The need for paediatric developments in PSC, trial duration and endpoints

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Paediatric onset PSC

- Age of onset and phenotype at onset
- Natural history of disease after paediatric onset
- Potential surrogate markers - (in)dependency from therapeutic interventions

Unique features of primary sclerosing cholangitis in children

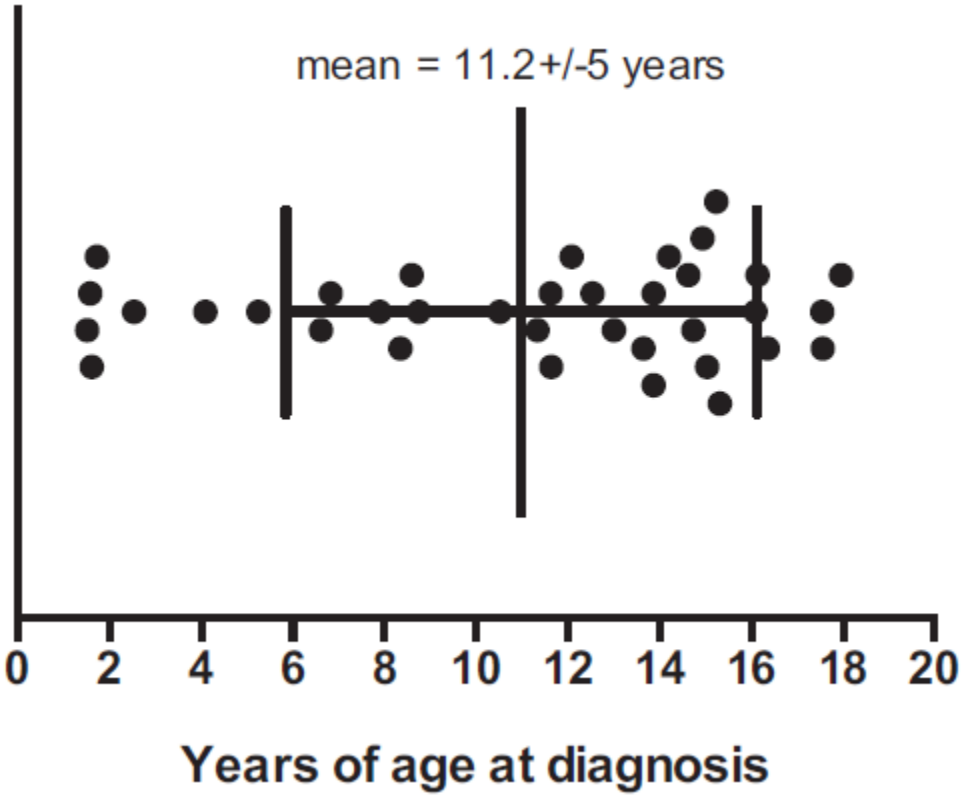
Giorgina Mieli-Vergani and Diego Vergani

Current Opinion in Gastroenterology 2010,
26:265–268

Conclusion

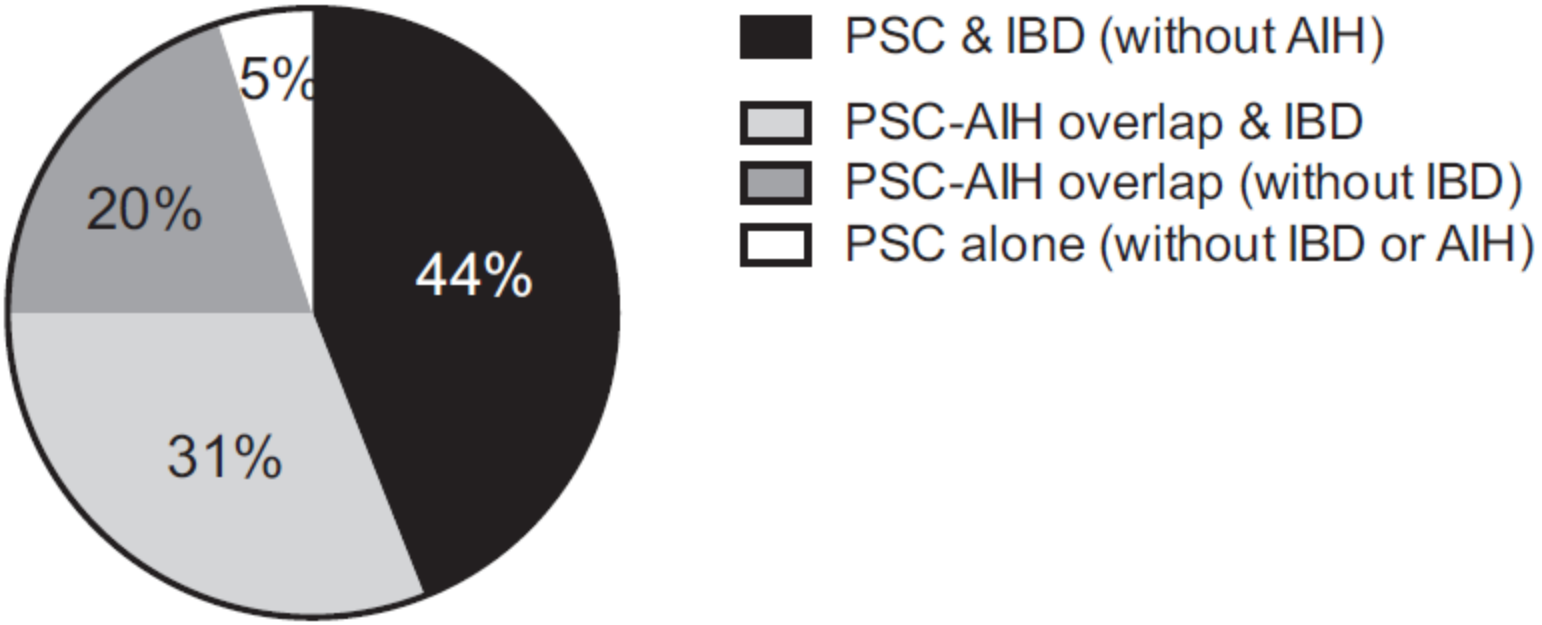
PSC remains underreported in paediatric hepatology, as reflected by the small number of papers published on this subject in the past 5 years. This is likely to be due to a persisting little awareness of this condition. Studies on large cohorts of children with PSC are needed for a better understanding and definition of pathogenic mechanisms, diagnostic pathways, response to treatment and outcome of this serious disease.

Majority of paediatric onset of PSC occurs in second decade, but it definitely can also occur in the first decade



Cotter et al. JPGN 2018;66: 227–233

Paediatric onset of PSC: ~50% with auto-immune characteristics



Cotter et al. JPGN 2018;66: 227–233

Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement

*Giorgina Mieli-Vergani, *Diego Vergani, †Ulrich Baumann, ‡Piotr Czubkowski, §Dominique Debray, ||Antal Dezsofi, ¶Björn Fischler, #Girish Gupte, **Loreto Hierro, ††Giuseppe Indolfi, ‡‡Jörg Jahnel, §§Françoise Smets, ||||Henkjan J. Verkade, and *Nedim Hadžić

Diagnosis of ASC requires cholangiography (magnetic resonance colangiopancreatography [MRCP], unless suspicion of distal biliary stricture, where endoscopic retrograde cholangiopancreatography [ERCP] is indicated). *(11 strongly agree, 1 agree)*

Parenchymal inflammation responds satisfactorily to standard immunosuppressive treatment with prednisolone/prednisone and azathioprine both in AIH and ASC, but the bile duct disease could progress in about 50% of the ASC cases, leading to end-stage liver disease requiring liver transplantation. *(7 strongly agree, 5 agree)*

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Mieli-Vergani et al;
JPGN 2018;66: 345–60

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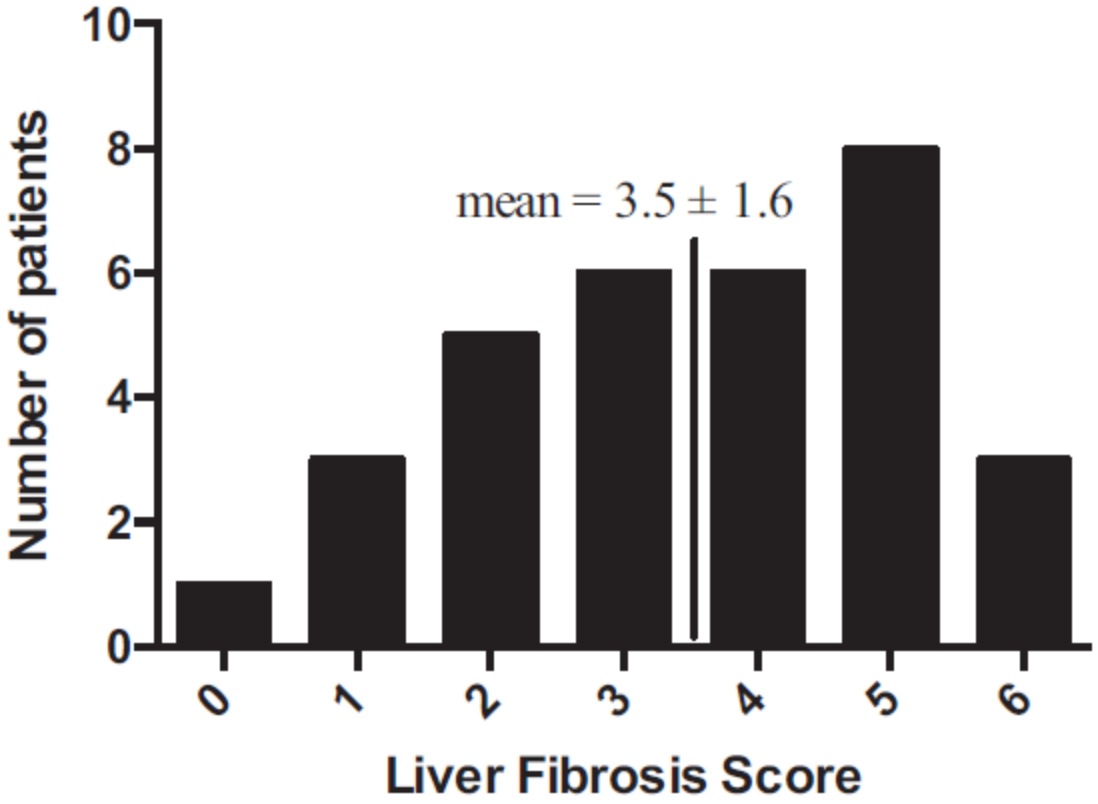
Severe fibrosis already at time of diagnosis (Ishak): 33% cirrhosis



Cotter et al. JPGN 2018;66: 227–233

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HEPATOLOGY, VOL. 66, NO. 2, 2017 AUTOIMMUNE, CHOLESTATIC AND BILIARY DISEASE

The Natural History of Primary Sclerosing Cholangitis in 781 Children: A Multicenter, International Collaboration

Mark R. Deneau,[1] Wael El-Matary,[2] Pamela L. Valentino,[3] Reham Abdou,[4] Khaled Alqoaer,[5] Mansi Amin,[6] Achiya Z. Amir,[7]

- 781 patients, median age 12 years, with 4,277 person-years of follow-up
- 33% +AIH, 76% +IBD, and 13% small duct PSC.
- after 10 years: portal hypertensive compl 38%; biliary compl 25%
- overall event-free survival was 70% at 5 years and 53% at 10 years.

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Deneau et al,
Hepatology 2017;66:518-527

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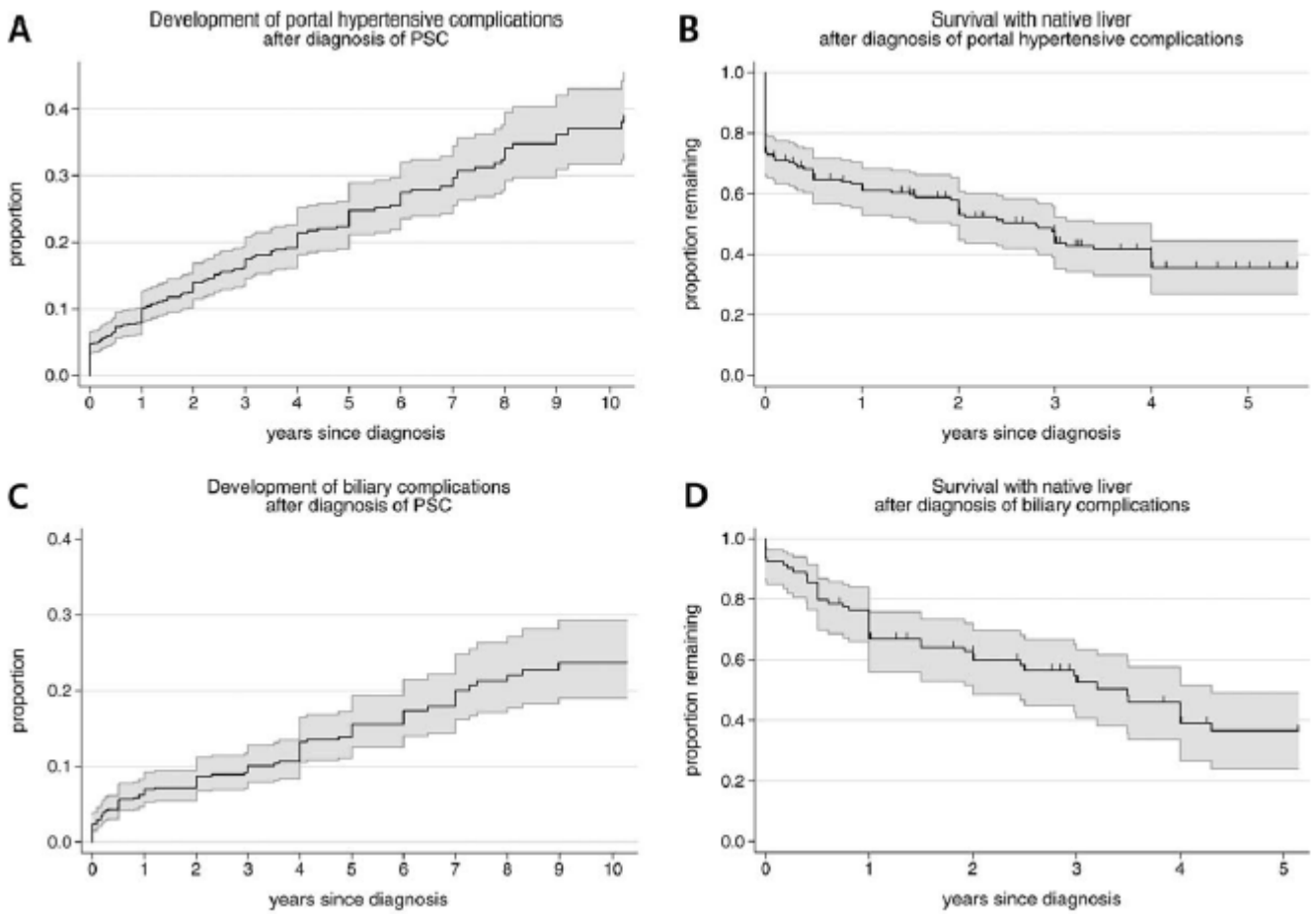
Portal hypertensive or biliary complications after pediatric onset of PSC is associated with >50% liver transplantation within 5 years



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Deneau et al,
Hepatology 2017;66:518-527

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Table 1. Comparison of clinical characteristics of PSC in children and adults.

	PSC in children	PSC in adults
Incidence	• 0.2 in 100,000 per year	• 1 in 100,000 per year
Median age at presentation	• 2nd decade of life	• 30 – 50 years
Clinical features	• Abdominal pain is more common • Dominant strictures are less commonly found in children • Strongly associated with IBD (55 – 81%) • Small duct and intrahepatic PSC occur more commonly in children and may less likely progress to large duct PSC • Overlap syndrome with AIH occurs more commonly in children than in adults, and PSC may mimic AIH (25–35%) • IgG4-associated cholangiopathy is rarely described in children, and it is unclear if IgG4 levels should be measured	• Pruritus is more common • Dominant strictures are more commonly found in adults • Strongly associated with IBD (60 – 100%) • Small duct and intrahepatic PSC occur less frequently in the adult population but may more likely progress to large duct PSC • Overlap syndrome occurs less commonly in adults than in children (7–10%) • It is reasonable to measure IgG4 levels in adults with PSC
Serology	• pANCA positive 53–74%	• pANCA positive 26–94%
Laboratory	• Alkaline phosphatase is less reliable because of the period of bone development. GGT is a more reliable marker of cholestasis in children • Alkaline phosphatase is not a good prognostic marker • More often present with a hepatocellular pattern of injury	• Alkaline phosphatase is more reliable • Alkaline phosphatase may be considered as a good prognostic marker • More often present with a cholestatic pattern of injury
Liver transplant rate	• 17–30%	• 1–2 %/year
Risk of recurrence post-liver transplant	• About 27%	• 20–40%
Response to therapy	• No definitive treatment	• No definitive treatment
Natural history	• 10-year survival of 70%	• 10-year survival of 61–64%
Surveillance for cholangiocarcinoma and gallbladder cancer	• Not recommended in children based on current practice guidelines	• Consider imaging (US/MR) and a CA 19–9 every 6–12 months • Cholecystectomy should be performed for patients with PSC and gallbladder polyps > 8 mm, to prevent the development of gallbladder adenocarcinoma.
Surveillance for colon cancer	• Colonoscopy should be performed at diagnosis. Unclear benefit for annual colonoscopy in children but should be considered in children older than 16 years of age with PSC-IBD.	• Annual colonoscopy is recommended at diagnosis in adults with PSC-IBD.

Abbreviations – primary sclerosing cholangitis (PSC), inflammatory bowel disease (IBD), autoimmune hepatitis (AIH), perinuclear antineutrophil cytoplasmic antibody (pANCA), carbohydrate antigen 19–9 (CA 19–9)

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Adike et al,
Exp Rev Gastro Hepatol 2018; 12:1025-32

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Variations in primary sclerosing cholangitis across the age spectrum

John E Eaton,* Bryan M McCauley,† Elizabeth J Atkinson,† Brian D Juran,* Erik M Schlicht,* Mariza de Andrade† and Konstantinos N Lazaridis*,†

Divisions of *Gastroenterology and Hepatology, and †Biomedical Statistics and Informatics, Mayo Clinic College of Medicine and Sciences, Rochester, Minnesota, USA

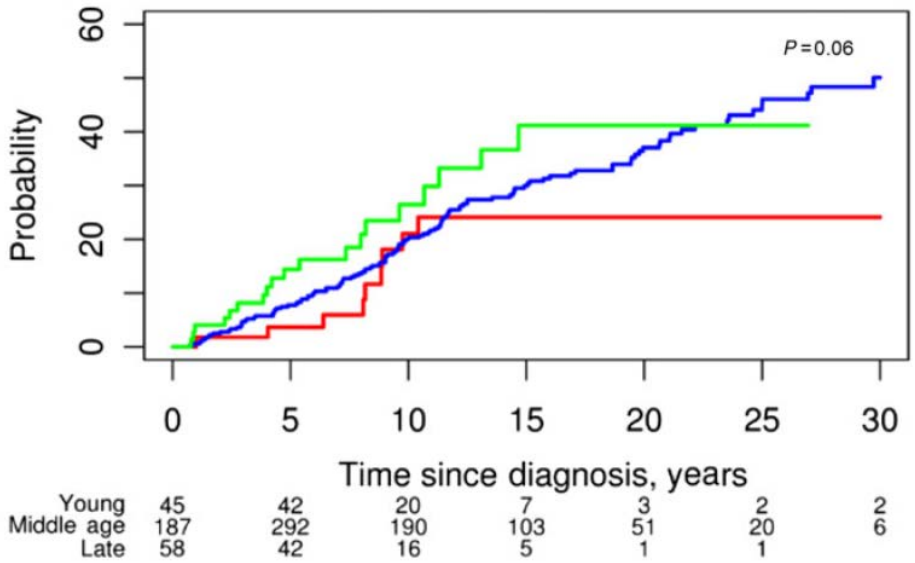
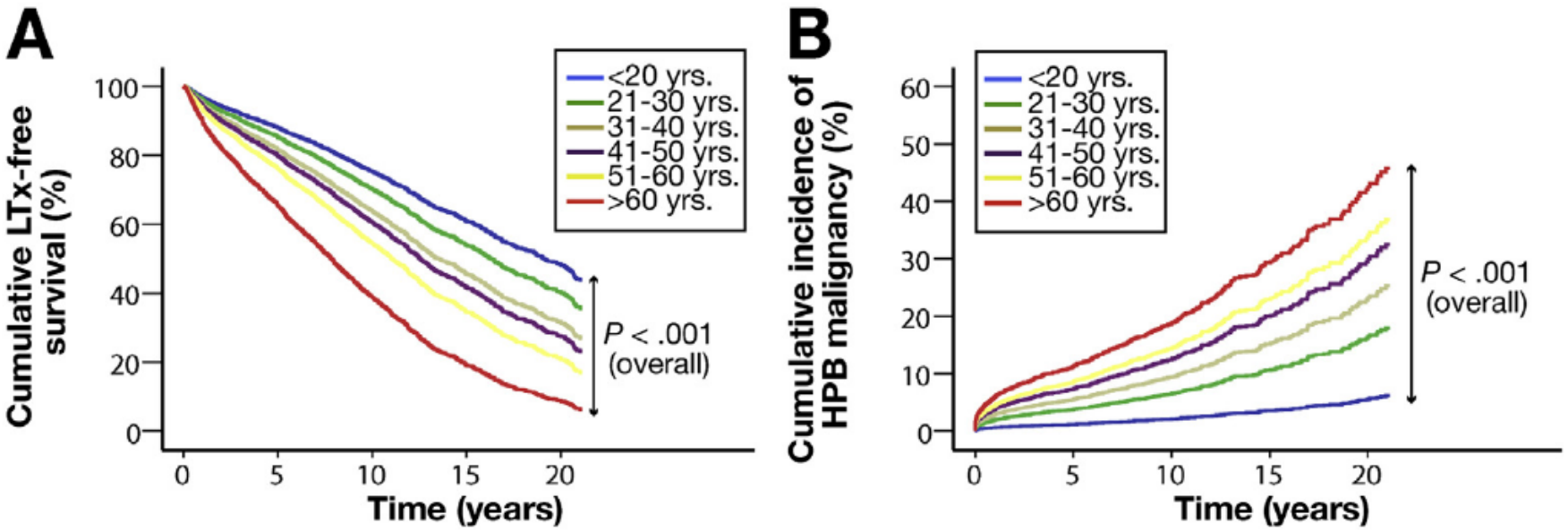


Figure 3 Development of hepatic decompensation. ——, young; ——, middle age; ——, late. [Color figure can be viewed at wileyonlinelibrary.com]

Pediatric onset PSC:
Higher LTx-free survival, but still <50% within 20 years!



Impact of patient age and gender on clinical outcome. Cox plots with regard to LT or HPB malignancy. All data are stratified by geographic region of referring center and year of diagnosis, presented according to patient age at diagnosis and weighted for patient gender, IBD phenotype at baseline, and PSC subphenotype

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Weismüller et al;
Gastroenterology 2017;152:1975–84

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HEPATOLOGY COMMUNICATIONS, VOL. 2, NO. 11, 2018

Gamma Glutamyltransferase Reduction Is Associated With Favorable Outcomes in Pediatric Primary Sclerosing Cholangitis

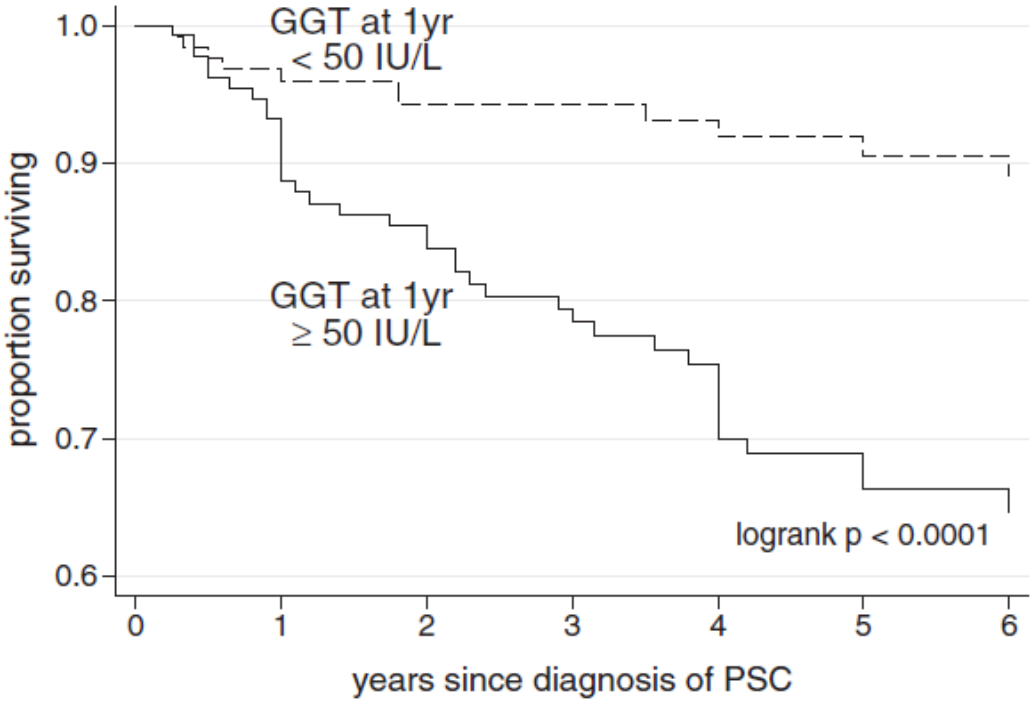
Mark R. Deneau,[1] Cara Mack,[2] Reham Abdou,[3] Mansi Amin,[4] Achiya Amir,[5] Marcus Auth,[6] Fateh Bazerbachi,[7]

- event-free survival (no portal hypertensive or biliary complications, cholangiocarcinoma, liver transplantation, or liver-related death)

- GGT < 50 and/or GGT reduction of > 75% by 1 year after PSC diagnosis predicts favorable 5-year outcomes in children.

- *“GGT has promise as a potential surrogate endpoint in future clinical trials for pediatric PSC.”*

Paediatric onset PSC: 1-year GGT <50 is associated with a better prognosis



Number at risk

GGT < 50	132	123	101	85	71	55	39
GGT ≥ 50	126	120	103	90	79	69	61

Ignoring treatment status and pooling treated and untreated patients together, patients with 1-year GGT < 50 had a 5-year event-free survival of 91% compared with 67% in patients with 1-year GGT ≥ 50 (P < 0.0001)

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Deneau et al., Hepatology Comm 2018;2:1369-1378

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Lower GGT associated with better outcome, but UDCA *not* associated with better outcome, despite lowering GGT.

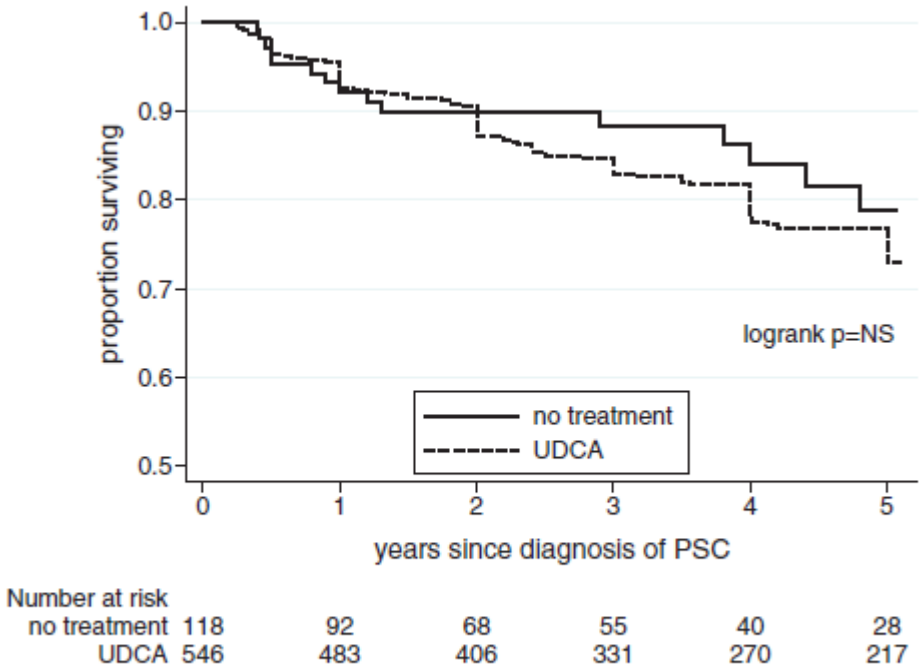

FIG. 1. Event-free survival based on UDCA treatment status.

Events: portal hypertensive or biliary complications, cholangiocarcinoma, liver transplantation, or liver-related death

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Deneau et al., Hepatology Comm 2018;2:1369-1378

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An “inconvenient” truth regarding GGT as potential surrogate marker

The relationship between biochemical response to UDCA and long-term liver outcomes seems paradoxical: (1) UDCA-treated patients had lower liver biochemistry levels on average compared with patients who were not treated; (2) lower liver biochemistry levels generally predicted a more favorable outcome; but (3) UDCA treatment did not result in improved outcomes compared with untreated patients. Analogous results have been seen in clinical trials involving adult patients: Lower or normal ALP levels were associated with improved outcomes,[15,16,39,40] regardless of whether UDCA was used or if the labs normalized without therapy.[16,17]

Deneau et al., Hepatology Comm 2018;2:1369-1378

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Future possibilities

- Support (consortia) for delineating the natural history, bridging paediatric and adult medicine
- Multiple n=1 trials with patient reported outcomes on symptom / quality issues
- After safety and tolerance assessment, allow broad-inclusion trials with *post-hoc* analysis of sub-group efficacy. Subsequently, regular trial in these sub-group(s)

Thank you for your attention

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Title

- Text