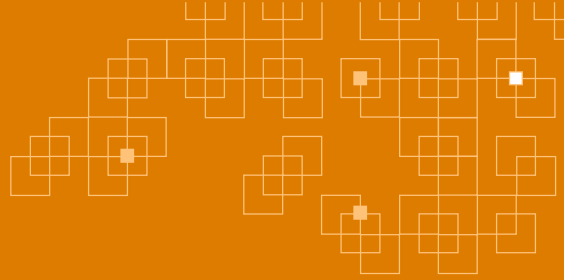

THE FORUM
For Collaborative Research℠

Phase 3 Trial Endpoints

Gideon Hirschfield, *University of Toronto*

Berkeley Public Health

Phase 3 Trial Endpoints

PSC Forum, September 2019

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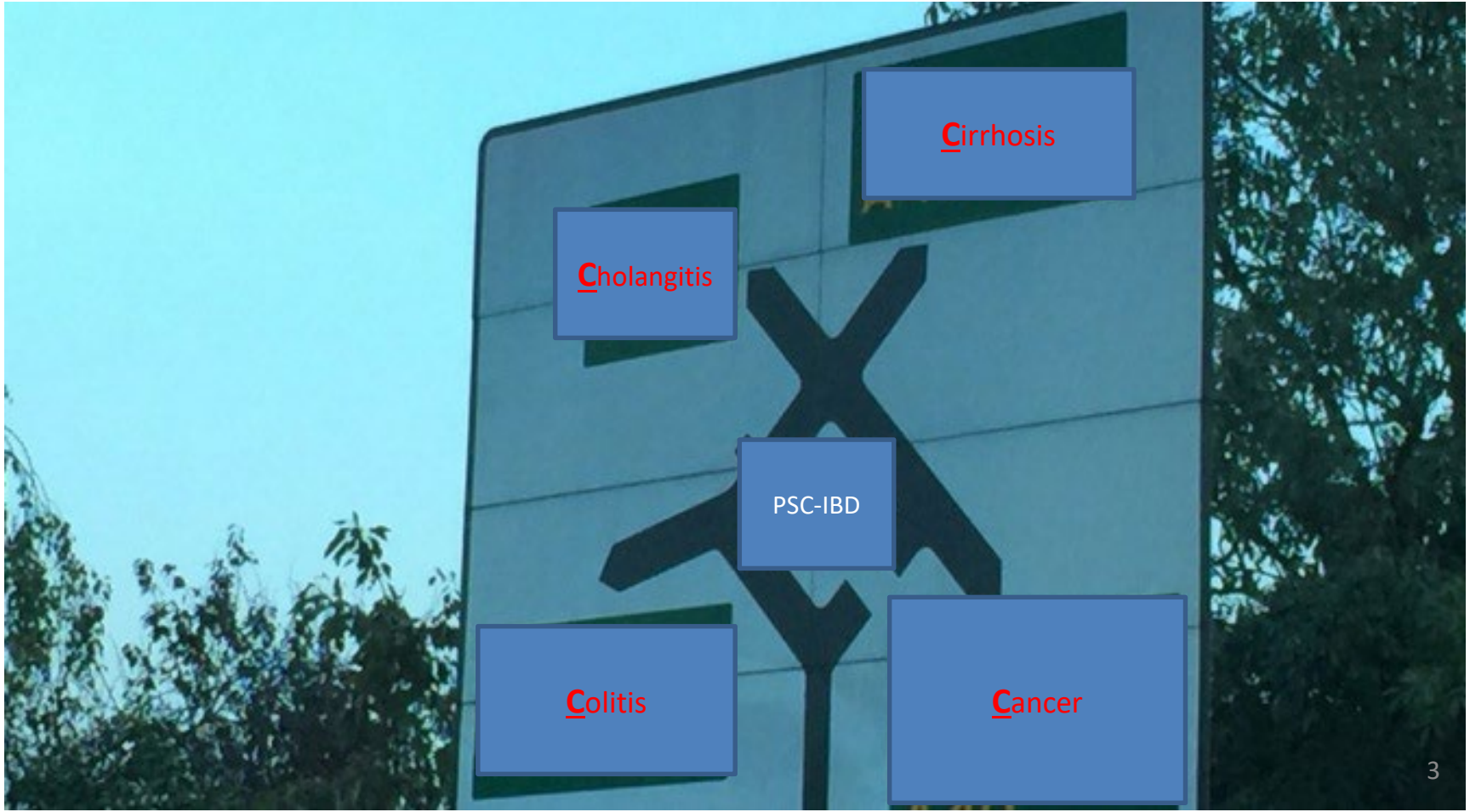
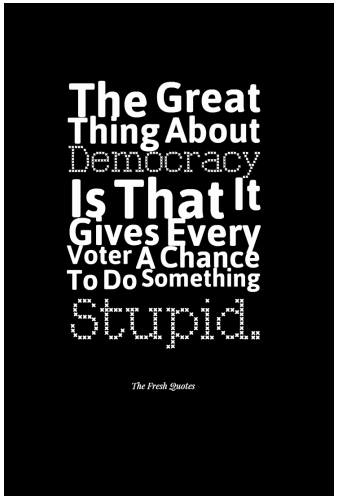
TORONTO CENTRE FOR LIVER DISEASE

Medicine
UNIVERSITY OF TORONTO

"If it looks good, you'll see it. If it sounds right, you'll feel it. If it's marketed right, you'll buy it. But...if it's real, you'll feel it." – Kid Rock "Let's rock on."

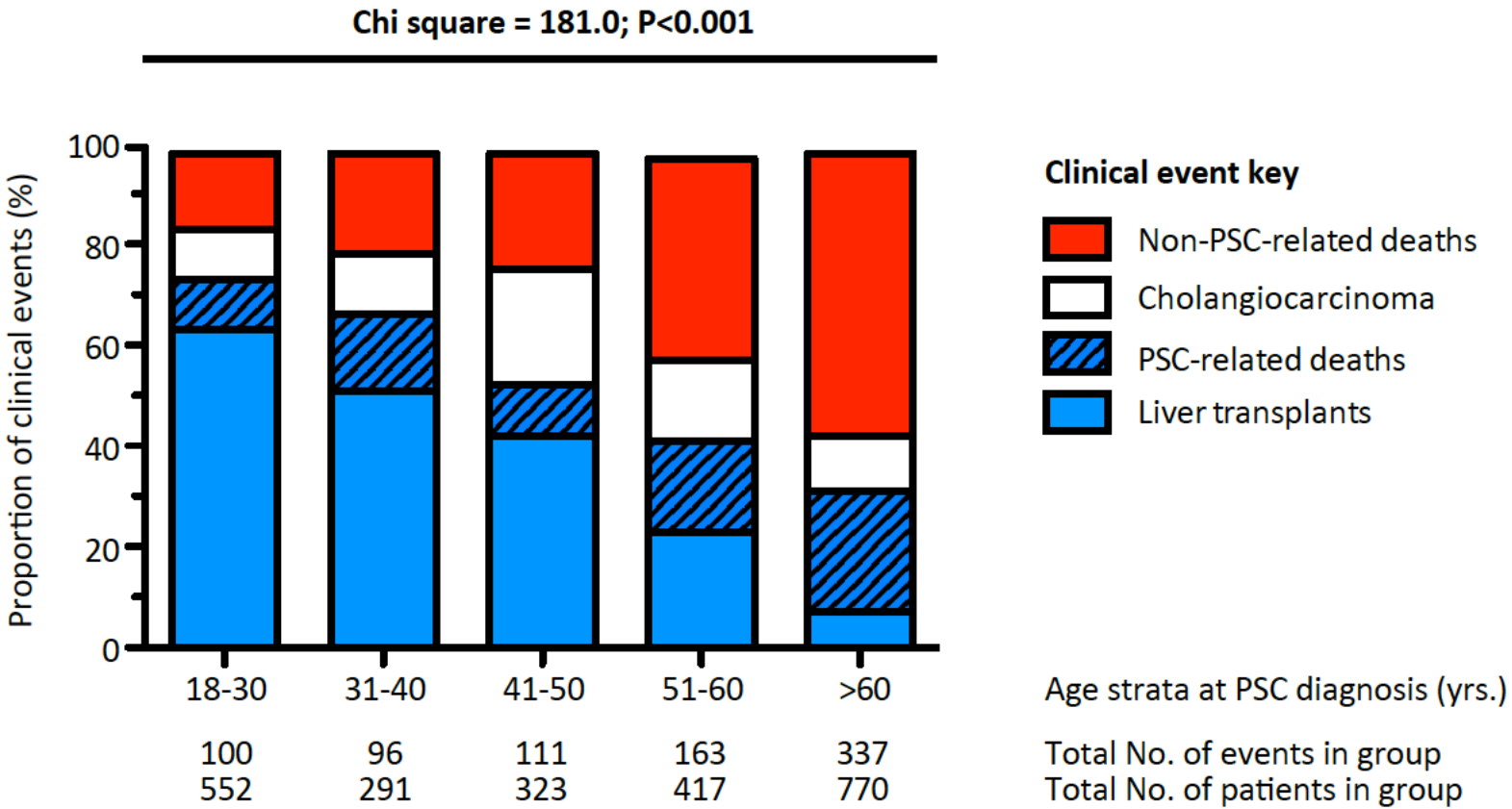


Hepatologists keep trying to leave UDCA zone..



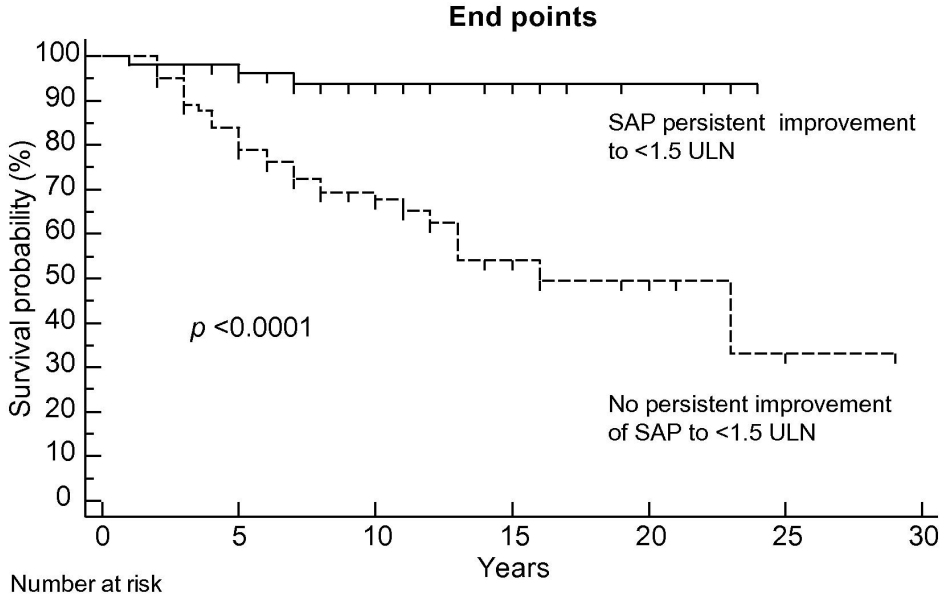
- "UDCA does work; the trials are just wrong"
- "We all know the trial is not going to be positive'
- "We can't take part in that trial because patients won't agree to biopsies…"
- "But clearly the disease is a consequence of xx so you can't treat with…"
- "I believe in early adoption as it is obvious yy works…"
- **"What is the pathway to approval?"**

The proportion of first clinical events attributable to liver transplantation, PSC-related death, cholangiocarcinoma and non-PSC-related death



Trivedi et al. In Prep.

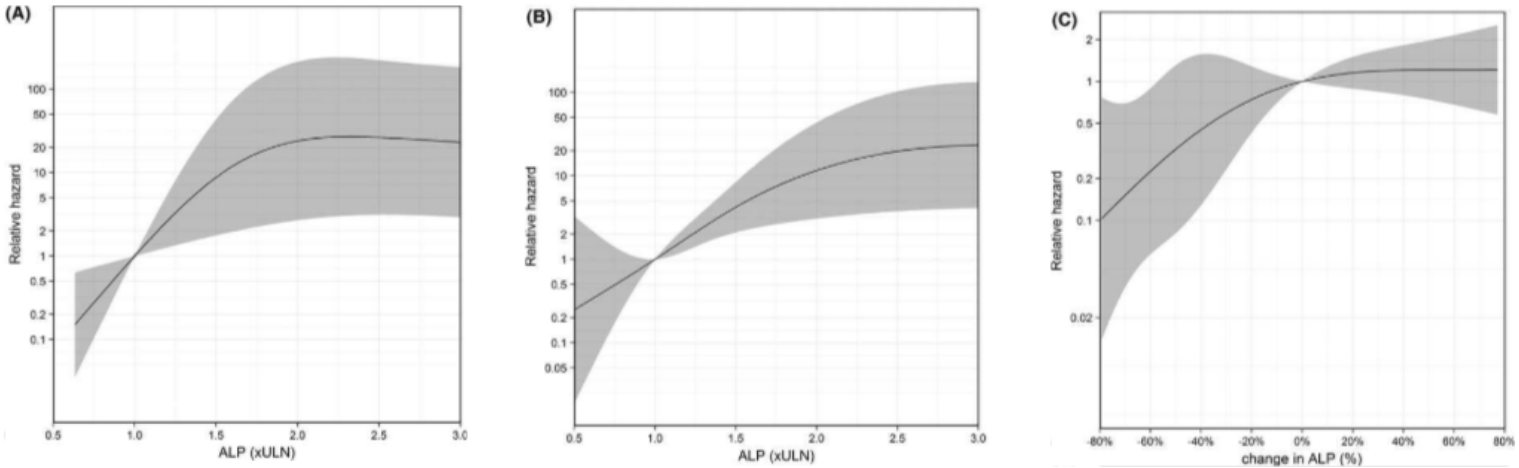
Survival in PSC and serum ALP values



Number at risk							
Group: No SAP improvement to <1.5 ULN	84	60	29	12	4	1	0
Group: SAP improvement to <1.5 ULN	55	46	22	12	5	0	0

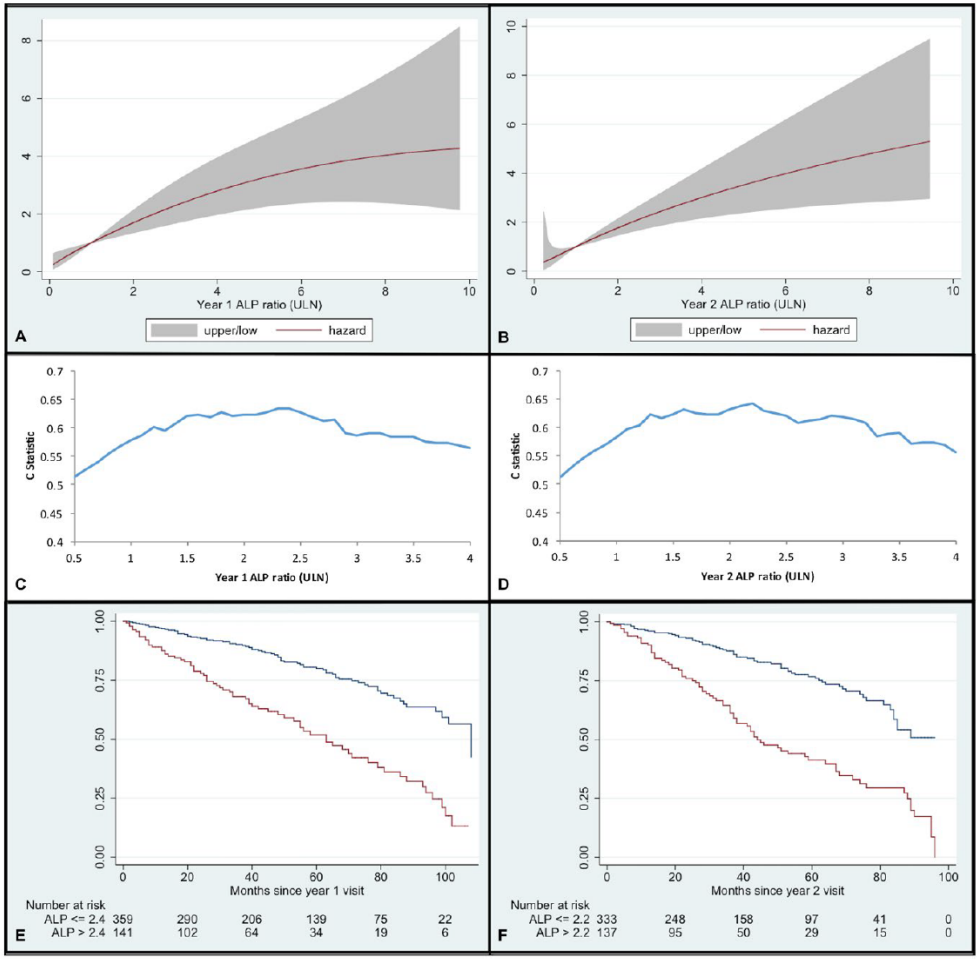
Journal of Hepatology 2013; 58:329-334

- Retrospective study, 366 patients with PSC were followed for a median of 100 months (67,150)
  - 66 (18%) had an outcome of PSC related death or liver transplant
- Hazard ratio increased with increasing ALP in a range from 0.5-2.5xULN at both T0 (Fig A) and T1 (Fig B), and patients with a reduction in ALP from T0 to T1 also had a reduction in hazard ratio (Fig C)
  - In this cohort of patients the optimal cutoff was found to be ALP <1.3xULN

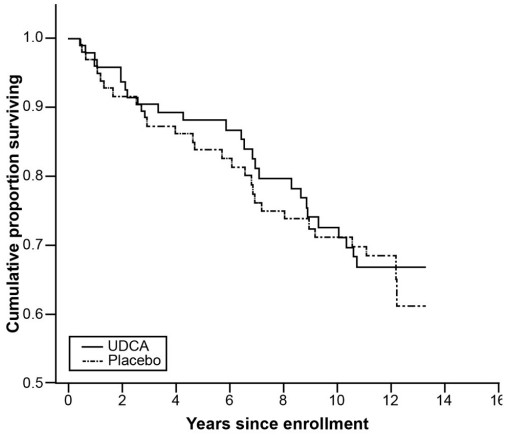


de Vries EMG, et al.. Liver Int. 2016;36:1867–1875.

Predictive value of ALP and outcome



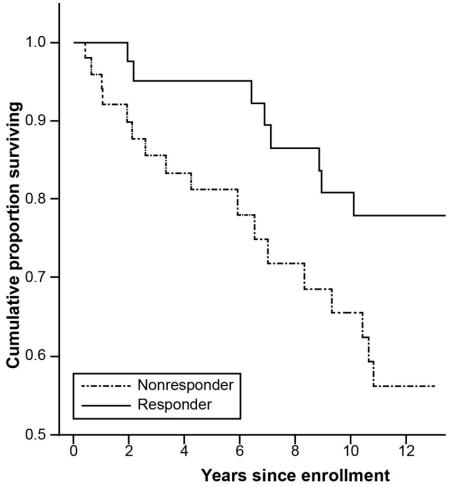
Association Between Reduced Levels of Alkaline Phosphatase and Survival Times of Patients With Primary Sclerosing Cholangitis



Numbers at risk

Years	0	2.5	5	7.5	10	12.5
UDCA	97	84	78	56	51	20
Placebo	101	84	72	59	56	19

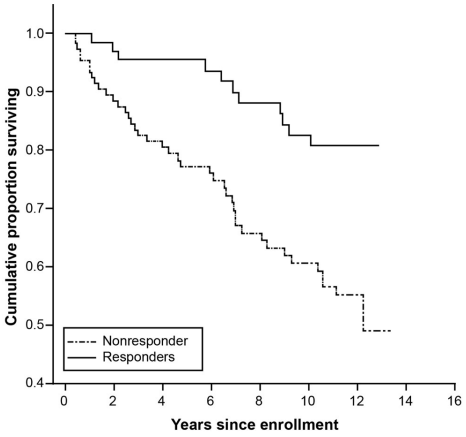
198 patients enrolled in the 5-year Scandinavian UDCA trial in 1996 randomized to UDCA vs placebo with extended follow-up



Numbers at risk

Years	0	2.5	5	7.5
Responder	43	40	34	24
Nonresponder	51	45	35	19

UDCA-treated patients with a biochemical response (ie, normal or ≥40% reduction in ALP after 1 year in the trial) vs nonresponders



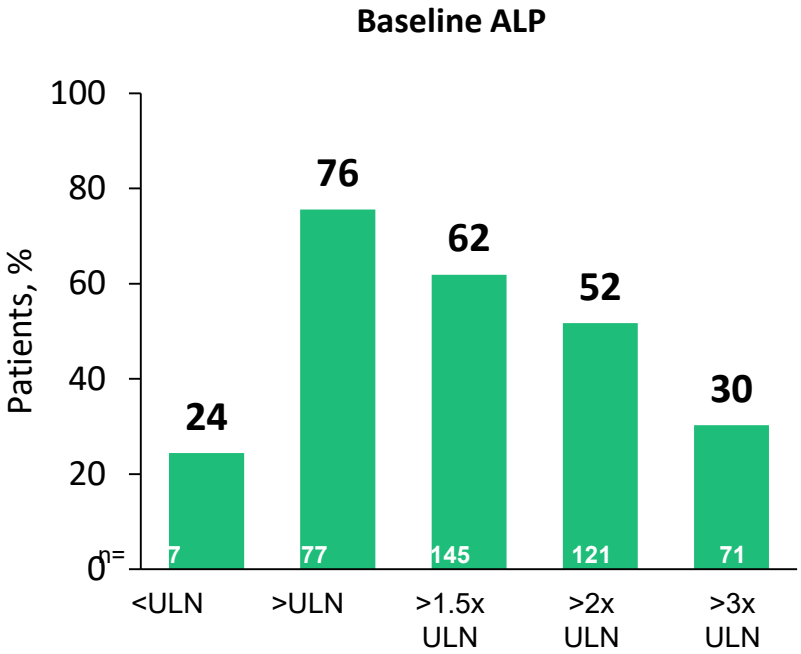
Numbers at risk

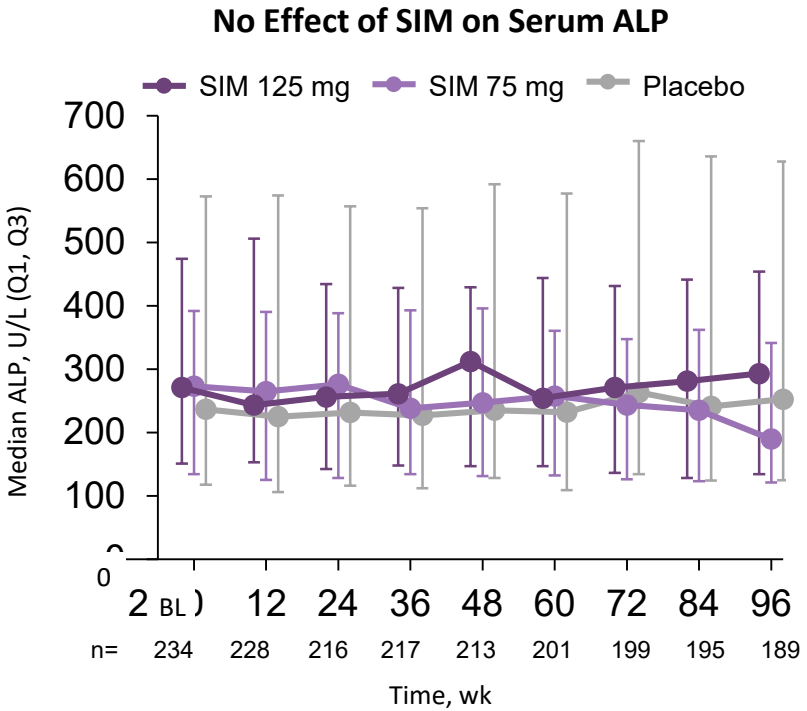
Years	0	2.5	5	7.5	10	12.5
Responders	79	72	69	56	53	17
Nonresponders	116	93	78	56	52	21

Biochemical responders vs nonresponders, regardless of treatment with UDCA (P = .0001, log-rank test)

Clinical Gastroenterology and Hepatology
Volume 11, Issue 7, Pages 841-846 (July 2013)

Serum ALP in SIM study

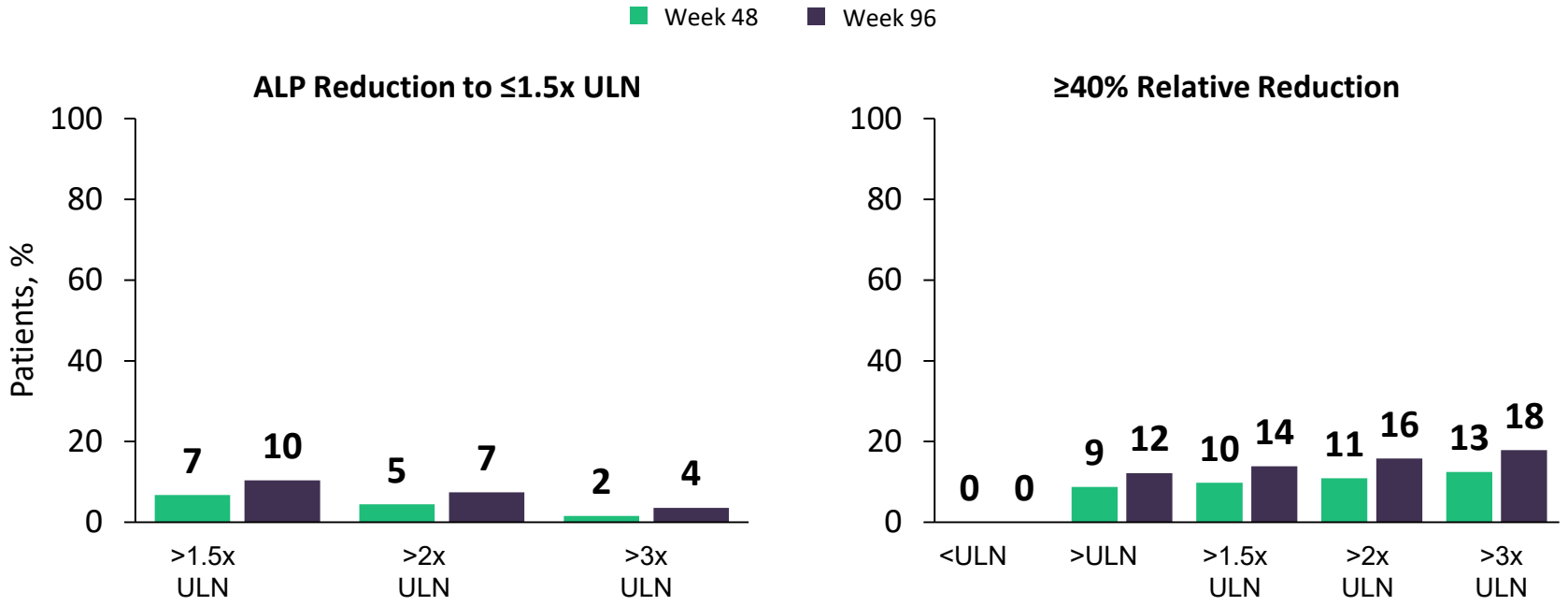




Muir AJ, et al. Hepatology 2019;69:684-98.

Trivedi et al. In Prep.

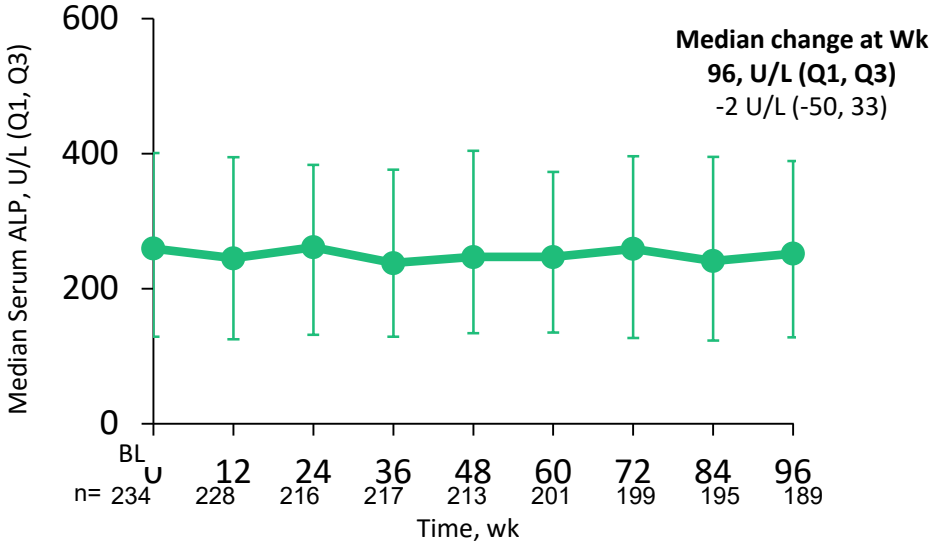
Spontaneous Reductions in Serum ALP



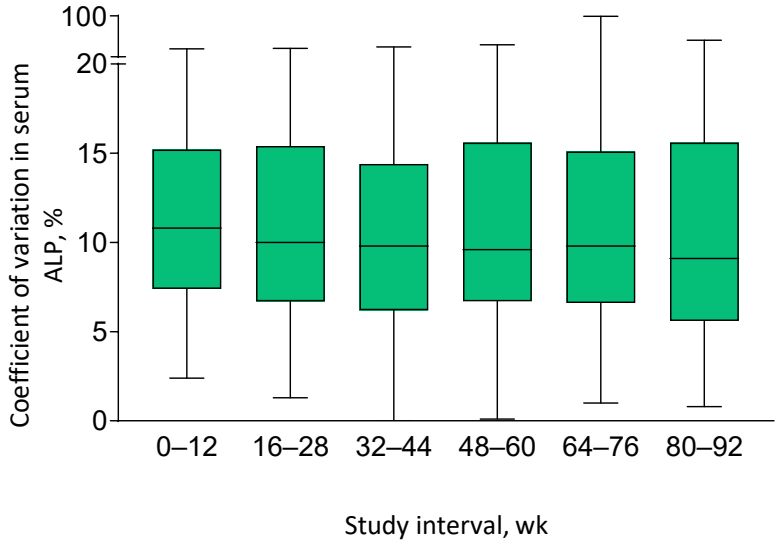
Trivedi et al. In Prep.

Serum ALP is Widely Variable

Inter-Individual Variability



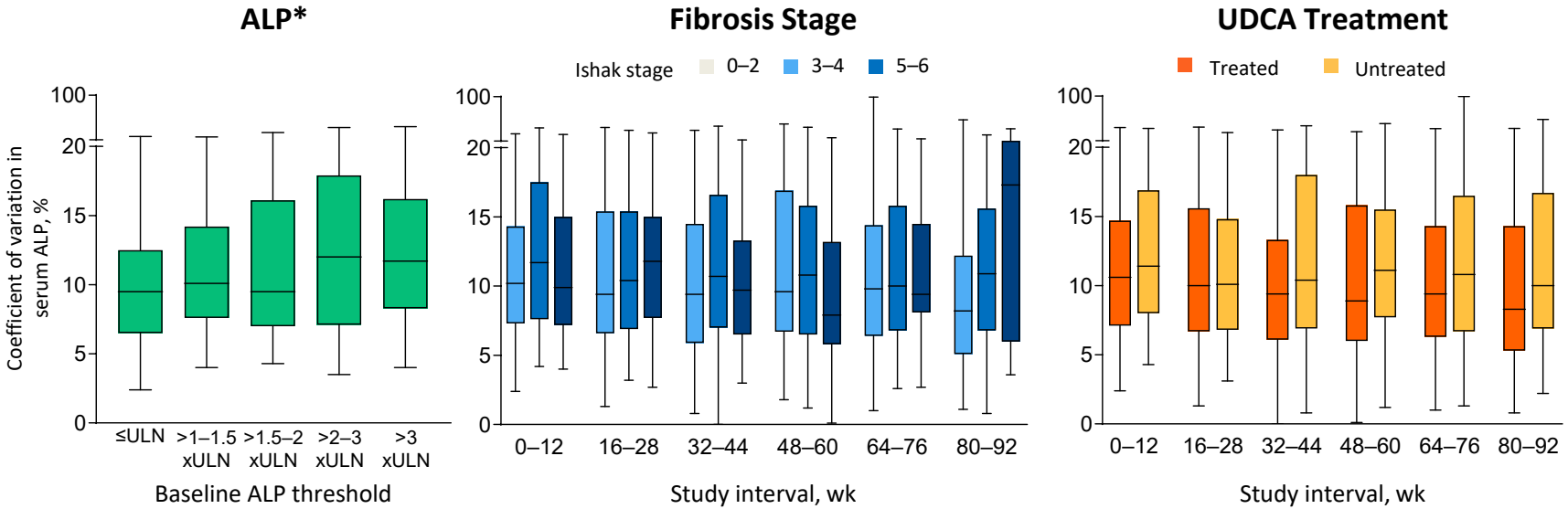
Intra-Individual Variability



- **Overall, ALP did not change between baseline and Wk 96**
- **Median per-patient CV was 11.5% (IQR 8.9, 14.2), but varied widely**

Trivedi et al. In Prep.

Impact of Baseline Factors on ALP Variability

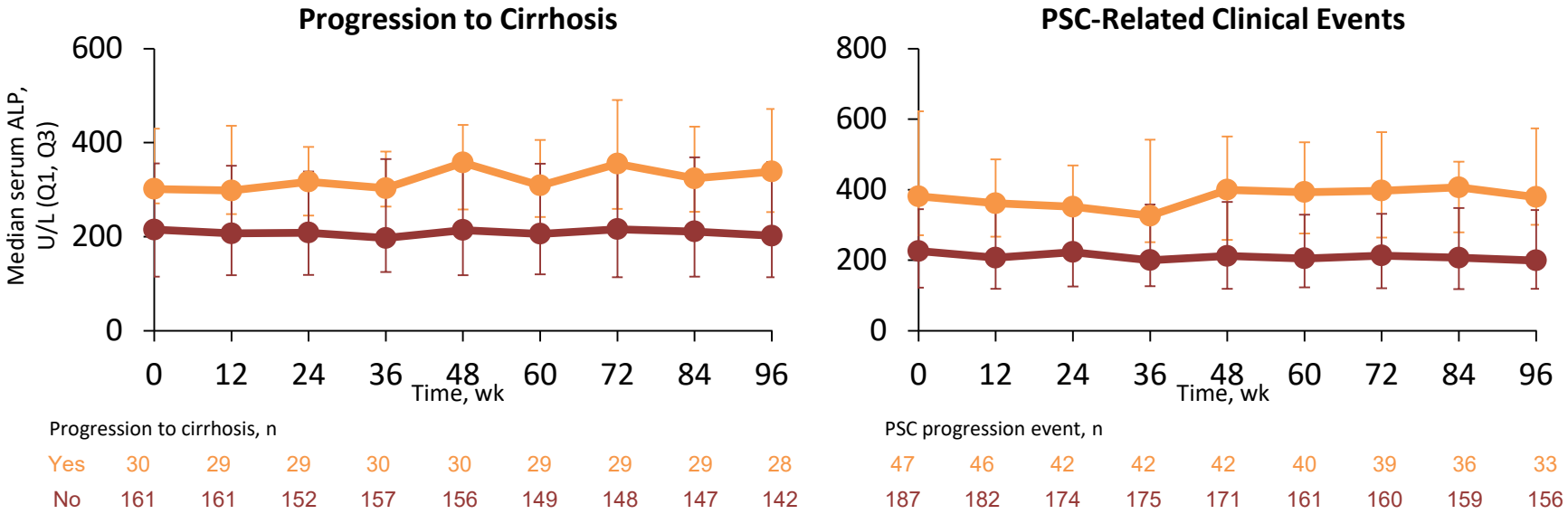


- **Variability in serum ALP was not influenced by baseline ALP, fibrosis stage, UDCA treatment, IBD phenotype, extent of ductal involvement, history of ascending cholangitis, or treatment arm**

* Data for study interval Wk 0–12.

Trivedi et al. In Prep.

Prognostic Utility of Serum ALP



Progression to cirrhosis, n									
Yes	30	29	29	30	30	29	29	29	28
No	161	161	152	157	156	149	148	147	142

PSC progression event, n								
47	46	42	42	42	40	39	36	33
187	182	174	175	171	161	160	159	156

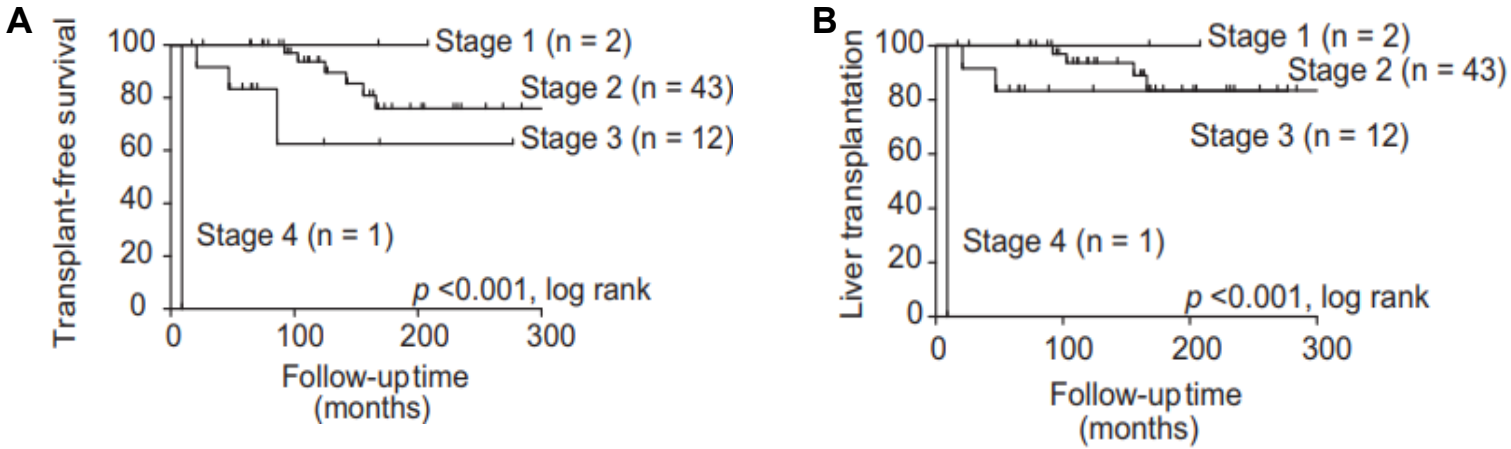
- **Baseline serum ALP was associated with:**
  - **Progression to cirrhosis (OR per 10-U/L: 1.02; 95% CI 1.00, 1.03)**
  - **PSC-related clinical events (HR per 10-U/L: 1.02; 95% CI 1.01, 1.02)**
- **Changes in serum ALP from baseline to Wk 12, 24, and 48 were not prognostic**

CI, confidence interval; OR, odds ratio; HR, hazard ratio.

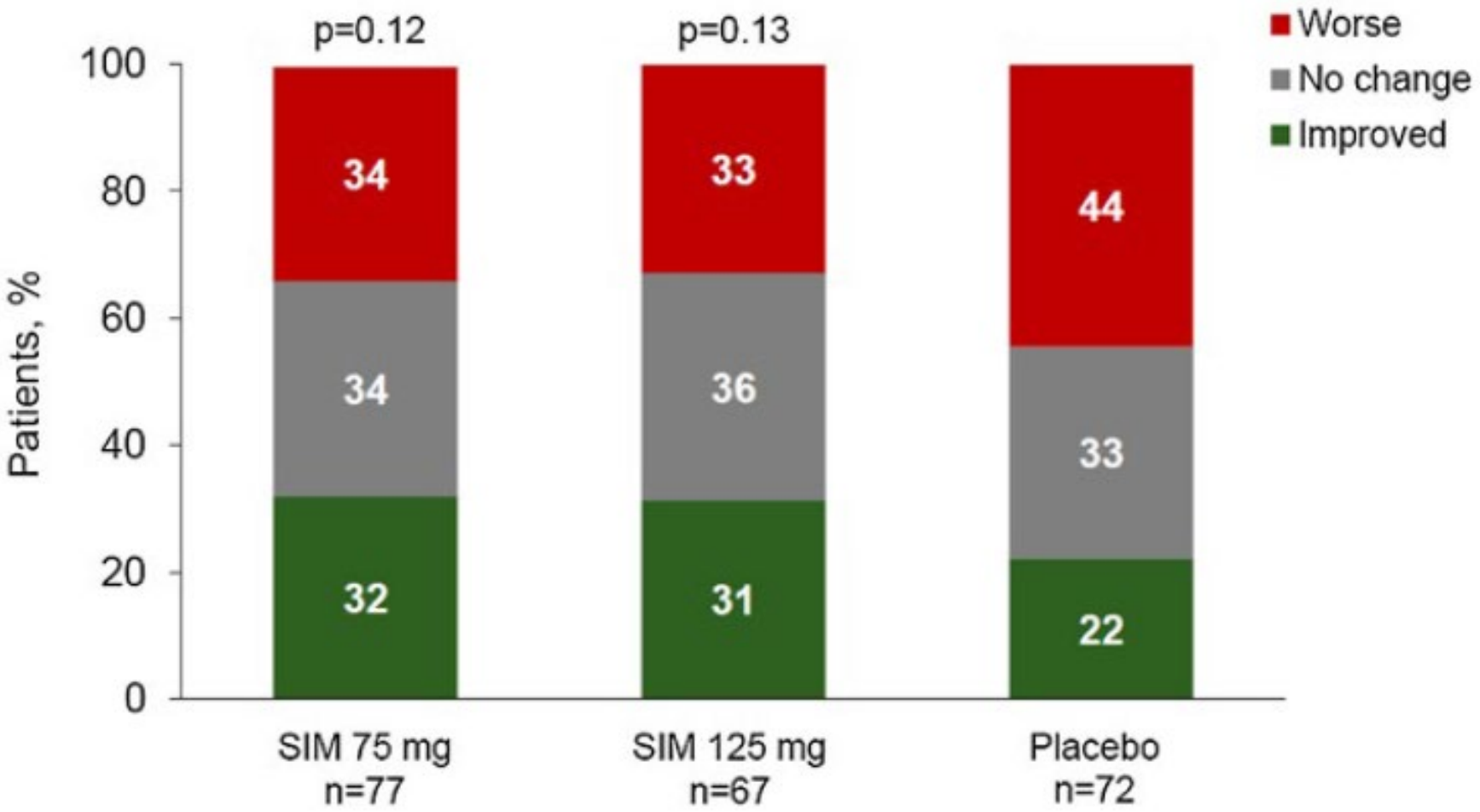
Trivedi et al. In Prep.

Liver histology and PSC outcome

- 4 observational publications with long-term follow-up comprising 826 cases demonstrated that Ludwig stage was independently associated with death/Ltx
- de Vries et al. assessed the prognostic value of Ludwig, Ishak, and Nakanuma scoring systems in 64 patients with PSC with a median follow up of 112 months
  - Outcomes included PSC related death, PSC related malignancies, LTx and cirrhosis-related symptoms
  - In univariate analysis, Ishak, Nakanuman and Ludwig stage all associated with transplant free survival and time to liver transplant but not cirrhosis related symptoms (Nakanuma KM Shown below)
  - Nakanuma staging had a larger hazard ratio than Ishak/Ludwig



de Vries EMG, et al J. *Hepatology*. 2015;63:1212-1219.



Muir et al. 2019

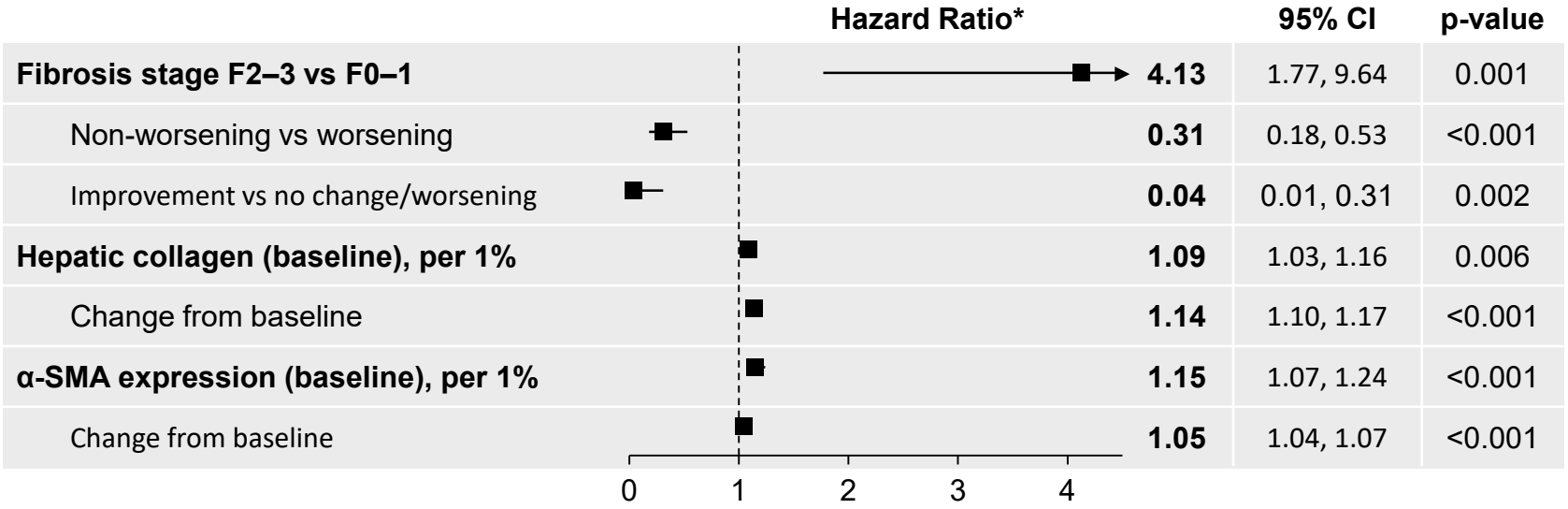
Changes in Ludwig Fibrosis Stage

	n (%)	Ludwig Stage at Week 96				
		F0 n=14	F1 n=43	F2 n=39	F3 n=49	F4 n=28
Baseline	F0 n=17	6 (35)	9 (53)	2 (12)	0	0
	F1 n=34	5 (15)	12 (35)	12 (35)	3 (9)	2 (6)
	F2 n=48	2 (4)	14 (29)	13 (27)	16 (33)	3 (6)
	F3 n=74	1 (1)	8 (11)	12 (16)	30 (41)	23 (31)

- **Fibrosis progression in 40% and fibrosis regression in 24% between baseline and Week 96**
  - **Progression to cirrhosis in 16%**

Bowlus et al.

Associations Between Histologic Features and Disease Progression



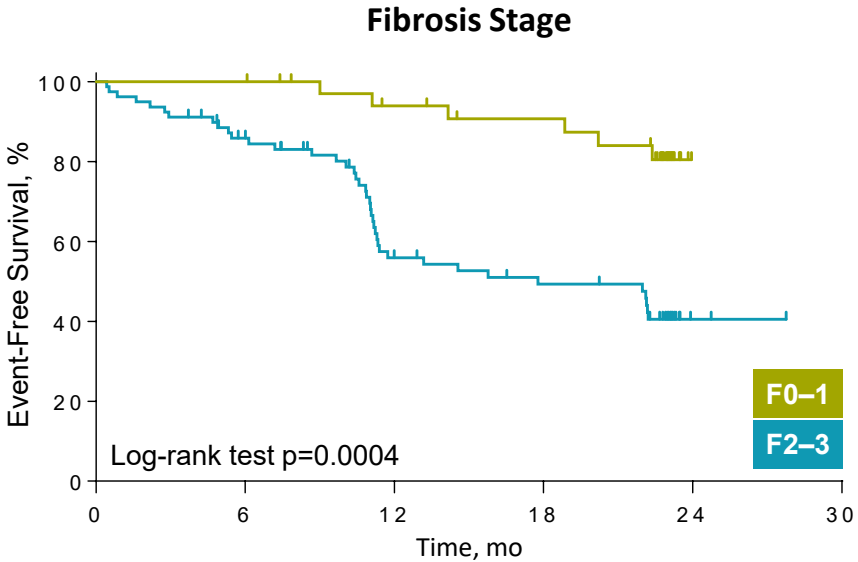
	Hazard Ratio*	95% CI	p-value
Fibrosis stage F2–3 vs F0–1	**4.13**	1.77, 9.64	0.001
Non-worsening vs worsening	**0.31**	0.18, 0.53	<0.001
Improvement vs no change/worsening	**0.04**	0.01, 0.31	0.002
Hepatic collagen (baseline), per 1%	**1.09**	1.03, 1.16	0.006
Change from baseline	**1.14**	1.10, 1.17	<0.001
α-SMA expression (baseline), per 1%	**1.15**	1.07, 1.24	<0.001
Change from baseline	**1.05**	1.04, 1.07	<0.001

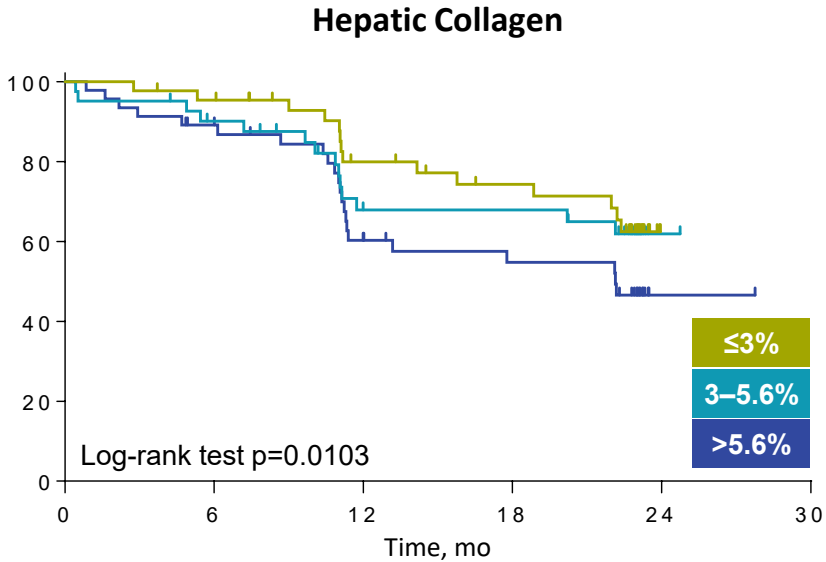
- **Increased risk of events associated with:**
  - **More severe fibrosis at baseline (F2–3; greater collagen and α-SMA expression)**
  - **Worsening of fibrosis (by Ishak stage, collagen content, α-SMA)**

* Separate multivariate models run with baseline and change from baseline for each variable.
Hazard ratios for changes from baseline adjusted for baseline value.

Bowlus et al.

F2-3 Fibrosis and Greater Hepatic Collagen Associate with Increased Risk of Disease Progression





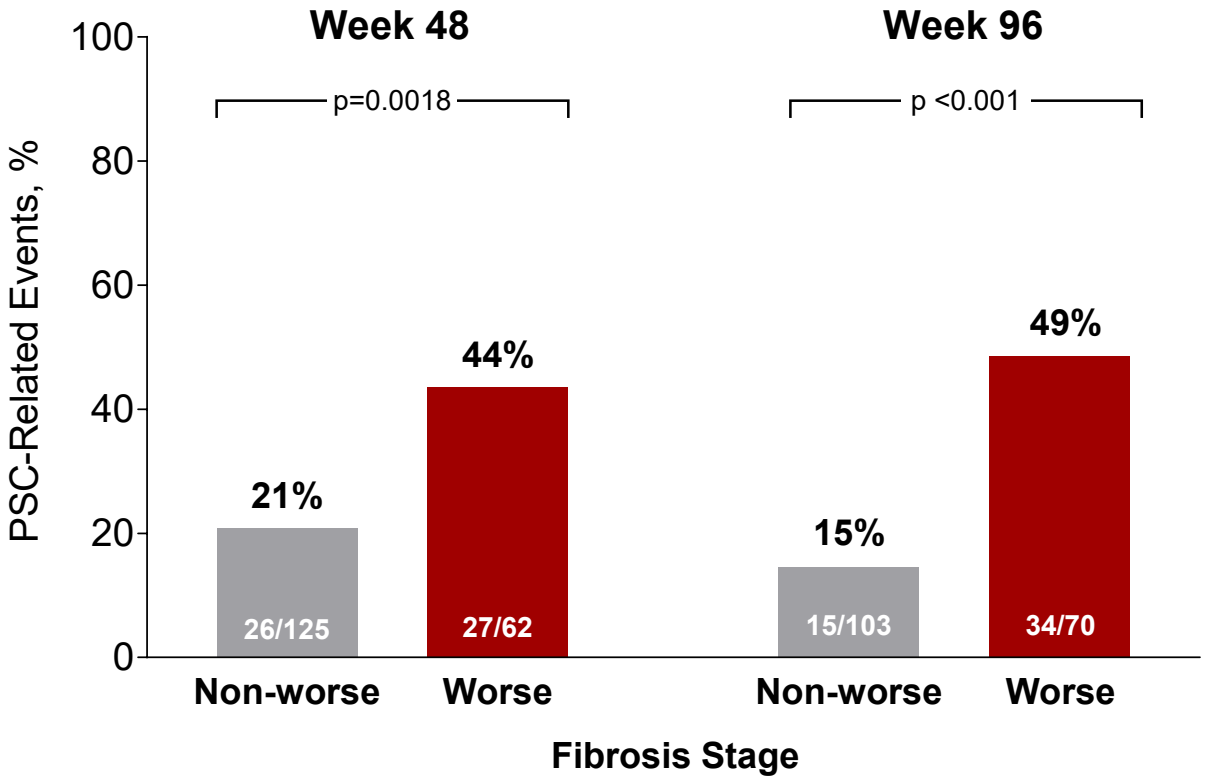
N at risk (Events)

60 (0)	60 (0)	60 (0)	57 (0)	54 (2)	51 (3)	51 (3)	49 (5)	0 (6)	0 (6)	0 (6)
149 (0)	142 (7)	133 (11)	125 (14)	97 (39)	93 (41)	90 (43)	89 (43)	2 (50)	1 (50)	0 (50)

71 (0)	70 (1)	68 (2)	64 (2)	57 (8)	54 (9)	52 (10)	51 (11)	0 (14)	0 (14)	0 (14)
67 (0)	65 (2)	61 (4)	58 (5)	49 (12)	49 (12)	49 (12)	47 (13)	1 (14)	0 (14)	0 (14)
68 (0)	64 (4)	61 (5)	57 (7)	42 (21)	39 (22)	38 (23)	38 (23)	1 (27)	1 (27)	0 (27)

Bowlus et al.

Non-Worsening of Fibrosis Is Associated with a Reduced Incidence of Disease Progression

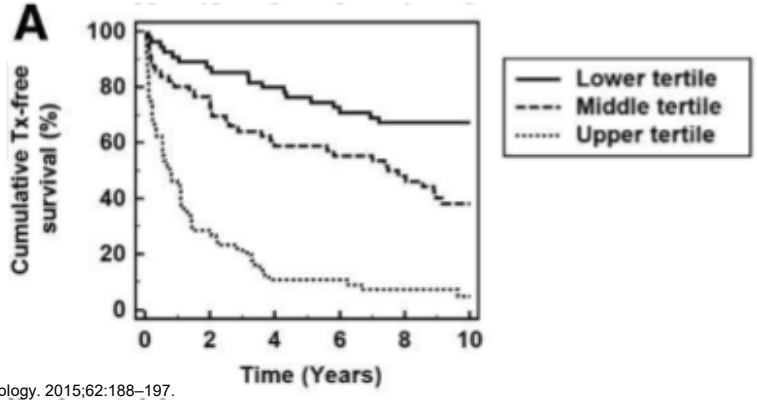


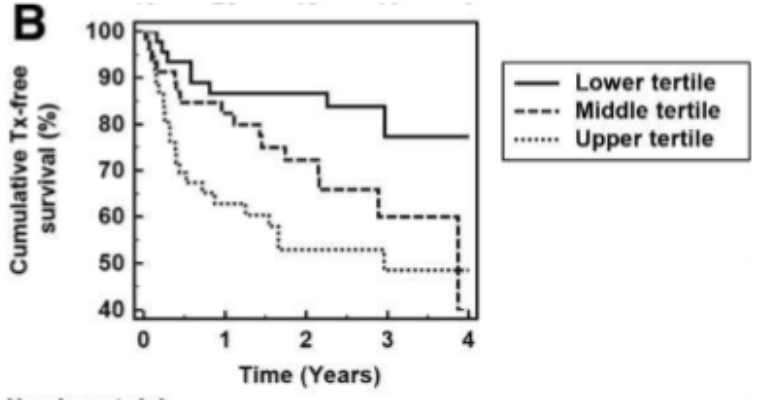
P-values by Fisher's exact test.

Bowlus et al.

Serum fibrosis markers

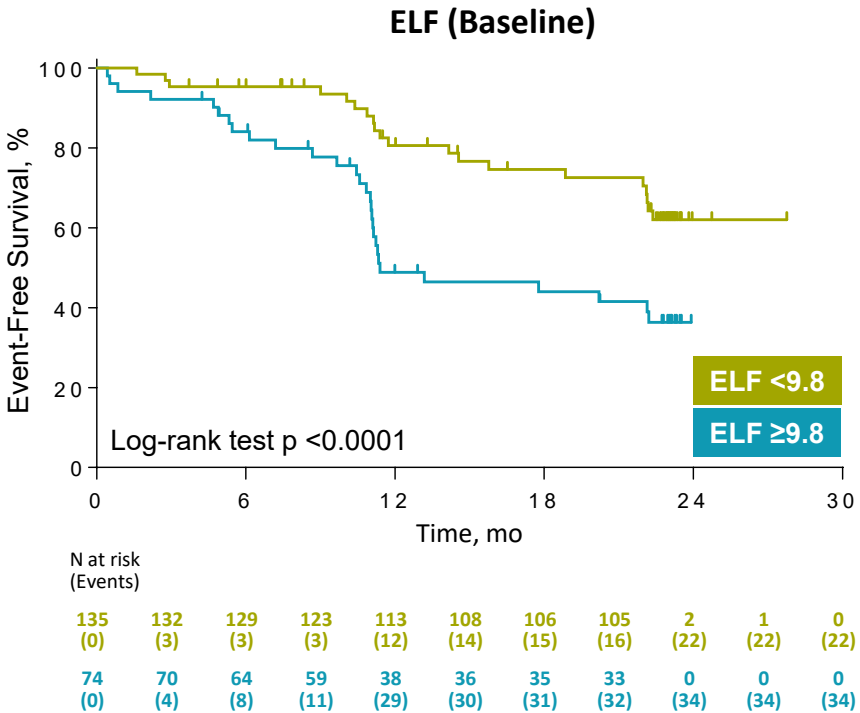
- Vesterhus et al. performed a retrospective analysis of ELF on two cohorts of patients with large duct PSC
  - Cohort 1: N=167, Median follow up of 4 years; Serum collected 1992-2006
  - Cohort 2: N=138, Median follow up of 2.2 years; serum collected 2008-2012
  - Actual tertile values not provided, but Youdon Index values were at 11.1 and 11.2 for the respective cohorts
  - n multivariate cox regression ELF (and also Mayo Score) showed independent associate with transplant free survival in both cohorts of patients

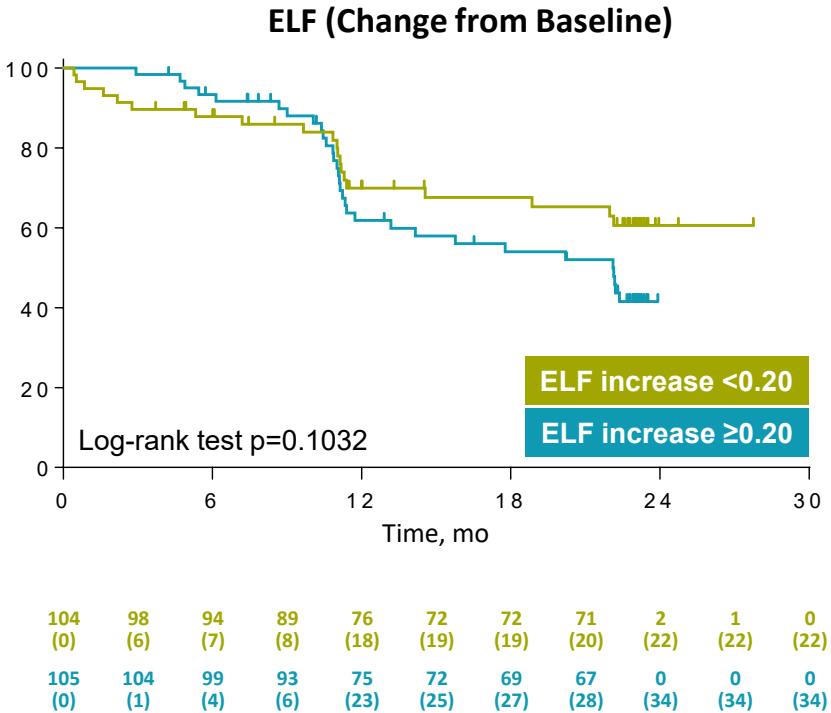




Vesterhus M, et al. Hepatology. 2015;62:188–197.

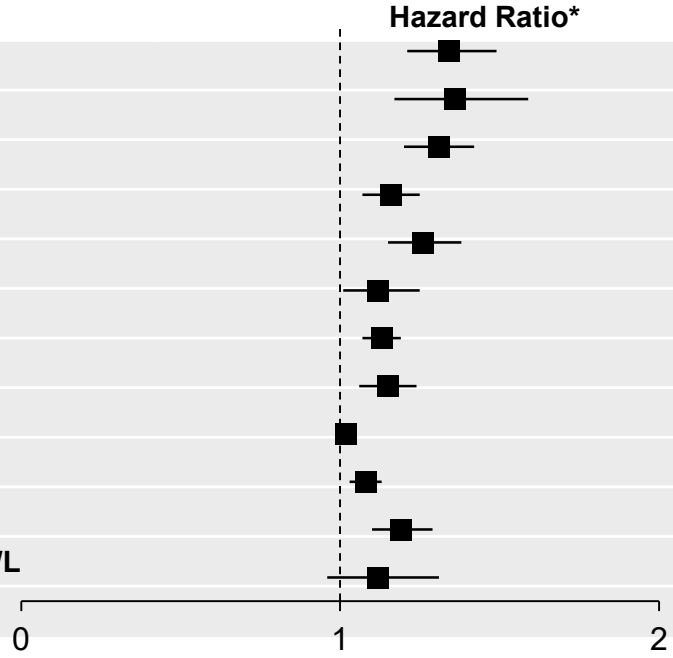
Association Between ELF and Disease Progression





Bowlus et al.

Associations Between Fibrosis Markers, ALP, and Disease Progression



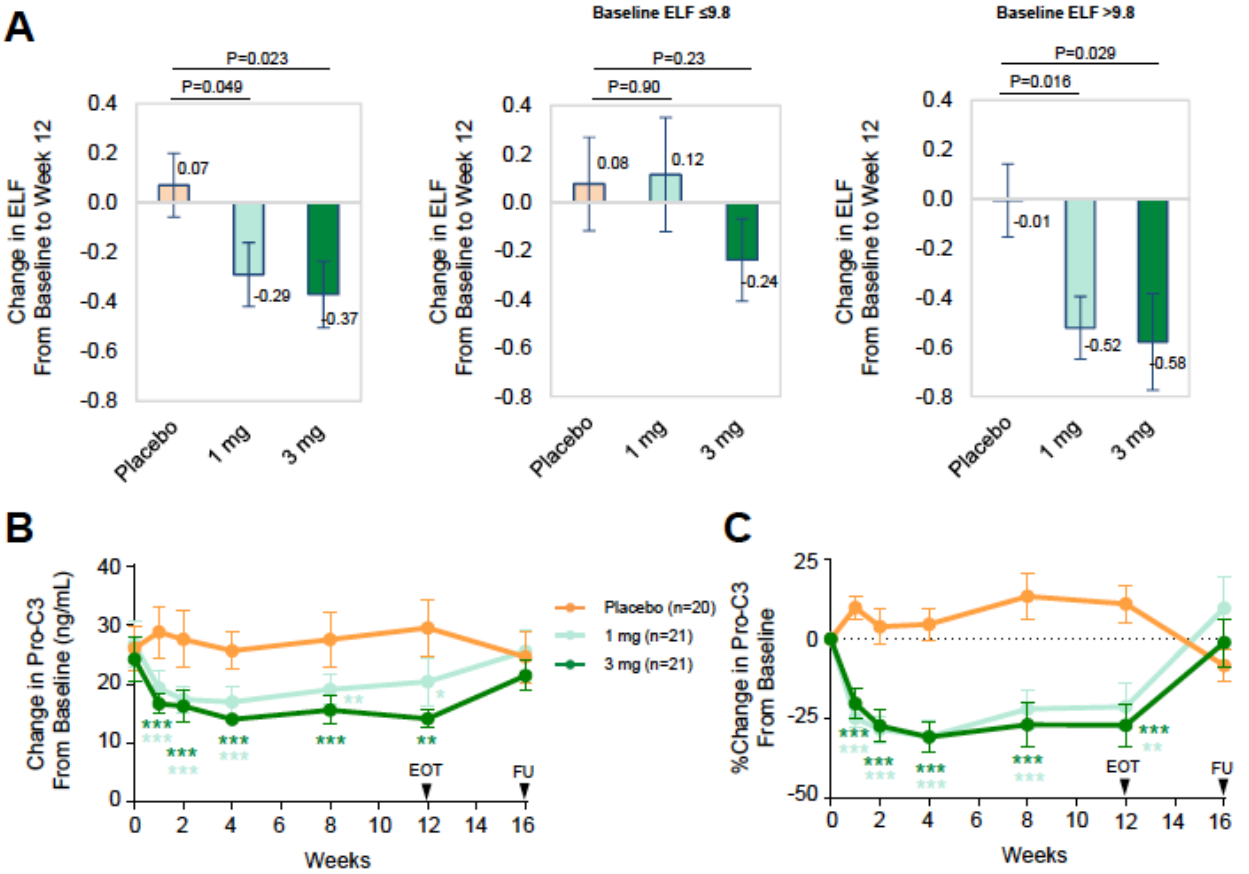
	Hazard Ratio*	95% CI	p-value
ELF (baseline), per 0.5-units	**1.34**	1.21, 1.49	<0.001
Change from baseline	**1.36**	1.17, 1.59	<0.001
TIMP-1 (baseline), per 50-ng/mL	**1.31**	1.20, 1.42	0.0000
Change from baseline	**1.16**	1.07, 1.25	0.0004
PIII-NP (baseline), per 2.5-ng/mL	**1.26**	1.15, 1.38	0.0000
Change from baseline	**1.12**	1.01, 1.25	0.0320
HA (baseline), per 50-ng/mL	**1.13**	1.07, 1.19	0.0000
Change from baseline	**1.15**	1.06, 1.24	0.0005
LS by TE (baseline), per 1-kPa	**1.02**	0.99, 1.05	0.21
Change from baseline	**1.08**	1.03, 1.13	0.003
Serum ALP (baseline), per 100-U/L	**1.19**	1.10, 1.29	<0.001
Change from baseline	**1.12**	0.96, 1.31	0.16

- Increased risk of events with:
  - Higher baseline ELF (and components) and serum ALP
  - Increases of ELF and liver stiffness, but not serum ALP

* Separate multivariate models run with baseline and change from baseline for each variable.

Bowlus et al.

Pro-C3 and ELF in the NGM282 study



Hirschfield et al. *J Hep* 2019.

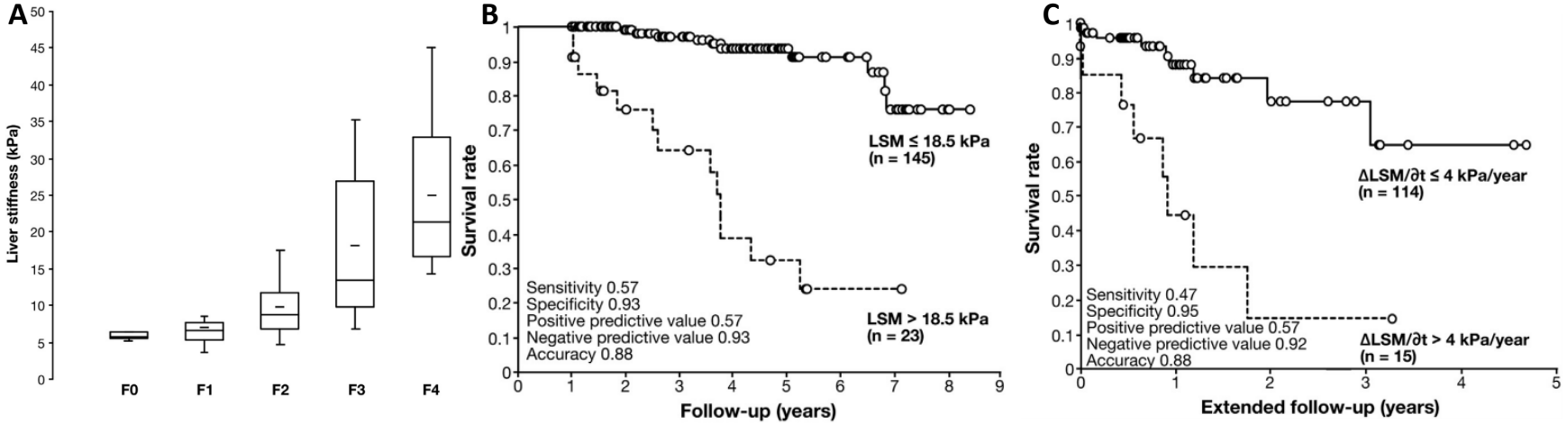
Potential Biomarkers- Transient Elastography

The thresholds that predicted fibrosis stages F1, F2, F3, and F4 were 7.4, 8.6, 9.6, and 14.4 kPa (Figure A)

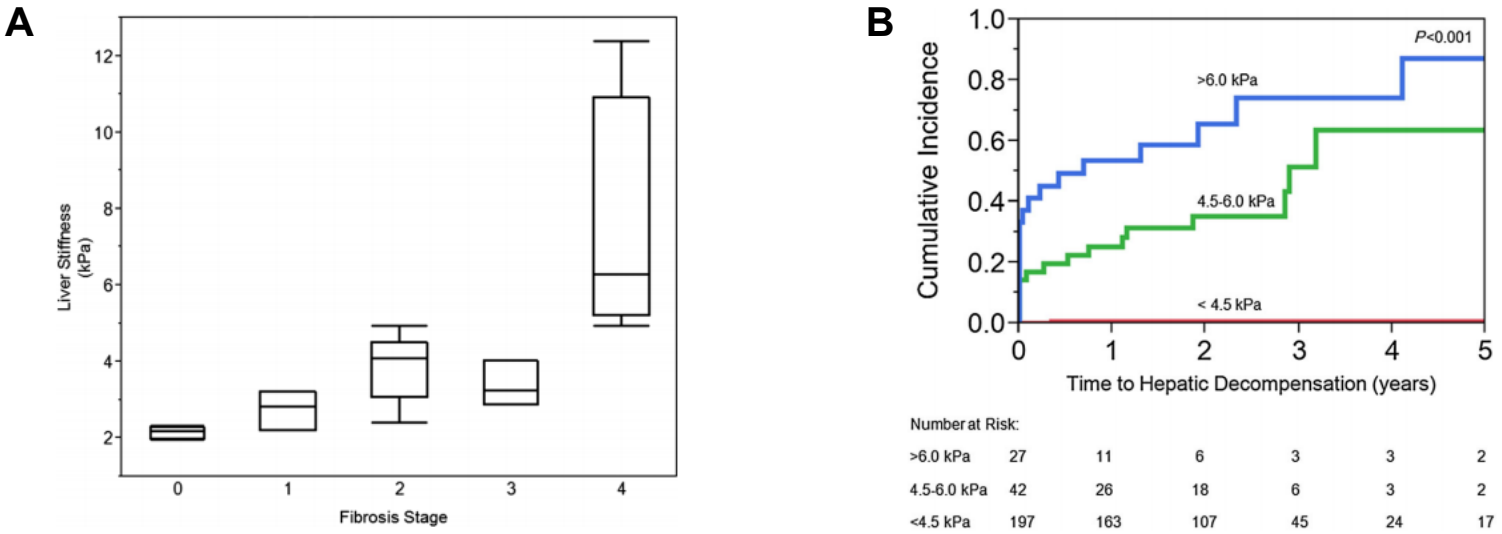
Evaluated Clinical outcomes in 168 patients with PSC with a mean follow up of 3.9 ± 1.9 years

- 23 (14%) experienced clinical outcomes
  - 11 liver transplantations, 6 deaths (2 from cholangiocarcinoma, 2 from hepatocellular carcinoma, and 1 from liver failure), 6 hepatic complications (3 cases of ascites, 2 cases of variceal bleeding, and 1 case of hepatic encephalopathy)
- Both baseline and rate of change in liver stiffness where shown to be prognostic of outcomes (Figure B/C)

TE has limitations: operator inexperience, large increase with inflammation/acute episodes/dominant strictures



MRE



- Only 20 patients had biopsy info (F0, n=4; F1, n=3; F2, n=6, F3, n=3, F4, n=4); however, liver stiffness was still found to be strongly correlated with fibrosis stage (R=0.84, P< 0.001, Fig A)
- Patients who had baseline liver stiffness >4.5kPa had significantly increased risk of hepatic decompensation (Fig B)
- These results require further validation (this is the only paper on MRE in PSC)
- MRE has high cost/limited availability but may be more accurate than TE and can be combined with MRCP in a single visit for more

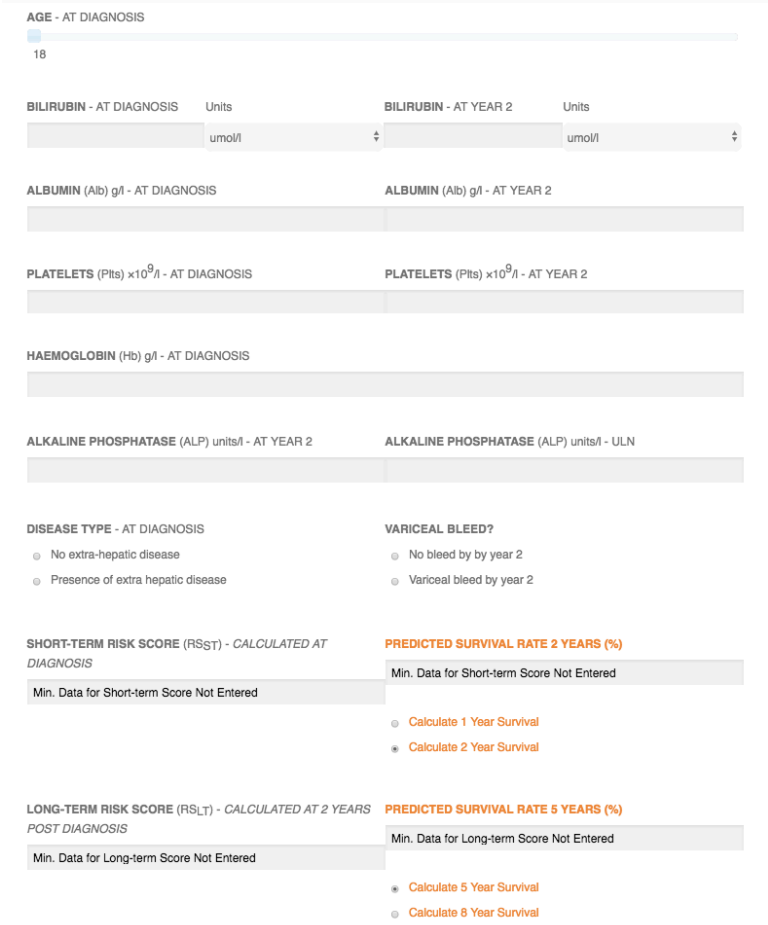
Eaton JE, et al. *Journal of Gastroenterology and Hepatology*.2016;31:1184-1190.

Prognostic Models

Mayo Clinic Model	King's College Model	Multicenter Model	Revised Mayo Model	Amsterdam-Oxford Model	PREsTo
		Predictors of Survival			
Age	Age	Age	Age	Age	Age
Bilirubin	Hepatomegaly	Bilirubin	Bilirubin	Bilirubin	Bilirubin
Histologic stage	Histologic stage	Histologic stage	Albumin	Albumin	Albumin
Hgb	Splenomegaly	Splenomegaly	AST	AST	AST
IBD	Alkaline phosphatase		Variceal bleeding	Alkaline phosphatase	Alkaline phosphatase
				Platelets	Platelets
				PSC subtype	Duration of PSC
					Sodium
					Hemoglobin

Slide courtesy Cynthia Levy

UK-PSC score


AGE - AT DIAGNOSIS
18
BILIRUBIN - AT DIAGNOSIS
Units
umol/l
BILIRUBIN - AT YEAR 2
Units
umol/l
ALBUMIN (Alb) g/l - AT DIAGNOSIS
ALBUMIN (Alb) g/l - AT YEAR 2
PLATELETS (Plts) ×10^9/l - AT DIAGNOSIS
PLATELETS (Plts) ×10^9/l - AT YEAR 2
HAEMOGLOBIN (Hb) g/l - AT DIAGNOSIS
ALKALINE PHOSPHATASE (ALP) units/l - AT YEAR 2
ALKALINE PHOSPHATASE (ALP) units/l - ULN
DISEASE TYPE - AT DIAGNOSIS
No extra-hepatic disease
Presence of extra hepatic disease
VARICEAL BLEED?
No bleed by by year 2
Variceal bleed by year 2
SHORT-TERM RISK SCORE (RS_ST) - CALCULATED AT DIAGNOSIS
Min. Data for Short-term Score Not Entered
PREDICTED SURVIVAL RATE 2 YEARS (%)
Min. Data for Short-term Score Not Entered
Calculate 1 Year Survival
Calculate 2 Year Survival
LONG-TERM RISK SCORE (RS_LT) - CALCULATED AT 2 YEARS POST DIAGNOSIS
Min. Data for Long-term Score Not Entered
PREDICTED SURVIVAL RATE 5 YEARS (%)
Min. Data for Long-term Score Not Entered
Calculate 5 Year Survival
Calculate 8 Year Survival

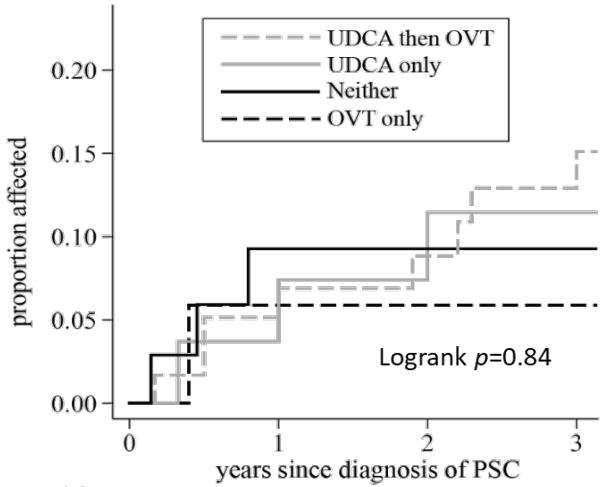
Clinical outcomes of oral vancomycin therapy in pediatric primary sclerosing cholangitis

Objective:
To assess whether oral vancomycin therapy (OVT) prevents adverse liver outcomes in children with PSC

Methods:
Multicenter analysis of the occurrence of portal hypertensive complications, dominant stricture interventions, or liver transplantation within 3 years of PSC diagnosis in children treated with ursodeoxycholic acid (UDCA), OVT only, OVT after a UDCA trial, or nothing

Conclusions:
We reported the largest cohort of children with PSC treated with OVT to date. Adverse outcomes occurred at similar rates regardless of treatment with OVT, UDCA, or nothing.

Event-free survival after diagnosis of PSC



Number at risk				
UDCA then OVT	27	26	23	17
UDCA only	60	54	46	40
Neither	35	27	20	15
OVT only	22	16	12	9

Deneau MR, et al., Abstract 182

Proving It Works…

IPSCSG statement 2

Alkaline phosphatase is widely recognized as a clinical measure of cholestasis. Currently, albeit not formally validated, it is regarded as a potential surrogate outcome parameter *[EL 4, RG D]*

In early phase studies bloods alone are ok to show a drug may work

IPSCSG statement 4

Liver histology has the potential to be a robust surrogate endpoint for clinical trials in PSC *[EL2b, RG B]*

Liver biopsy is likely solid evidence a treatment works

IPSCSG statement 5

In the absence of a convincing single surrogate endpoint combining multiple endpoints is considered advisable and should be explored further *[EL 5, RG D]*

The next drug will probably be shown to work by looking at a combination of end-points alongside long term extension studies