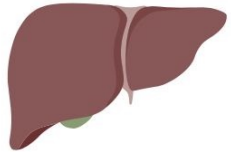
Image courtesy of Karen Matsukuma, MD.

# PSC-IBD

- 70-80% of patients with PSC have IBD
  - 2/3 ulcerative colitis
  - 1/3 Crohn’s disease or indeterminate colitis.
- Frequently localized to the right colon and asymptomatic
- Histological evidence of IBD without endoscopic changes of IBD occurs

*Hepatology*. 2023;77(2):659-702.

# PSC Natural History

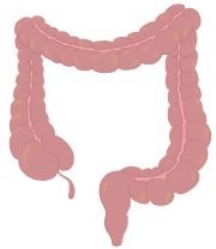


Ascites
Variceal Bleeding
Encephalopathy

→ Liver Tx
→ Liver Related Death

→ Cholangiocarcinoma → Liver Tx
→ PSC-Cancer Related Death

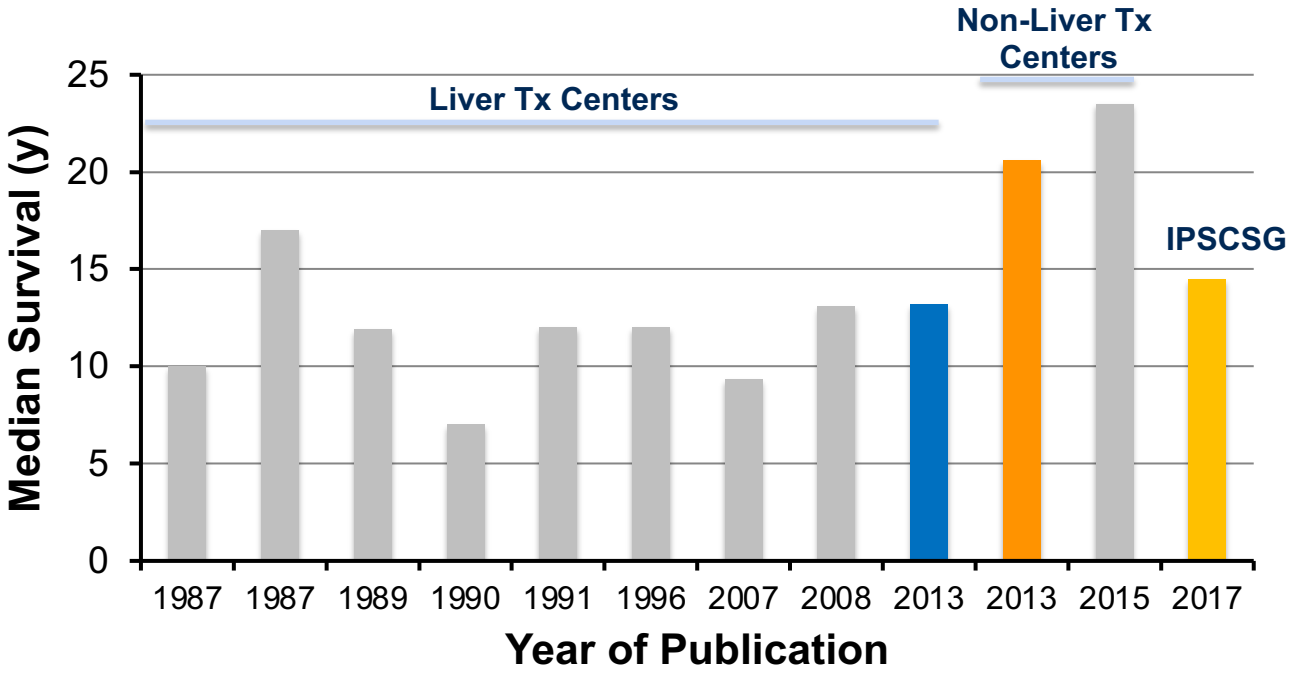
→ Cholangitis
Jaundice → Liver Tx
→ Liver Related Death



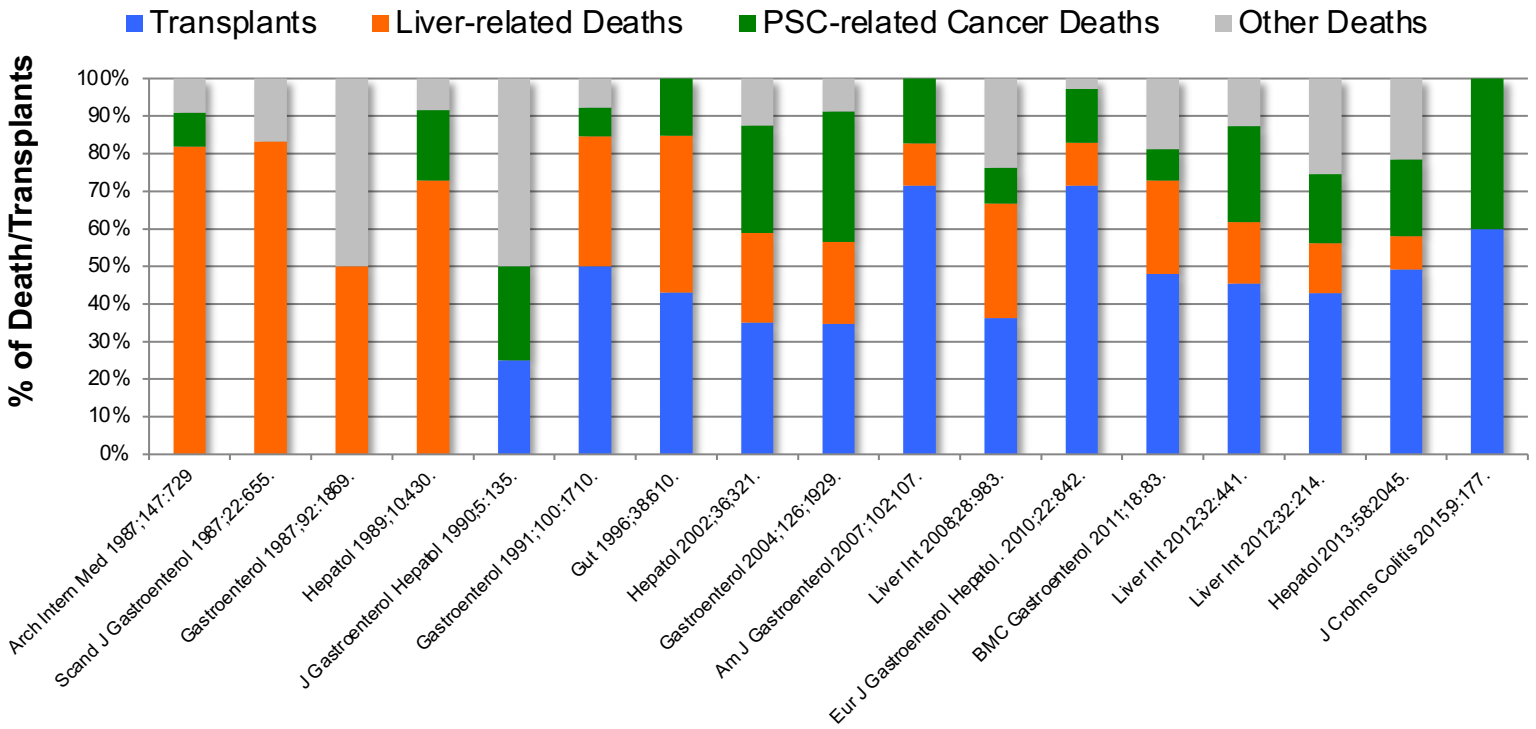
→ Colon Cancer → PSC-Cancer Related Death
→ Colectomy

→ Refractory Colitis → Colectomy

# Transplant-Free Survival in PSC



# Distribution of Death/Transplant in PSC Over Time



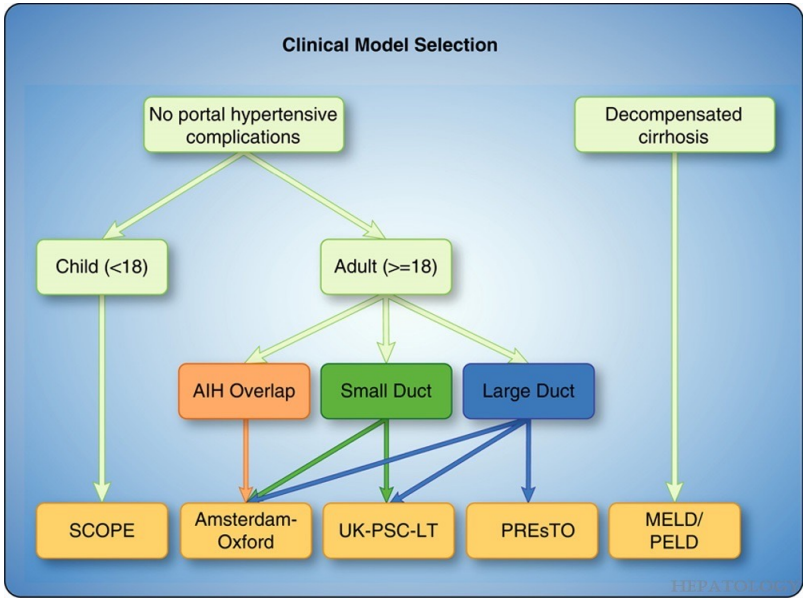
# PSC Prognostic Models

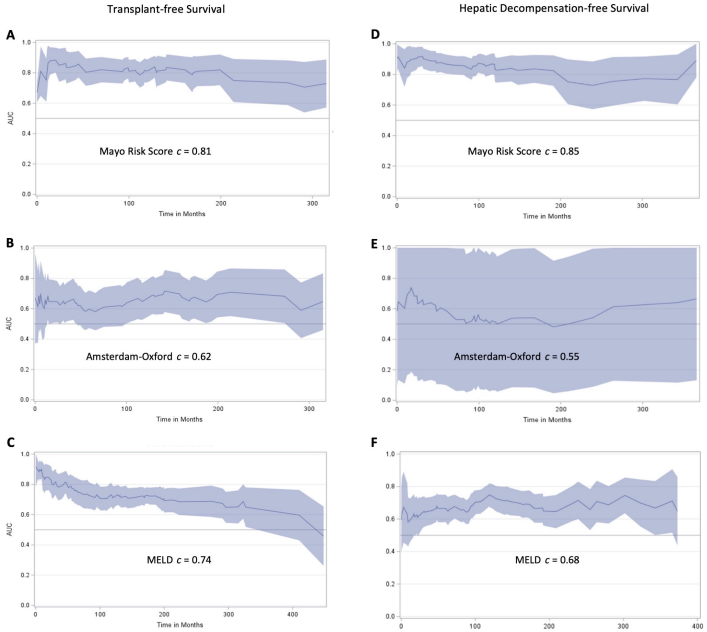
| | Revised Mayo (n = 405; 124) | Amsterdam-Oxford (n = 692; 264) | UK-PSC (n = 1,001; 451) | PREsTO (n = 509; 278) | SCOPE (n = 1,012; 240) |
|---|---|---|---|---|---|
| **Endpoint** | **Death or Transplant** | **PSC-related Death or Transplant** | **Death or Transplant** | **Variceal hemorrhage, ascites, or hepatic encephalopathy** | **Death or Listing for Transplant** |
| Age/Age at diagnosis | X | X | X | X | |
| Disease Duration | | | | X | |
| Alkaline Phosphatase/GGT | | X | X | X | X |
| AST | X | X | | X | |
| Total Bilirubin | X | X | X | X | X |
| Albumin | X | X | | X | X |
| Platelets | | | X | X | X |
| Hemoglobin | | | | X | |
| Sodium | | | | X | |
| PSC Subtype | | X[1] | X[2] | | X[1] |
| Variceal Bleeding | X | | X | | |

[1]Small duct v large duct; [2]Extrahepatic involvement.

De Vries EM et al. *Gut*. 2018;67:1864-1869; Goode EC et al. *Hepatology*. 2019;69:2120-2135; Eaton JE et al. *Hepatology*. 2020;71:214-224; Deneau ML et al. *Hepatology*. 2021;73:1074-1087.

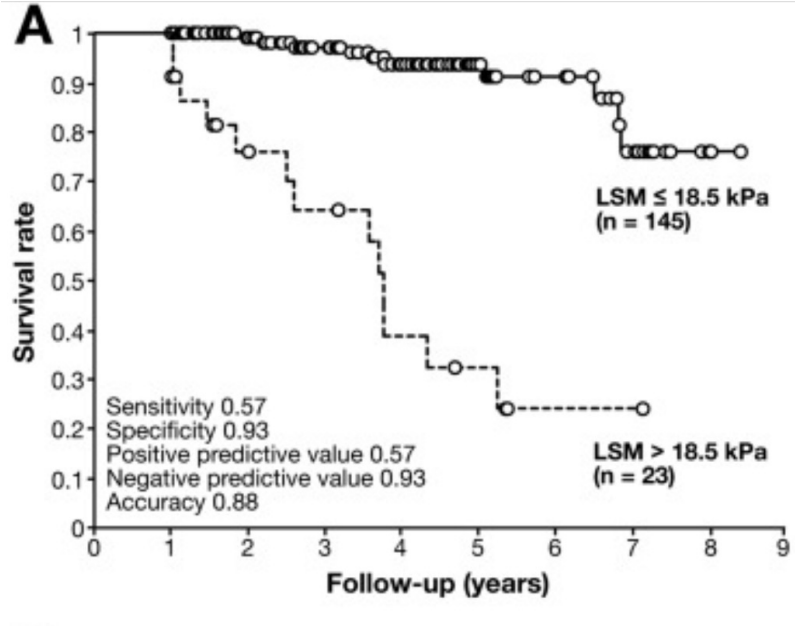
# Prognostic Models

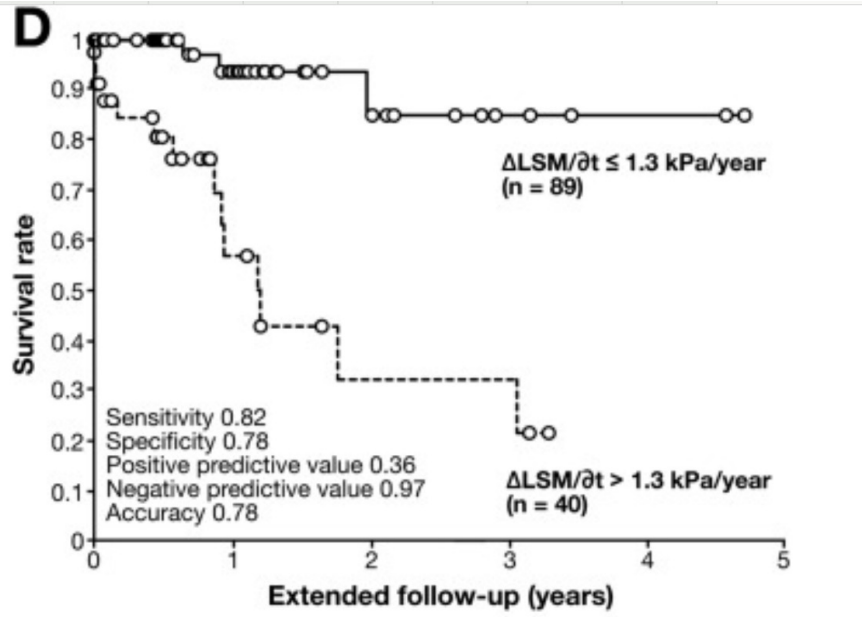



*Hepatology*. 2023;77(2):659-702. Hep Comm in press.

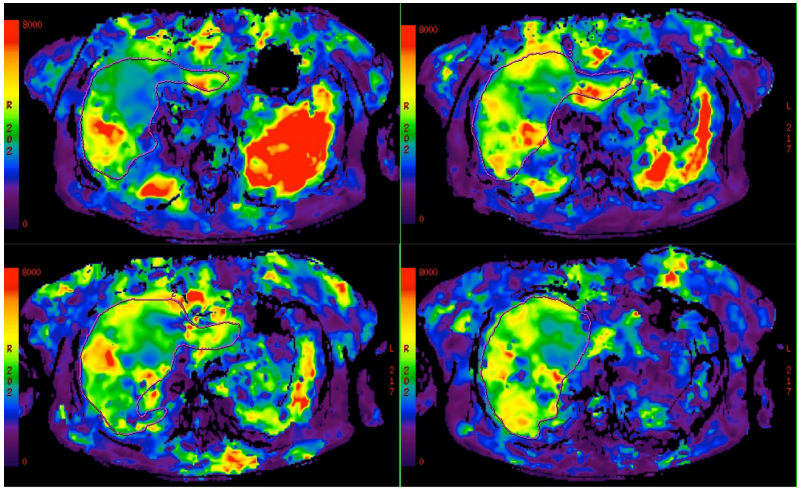
# Baseline and Change in Liver Stiffness Predicts Death, Transplant or Hepatic Decompensation

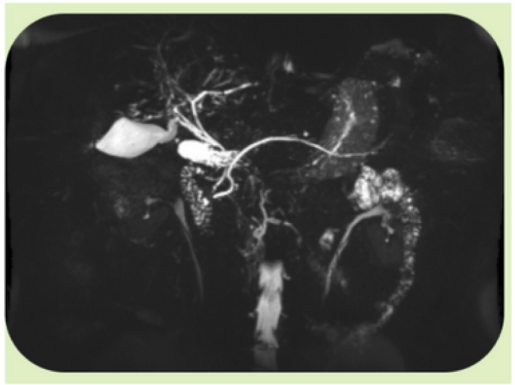


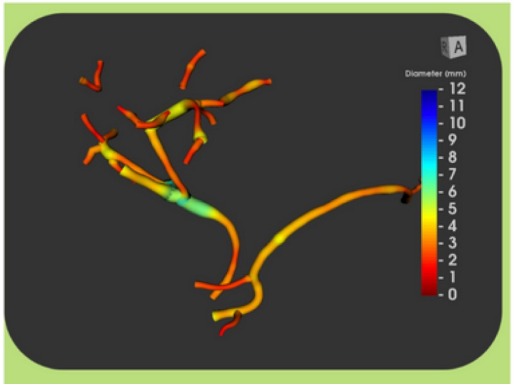




Corpechot C et al. *Gastroenterology*. 2014;146:970-9.

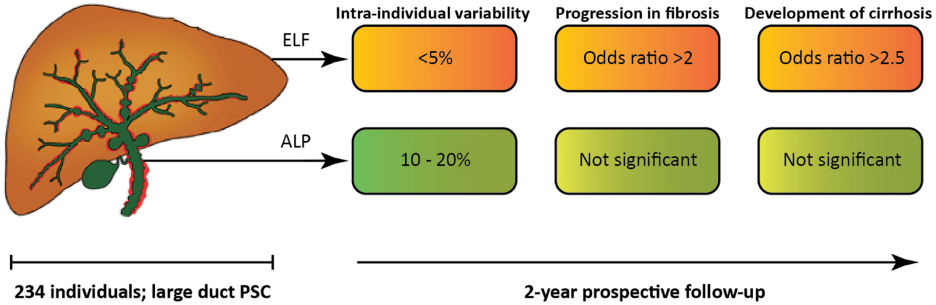
# MR Elastography and MRCP+® in PSC

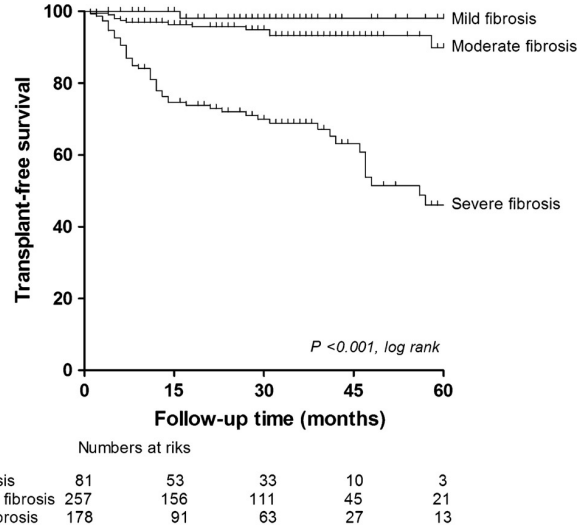






# Enhanced Liver Fibrosis (ELF) Test




*Clin Gastroenterol Hepatol*. 2021 Jun;19(6):1248-1257; *Liver Int*. 2017 Oct;37(10):1554-1561.

# Ursodeoxycholic Acid – Lots of Data; Lack of Results

- UDCA (13–15 mg/kg/day) has shown improvement in ALP by 12 months but no improvement in liver histology or transplant-free survival
- Intermediate-dose UDCA (17–23 mg/kg/day) has been inconclusive.
  - Largest study to date did not achieve statistical significance for reduction in the need for LT, CCA, or overall mortality.
  - Underpowered with only 63% of target enrollment
- High-dose UDCA (28–30 mg/kg/day) study was terminated early due to futility.
  - Post hoc, UDCA was associated with an increased risk of serious adverse events.
  - Increased risk of colorectal neoplasia with UDCA in patients with UC

# Arguments for Ursodiol in PSC

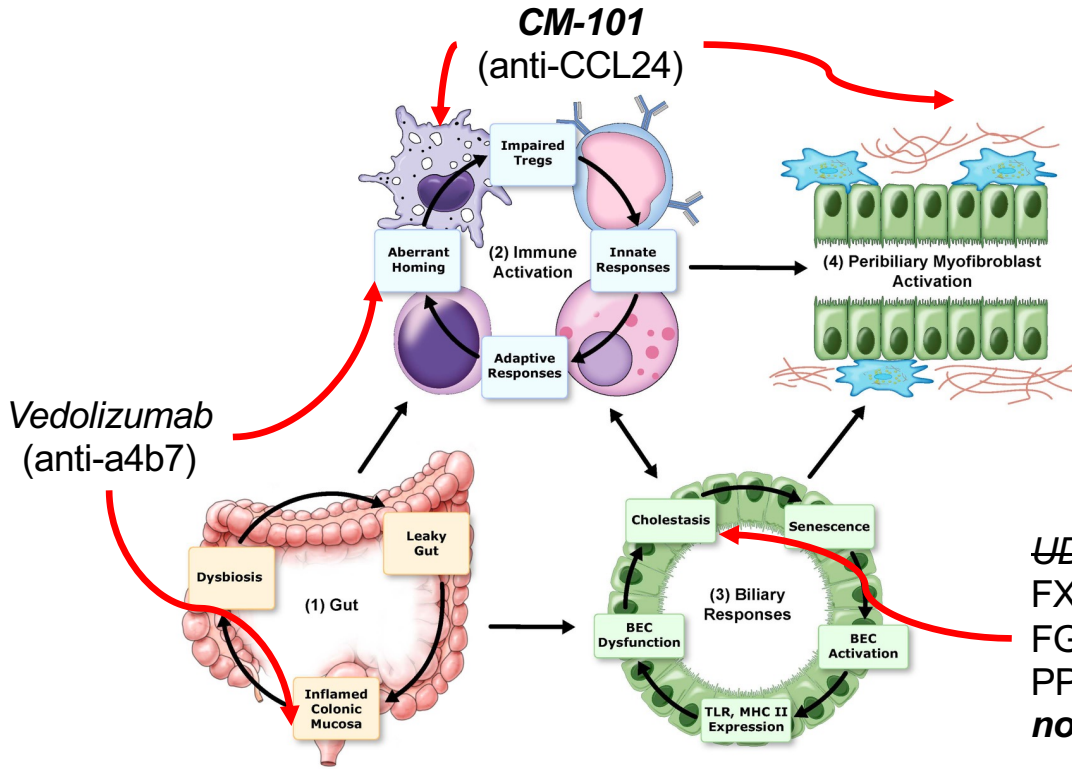
- Reductions in ALP have been associated with significantly better outcomes
  - Reduction of ALP to < 1.5 × ULN
  - 40% reduction or normalization of ALP
  - Normalization of ALP
- Ursodiol improves ALP
  - Demonstrated in nearly all RCTs at all doses
- Ursodiol demonstrated to be safe at doses of 13-23 mg/kg/d
- Removal of ursodiol results is worsening of symptoms, liver tests, and Mayo risk score

*N Engl J Med*. 1997;336:691-5; *Gastroenterology*. 2001;121:900-7; *Am J Gastroenterol*. 2001;96:1558-62; *Gastroenterology*. 2005;129:1464-72; *Hepatology*. 2014;60:931-40; *Hepatology*. 2009;50:808-14.

# Oral Vancomycin – Lack of Data

1. Randomized Controlled Trial
   - Randomized 29 patients to OV or placebo for 12 weeks and reported an improvement in Mayo Risk Score
2. Open Label Trial
   - 8 and 9 patients received low or high dose OV for 12 weeks. Compared with baseline, alkaline phosphatase decreased in both group
3. “Open” Label Trial
   - 30 patients enrolled and 29 patients treated outside protocol. 25 (42%) had small duct PSC and included patients previously treated with OV.
4. Retrospective studies
   - 264 patients found neither OV nor ursodiol were associated with clinical improvements compared with observation in pediatric patients with PSC
   - *7 patients treated with OV for at least 6 months. All achieved complete remission of UC. None developed VRE by rectal swab.*

# PSC Future Treatments?




***CM-101***
(anti-CCL24)

*Vedolizumab*
(anti-a4b7)

~~*Simtuzumab*~~
(anti-LOXL2)
***Bexotegrast***
(anti-avb6)

~~*UDCA*~~
FXR Agonists (*OCA/~~Cilofexor~~*)
FGF-19 analogue (*Aldefermin*)
PPAR Agonists (***Bezafibrate/Elafibranor***)
***nor-Urso***

*Hepatology*. 2023;77(2):659-702.

# PSC Symptoms

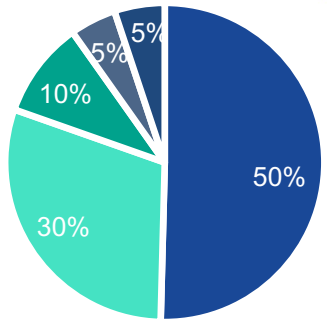
PSC PARTNERS PATIENT REGISTRY

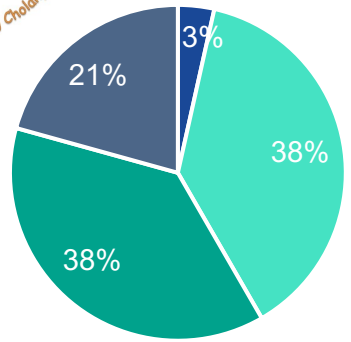
**Symptoms Reported by US vs Non-US Registrants**

| | US (n = 486) | Non-US (n = 192) |
|---|---|---|
| Fatigue | 360 (74.1%) | 151 (78.6%) |
| Abdominal pain | 354 (72.8%) | 139 (72.4%) |
| Itching | 318 (65.4%) | 113 (58.9%) |
| Sleep disturbances | 264 (54.3%) | 103 (53.6%) |
| Depression | 165 (34.0%) | 77 (40.1%) |

Investigating the Cholestatic Pruritus of Primary Sclerosing Cholangitis

ItCH-PSC




0 Encounters
1-2 Encounters
3-4 Encounters
5-6 Encounters
>6 Encounters

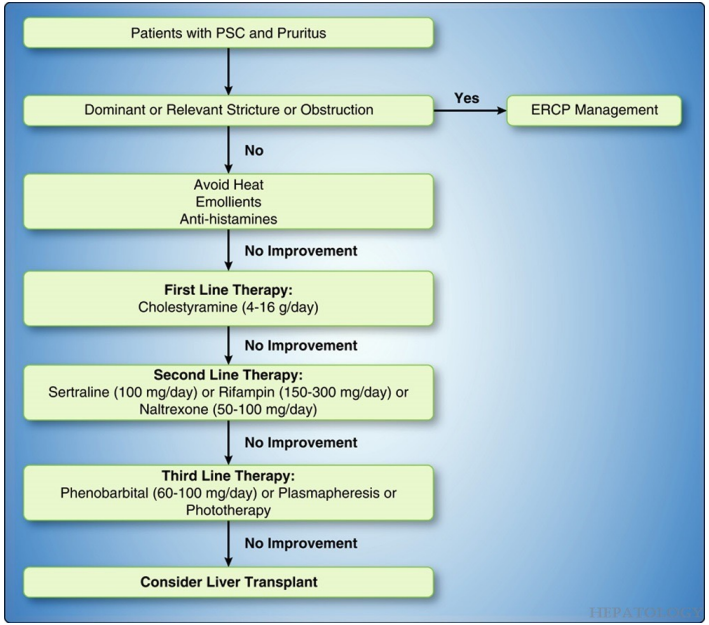
Absent
Mild
Moderate
Severe

*Clin Gastroenterol Hepatol*. 2019;17:1372-1378. ILC 2023.

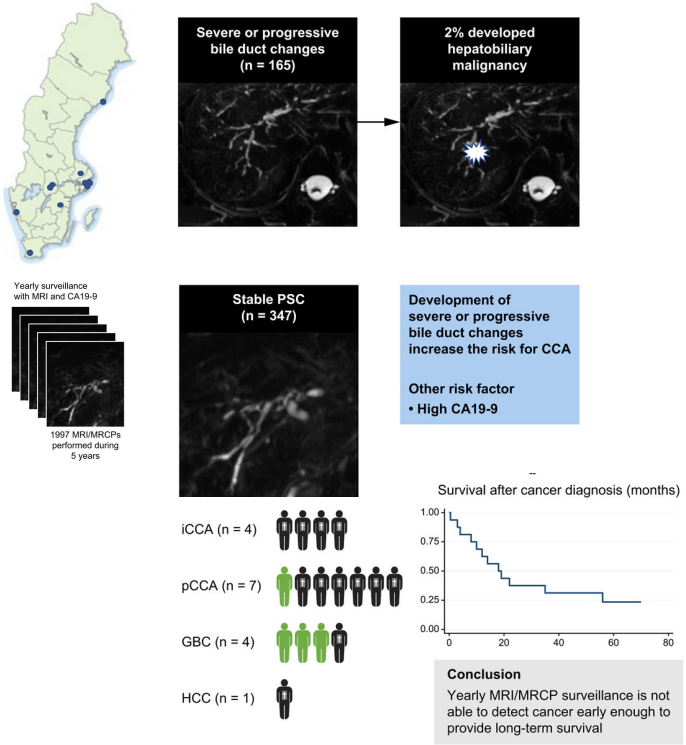
# Itch Management

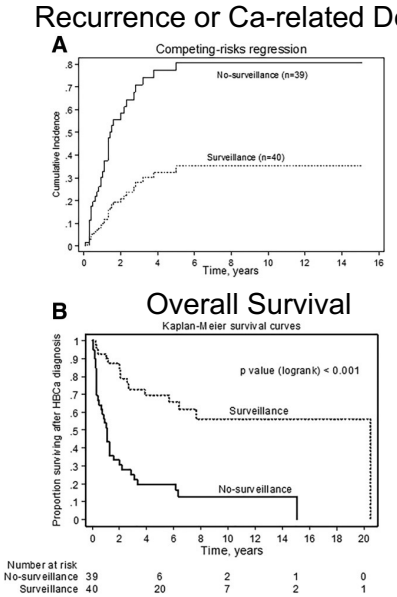
**Anti-pruritic medication ever used**

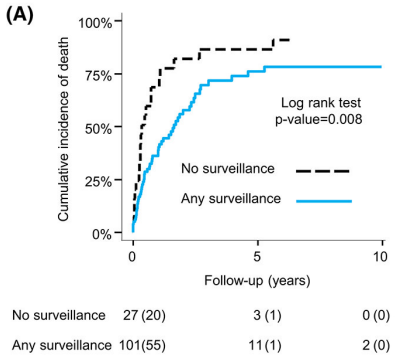
| Medication | No itch N=365 | Mild N=142 | Moderate N=140 | Severe N=77 |
|---|---|---|---|---|
| Bile acid binding resin | 26 (7%) | 34 (24%) | 61 (44%) | 36 (47%) |
| Hydroxyzine | 20 (5%) | 26 (18%) | 29 (21%) | 26 (34%) |
| Doxepin | 7 (2%) | 6 (4%) | 7 (5%) | 13 (17%) |
| Rifampin | 4 (1%) | 4 (3%) | 16 (11%) | 21 (27%) |
| Sertraline | 22 (6%) | 8 (6%) | 15 (11%) | 12 (16%) |
| Gabapentin | 44 (12%) | 13 (9%) | 13 (9%) | 10 (13%) |
| Fenofibrate | 10 (3%) | 6 (4%) | 6 (4%) | 4 (5%) |



# Surveillance for CCA in PSC

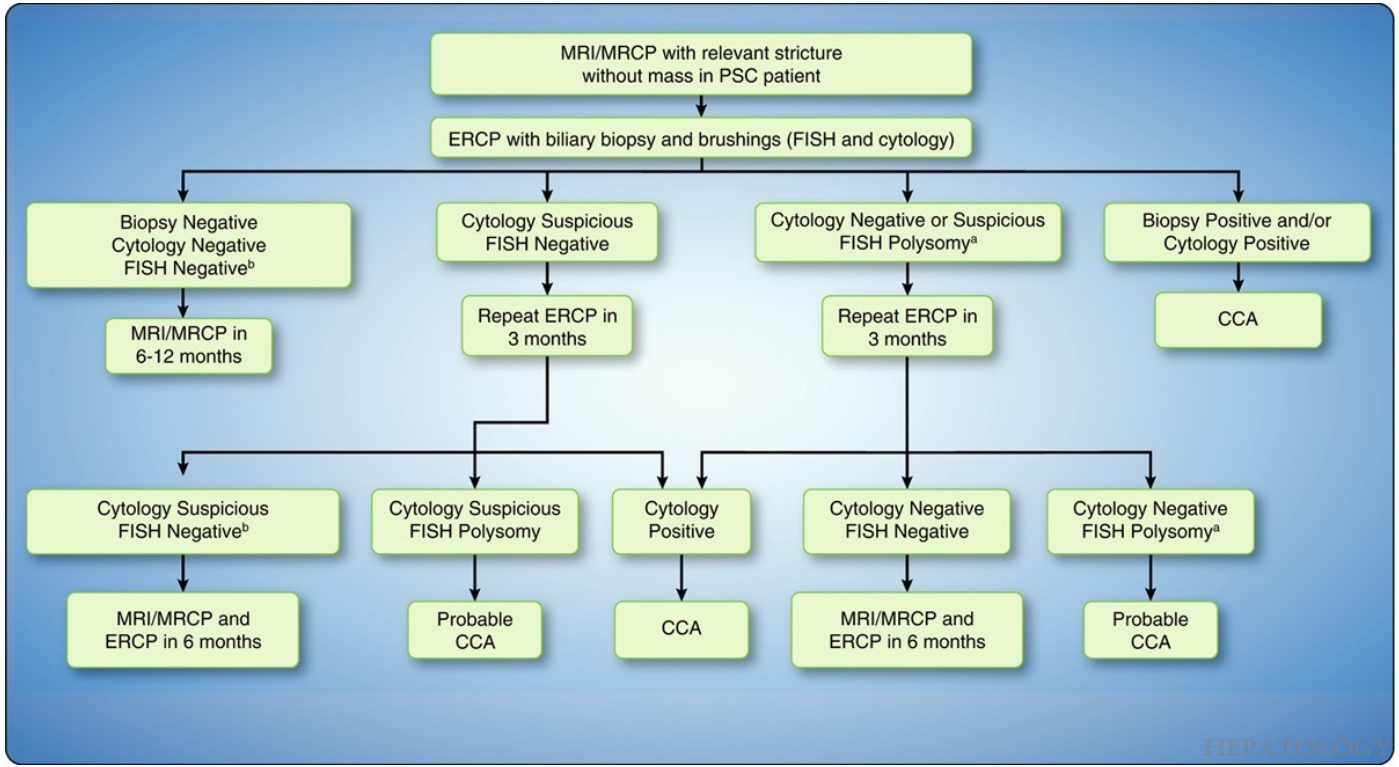



*J Hepatol*. 2023;78:604-613; *Hepatology*. 2018;67:2338-2351; *Liver Int*. 2023;43:127-138.

# Perihilar/Distal Cholangiocarcinoma Diagnosis




*Hepatology*. 2023;77(2):659-702.

# Colorectal Cancer in PSC

- 5–12 times greater compared to the general population
- 3 times greater compared to patients with IBD without PSC
  - Tendency toward right-sided lesions and younger age at onset
- Cumulative incidence of CRC in PSC-IBD of up to 40% after 20 years of disease
  - More recent study 5-year and 10-year CRC incidence rates of 7% and 9%, respectively.
- Children develop CRC with 5% affected at 10 years.
- More frequently endoscopically invisible dysplasia
  - Low-grade dysplasia progresses to high-grade dysplasia (HGD) or CRC more rapidly compared to IBD alone.
- Risk of CRC in patients with PSC without IBD relative to the average-risk population is unknown

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# Take Home Messages

- Diagnosis is based upon MRI/MRCP
  - Liver biopsy only to exclude AIH or diagnose small-duct PSC
  - ERCP only for therapeutic intervention
- Urso (or nothing) is OK, oral vanco is not
- Ask about and treat itch and other symptoms
- Cancer surveillance for CCA, colon cancer
- Future treatments remain elusive…but there is hope.