21ST ANNUAL PSC PARTNERS SEEKING A CURE CONFERENCE

Pediatric Primary Sclerosing Cholangitis

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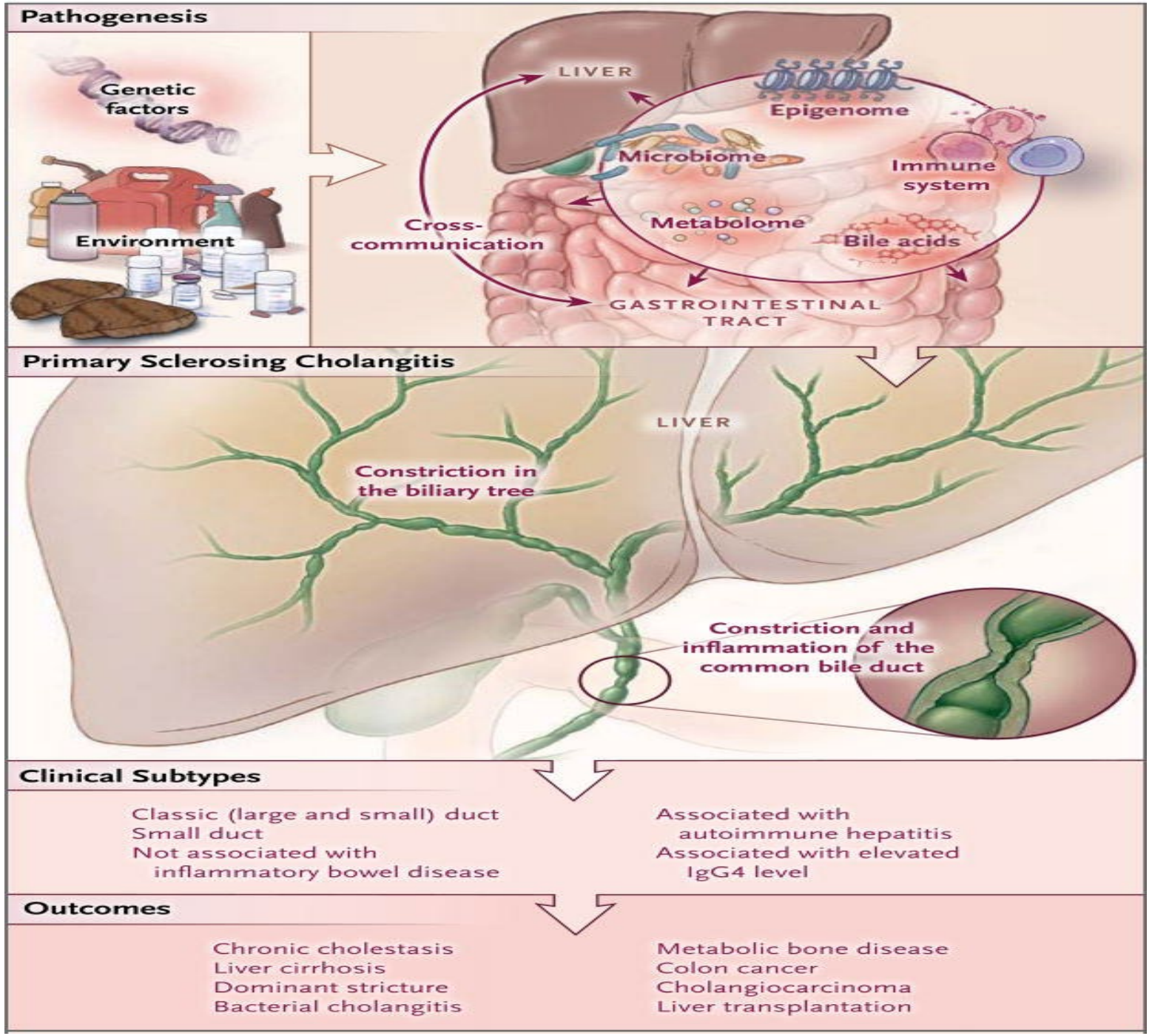
Background

- Primary sclerosing cholangitis (PSC) is a chronic and progressive fibrosing cholangiopathy characterized by inflammation, injury and scarring of the intra- and/or extrahepatic bile ducts
- Rare disease: Prevalence of 1.5 per 100,000
- PSC is associated with ulcerative colitis (UC) in ~80% of cases, while only ~5% of patients with UC will have PSC
- Important clinical differences in pediatric vs. adult PSC
  - Small duct phenotype: 20% pediatrics vs 10%adults
  - Autoimmune Sclerosing Cholangitis: 33% pediatrics vs. 7% adults
  - Dominant strictures: 4% pediatrics vs 45% in adults
  - Cholangiocarcinoma in children 1% by 10 years vs. 7-13% in adults

- Within 10 years of diagnosis, 30% of patients will require liver transplantation.

Lazardis et al. *NEJM,* 2016
Deneau et al Hepatology 2021



Lazardis et al. *NEJM*, 2016

Key Questions

What is the natural history of pediatric PSC?

How do we predict prognosis?

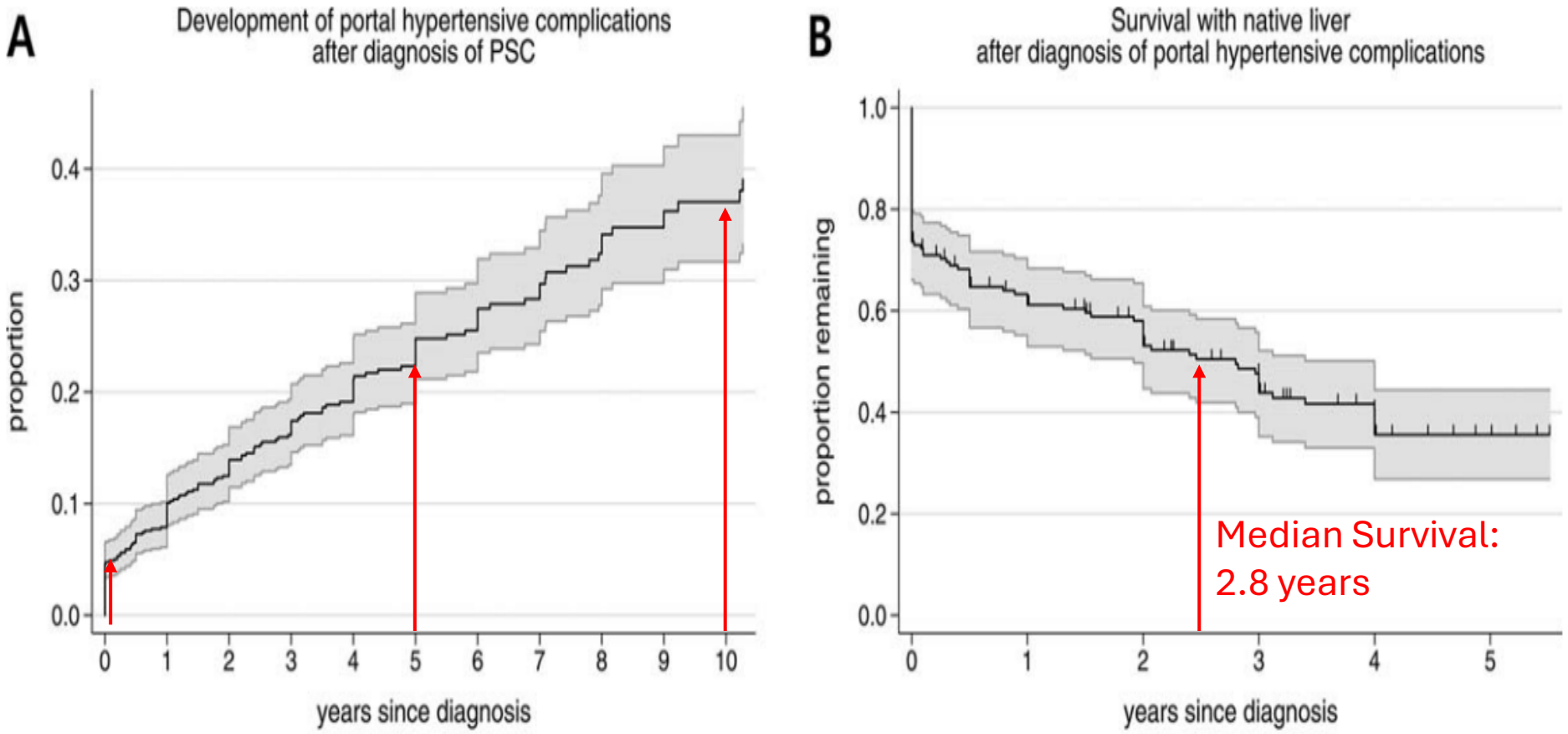
What therapeutic options exist?

How do we think about the need for liver transplant?

WHAT IS THE NATURAL HISTORY OF PEDIATRIC PSC?

781 pediatric PSC patients from 36 countries; Median age: 12 years

Development of Portal Hypertension (n=163)



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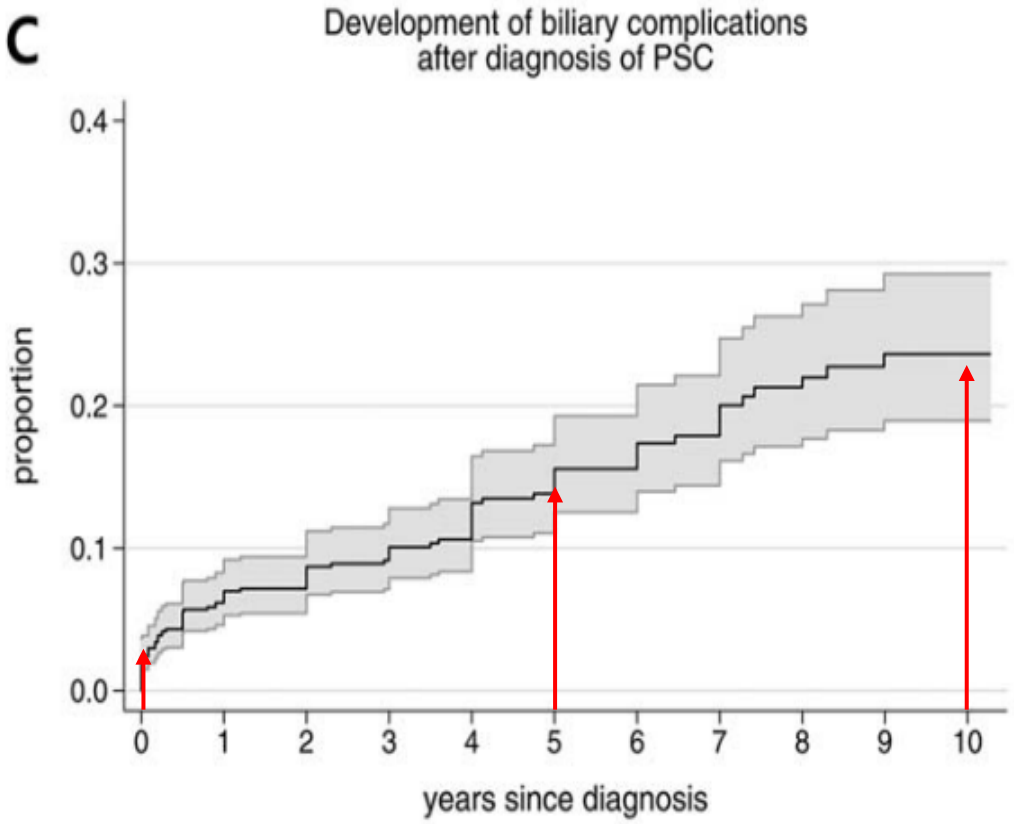
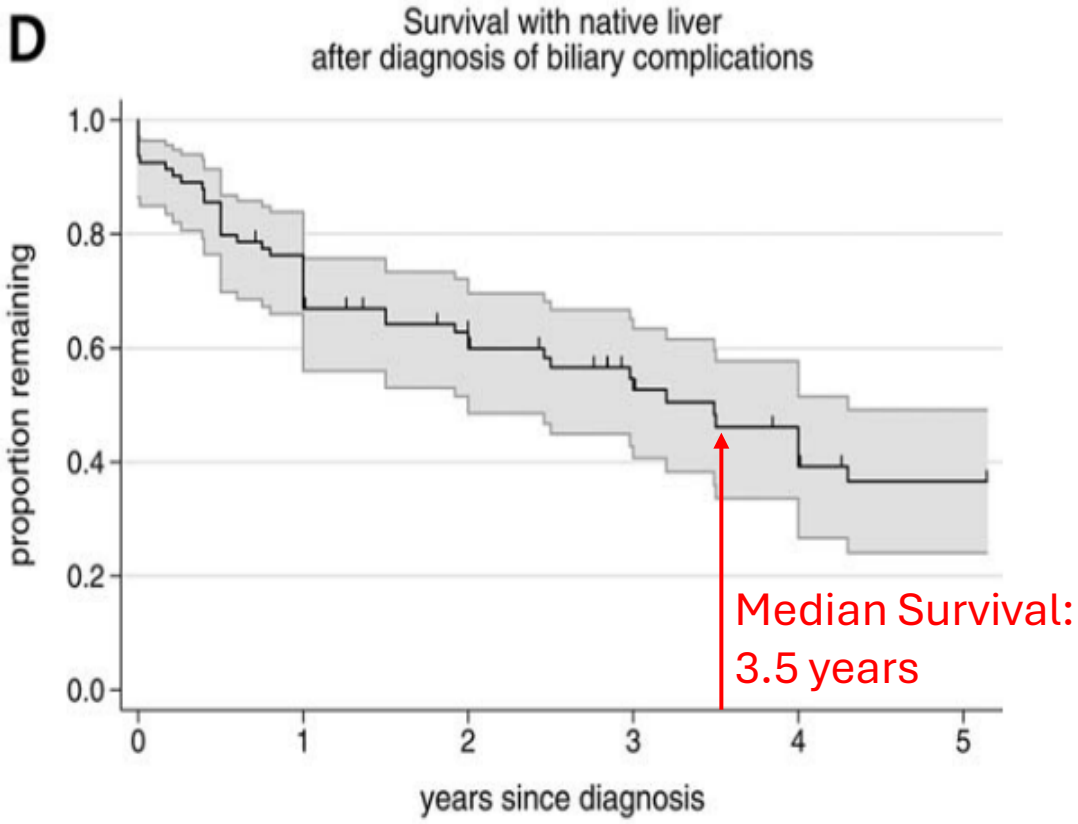
Development of Biliary Complications (n=95)





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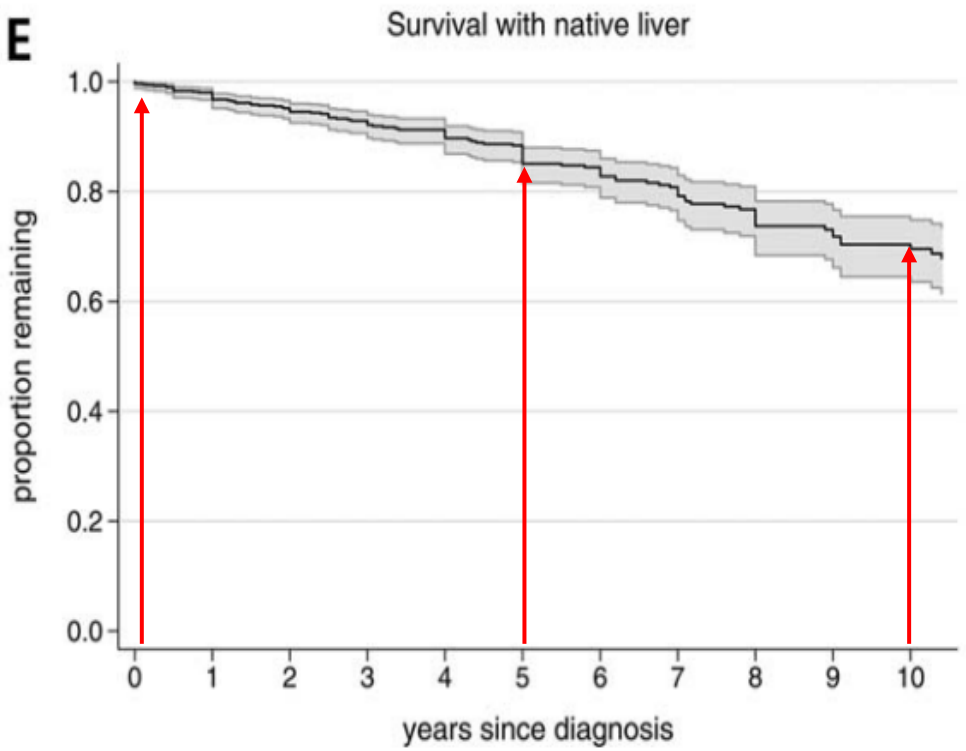
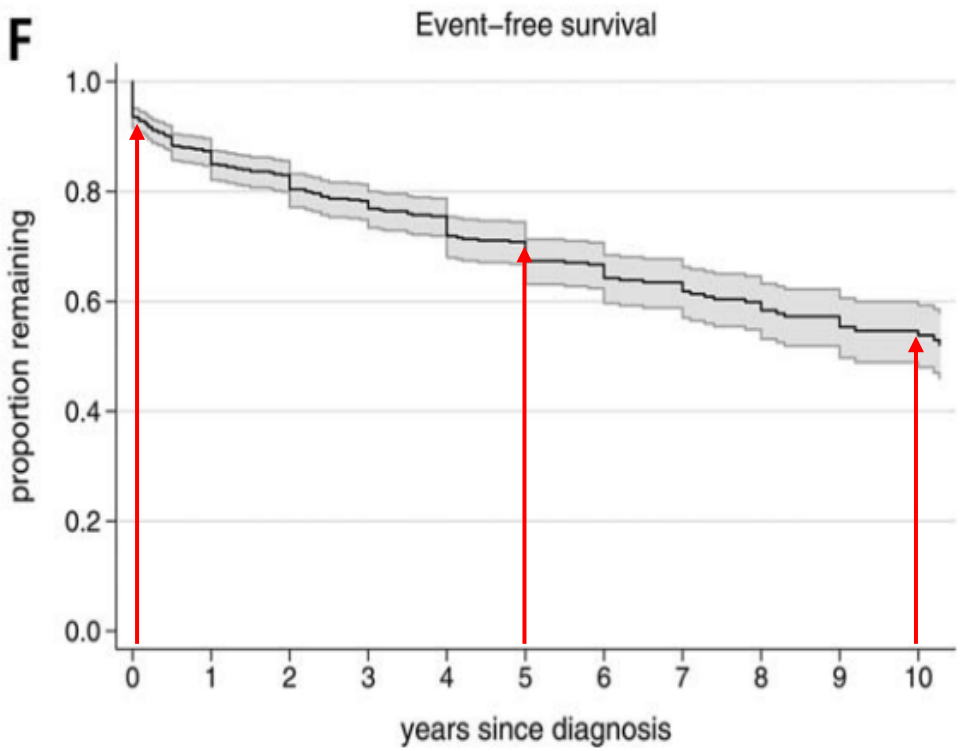
Liver Transplant



- 14% population
- Median age 15 years
- Median 4 years after diagnosis

Event Free Survival



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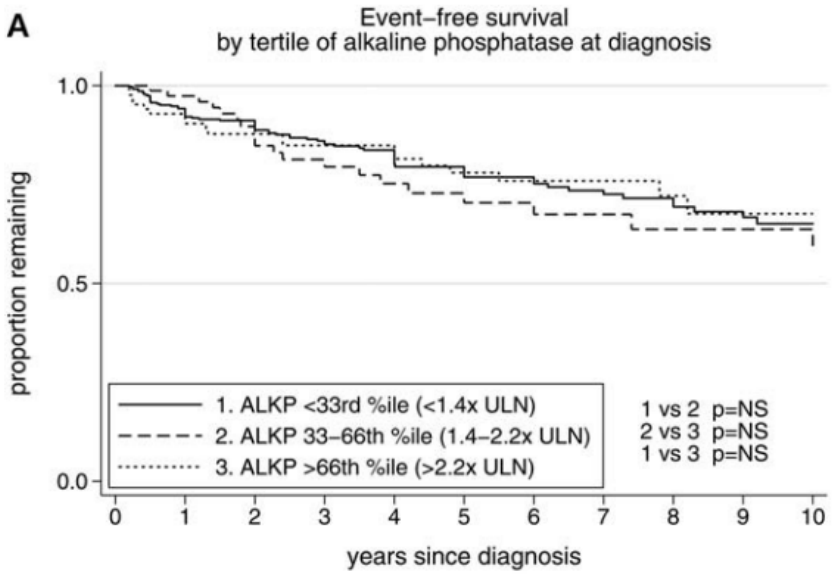
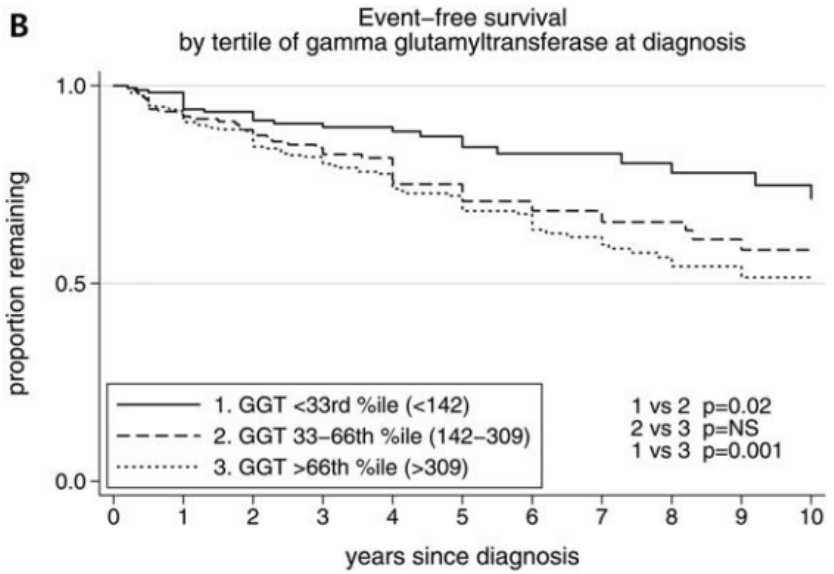
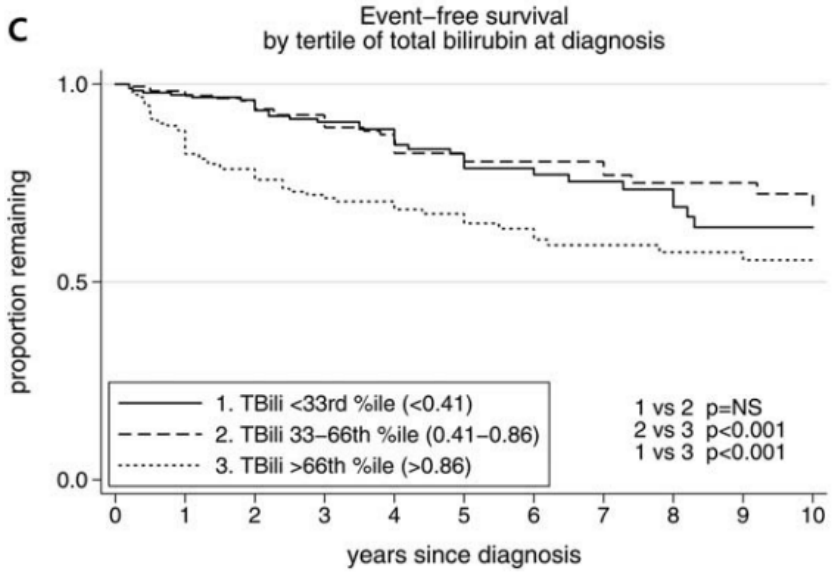
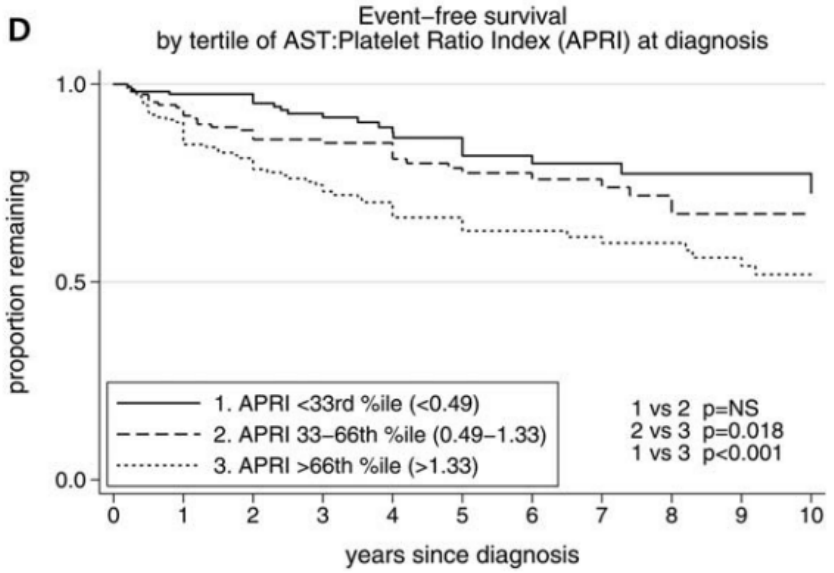
Predictors of Outcomes: labs at diagnosis









Favorable Subtypes:
SMALL> large duct
PSC-IBD>no IBD

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HOW DO WE PREDICT PROGNOSIS?

SCOPE SCORE
(SCLEROSING CHOLANGITIS OUTCOMES IN PEDIATRICS)

Attribute	Value		Points
	Traditional Units	SI Units	
	mg/dL	µmol/L	
Total bilirubin	≤0.6	≤11	0
	0.7–2.7	11.1–46.7	+1
	2.8–4.8	46.8–82.4	+2
	≥4.9	≥82.5	+3
	g/dL	g/L	
Albumin	≥4	≥40	0
	3.2–3.9	32–39	+1
	≤3.1	≤31	+2
	$\times 10^3$/µL	$\times 10^9$/L	
Platelet count	≥225	≥225	0
	136–224	136–224	+1
	≤135	≤135	+2
	U/L	U/L	
GGT	≤100	≤100	0
	101–249	101–249	+2
	≥250	≥250	+3
Cholangiography	Normal		0
	Large-duct involvement		+ 1

Total	
Low risk	0–3
Medium risk	4–5
High risk	6–11

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SCOPE risk group	SCOPE index	probability (0-100%) of transplant or death† in the next 5 years					probability (0-100%) of any hepatobiliary complication* in the next 5 years				
		1 year	2 years	3 years	4 years	5 years	1 year	2 years	3 years	4 years	5 years
LOW	**0**	<1	<1	<1	<1	<1	<1	1	2	2	3
	1	<1	<1	<1	<1	1	2	3	4	5	6
	2	<1	<1	1	1	2	3	4	6	7	9
	3	<1	1	2	2	3	4	5	7	9	15
MEDIUM	**4**	1	2	3	4	6	5	7	10	12	16
	5	2	3	5	7	10	8	12	16	20	25
HIGH	**6**	3	5	9	13	18	13	19	26	32	39
	7	6	10	18	23	31	20	28	37	45	53
	8	10	17	30	38	50	31	43	54	64	73
	9	17	28	46	56	69	36	48	59	68	76
	10	33	52	75	84	93	48	62	75	84	93
	11	44	65	86	93	97	56	71	86	93	97

†**transplant or death** includes either of:
listing for liver transplantation
death from liver disease

*__hepatobiliary complications__ include any of:
portal hypertensive complications
- esophageal varices
- ascites
- hepatic encephalopathy

biliary complications
- stricture requiring balloon dilation, stenting or external drainage
- hospitalization for acute cholangitis

cholangiocarcinoma
listing for liver transplantation
death from liver disease

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WHAT THERAPEUTIC OPTIONS ARE AVAILABLE?

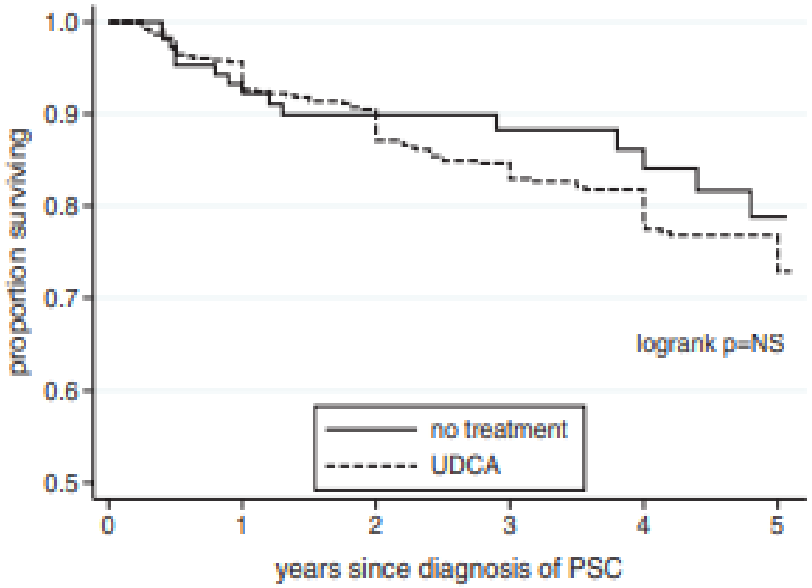
URSODIOL

- High concentrations of hydrophobic (water fearing) bile acids care present in PSC and can be damaging to the liver
- Ursodiol is a hydrophilic (water loving) bile acid and may be protective for the liver.
- Low, intermediate and high doses have been studied
  - High Dose: Adult study terminated early for futility and increased risk of serious adverse events
  - Medium Dose: Adult study inconclusive-no change in need for liver transplant, cholangiocarcinoma or overall mortality
  - Low dose: Improved alkaline phosphatase but not transplant free survival

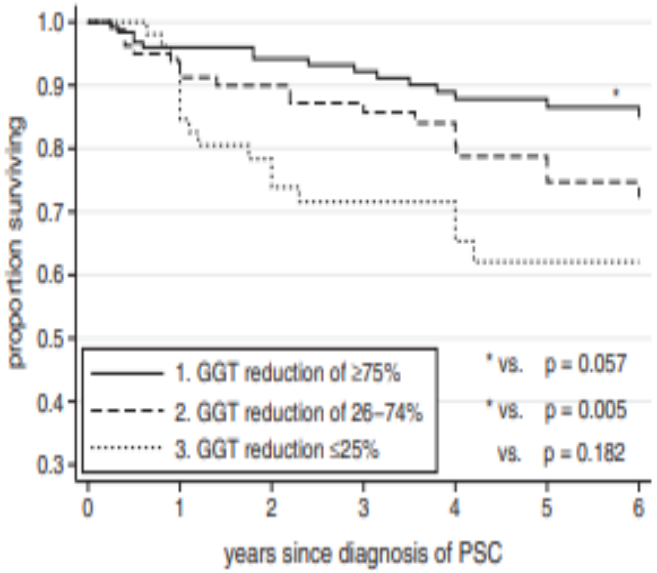
Lindor NEJM 1997
Olsson Gastro 2005
Imam Aliment Pharm 2011

URSODIOL

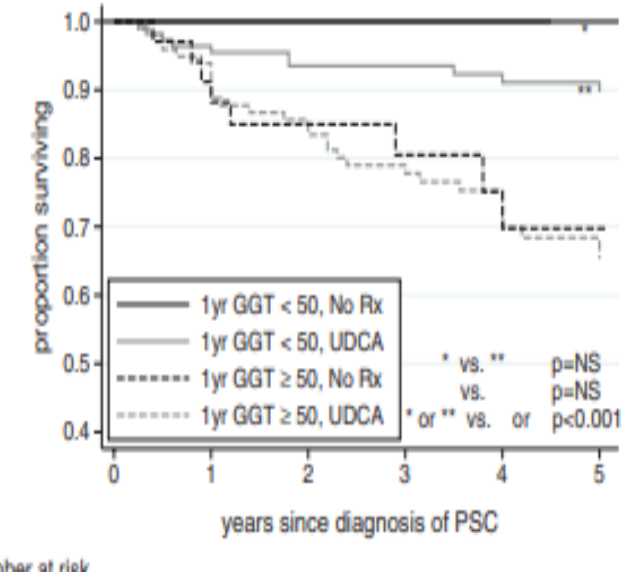
Event free survival: UDCA vs no treatment



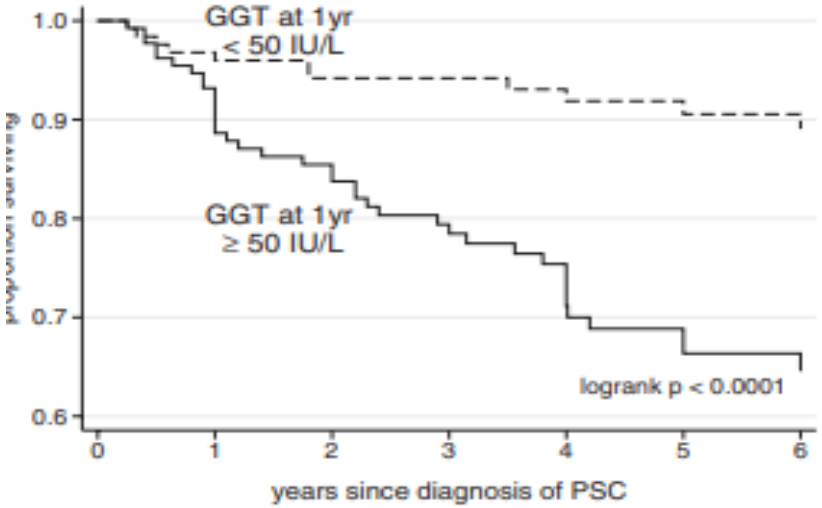
Event free survival: GGT decrease



Event free survival: GGT and treatment



Event free survival: normalizing GGT



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ORAL VANCOMYCIN

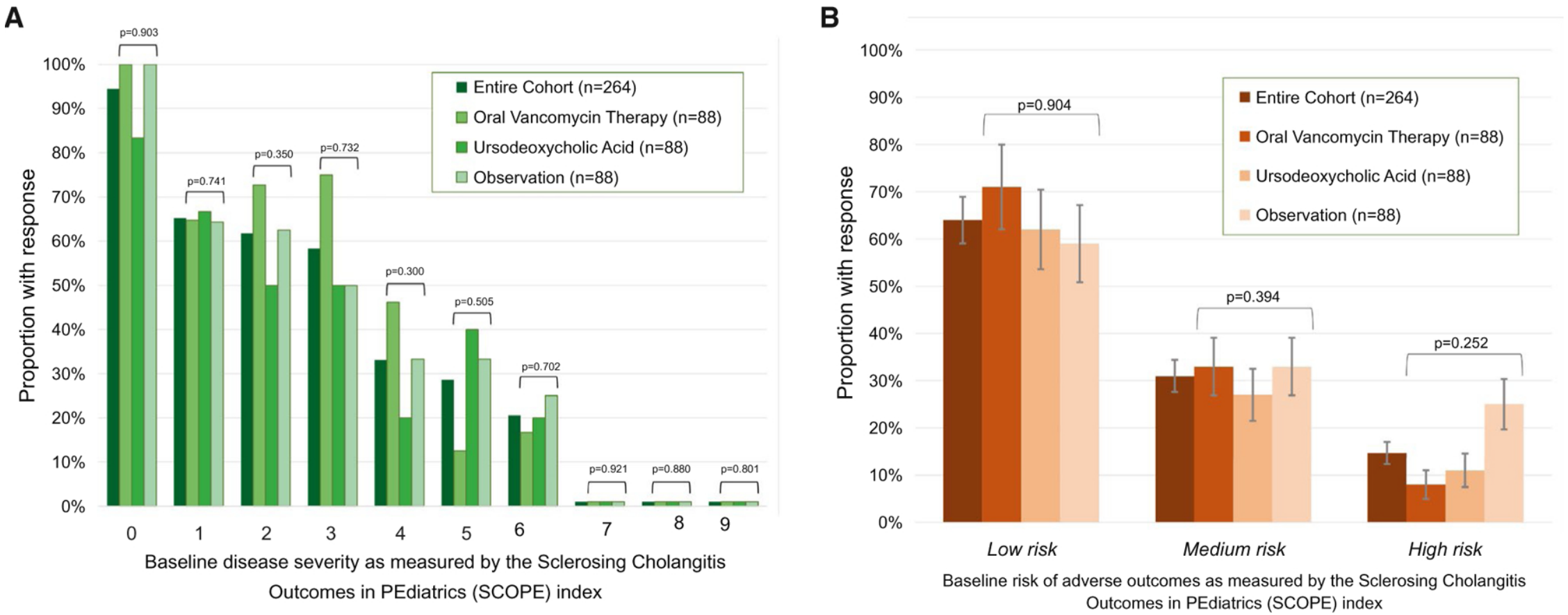
- PSC patients have reduced bacterial diversity and microbiome compared to health y patients.
- Driven interest in antibiotics- like Vancomycin, which may also act as an immunomodulator.
- Pediatric data limited: 2 studies with 14 patients (6 in both studies)
  - 50 mg/kg/day: 1-2 months post treatment, all lowered GGT. With 9/14 normalizing GGT to < 50.
    - The 4 non-responders were all cirrhotic.
    - GGT climbed with stopping Vanco in responders, and dropped when restarted
  - Describe non-specific improvements in histology and/or cholangiogram

Davies JPGN 2008
Abarbanel JCI 2013

Oral Vancomycin

- Current data suggest about 7% of pediatric PSC patients may be getting oral vancomycin
- We need more data
  - Optimal dose
  - Efficacy at different stages of disease
  - Efficacy with and without IBD
  - Risk of vancomycin resistant organisms

Pediatric PSC Consortium Analysis of Treatment



Baseline disease severity and risk of adverse outcomes similar

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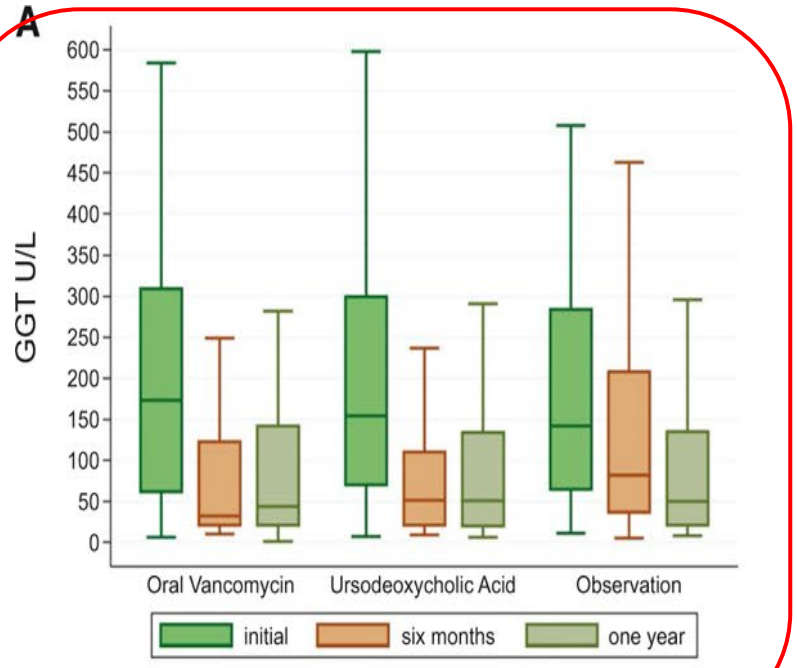
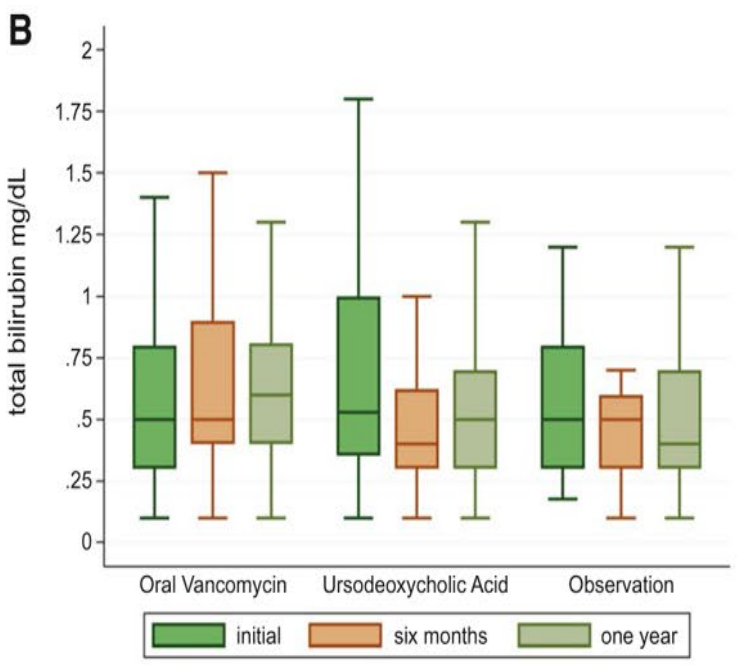
Biochemical Response to Treatment

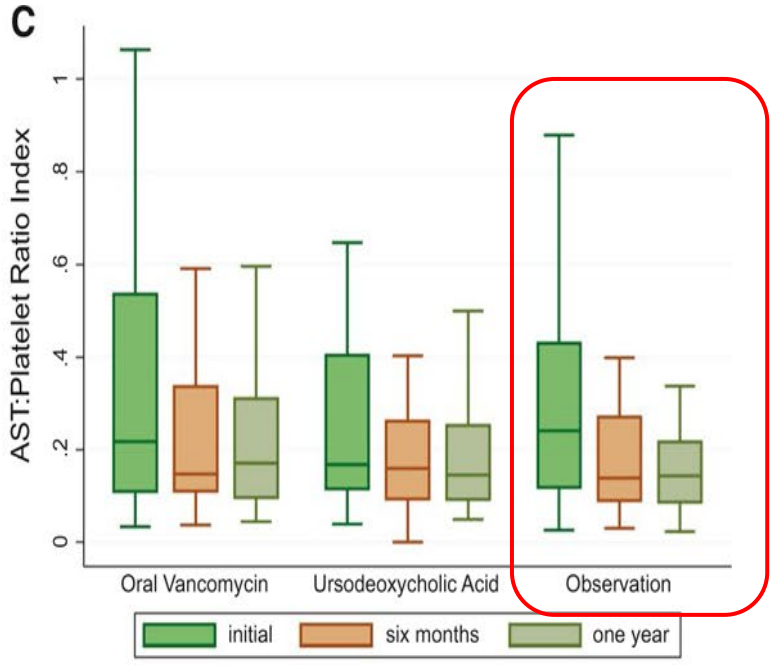
GGT



Bilirubin



AST: Platelet Ratio



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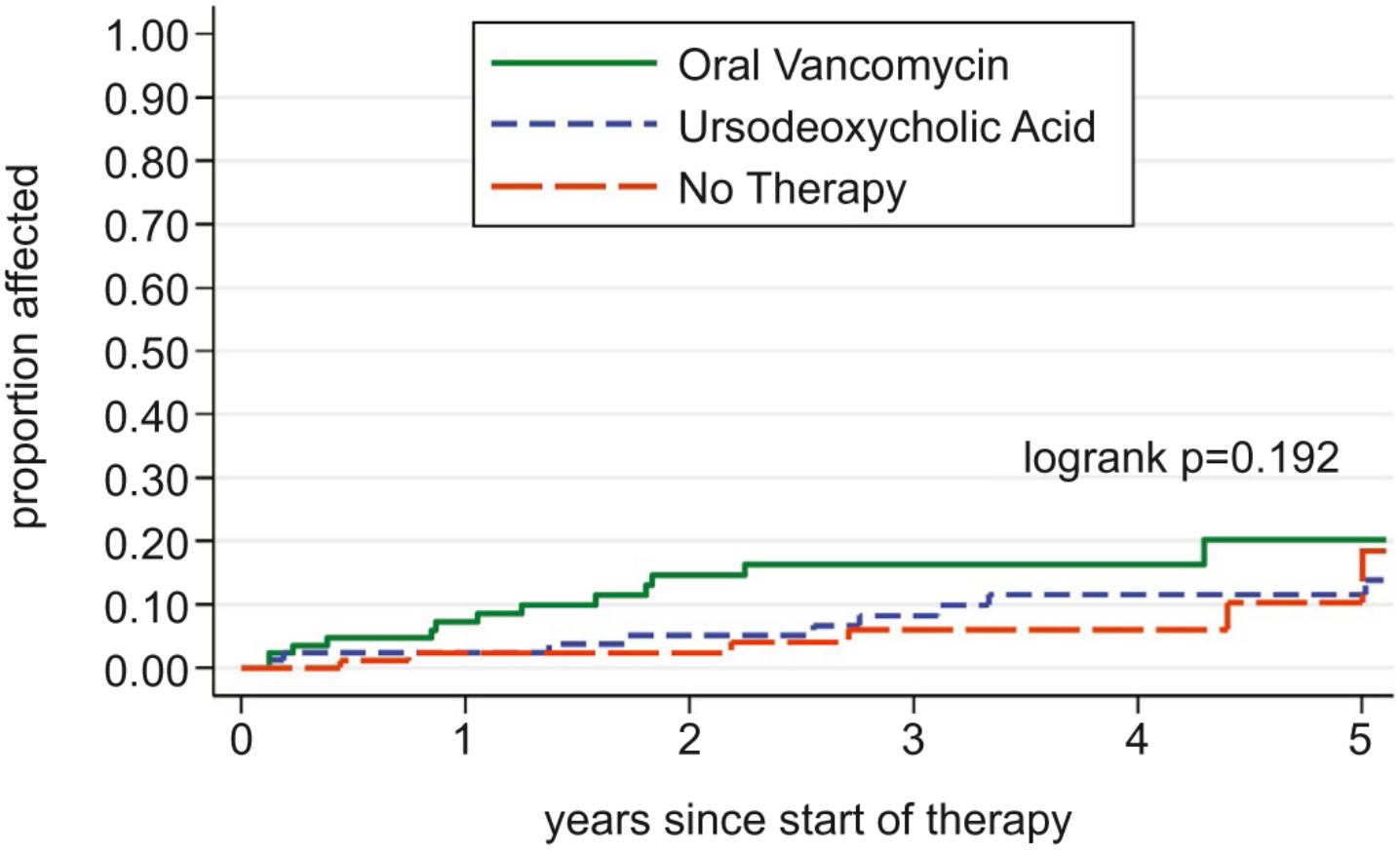
Biochemical Response at 1 Year, by Subgroup

	Oral Vanco	UDCA	Observation	*P* Value
Overall n = 264	53% (47/88)	52% (46/88)	50% (44/88)	0.918
IBD n = 227	58% (44/76)	55% (41/75)	50% (38/76)	0.678
No IBD n = 37	25% (3/12)	33% (4/13)	50% (6/12)	0.467
Large duct n = 218	46% (33/72)	47% (34/73)	52% (38/73)	0.788
Small duct n = 46	83% (13/16)	73% (11/15)	38% (6/15)	0.126
AIH n = 101	50% (18/36)	38% (11/30)	41% (14/35)	0.586
No AIH n = 163	56% (29/52)	59% (34/58)	57% (30/53)	0.935

Probability of Being Listed for Liver Transplant



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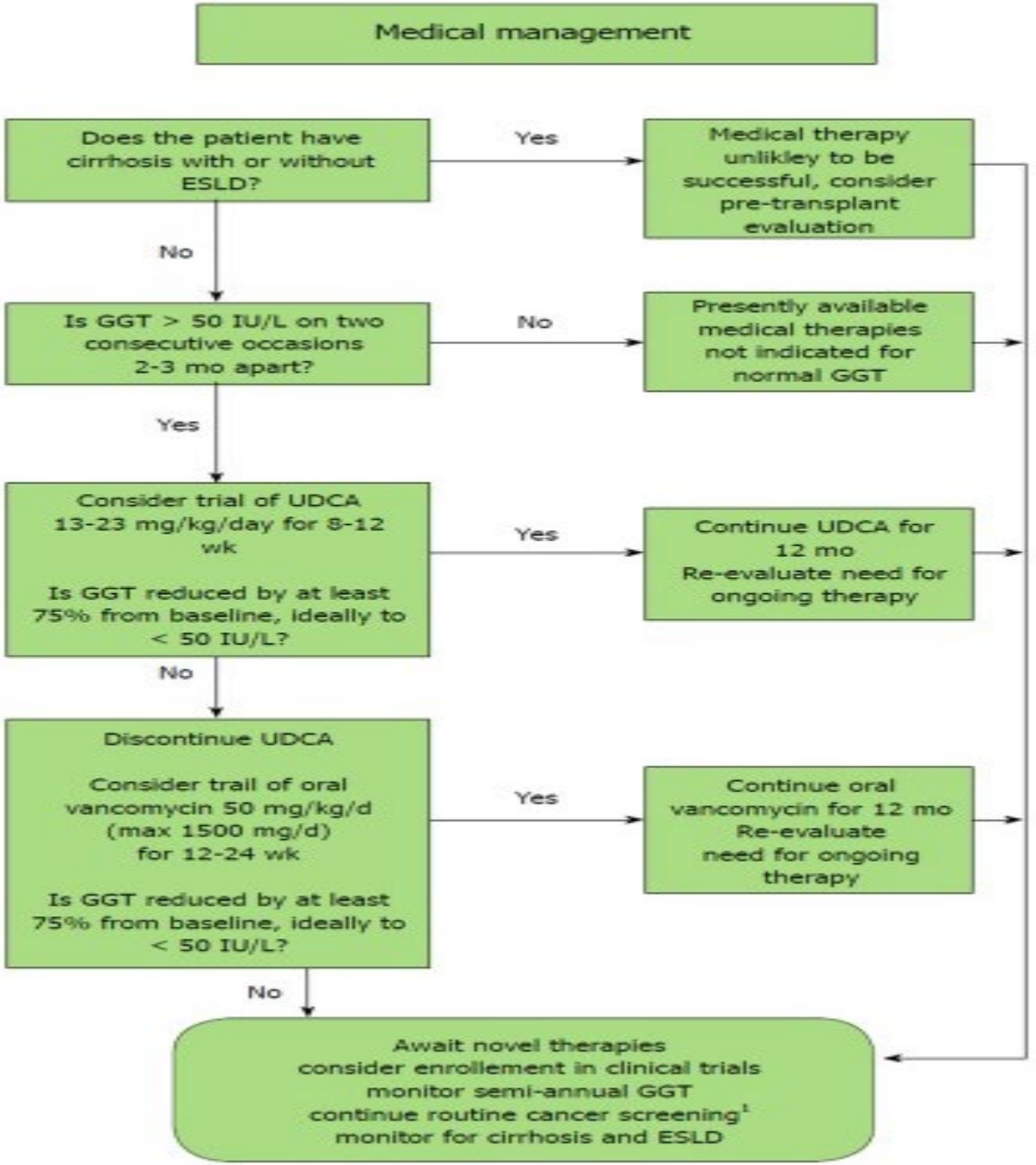
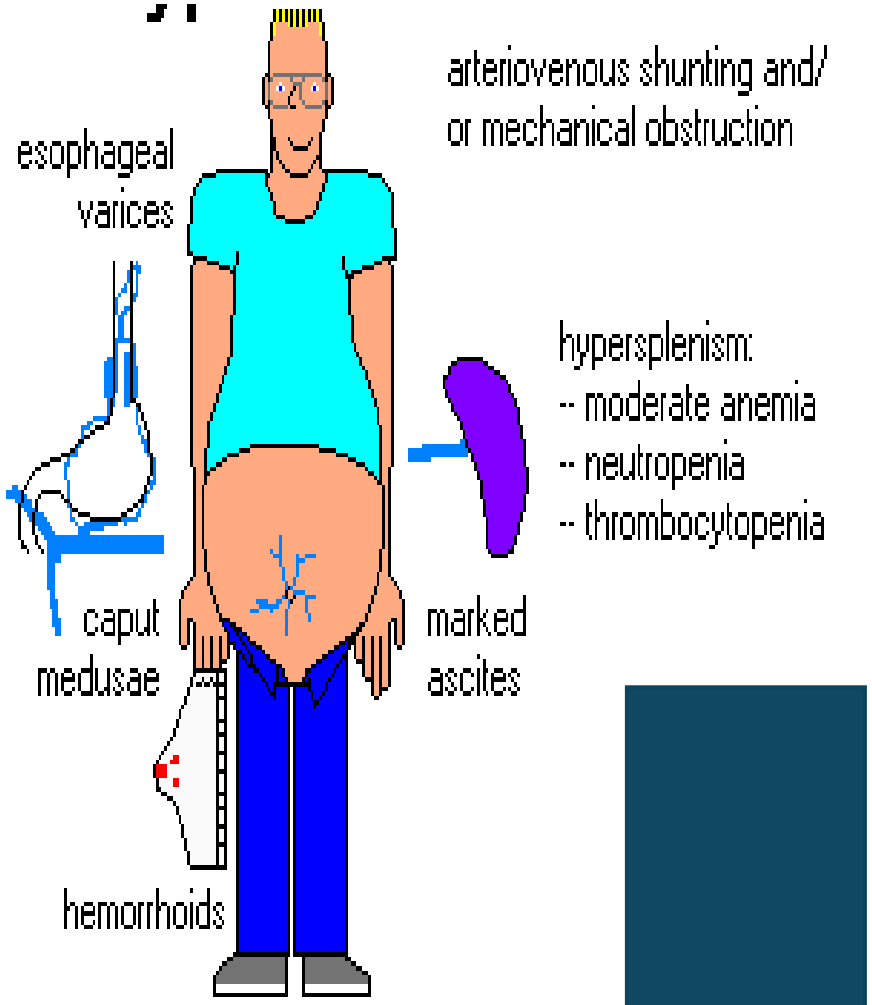


Laborda W J Hepatology 2019

HOW DO THINK ABOUT THE NEED FOR LIVER TRANSPLANT?

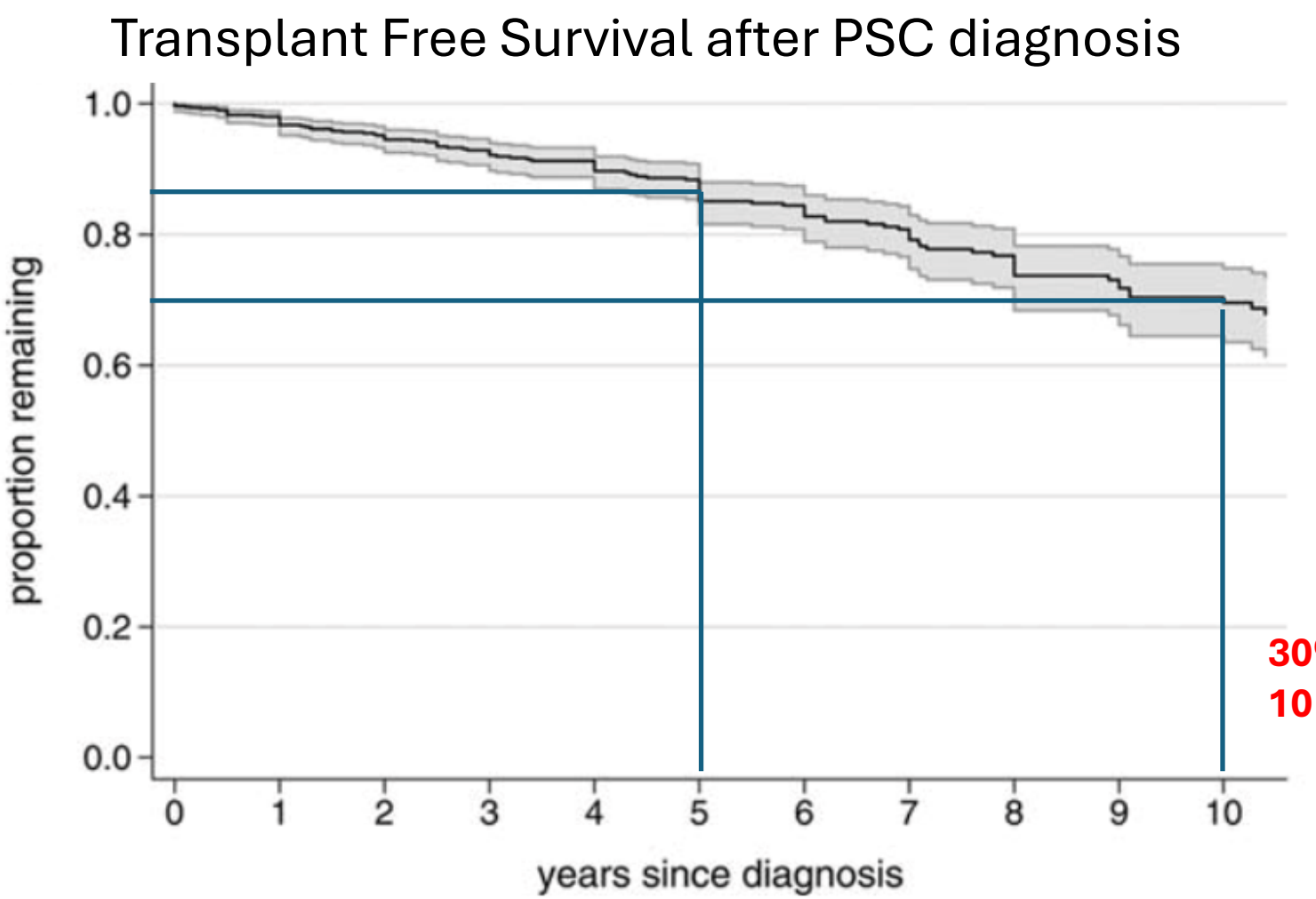
Indications for Liver Transplant in PSC

- Complications of end stage liver disease
  - Portal Hypertension
  - Bleeding
  - Intractable Ascites
  - Severe Fatigue
  - Itching
  - Encephalopathy
- Recurrent infection/cholangitis
- Early Stage Cholangiocarcinoma



discourseafghanistan.com

How common is LT for Pediatric PSC?



<3% of all pediatric LT is for PSC

30% LT at 10 years

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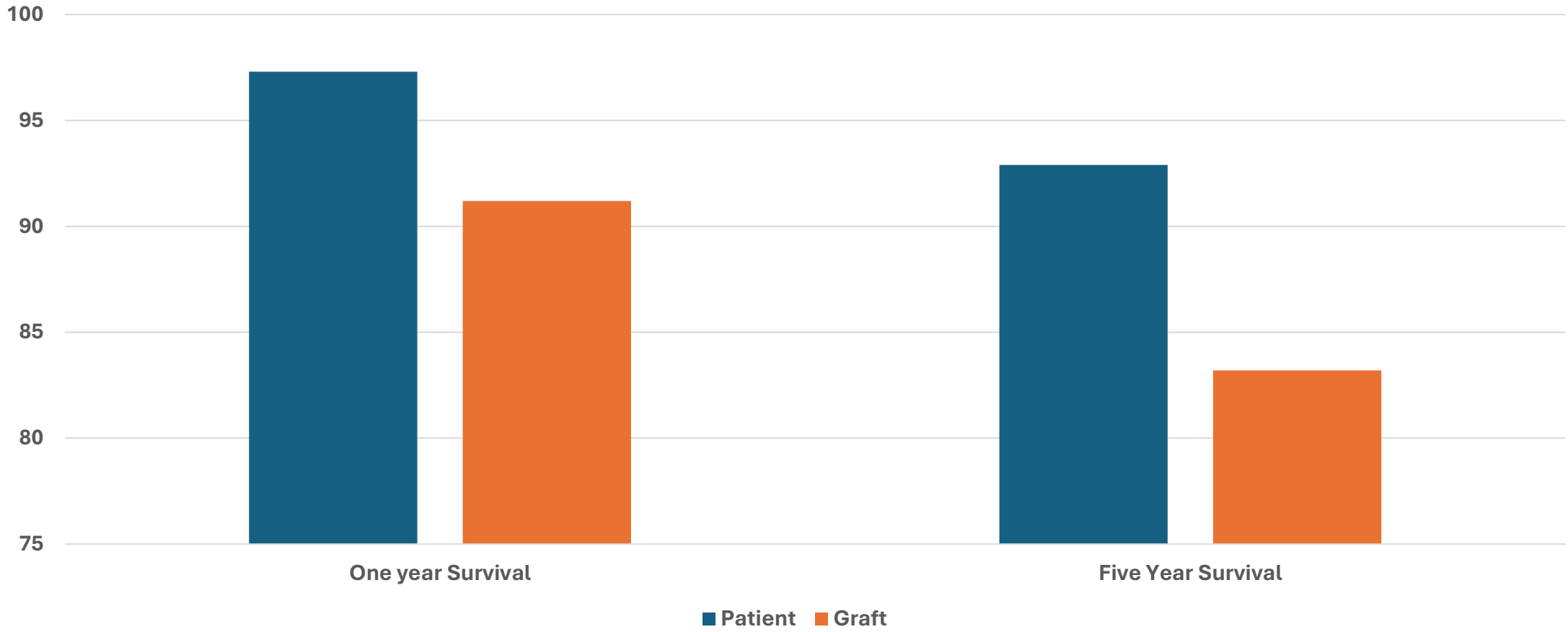
Does Inflammatory Bowel Disease (IBD) Change the Possibility of Liver Transplant?

- IBD is present in 76-81% of all PSC
  - 70-80% Ulcerative colitis/indeterminate
  - 20-30% Crohn's disease
  - May be diagnosed before or after PSC diagnosis
  - May be asymptomatic or symptomatic
  - Screening for IBD/PSC in affected patients is important
- Boston: LT 22% PSC with IBD vs 41% PSC without IBD
- PSC Consortium: PSC with IBD less likely (HR 0.63) to develop end stage liver disease needing LT vs PSC without IBD

Valentino JPGN 2016
Deneau Hepatology 2017

Post-Transplant Outcomes in Pediatric PSC



Jossen JPGN 2017

Post-Transplant: PSC Disease Recurrence

- Liver Transplant complication versus PSC recurrence
  - At least 6 months post-transplant
  - Cholestatic biochemical profile
    - Elevated GGTT, aminotransferases, bilirubin and bile acids
  - Multi-focal bile duct irregularity, beading, stricture
  - Exclusion:
    - Anastomotic biliary stricture
    - Hepatic artery thrombosis (vascular/ischemic stricture)
    - Chronic/ductopenic rejection
    - ABO incompatibility

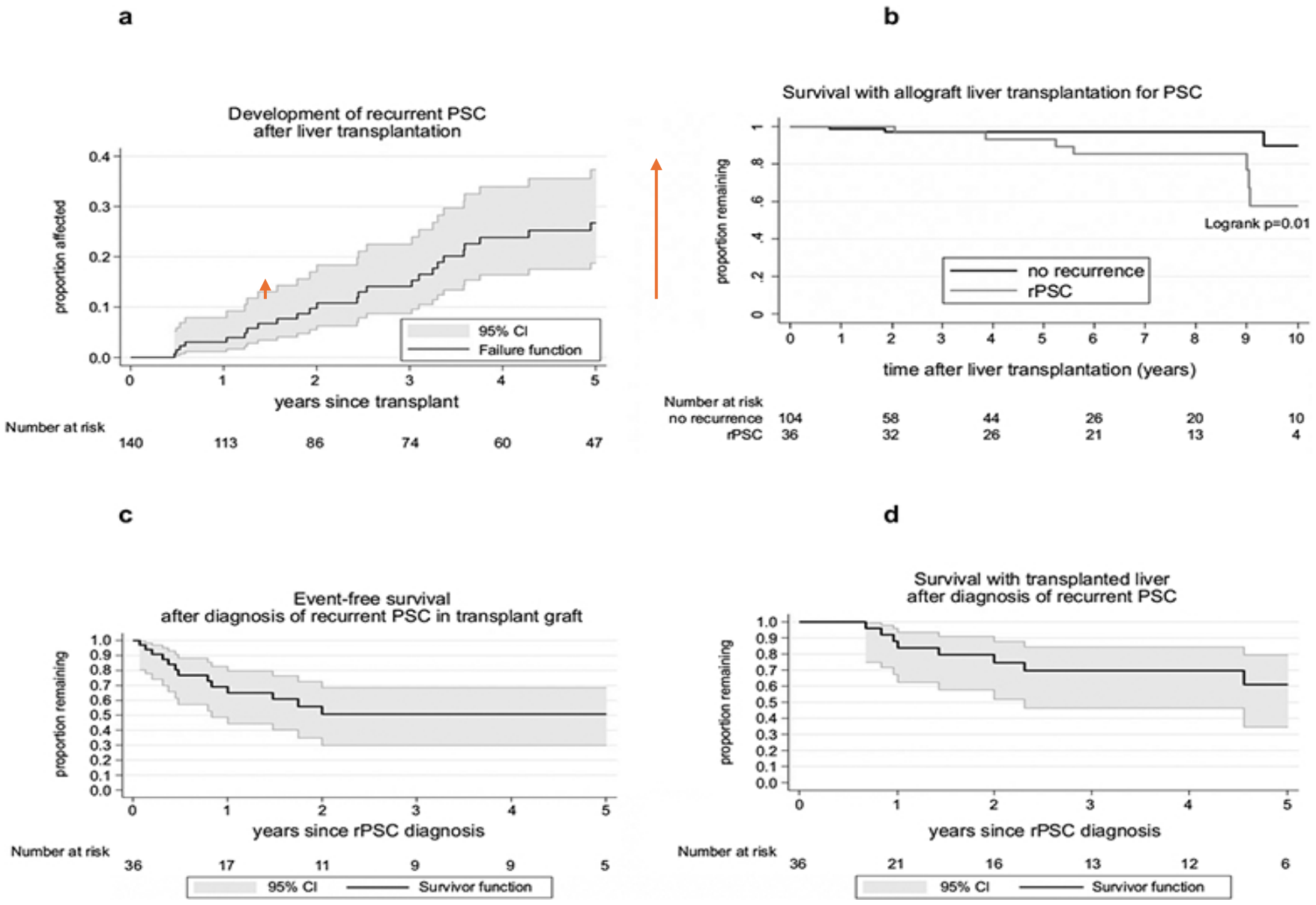
Soufi Current Gastro Reports 2018

Risk Factors for Recurrent PSC

- Younger age at transplant (not diagnosis): 12 vs 15 years
- Shorter duration between diagnosis and LT (2.2 vs 4.5 years)
- Overlaps syndrome (autoimmune hepatitis and PSC)
- Extended criteria donors
- Immunosuppression: thymoglobulin induction
- Recurrent acute cellular rejection
- Presence of IBD (86% in rPSC vs 66% in no recurrence)
  - Colectomy before or at the time of LT **may have a protective effect against recurrent PSC** by removing inflammatory triggers
  - The presence of an intact colon post-LT **increases rPSC risk**, suggesting a gut-liver axis involvement in disease recurrence

Soufi Current Gastro Reports 2018
Venkat Expert Reviews in Gastro and Hep 2018
Liberal Liver Tran 2016
Martinez Hepatology 2022

Recurrent PSC: Impact on Outcomes



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Thank You!
Questions?
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