Transforming Primary Sclerosing Cholangitis: From Treatment to Transplantation

Kris Kowdley, MD, FAASLD

Director of Liver Institute Northwest

Professor, Elson Floyd College of Medicine

Washington State University

Spokane, WA, USA

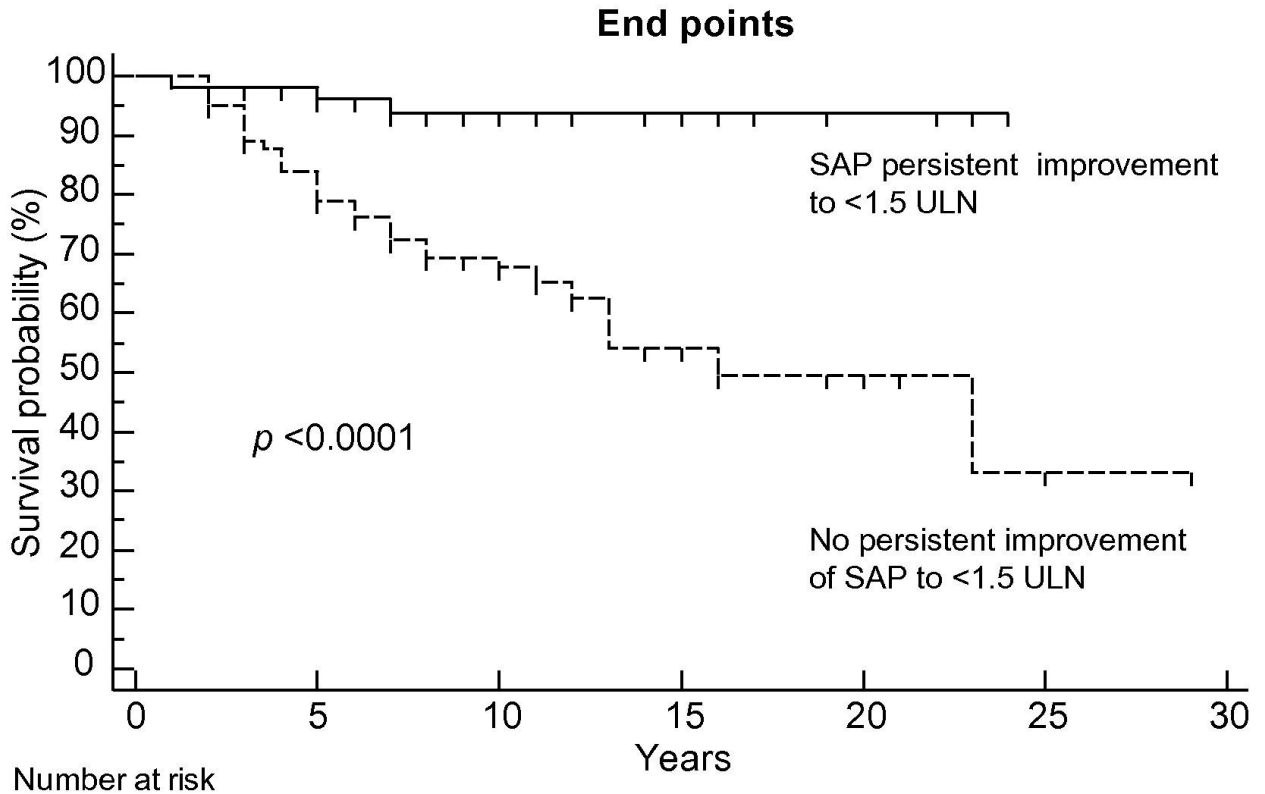
Primary Sclerosing Cholangitis

- Long natural history
- Median survival free of transplant 15-20 years
- Small-duct and large duct varieties
- Genetic and Autoimmune associations
- Presence and type of IBD may influence clinical events
- Possible association with IgG4 Autoimmune cholangiopathy
- Histologic features may be non-specific, sampling and biological variability
- Need surrogates for clinical events to:
  - Optimize clinical follow up
  - Identify patients at high risk
  - Design and endpoint selection in clinical trials

Possible Risk Predictors

- ALP
- Mayo Risk score
- UK-PSC score
- Amsterdam-Oxford model
- Serum fibrosis markers
  - ELF, APRI, FIB-4
- Imaging based markers
  - MRE
  - MRI/MRCP
  - VCTE
- Liver Biopsy

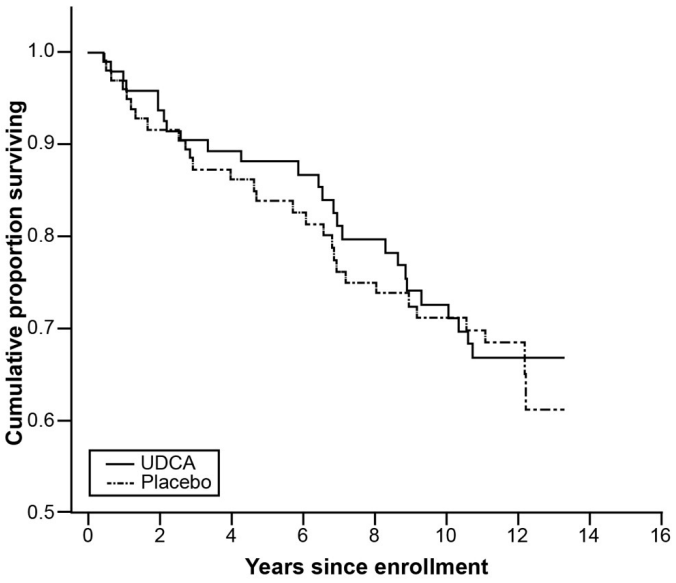
Survival in PSC and serum ALP values



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

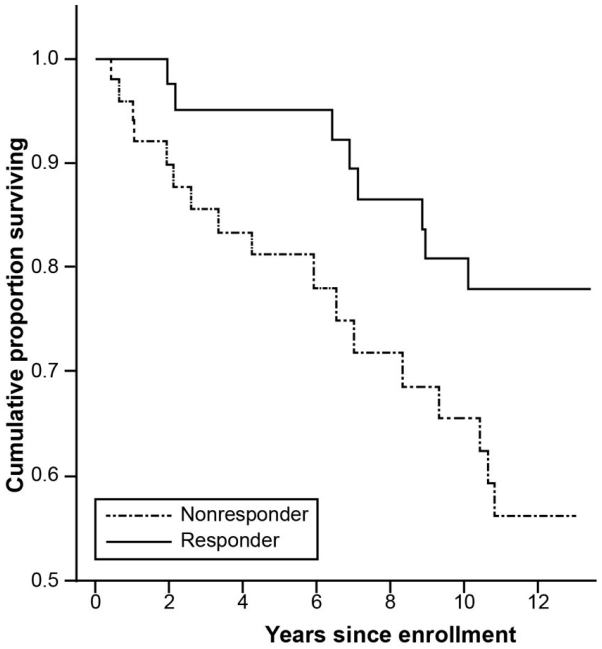
Association Between Reduced Levels of Alkaline Phosphatase and Survival Times of Patients With Primary Sclerosing Cholangitis



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

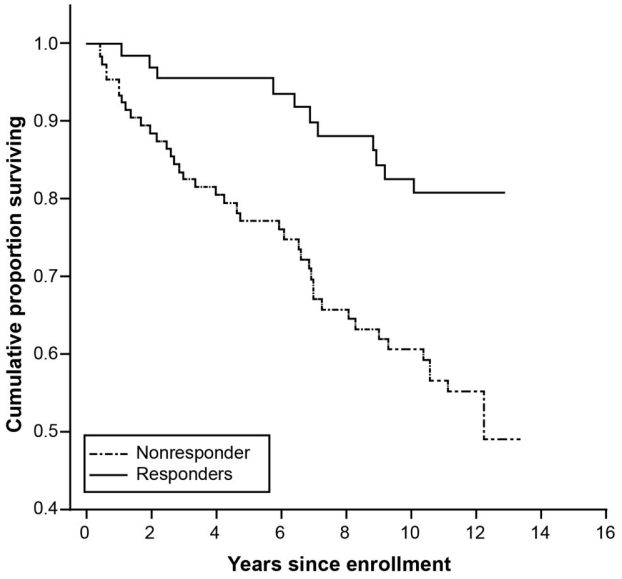
198 patients enrolled in the 5-year Scandinavian UDCA trial in 1996 randomized to UDCA vs placebo with extended follow-up



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

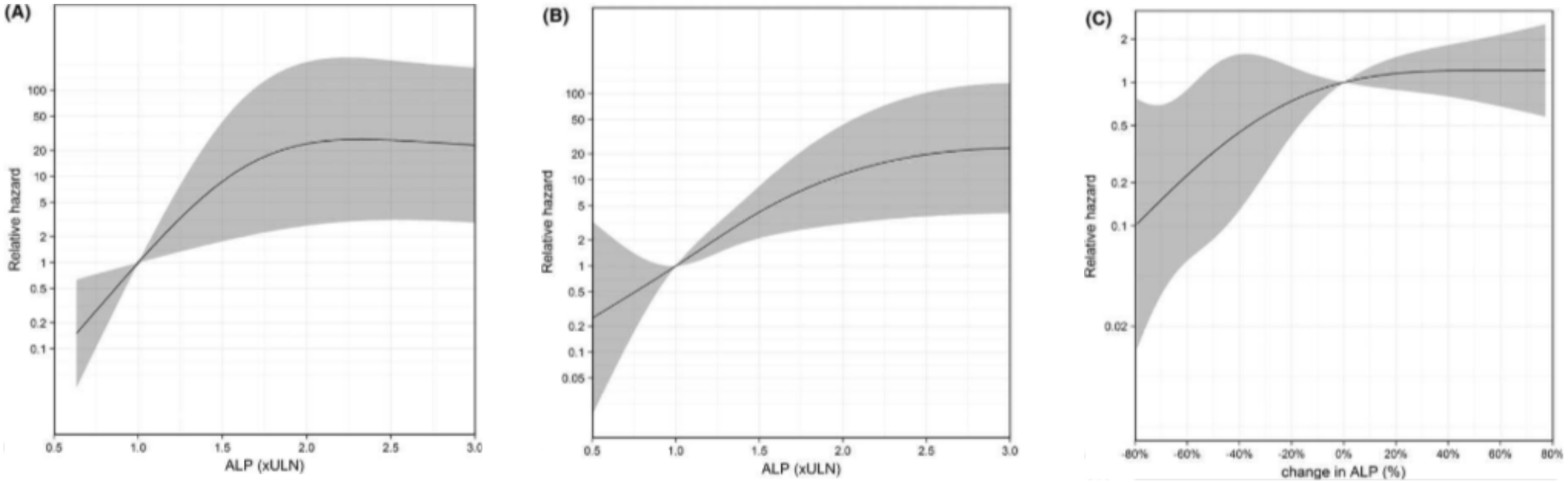
Biochemical responders vs nonresponders, regardless of treatment with UDCA (P = .0001, log-rank test)

Courtesy of Gideon Hirschfield

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

Alkaline Phosphatase as a Biomarker for Prognosis in PSC

- 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



Courtesy of Gideon Hirschfield

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

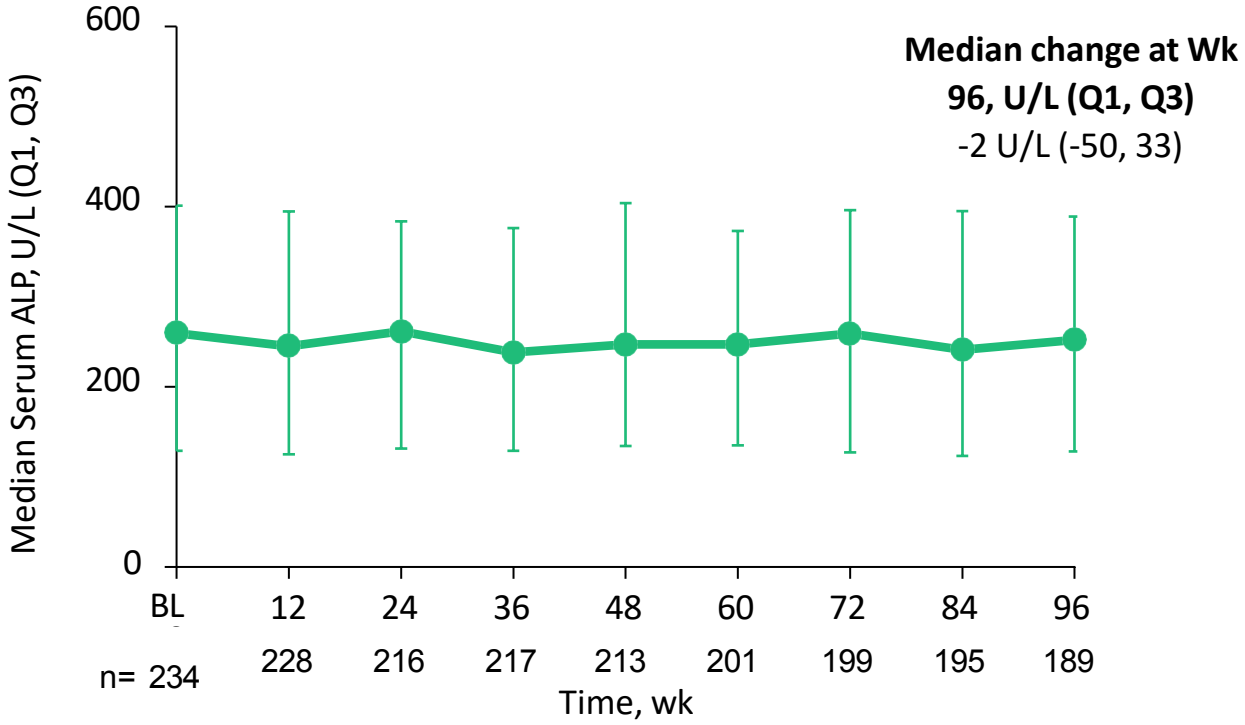
Prognostic Models

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

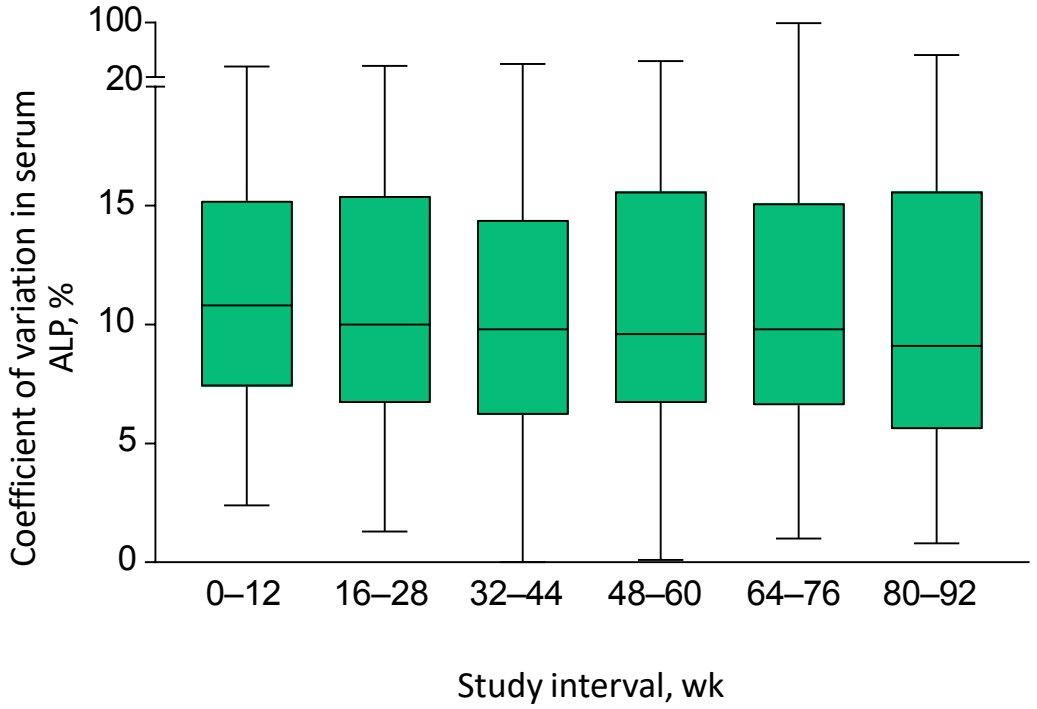
Slide courtesy Cynthia Levy

Serum ALP has Substantial Variability

Inter-Individual Variability



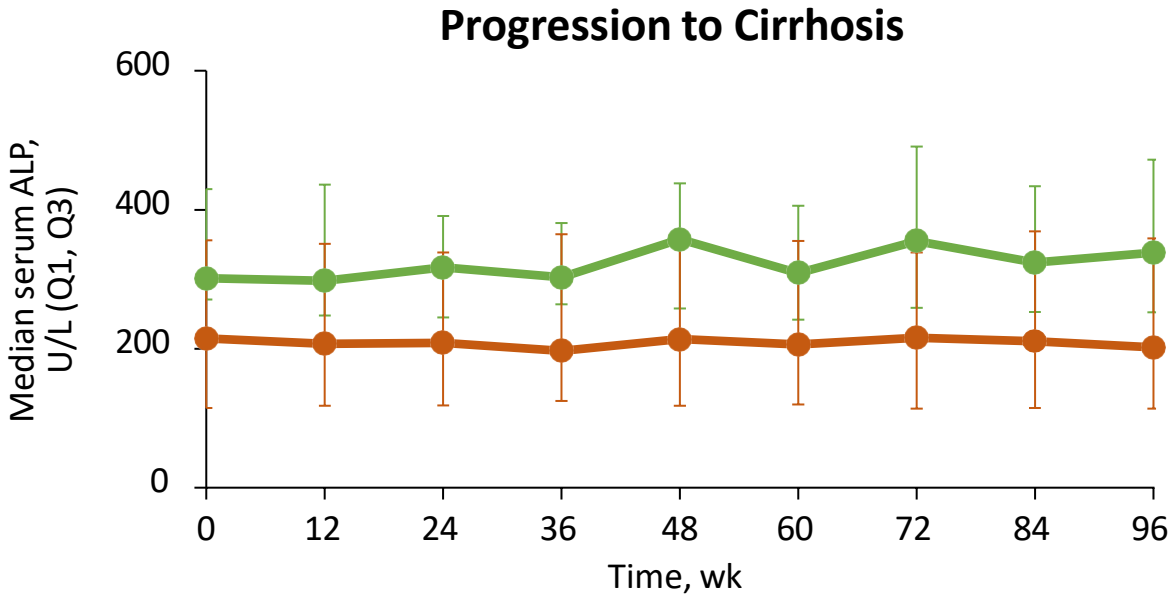
Intra-Individual Variability

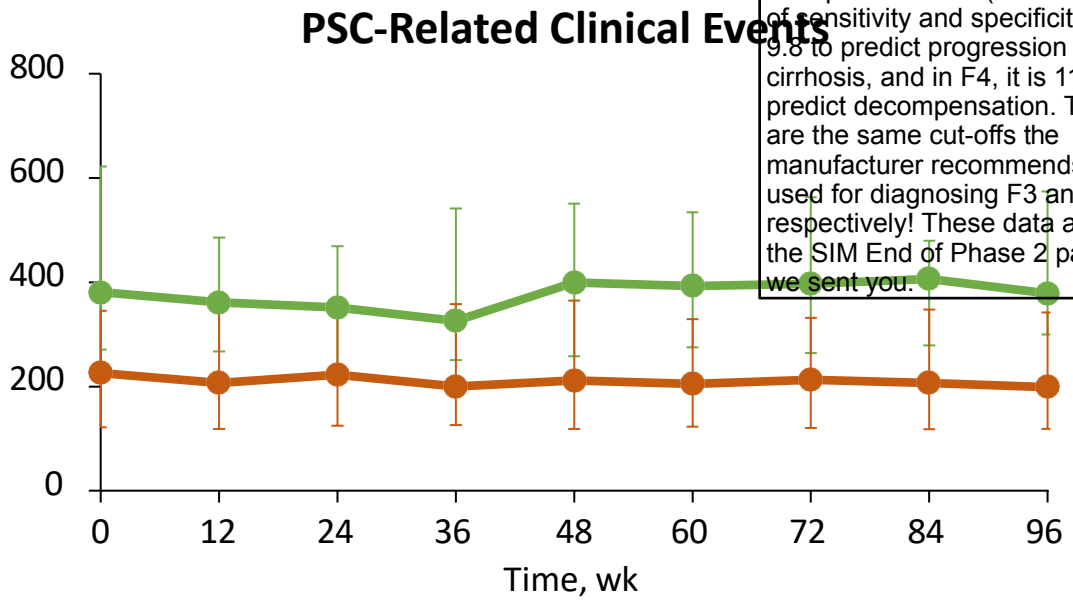


- **Overall, ALP did not change between baseline and Wk 96**
- **Median per-patient CV was 11.5% (IQR 8.9, 14.2), but varied widely**

CGH 2020:S1542-3565

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**

CGH 2020:S1542-3565

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

Presenter Notes
2024-03-09 09:58:36

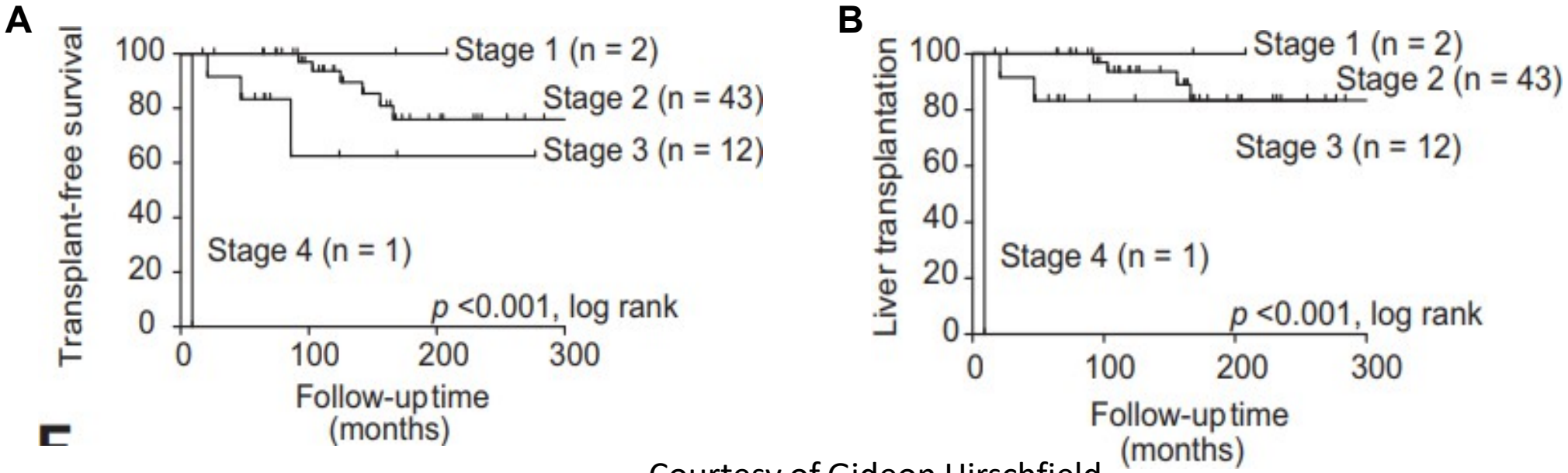
At AASLD, we will describe optimal cutoffs for ELF and hepatic collagen that are associated with clinical events. Preliminary data show that in F3, the optimal cut-off (maximal sum of sensitivity and specificity) is 9.8 to predict progression to cirrhosis, and in F4, it is 11.3 to predict decompensation. These are the same cut-offs the manufacturer recommends to be used for diagnosing F3 and F4, respectively! These data are in the SIM End of Phase 2 package we sent you.

Liver histology and PSC outcome

Presenter Notes
2024-03-09 09:58:37

Endpoints transplant-free survival and time to liver transplantation shown for Nakanuma staging system.

- 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



Courtesy of Gideon Hirschfield

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

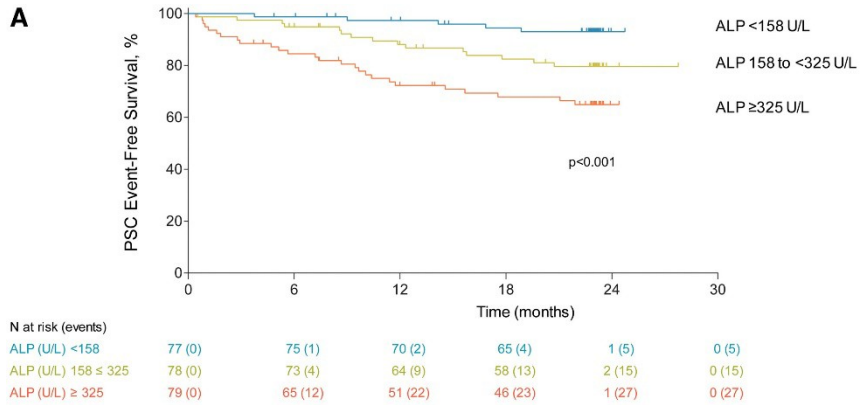
Evaluation of biochemical tests in predicting outcomes in PSC: Simtuzumab trial

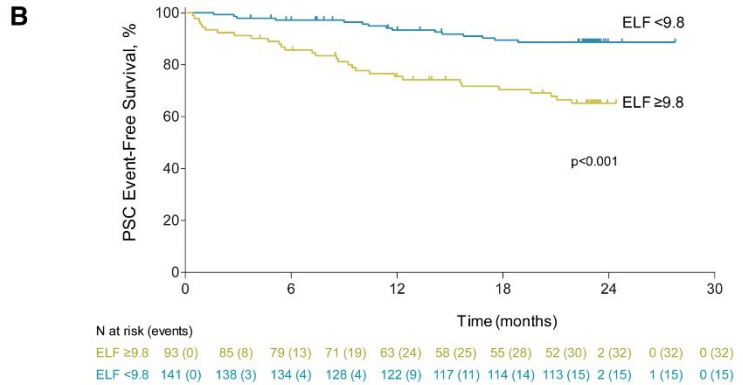
PSC event-free survival by baseline ALP, baseline ELF score, and change in ELF score at week 12.

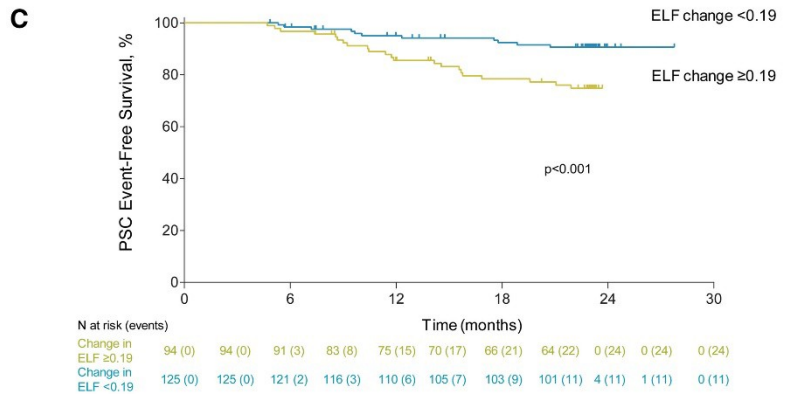
(A) Survival free of PSC-related clinical events by baseline ALP tertile.

(B) Survival free of PSC-related clinical events by baseline ELF score.

(C) Survival free of PSC-related clinical events by change in ELF score at week 12





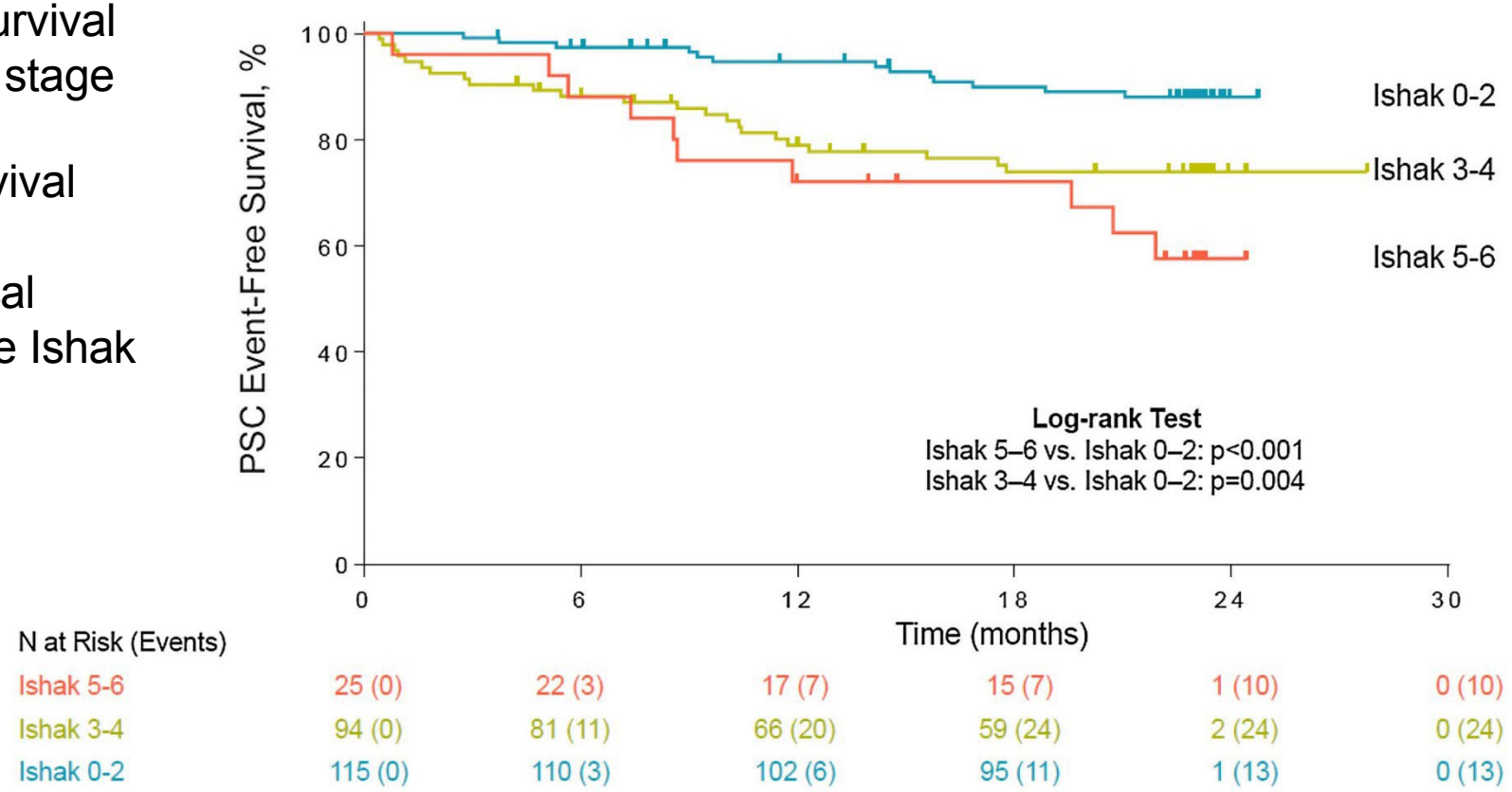


Hepatology 2019;69:684-698

Relationship between baseline histology and clinical events

PSC event-free survival by baseline Ishak stage

Figure shows survival free of PSC-related clinical events by baseline Ishak stage.

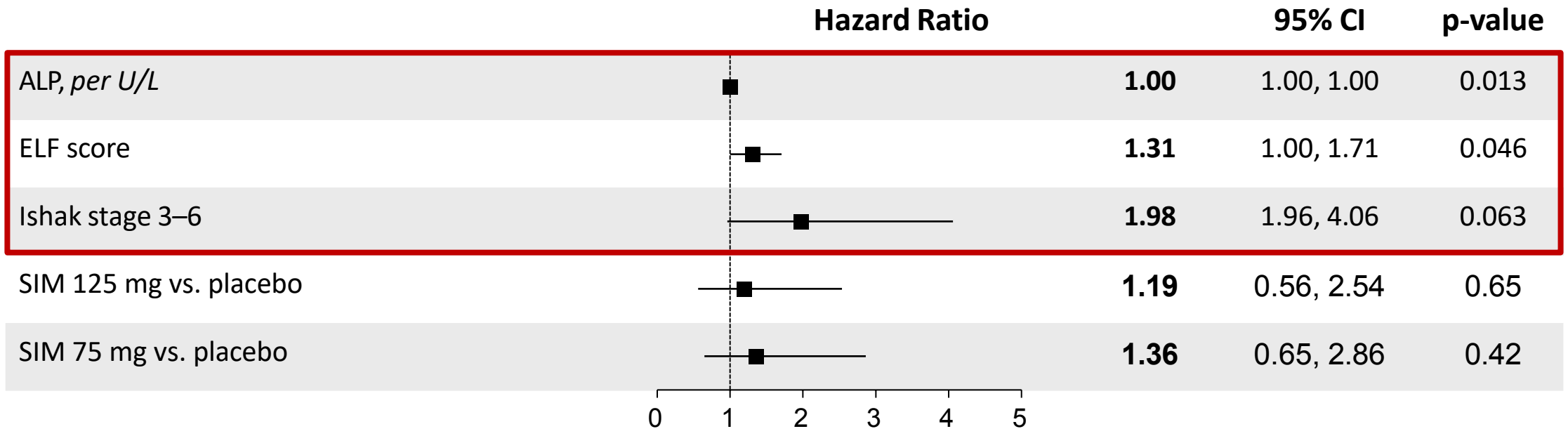


Hepatology 2019;69:684-698

Baseline Predictors of PSC-Related Clinical Events Multivariate Analysis

Presenter Notes
2024-03-09 09:58:37

Baseline ALP, ELF, and Ishak stage predicted events.
SIM treatment did not independently predict PSC related events.



Bowlus C, et al. EASL 2017 (#FRI-382).

Stepwise Cox regression analysis with treatment assignment forced into the model.

Serum Fibrosis Markers Effectively Exclude PSC-Related Cirrhosis

Test	AUROC	Cut-off *	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
sLOXL2	0.81 (0.71-0.90)	≥164	67 (45-84)	85 (80-90)	35 (21-50)	96 (92-98)
APRI	0.81 (0.71-0.91)	>2.0	38 (19-59)	97 (93-99)	56 (30-80)	93 (89-96)
FIB-4	0.81 (0.70-0.91)	>3.25	26 (15-39)	99 (96-100)	88 (64-98)	80 (74-85)
FibroTest	0.84 (0.76-0.92)	≥0.73	58 (37-78)	91 (86-95)	44 (26-62)	95 (91-98)
ELF	0.82 (0.73-0.91)	≥9.8	79 (58-93)	64 (57-71)	21 (13-30)	96 (92-99)

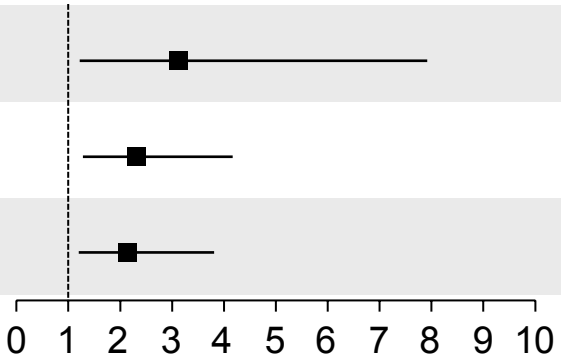
- AUROCs sub-optimal for prediction of bridging fibrosis (0.62-0.77)

Bowlus CL, et al. EASL 2015 (Abstr #FRI-624).

MRCP Predictors of PSC-Related Clinical Events

Multivariate Analysis

	HR (95% CI)	p-value	β Coefficient
Hepatic dysmorphy	**3.11** (1.22, 7.92)	**0.018**	**1.13**
Portal HTN	**2.31** (1.28, 4.17)	**0.005**	**0.84**
Perihepatic nodes ≥10 mm	**2.14** (1.20, 3.81)	**0.010**	**0.76**



MRCP Risk Score (MRCP-RS)

= 1 x Hepatic dysmorphy + 1 x Portal HTN + 1 x Perihepatic nodes

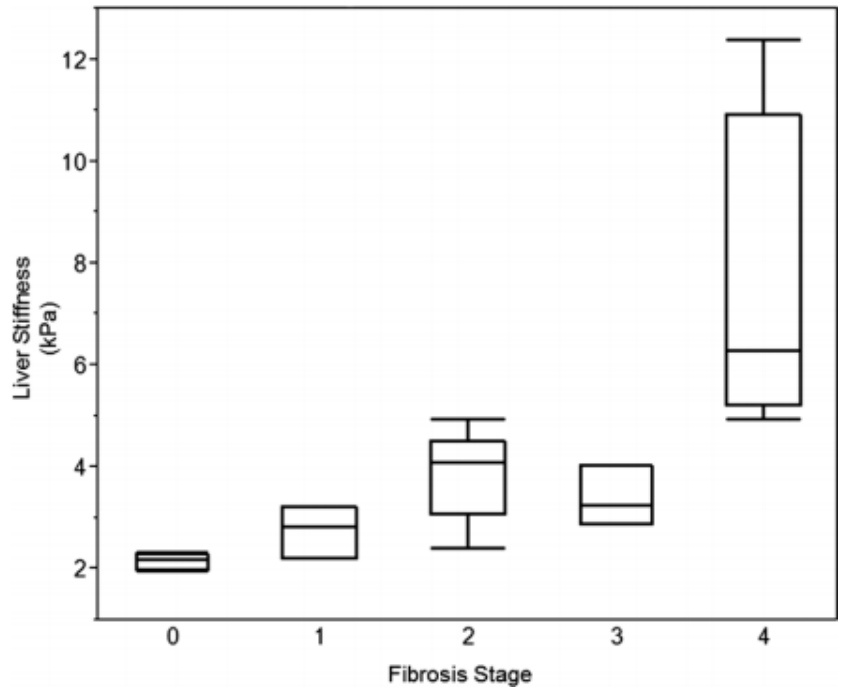
Hepatic dysmorphy = liver atrophy, caudate lobe hypertrophy, and/or marked lobulation of the liver contour.
Multivariate Cox regression with backward selection ($p<0.05$ for variable retention).
Muir AJ, et al. AASLD 2017 (Presidential Plenary Presentation #140).

MRE

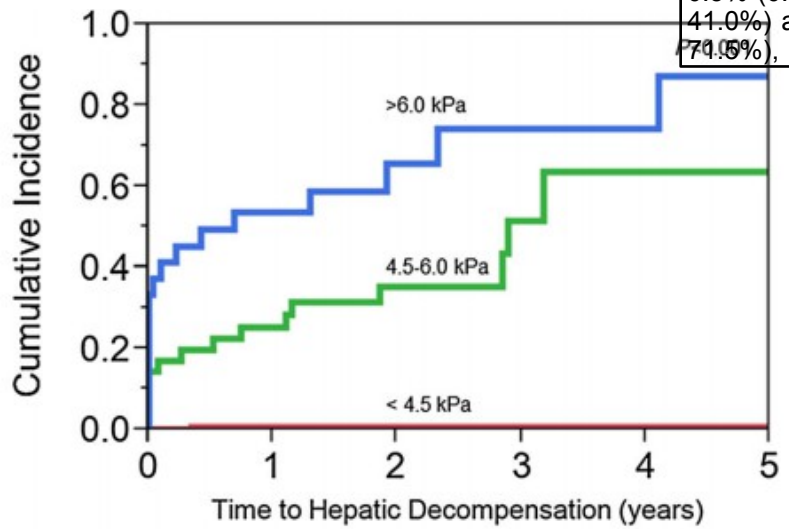
Presenter Notes
2024-03-09 09:58:38

Patients with a LS of less than 4.5, 4.5–6.0 and greater than 6.0 kPa had a 1-year cumulative incidence (95%CI) of hepatic decompensation, which was 0.5% (0.0–4.0%), 25.2% (14.1–41.0%) and 54.0% (34.6–71.5%), respectively

A



B



Number at Risk:

>6.0 kPa	27	11	6	3	3	2
4.5-6.0 kPa	42	26	18	6	3	2
<4.5 kPa	197	163	107	45	24	17

- 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.

Courtesy of Gideon Hirschfield

FICUS Study: Prognostic Factors at Baseline: Multivariate Analysis (without Liver Histology)

Parameters	HR (95% CI)	P
Bilirubin (mg/dL)	1.31 (1.16 – 1.46)	< 0.0001
ALP (ULN)	1.21 (1.04 – 1.38)	0.0091

Parameters	HR (95% CI)	P
Mayo Risk Score	2.28	< 0.0001
LS (kPa)	1.04 (1.02 -1.06)	< 0.0001

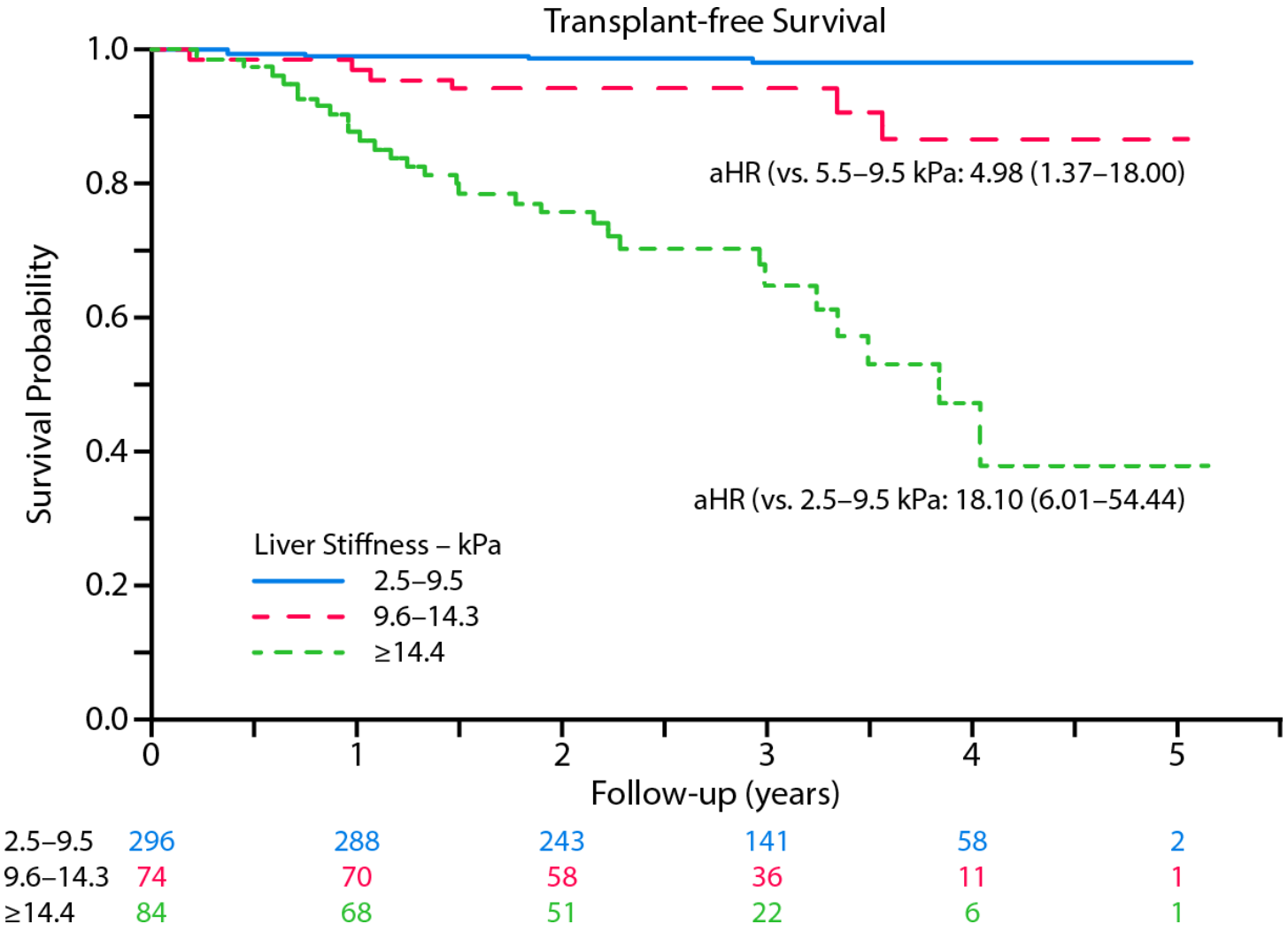
MRS: age, bilirubin, albumin, AST, variceal bleeding

Parameters	HR (95% CI)	P
Amsterdam Oxford Score	2.58 (1.44 – 4.47)	0.0010
LS (kPa)	1.04 (1.03 -1.06)	< 0.0001

Amsterdam Oxford Score: PSC subtype, AST, ALP, bilirubin, albumin, platelets

Chazouilleres et al., AASLD 2019, Abstract #47

Prognostic Value of LS according to Pre-established Cut-Offs



Predictive performance of LS assessed by the time-dependent area under the ROC curve: 0.87

Chazouilleres et al., AASLD 2019, Abstract #47

Assessment of liver disease severity in PSC: summary of evidence

- Studies on NITs generally involve small numbers of patients
- Good accuracy of LSM by TE has been reported
  - Diagnostic performance for optimal cut-offs for advanced fibrosis/cirrhosis were good/excellent
    - Advanced fibrosis (≥9.6 kPa): AUROC, 0.80; sensitivity, 74%; specificity, 74%
    - Cirrhosis (≥14.4 kPa): AUROC, 0.95; sensitivity, 100%; specificity, 83%
- LSM by MRE in patients with biopsy-proven PSC reported excellent diagnostic accuracy
  - AUROC of ≥0.97, irrespective of severity of disease
- Preliminary data on spleen length measurement by ultrasound suggested a good diagnostic performance to identify cirrhosis when an optimal cut-off of 120 mm was applied
  - AUROC 0.85, sensitivity 73%, specificity 73%

In patients with increased serum bilirubin due to the high-grade stenosis in the extrahepatic bile ducts, LSM values need to be carefully interpreted due to the risk of overestimation of fibrosis stage

Courtesy of EASL

EASL CPG: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2021;73(3):659–689.

Presenter Notes
2024-03-09 09:58:39

Abbreviations: AUROC, area under the receiver operator characteristic curve; kPa, kilopascal; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NITs, non-invasive tests; PSC, primary sclerosing cholangitis; TE, transient elastography

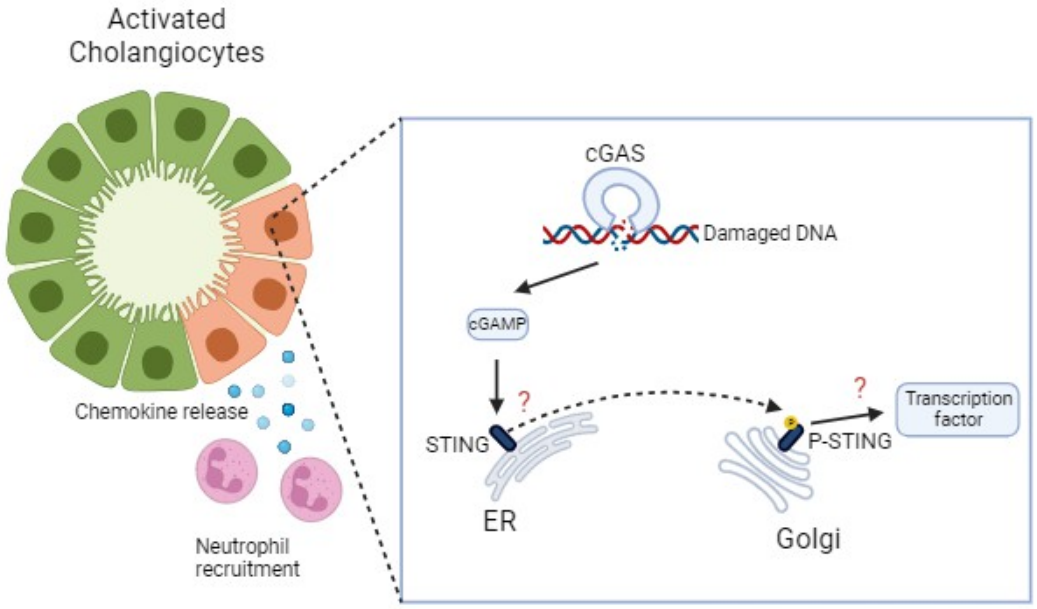
Summary

- Important to risk stratify PSC patients
- Available tools to predict clinical course
  - UK-PSC score
  - Amsterdam-Oxford model
  - Serum fibrosis markers
  - ELF, APRI, FIB-4
  - Imaging based markers
  - MRE
  - MRI/MRCP
  - VCTE
- Liver Biopsy
- Combination of imaging and functional tests may be needed

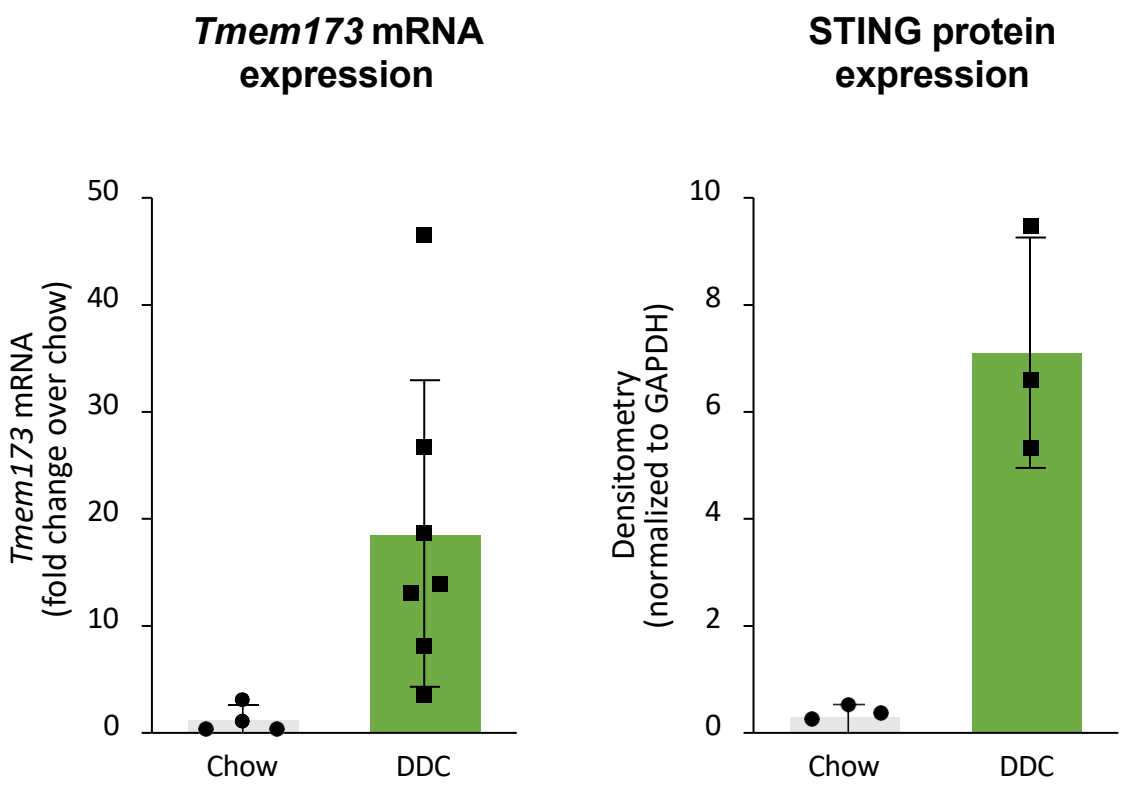
Cholangiocyte-mediated infiltration of neutrophils in the peri-portal region induces oxidative stress in PSC

- Neutrophil infiltration is associated with PSC
- Levels of chemo-attractants are increased in patients with PSC

Is there increased expression and phosphorylation of STING in PSC models?



Upregulation of STING expression in a mouse PSC model



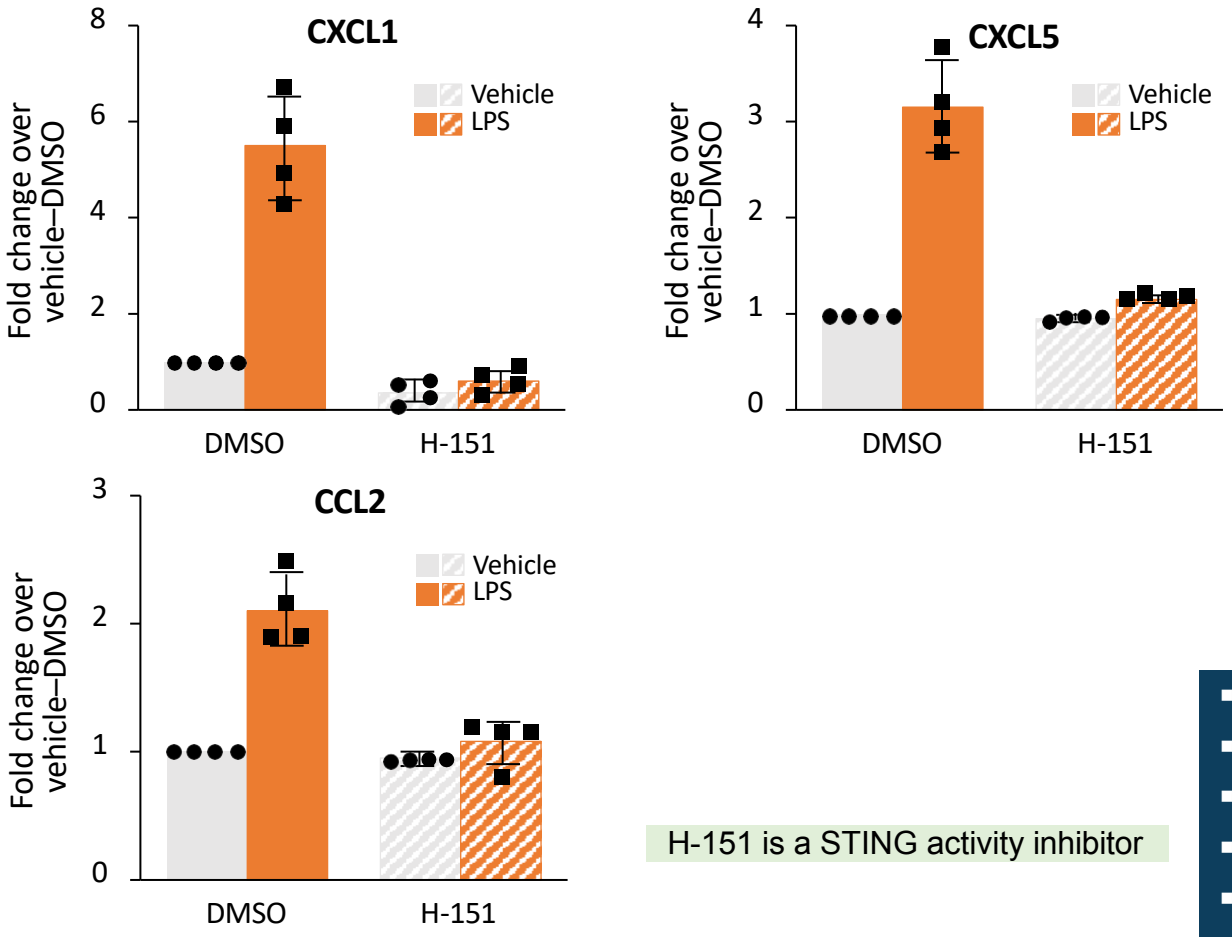
Tmem173 encodes STING protein

DDC, 3,5-diethoxycarbonyl-1,4-dihydrocollidine; STING, stimulator of interferon genes

Anwar A, et al. AASLD 2023. Oral presentation #107

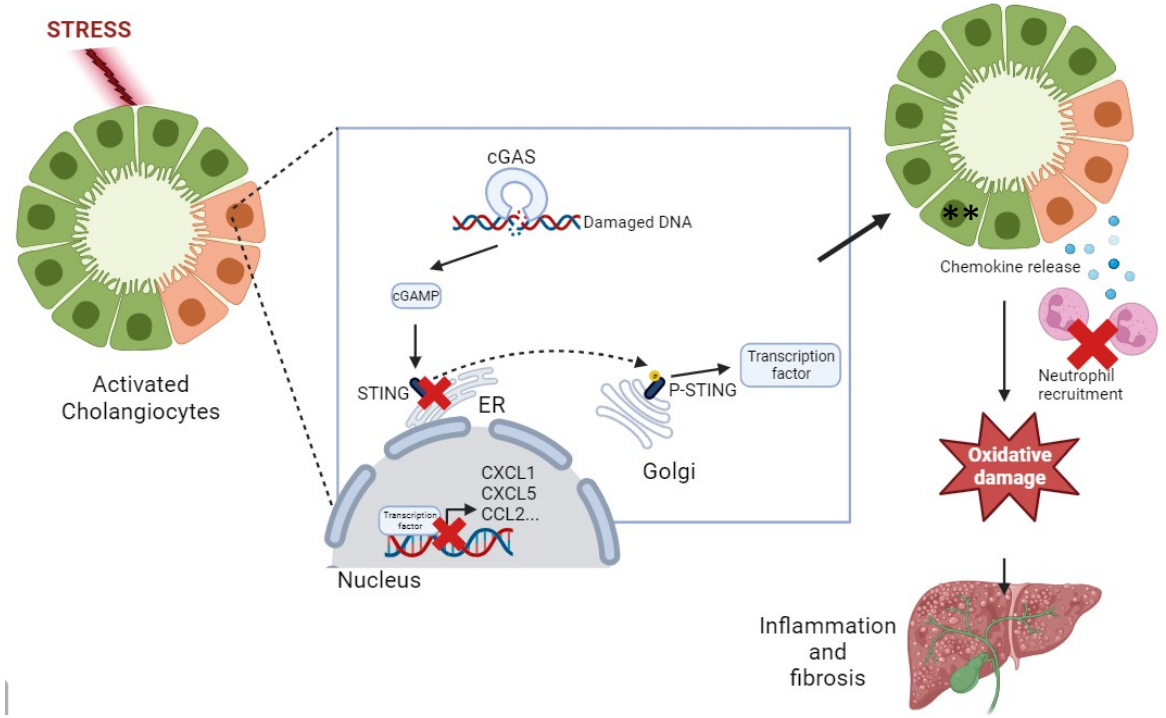
Cholangiocyte-mediated infiltration of neutrophils in the peri-portal region induces oxidative stress in PSC

Attenuation of proinflammatory cytokine expression in cholangiocytes by STING inhibition



H-151 is a STING activity inhibitor

Summary of proposed mechanisms

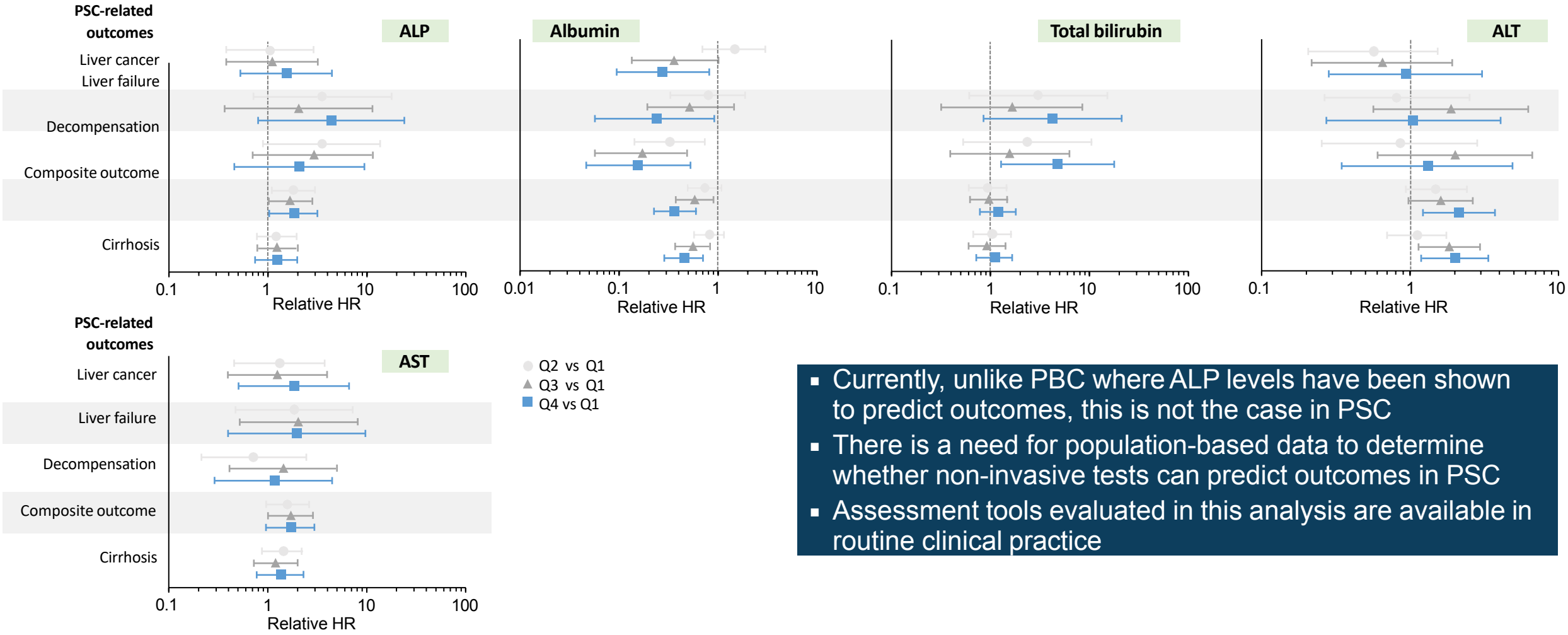


- Potential proof-of-concept study
- PSC – increase in neutrophil chemo-attractants
- STING inhibitor (chemotaxis inhibition) showed reversal of inflammation
- CCL2, CXCL5 and CXCL1 are potential targets for future therapeutics
- Only affects the fibrosis/cholangitis PSC phenotype? How about liver failure? Any role in cholangiocarcinoma?

Anwar A, et al. AASLD 2023. Oral presentation #107

Associations between liver biomarkers and clinical outcomes in patients with PSC: A retrospective real-world study

Associations of biomarker levels at outcomes with PSC-related events



- Currently, unlike PBC where ALP levels have been shown to predict outcomes, this is not the case in PSC
- There is a need for population-based data to determine whether non-invasive tests can predict outcomes in PSC
- Assessment tools evaluated in this analysis are available in routine clinical practice

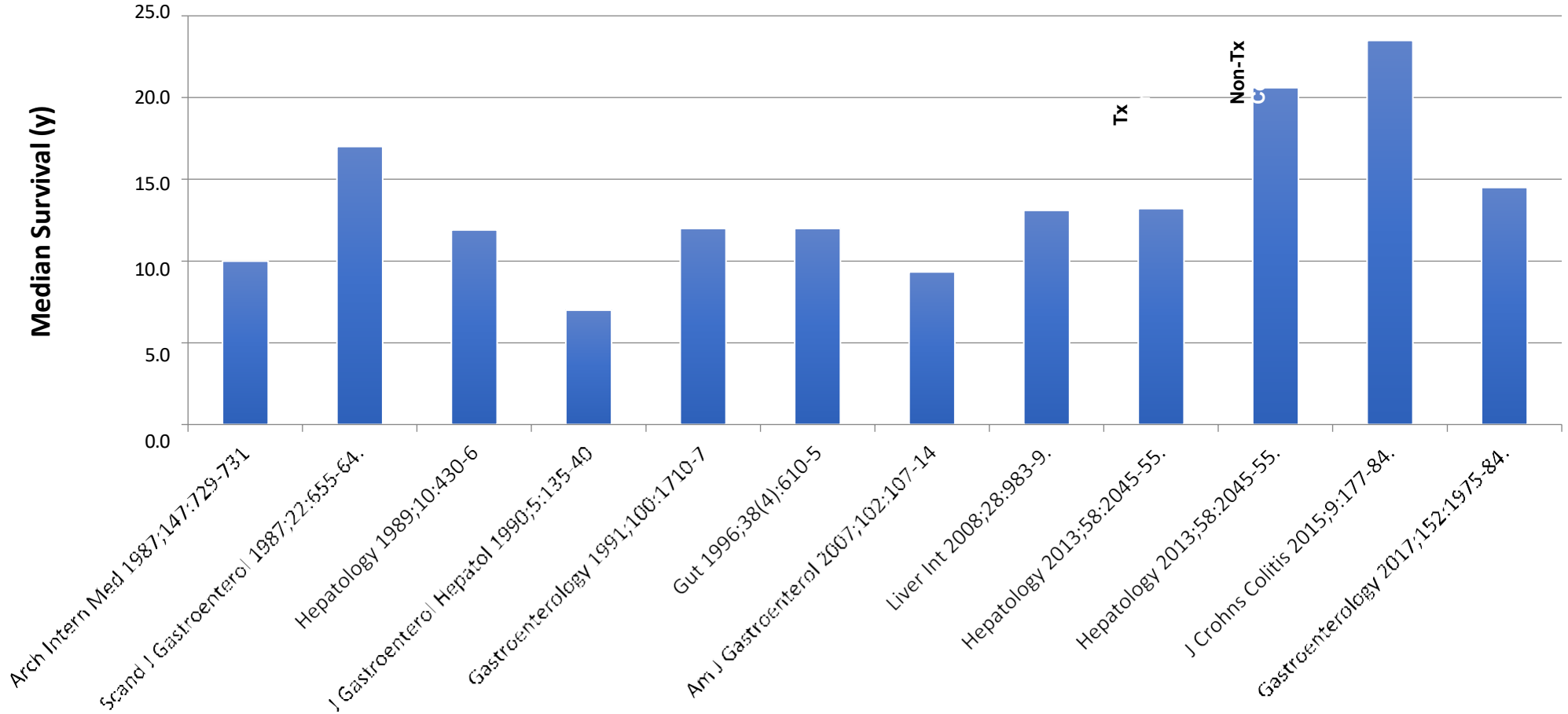
[a]Data shown as adjusted HR (95% CI). Outcome associations were not available for some biomarkers owing to missing data.

Xu J, et al. AASLD 2023. Poster presentation #4534-C. Sponsored by Gilead Sciences, Inc

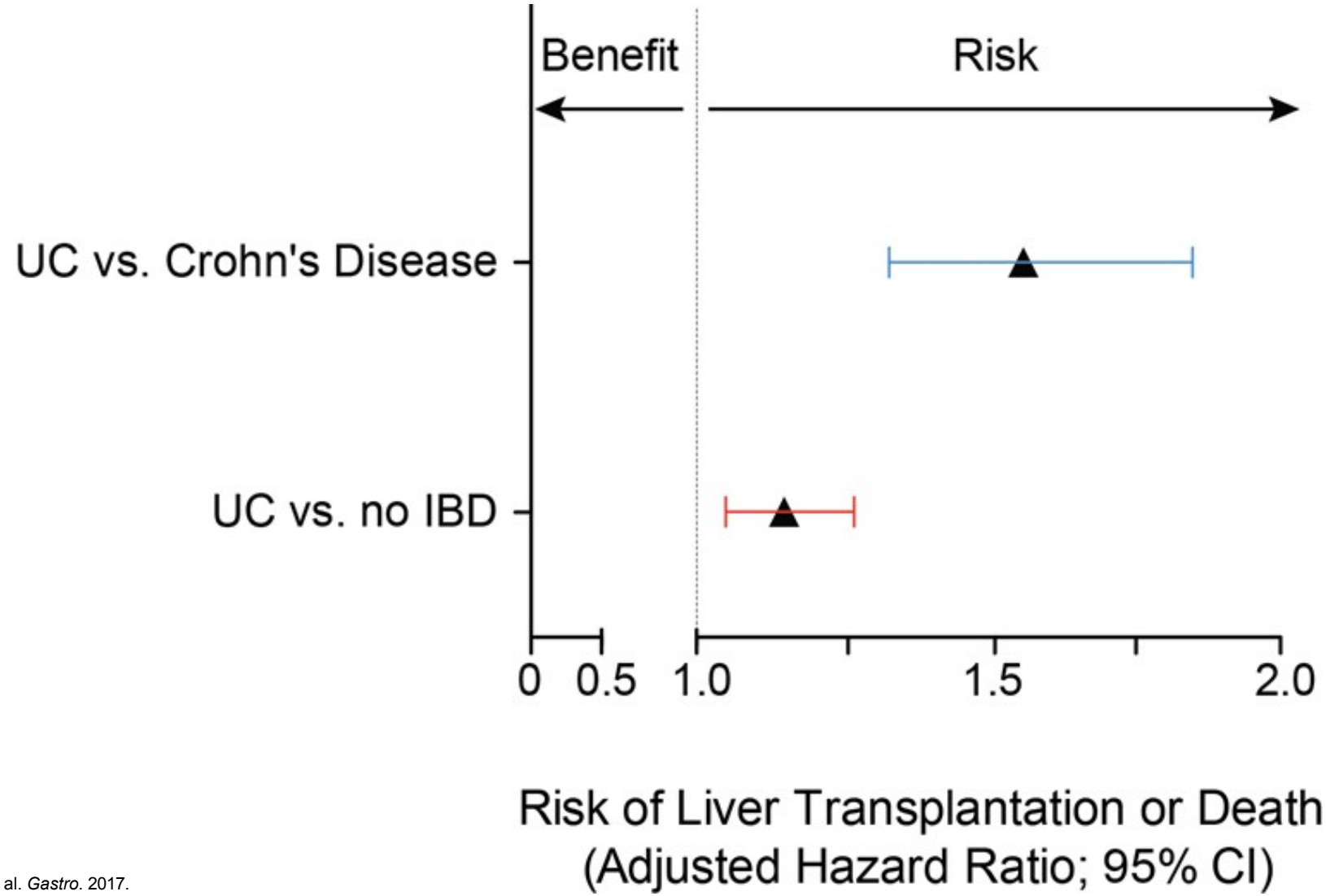
Treatment Considerations in PSC

- Assessment of stage and risk
- Noninvasive tools are limited
- Effect of IBD and risk of colon CA
- Risk of cholangitis, cholangiocarcinoma
  - May confound evaluation of efficacy and safety
- Limitations of liver biopsy
- Pathophysiology remains unclear
- No proven effective therapy

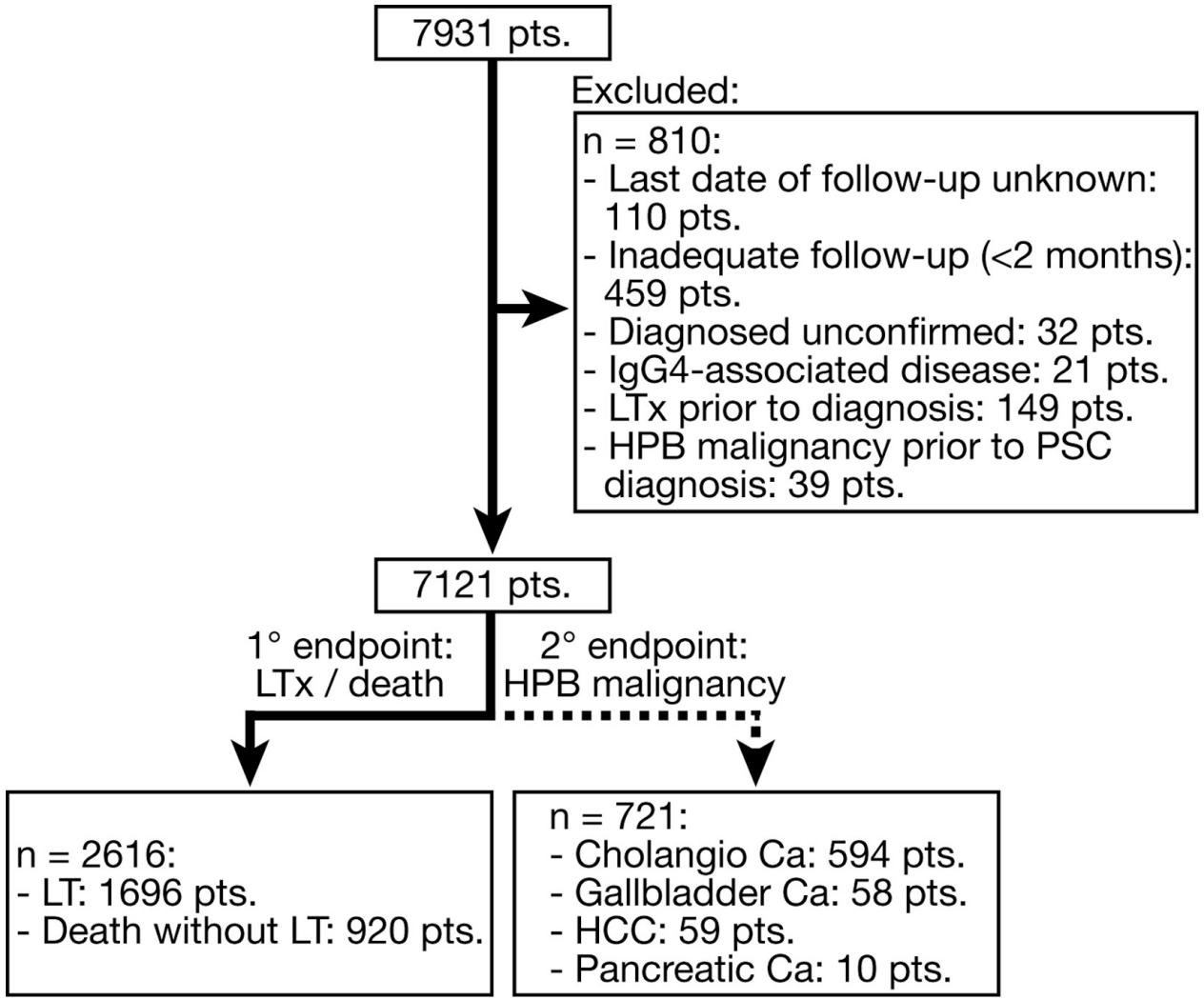
TRANSPLANT-FREE SURVIVAL IN PSC



Pre-transplant Clinical Course Is Impacted by IBD Phenotype



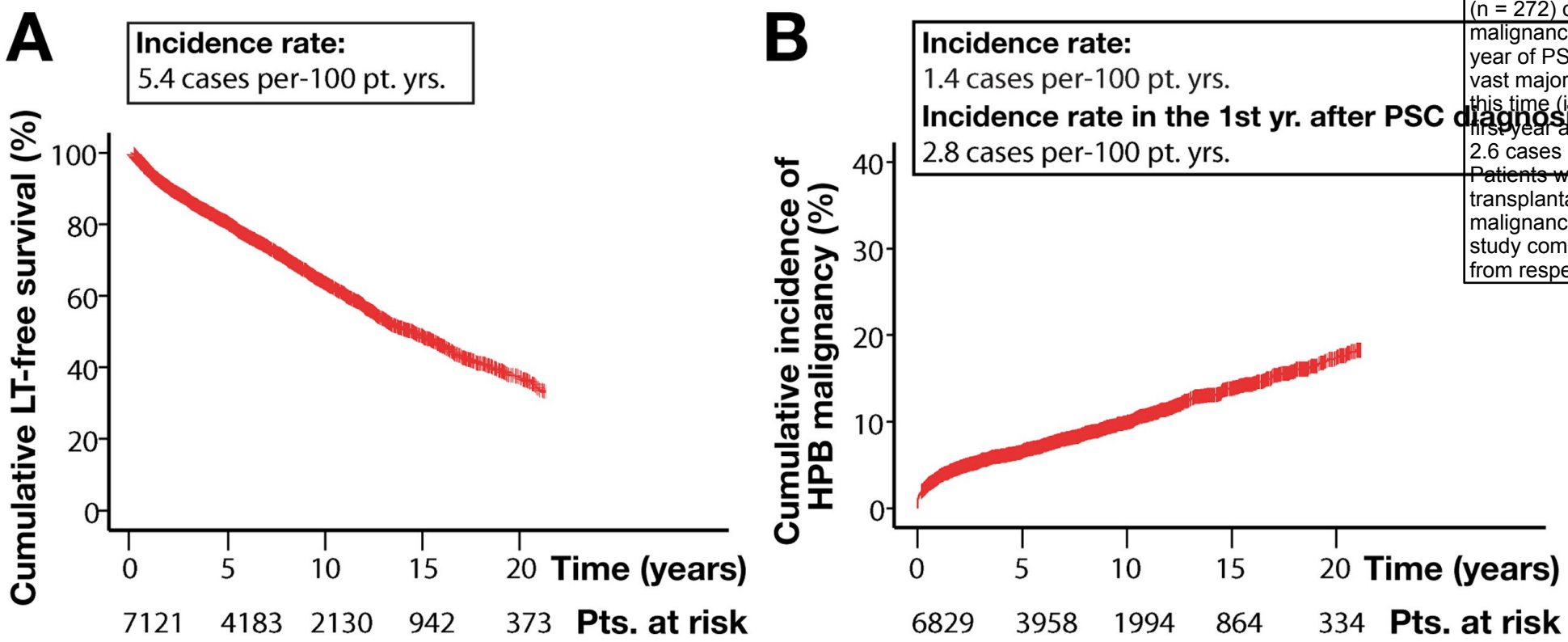
Weismueller, Trivedi, et al. *Gastro*. 2017.



Gastroenterology 2017

Presenter Notes
2024-03-09 09:58:41

Study cohort: At the time of analysis data were available for 7931 patients. However, following exclusion of groups with an alternate diagnose or inadequate follow-up, the final study group consisted of 7121 patients, of which 2616 underwent LT or died, with a total of 721 developing primary HPB malignancy.

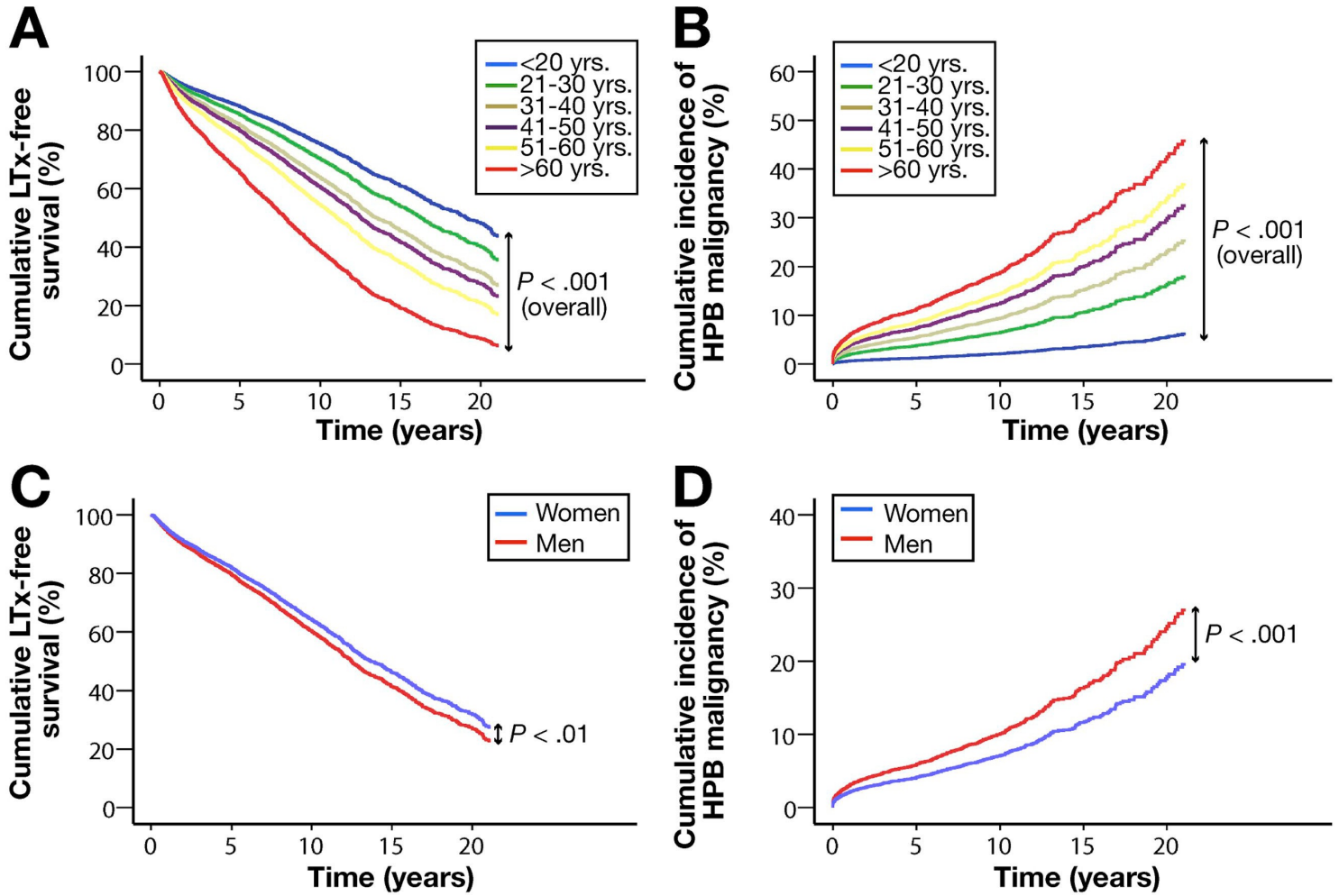


Gastroenterology 2017

Presenter Notes
2024-03-09 09:58:41

Cumulative incidence of clinical events. Kaplan-Meier estimates of (A) LT-free survival rate across the patient population and (B) incidence of all HPB malignancies. Notably, 37.8% (n = 272) of all HPB malignancies occurred in the first year of PSC diagnosis, with the vast majority being CCA during this time (incidence rate in the first year after PSC diagnosis: 2.6 cases per 100 patient-years). Patients with unknown transplantation, mortality, or malignancy status at the time of study completion were excluded from respective analysis.

Patient age and gender and clinical outcome

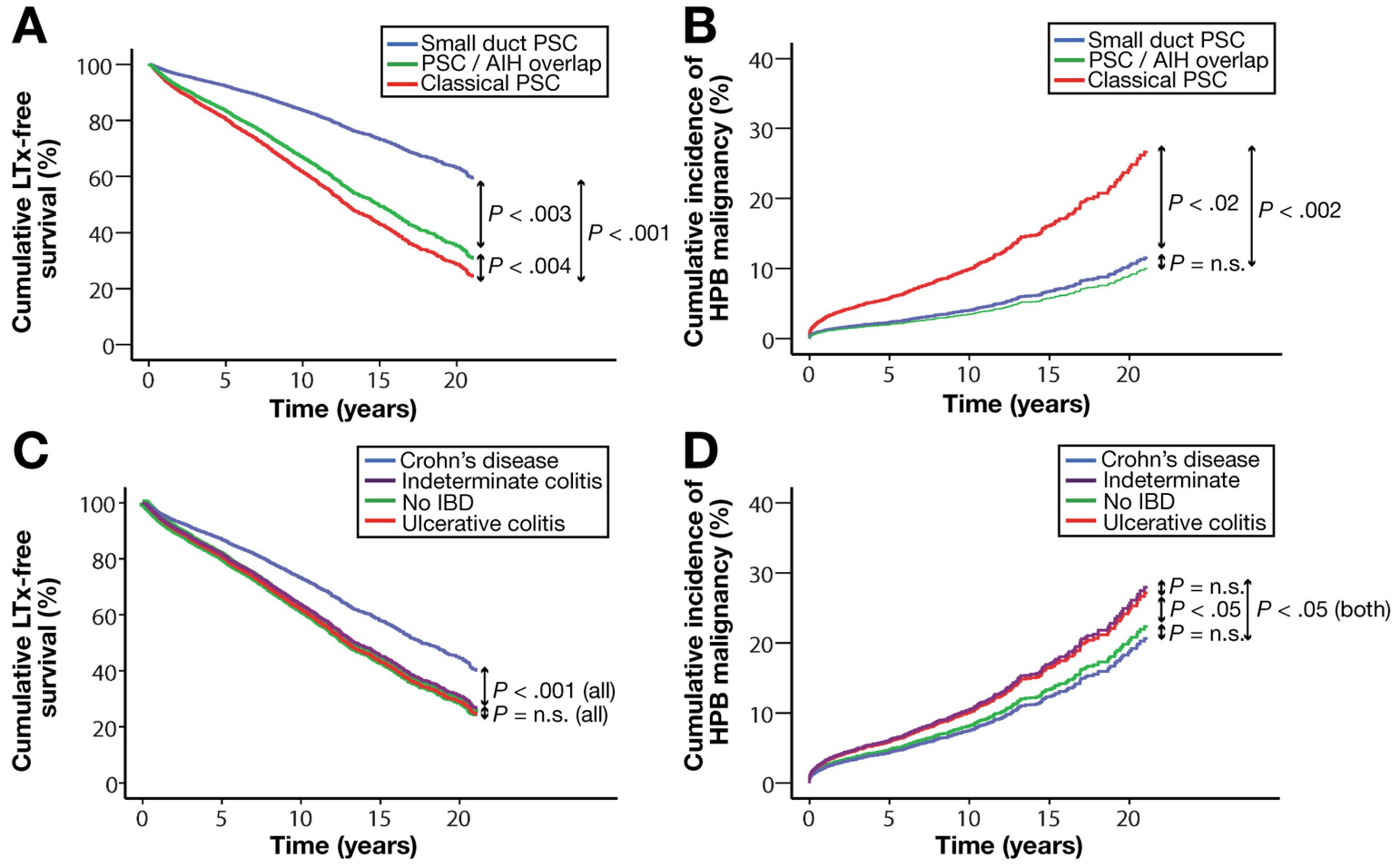


Gastroenterology 2017

Presenter Notes
2024-03-09 09:58:41

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 sub-phenotype (A and B); or patient gender weighted for patient age at diagnosis, IBD phenotype at baseline, and PSC sub-phenotype (C and D).

Cumulative Incidence of Clinical Events



Gastroenterology 2017

38% of HPB Malignancies in first year after diagnosis

Presenter Notes
2024-03-09 09:58:42

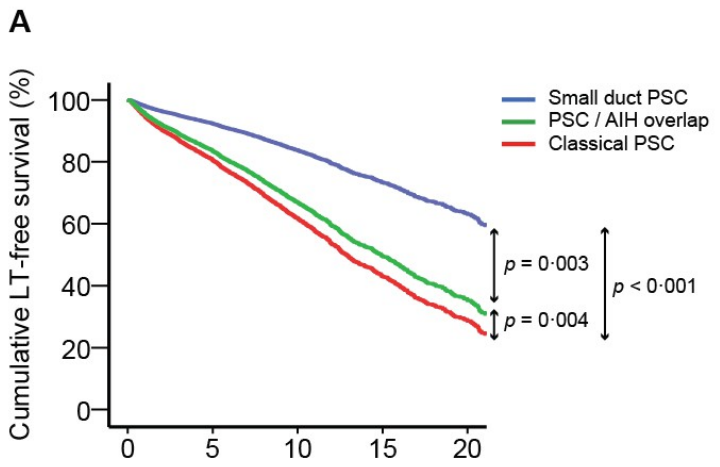
Impact of variant PSC sub-phenotypes and IBD phenotypes on clinical outcome. Cox plots with regard to LT or HPB malignancy. All data are stratified by geographic region of referring center and year of diagnosis, presented according to PSC sub-phenotype weighted for patient age at PSC diagnosis, gender, and IBD phenotype at baseline (A and B); or patient IBD phenotype at baseline weighted for age at PSC diagnosis, gender, and PSC sub-phenotype (C and D).

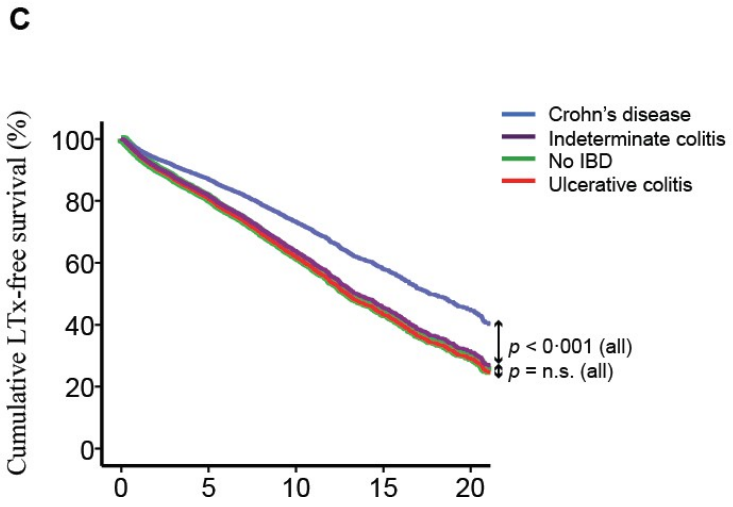
Heterogeneity of Disease

Ductal phenotype

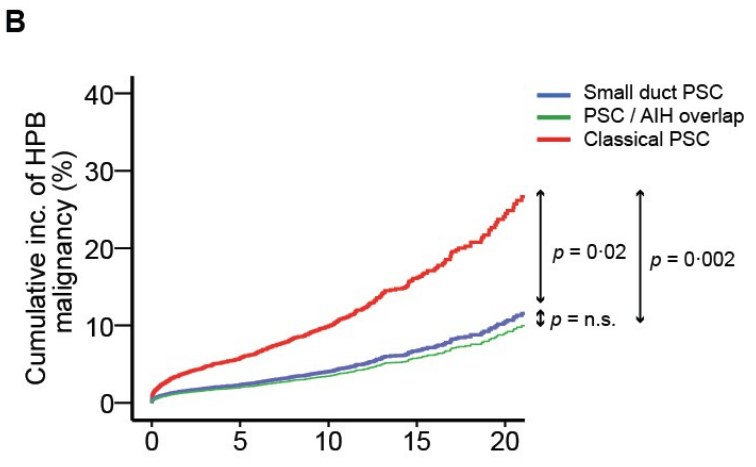
IBD phenotype

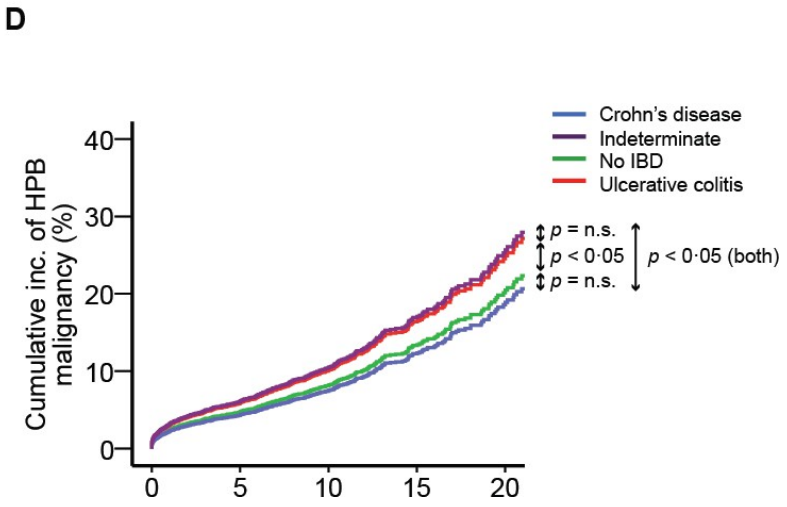
LT-free survival





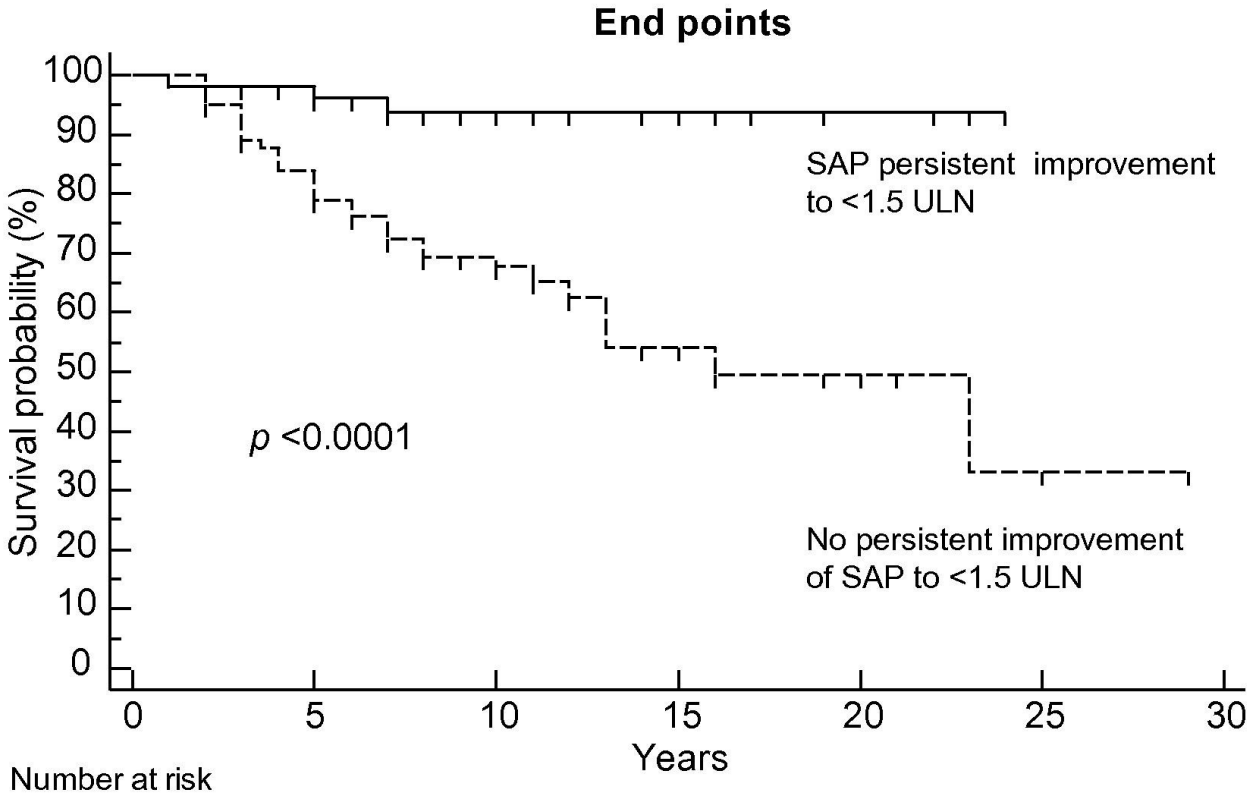
HPB malignancy





Weismueller, Trivedi, et al. *Gastro*. 2017.

Survival in PSC and Serum ALP Values



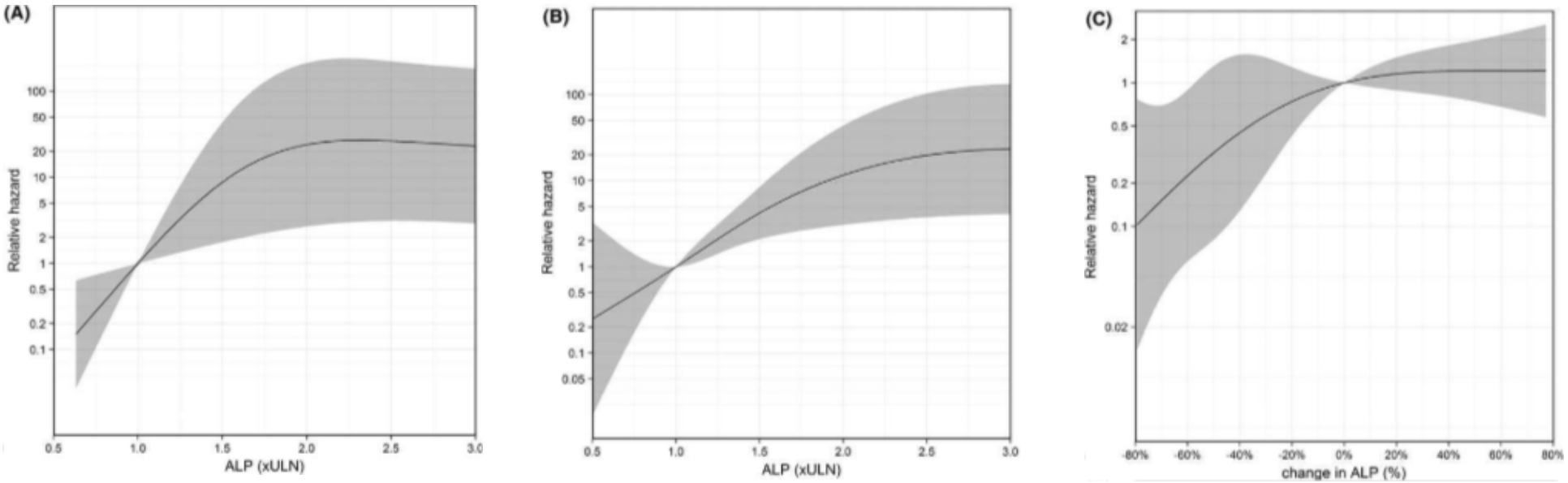
Number at risk

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.

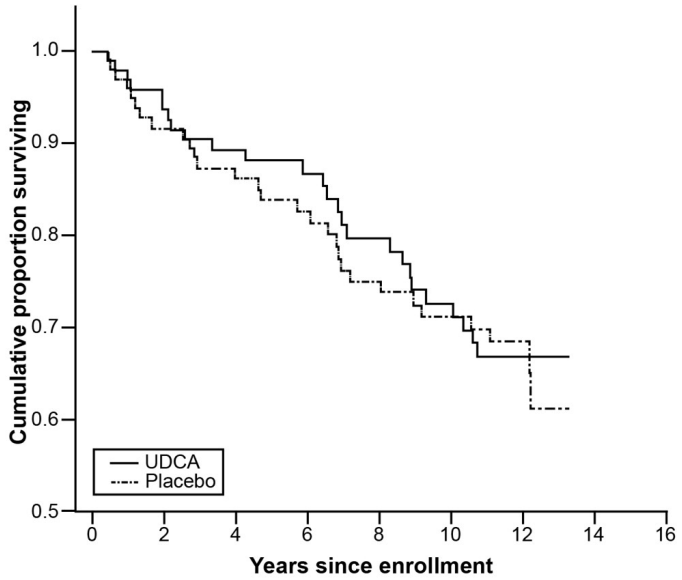
Potential Biomarkers – ALP

- 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 0.5-2.5x ULN 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 <1.3x ULN



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

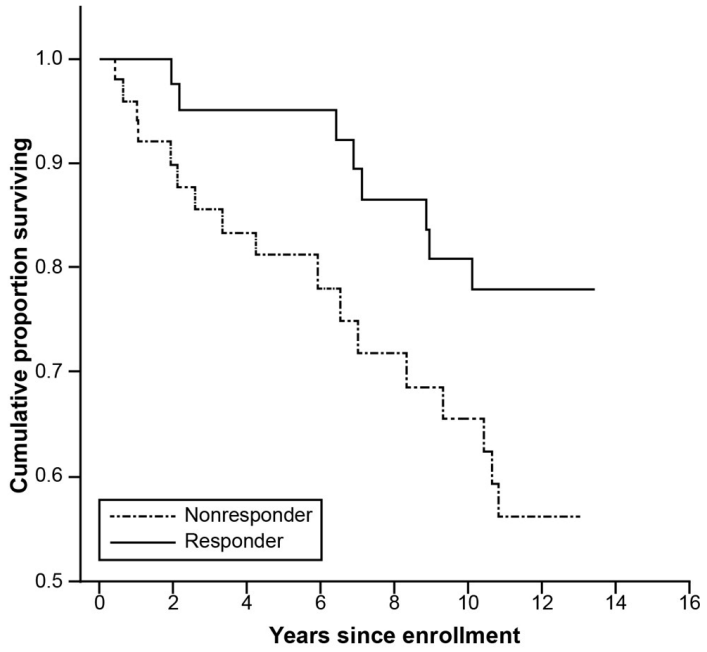
Association Between Reduced Values of ALP and Survival Times of Patients With Primary Sclerosing Cholangitis



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

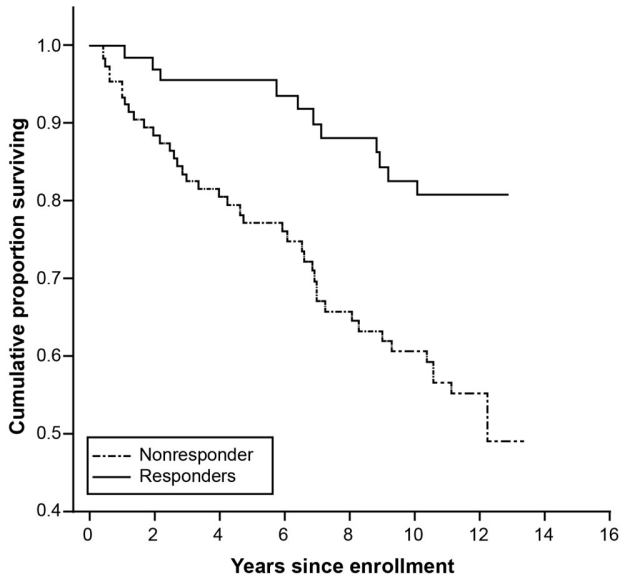
198 patients enrolled in the 5-year Scandinavian UDCA trial in 1996 randomized to UDCA vs placebo with extended follow-up



Numbers at risk

Years	0	2.5	5	7.5	10
Responder	43	40	34	24	23
Nonresponder	51	45	35	19	15

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=0.0001, log-rank test)

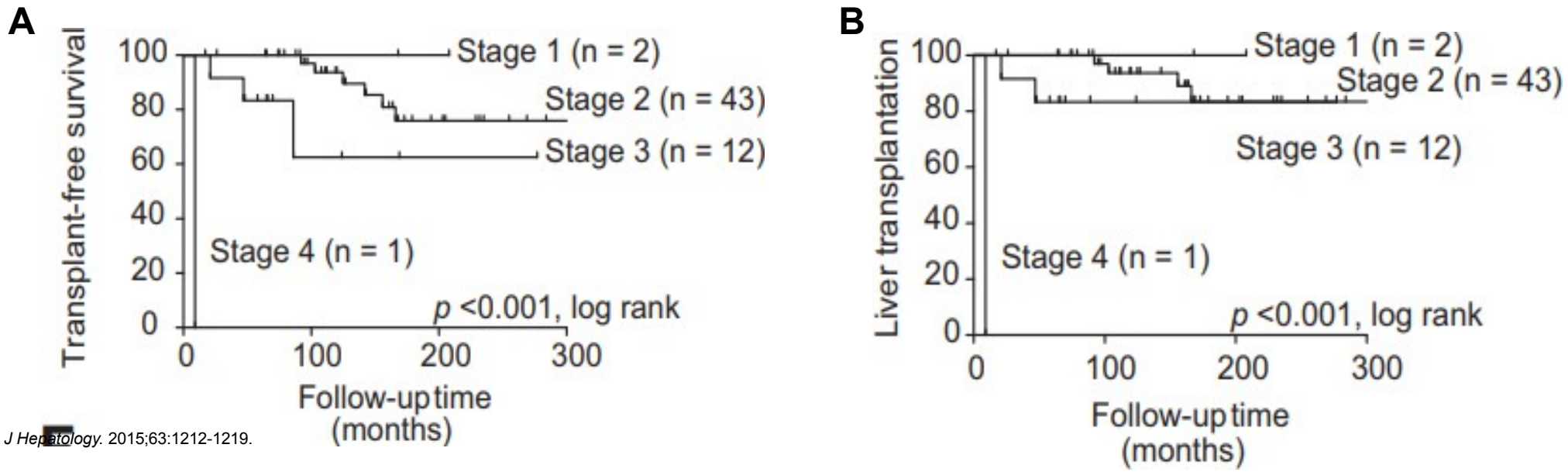
Clinical Gastroenterology and Hepatology. 2013;11(7):841-846.

Liver Histology and PSC Outcome

Presenter Notes
2024-03-09 09:58:42

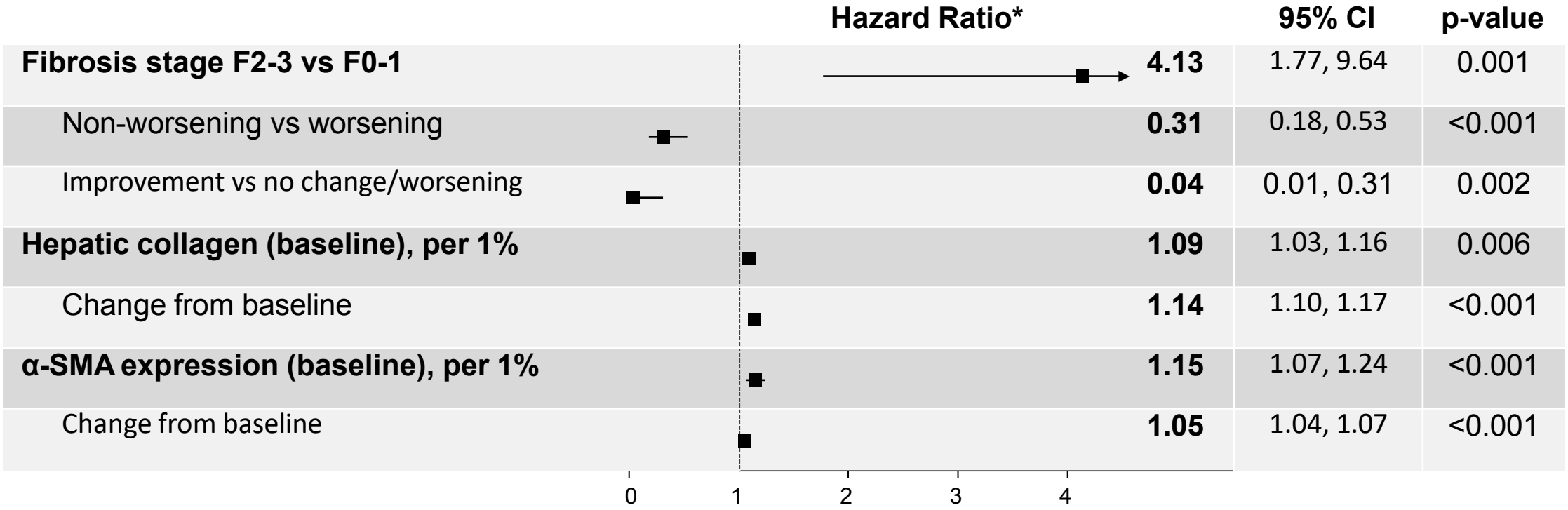
Endpoints transplant-free survival and time to liver transplantation shown for Nakanuma staging system.

- 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, Nakanuma, 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.

Associations Between Histologic Features on Disease Progression



- 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.

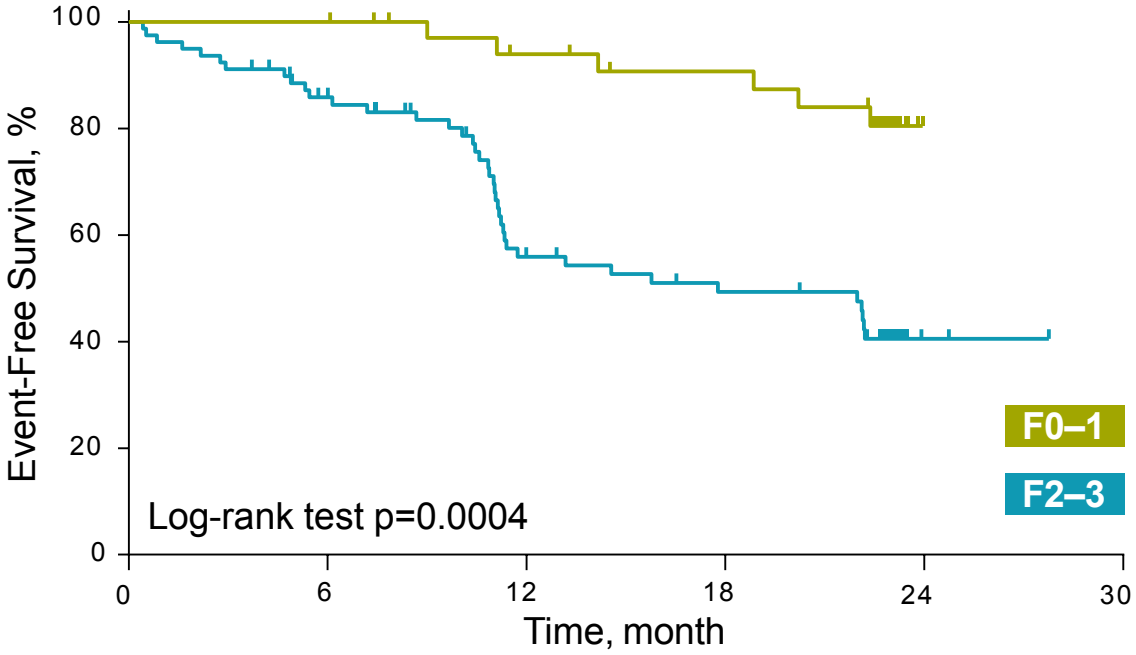
Bowlus et al.

F2-3 Fibrosis and Greater Hepatic Collagen Associated With Increased Risk of Disease Progression

Presenter Notes
2024-03-09 09:58:43

At AASLD, we will describe optimal cutoffs for ELF and hepatic collagen that are associated with clinical events. Preliminary data show that in F3, the optimal cut-off (maximal sum of sensitivity and specificity) is 9.8 to predict progression to cirrhosis, and in F4, it is 11.3 to predict decompensation. These are the same cut-offs the manufacturer recommends to be used for diagnosing F3 and F4, respectively! These data are in the SIM End of Phase 2 package we sent you.

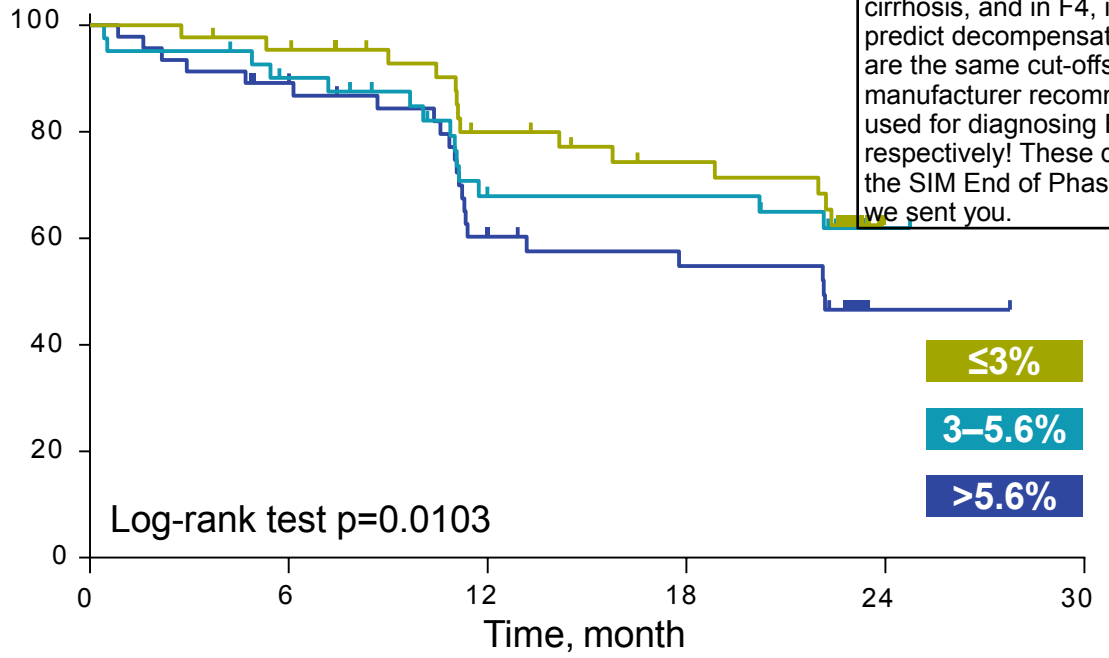
Fibrosis Stage



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)

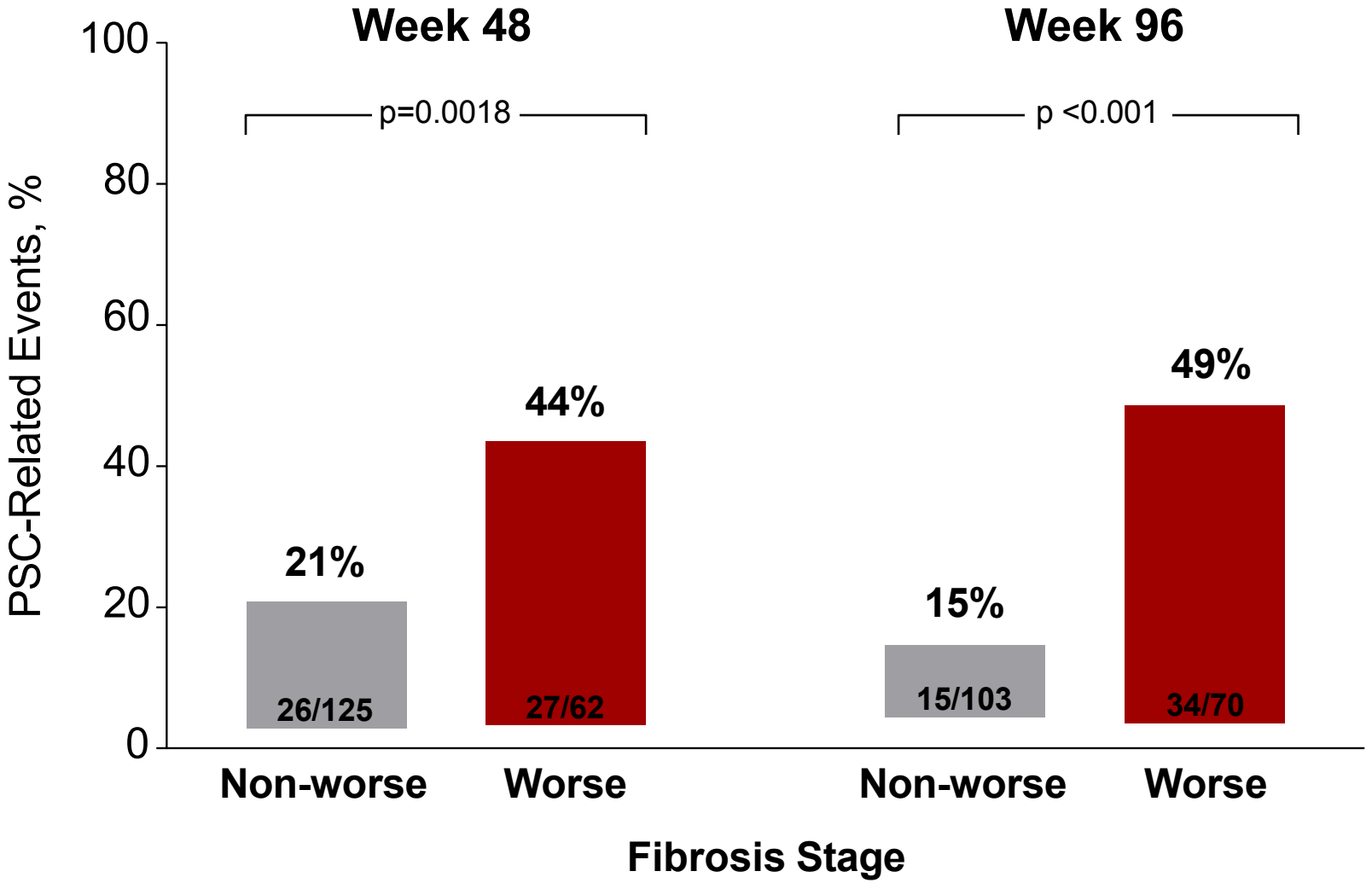
Hepatic Collagen



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



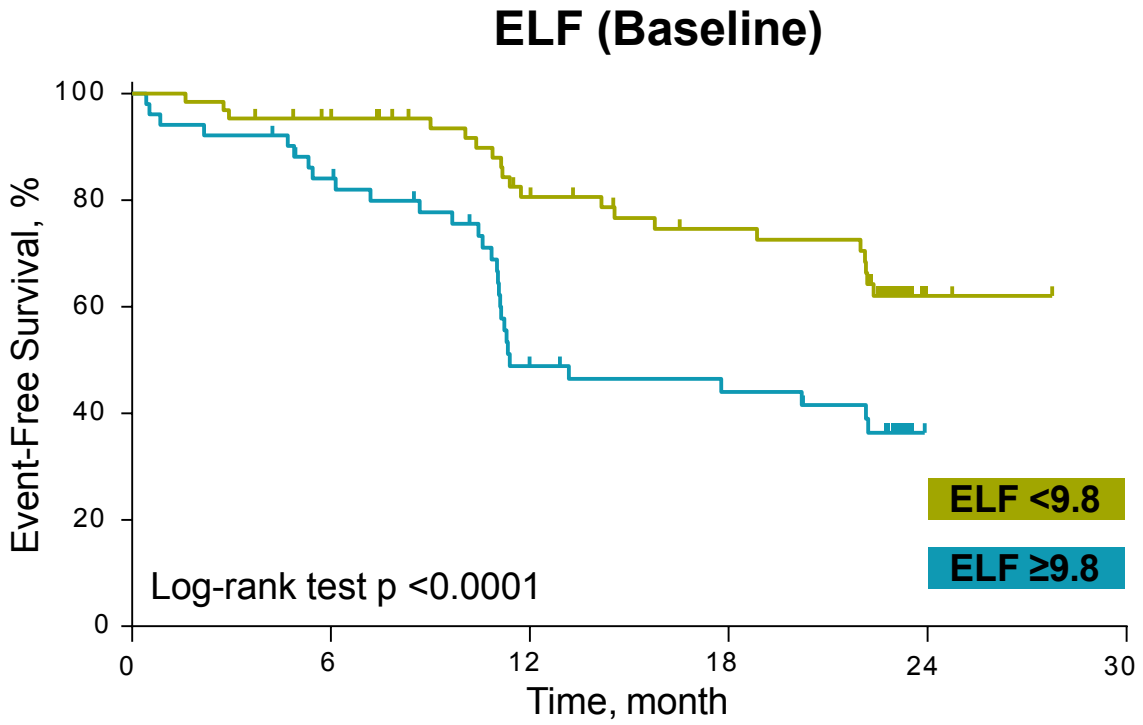
P-values by Fisher's exact test.

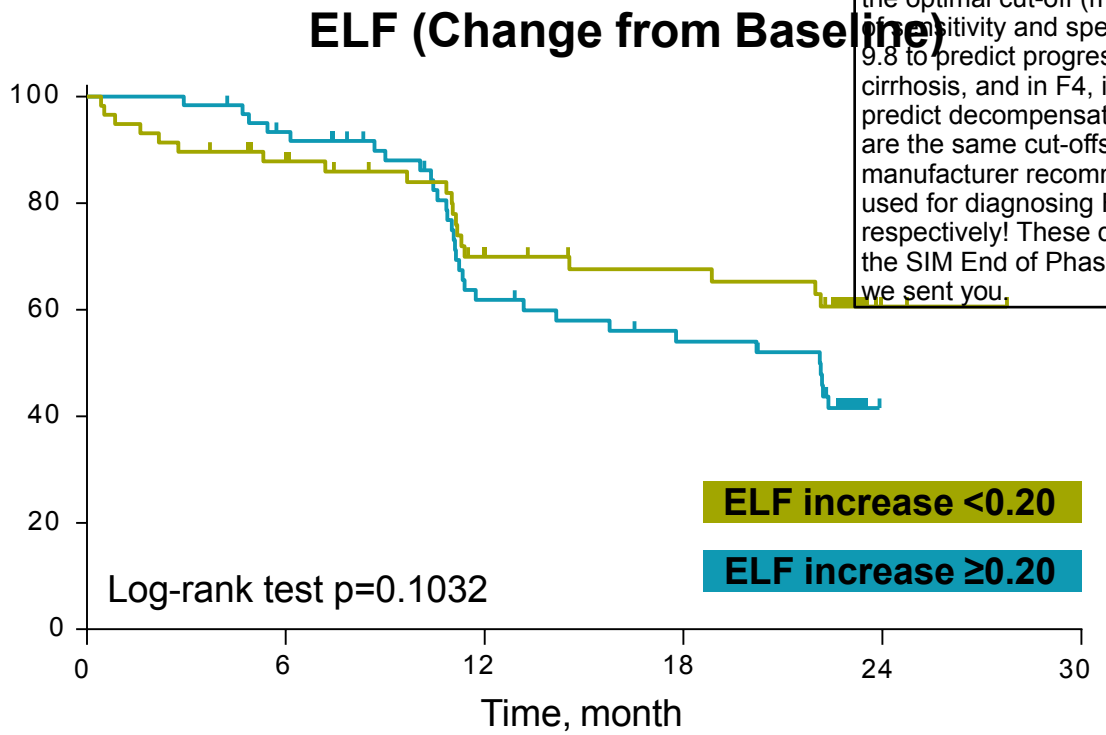
Bowlus et al.

Presenter Notes
Page 43

At AASLD, we will describe optimal cutoffs for ELF and hepatic collagen that are associated with clinical events. Preliminary data show that in F3, the optimal cut-off (maximal sum of sensitivity and specificity) is 9.8 to predict progression to cirrhosis, and in F4, it is 11.3 to predict decompensation. These are the same cut-offs the manufacturer recommends to be used for diagnosing F3 and F4, respectively! These data are in the SIM End of Phase 2 package we sent you.

Association Between ELF and Disease Progression in SIM Study





N at risk (Events)

135 (0)	132 (3)	129 (3)	123 (3)	113 (12)	108 (14)	106 (15)	105 (16)	2 (22)	1 (22)	0 (22)
74 (0)	70 (4)	64 (8)	59 (11)	38 (29)	36 (30)	35 (31)	33 (32)	0 (34)	0 (34)	0 (34)

104 (0)	98 (6)	94 (7)	89 (8)	76 (18)	72 (19)	72 (19)	71 (20)	2 (22)	1 (22)	0 (22)
105 (0)	104 (1)	99 (4)	93 (6)	75 (23)	72 (25)	69 (27)	67 (28)	0 (34)	0 (34)	0 (34)

Bowlus et al.

Presenter Notes
2024-03-09 09:58:43

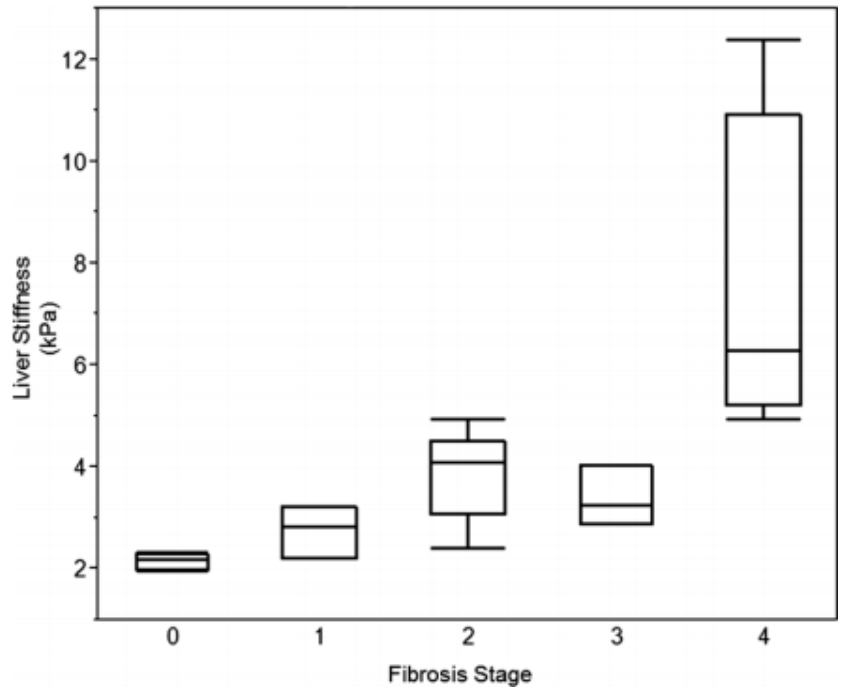
At MASLD, we will describe optimal cutoffs for ELF and hepatic collagen that are associated with clinical events. Preliminary data show that in F3, the optimal cut-off (maximal sum of sensitivity and specificity) is 9.8 to predict progression to cirrhosis, and in F4, it is 11.3 to predict decompensation. These are the same cut-offs the manufacturer recommends to be used for diagnosing F3 and F4, respectively! These data are in the SIM End of Phase 2 package we sent you.

MRE

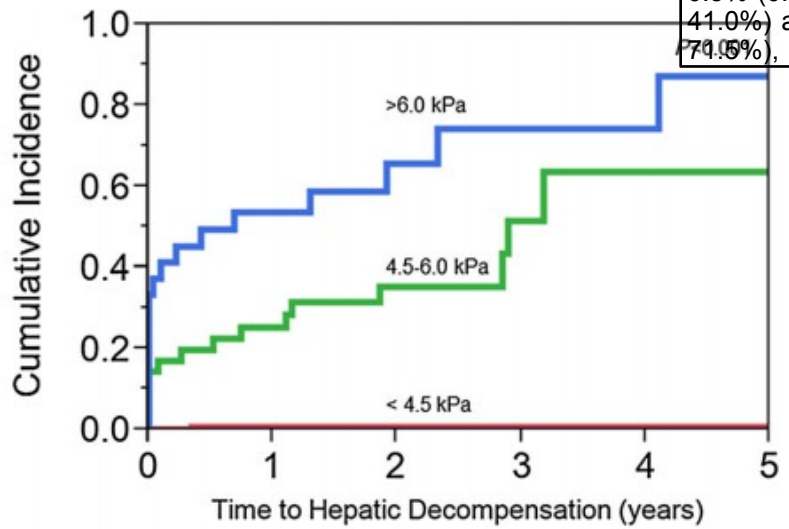
Presenter Notes
2024-03-09 09:58:43

Patients with a LS of less than 4.5, 4.5–6.0 and greater than 6.0 kPa had a 1-year cumulative incidence (95%CI) of hepatic decompensation, which was 0.5% (0.0–4.0%), 25.2% (14.1–41.0%) and 54.0% (34.6–71.5%), respectively

A



B



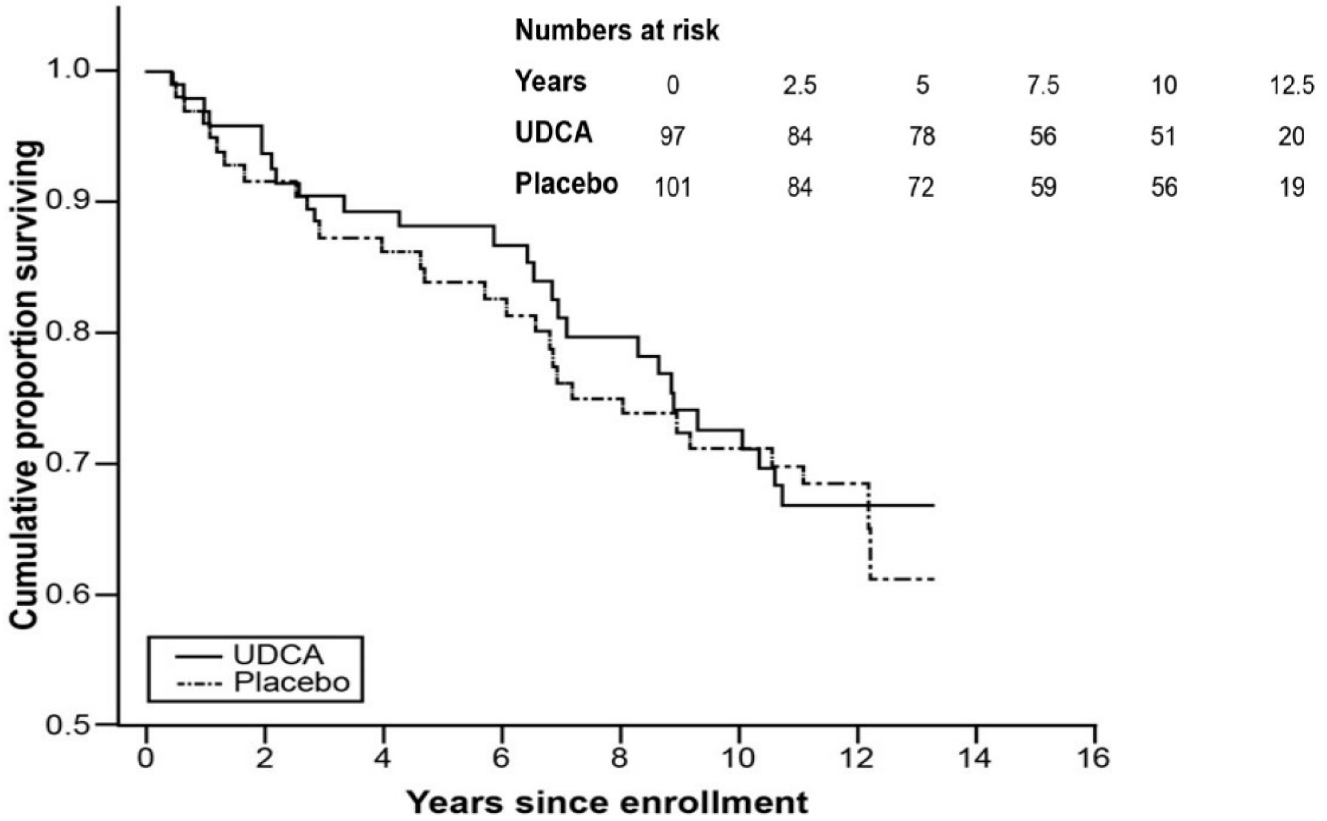
Number at Risk:						
>6.0 kPa	27	11	6	3	3	2
4.5-6.0 kPa	42	26	18	6	3	2
<4.5 kPa	197	163	107	45	24	17

- 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 >4.5 kPa 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.

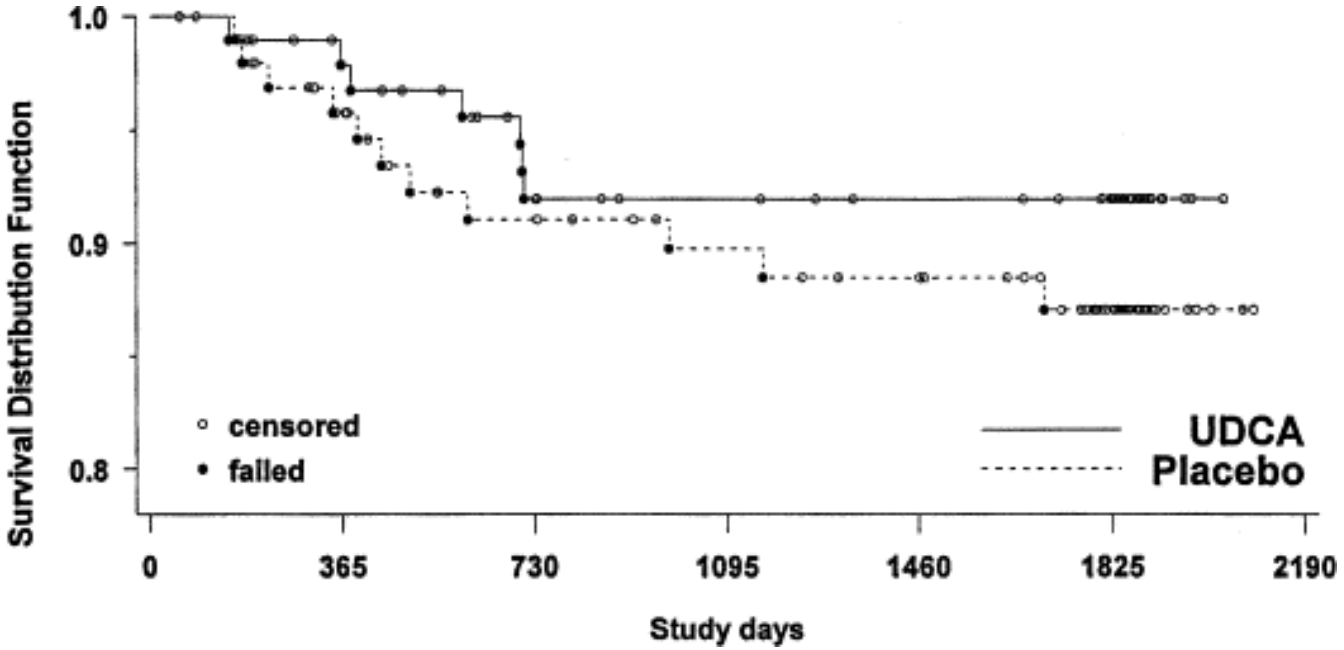
Ursodiol in PSC

Kaplan-Meier Survival Curve of 198 PSC Patients Enrolled in a 5 year UDCA Trial



Lindstrom L, Hultcrantz R, Boberg KM,, et al. Assoc. btwen reduced levels of ALK and Survival Times of Patients with PSC. Clin Gastro Hep. 2013;11(7):841-846.

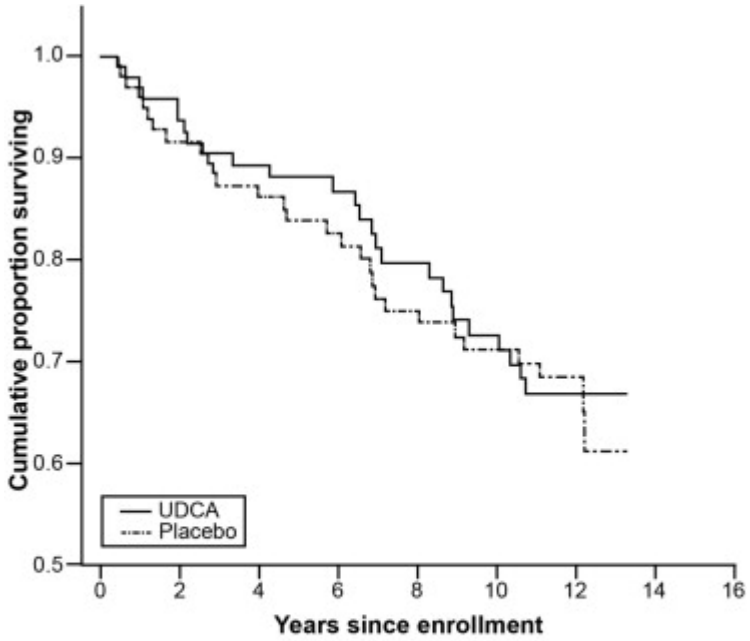
Intermediate Dose UDCA in PSC



Gastroenterology 2005 129, 1464-1472

Survival in Patients Treated With Ursodeoxycholic Acid vs Placebo

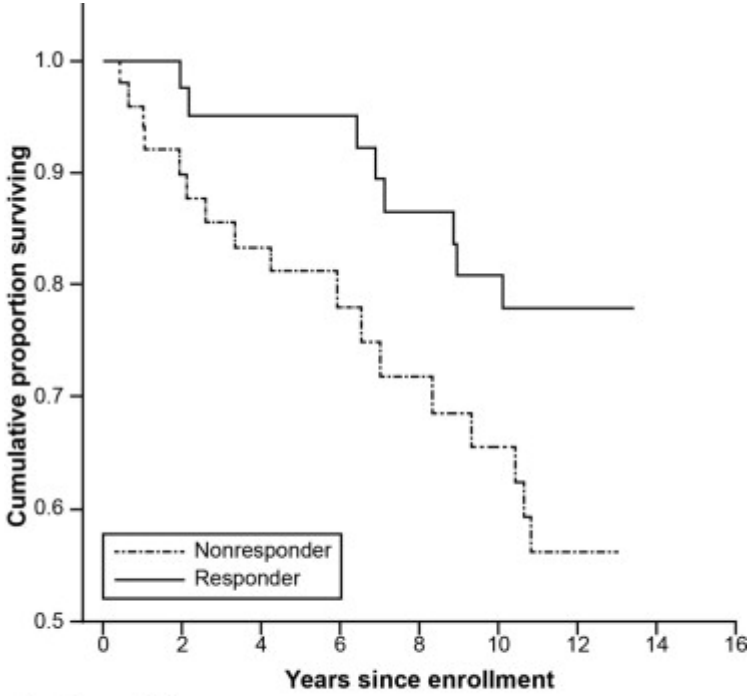
(*P* = .774, log-rank).



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

Survival in Biochemical Responders vs Nonresponders

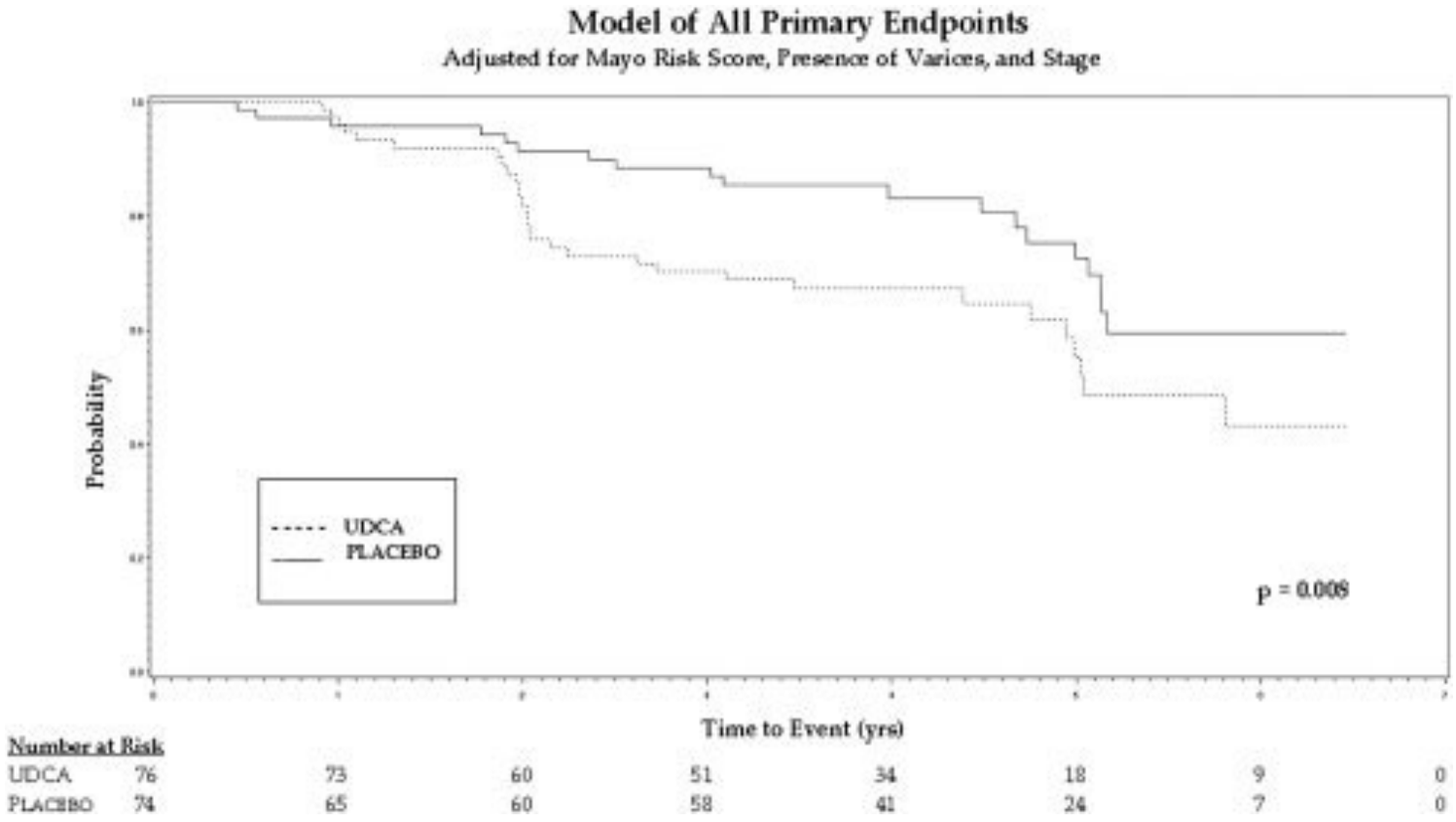


Numbers at risk

Years	0	2.5	5	7.5	10
Responder	43	40	34	24	23
Nonresponder	51	45	35	19	15

Clin Gastroenterol Hepatol. 2013;11:841-6

High-Dose UDCA (28-30 mg/kg) vs Placebo for PSC



Hepatology 2009; 50:808–814

High-dose Urso for PSC Results

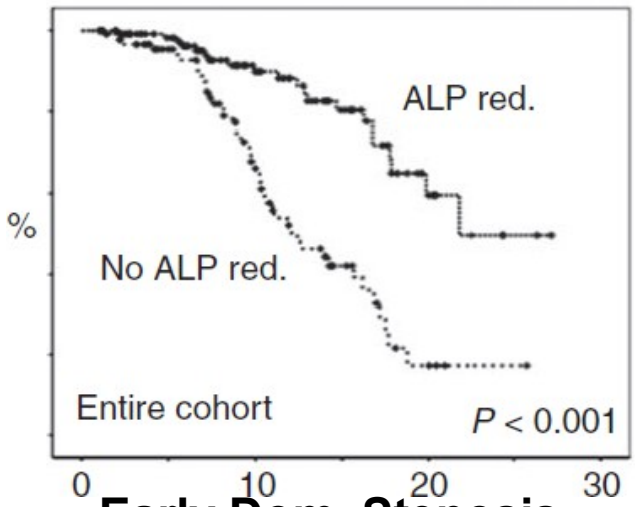
Primary Endpoints

Primary Endpoints	UDCA	Placebo
Death	5	3
Liver Transplant	11	5
Minimal Listing Criteria for Liver Transplant	13	10
Development of Cirrhosis	6	4
Esophageal and/or Gastric Varices	15	5
Cholangiocarcinoma	2	2
Total Endpoints	52	29

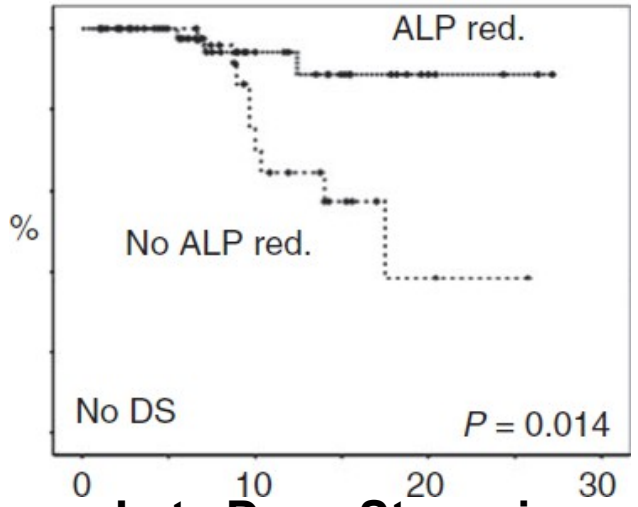
Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology 2009;50(3):808-14

Lower ALP Associated With Survival in Presence/Absence of Dominant Stenosis

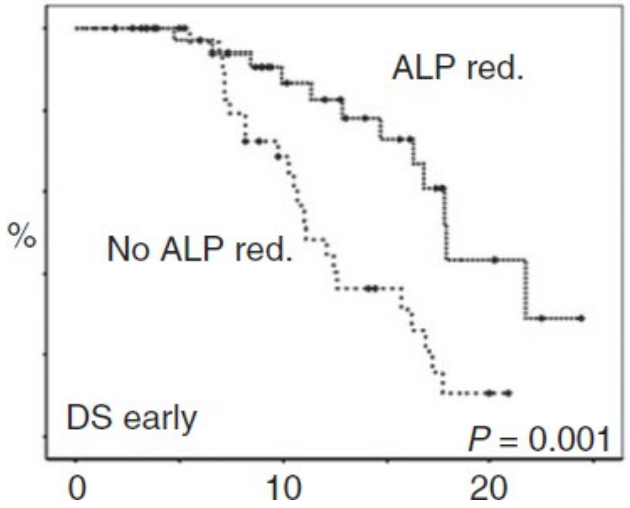
Overall



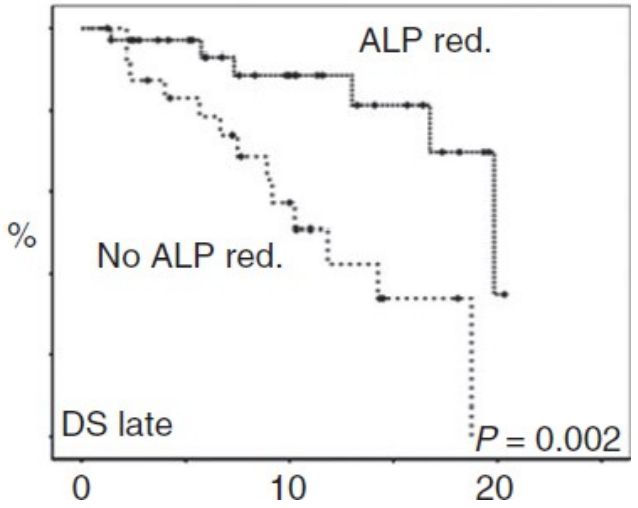
No Dom. Stenosis



Early Dom. Stenosis

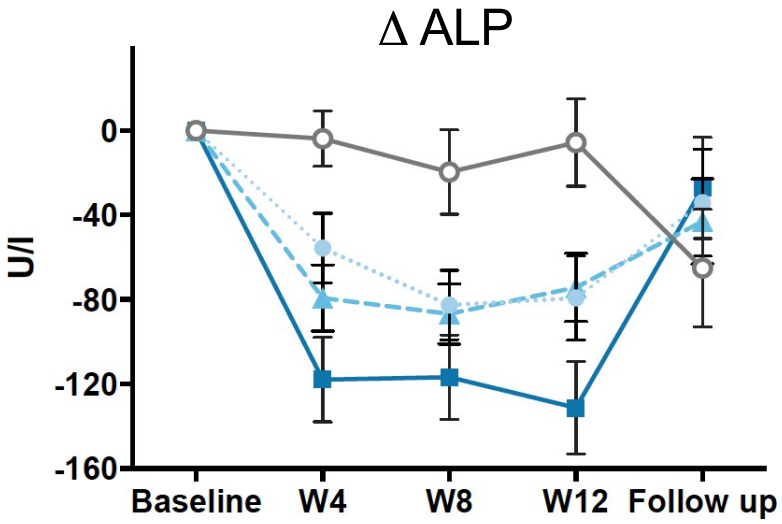


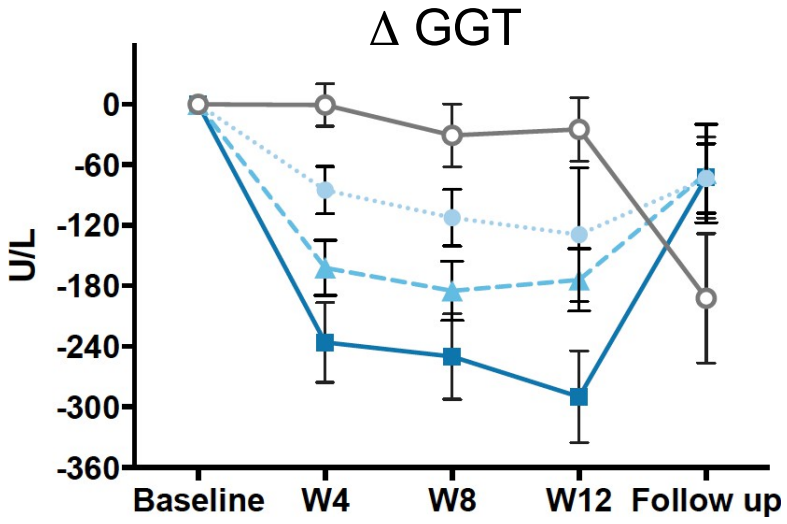
Late Dom. Stenosis

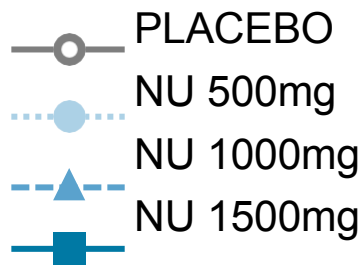


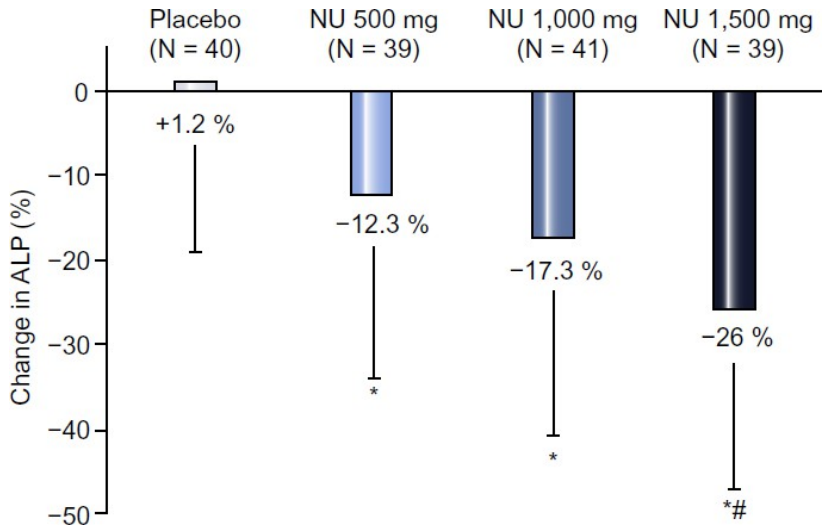
Rupp C, et al. *Aliment Pharmacol Ther*. 2014;40(11-12):1292-1301.

*nor*UDCA Improves Cholestasis in PSC: Results of a European Multicenter Phase II RCT (NUC-3)









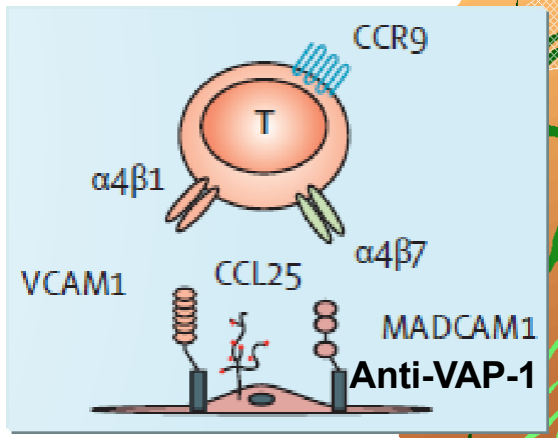
- *nor*UDCA resulted in a significant reduction of serum ALP within 12 weeks of treatment compared to placebo; n=161
- The effect occurred in a dose-dependent manner with the highest effect at 1500 mg/d - indep. of prev. UDCA response
- Safety profile of *nor*UDCA did not differ from placebo
- Phase III initiated (NUC-5): long-term treatment over 96 wks (DBE 192 wks); biochemical, histological & clinical endpoints; n=300

Fickert et al., *J Hepatol* 2017; 67: 549-558

Novel Therapeutic Strategies in PSC
Currently Tested in Clinical Trials - Overview

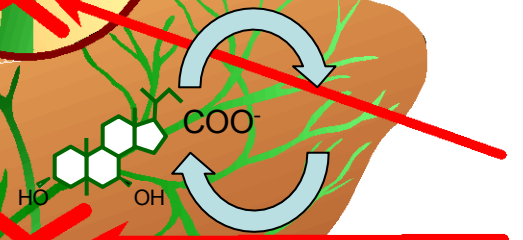
Cenicriviroc

Etrolizumab
Vedolizumab



Lancet 2013;382:1590

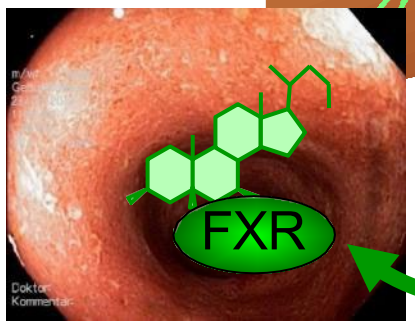
norUDCA



PPAR
FXR
RAR

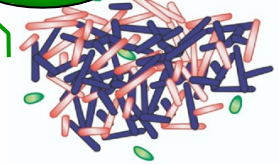
Simtuzumab

Antibiotics
(Vancomycin,
Minocyclin,
Metronidazol)



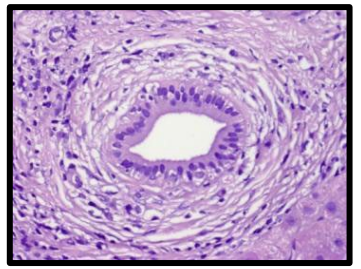
Colitis (~75%)

FXR



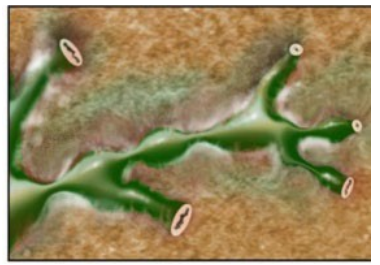
FMT?

Microbiota (Dysbiosis)

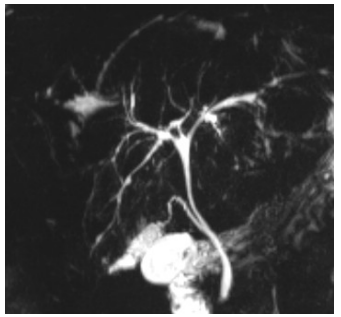


Small Duct PSC

Obliterative fibrosis
of bile ducts



www.mayoclinic.org



Large Duct PSC

Reviews: Hirschfield et al., *Lancet* 2013
Halilbasic et al., *Dig Dis* 2015
Ali et al., *Intract Rare Dis Res* 2015
Karlsen et al., *J Hepatol* 2017

Courtesy of Dr. Michael Trauner

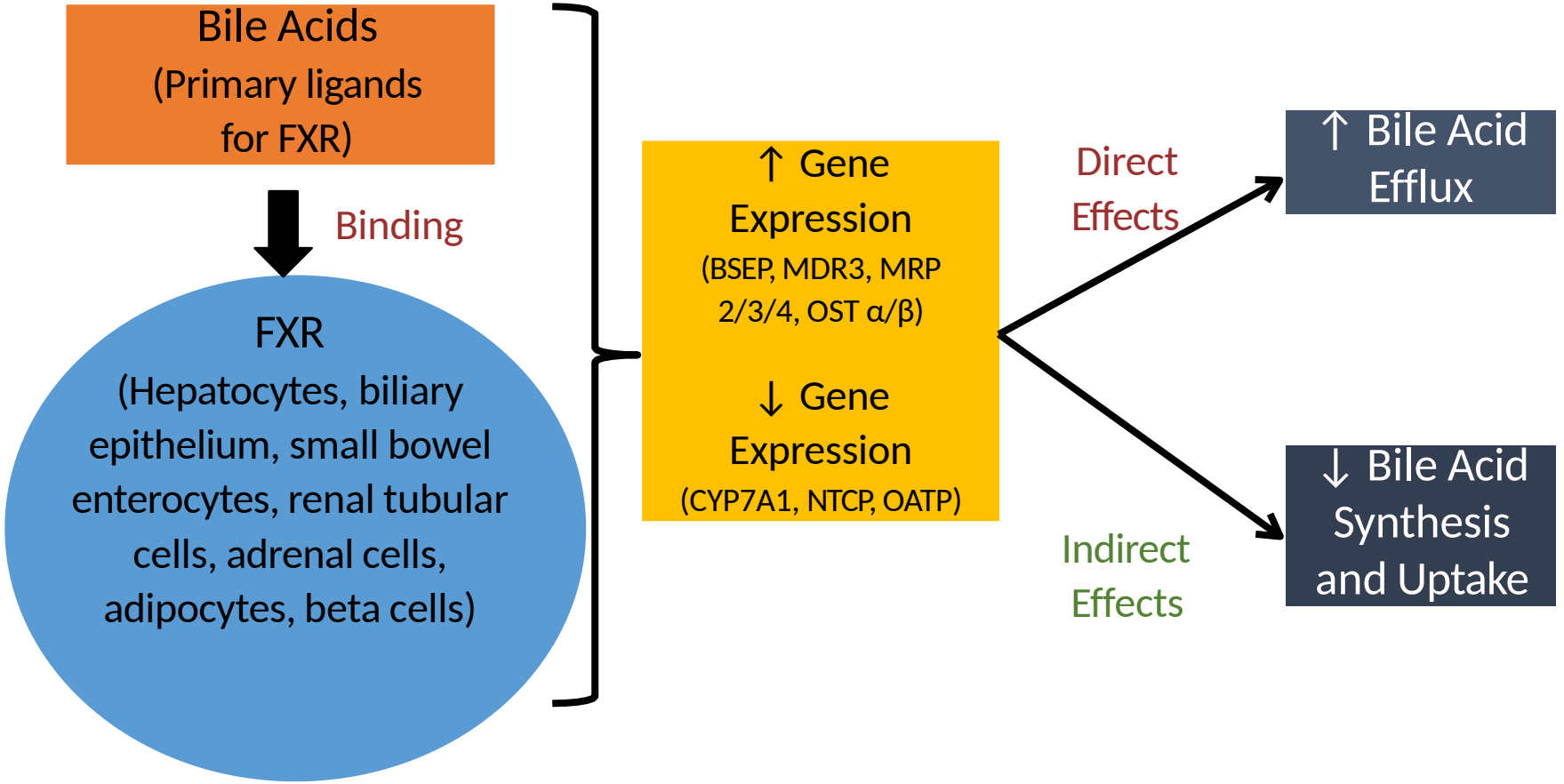
PBC Investigational Targets

Abbreviations: FGF, fibroblast growth factor; FXR, farnesoid X receptor; PBC, primary biliary cirrhosis; PPAR, peroxisome proliferator-activated receptor.

Presenter Notes
2024-03-09 09:58:46

See Neuschwander-Tetri2012.tiff

Farnesoid X Receptor Signaling



Abbreviations: BSEP, bile salt export pump; FXR, farnesoid X receptor; MRP 2/3/4, multidrug resistant protein 2/3/4; NTCP, sodium/taurocholate cotransporting polypeptide; OATP, organic anion transporting polypeptide; OST α/β, organic soluble transporter α/β.

Neuschwander-Tetri BA. *Curr Gastroenterol Rep*. 2012;14:55-62.

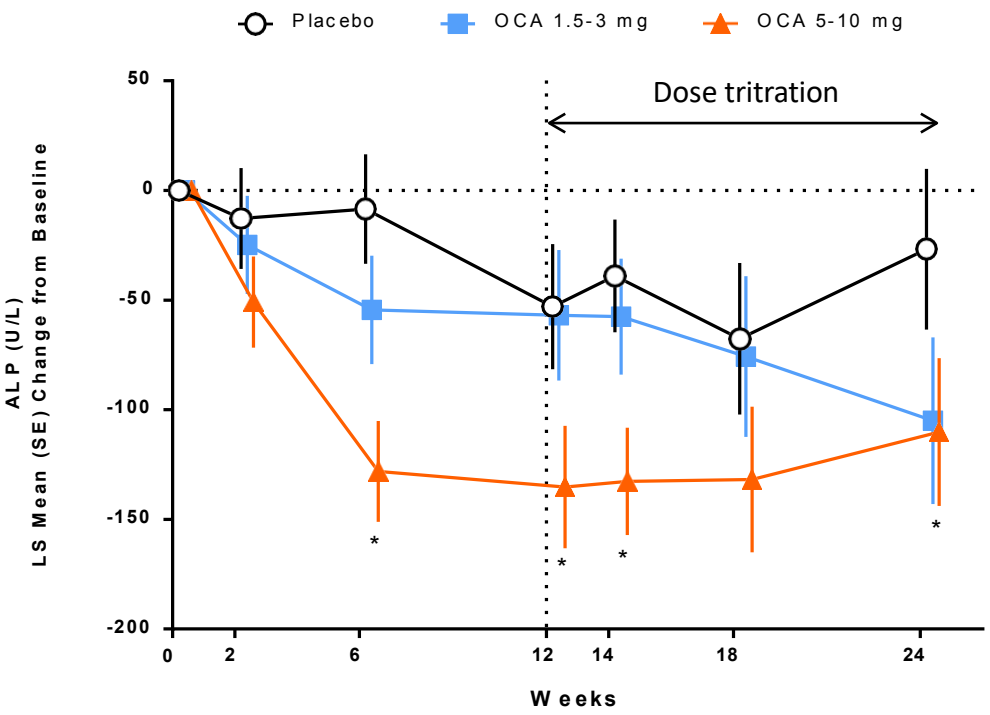
Bile Acid Receptor Signaling & Transport-based Drug Strategies in PSC

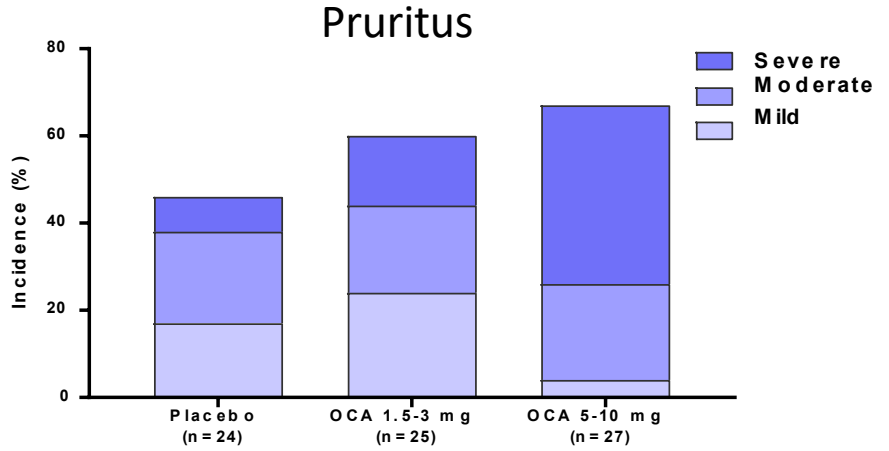
Drug (Target)	Phase	Outcome Parameters	ClinicalTrials.gov
OCA (FXR)	II RCT N=76 AESOP	Safety (pruritus) Reduction in ALP	NCT02177136 Completed Has results 1
GS-9674 (FXR)	II RCT N=52	Safety & efficacy 12 wks + 96 wks OLE	NCT02943460 Fully recruited
NGM282 (FGFR/β-klotho)	II RCT N=62	Biochemistry (ALP, AST @ 12 wks)	NCT02704364 Completed
LUM001/Lopixibat (ASBT)	II Open Lbl N=27 CAMEO	Safety Reduction in SBA & pruritus No change in ALP (14 wks)	NCT02061540 Completed Has results 2

1. Kowdley et al. AASLD 2017 LB-2 (Hepatology 2017, 66 (Suppl.1): 1254A)
2. Clinicaltrials.gov/ct2/show/results/NCT02061540

Courtesy of Dr. Michael Trauner

The AESOP Trial: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of OCA in Patients with PSC



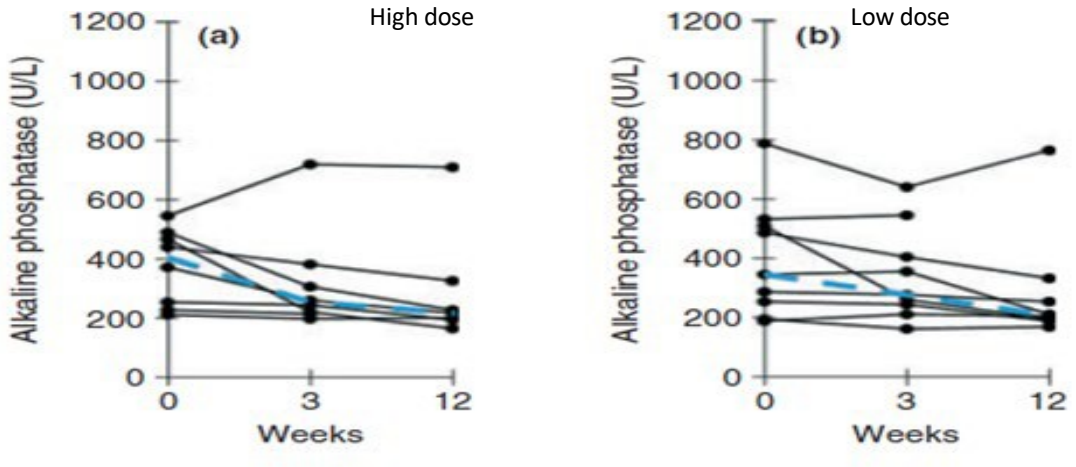


- OCA resulted in a significant reduction of serum ALP within 24 weeks of treatment compared to placebo; n=76
- The effect occurred in a dose-dependent manner, regardless of UDCA use (stable UDCA dose for 3 months required)
- Pruritus most common AE (increased with dose, few discontinuations n=4), no unexpected safety findings
- Findings warrant further investigation (OLE ongoing – 2 yrs)

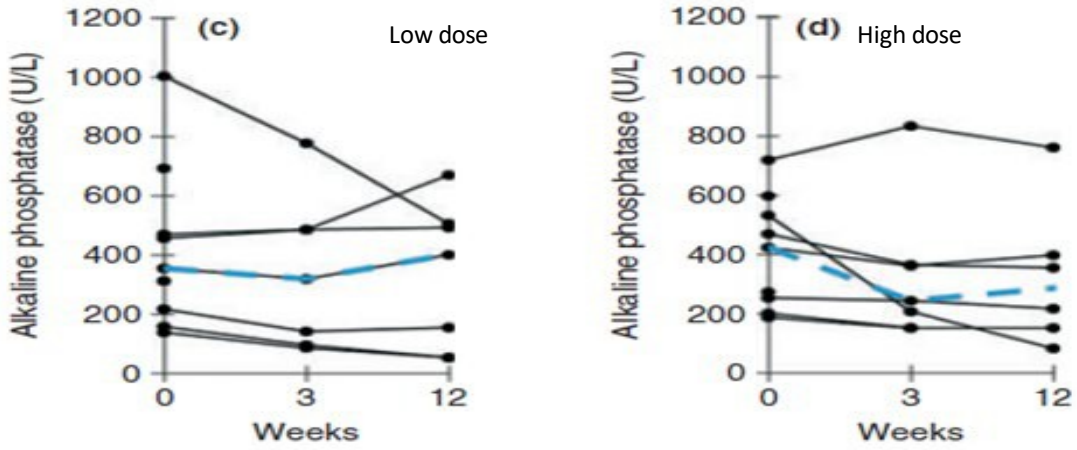
Kowdley et al., AASLD 2017 LB-2 (Hepatology 2017, 66 (Suppl.1): 1254A)

Vancomycin & Metronidazole in PSC

VANCOMYCIN



METRONIDAZOLE

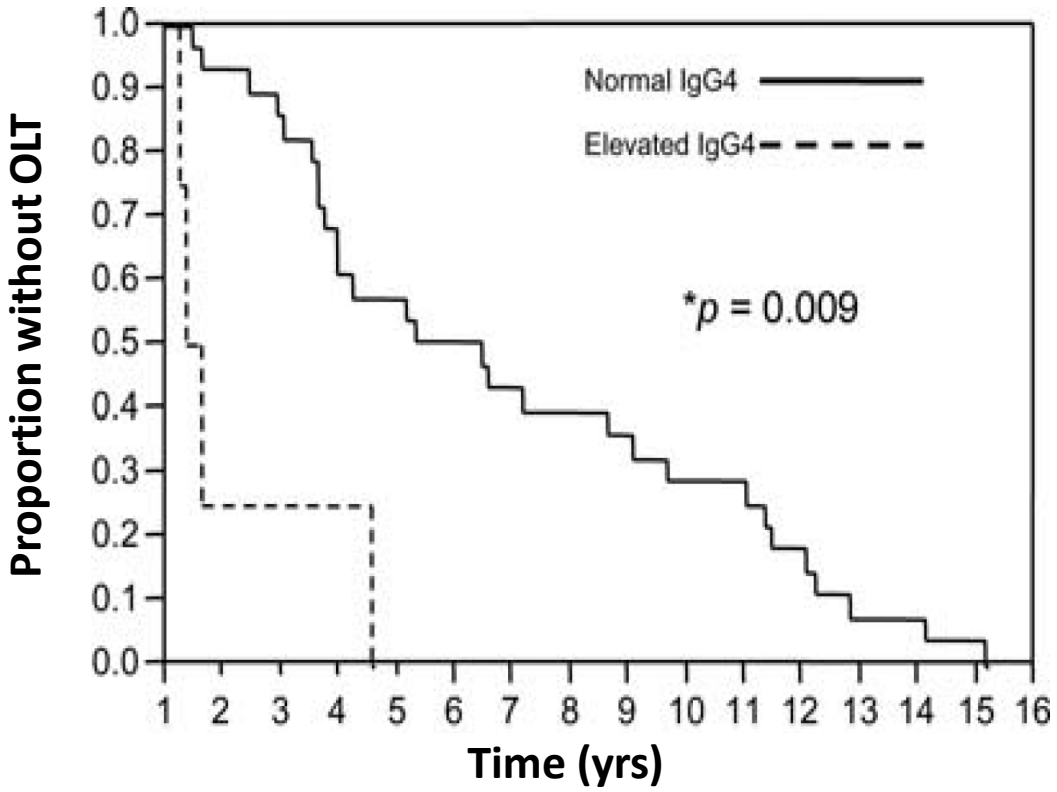


Tabibian JH, Weeding E, Jorgensen RA, et al. Randomized clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis – a pilot study. Aliment Pharmacol Ther. 2013; 37(6): 604-12.

Immunosuppressive and Other Agents

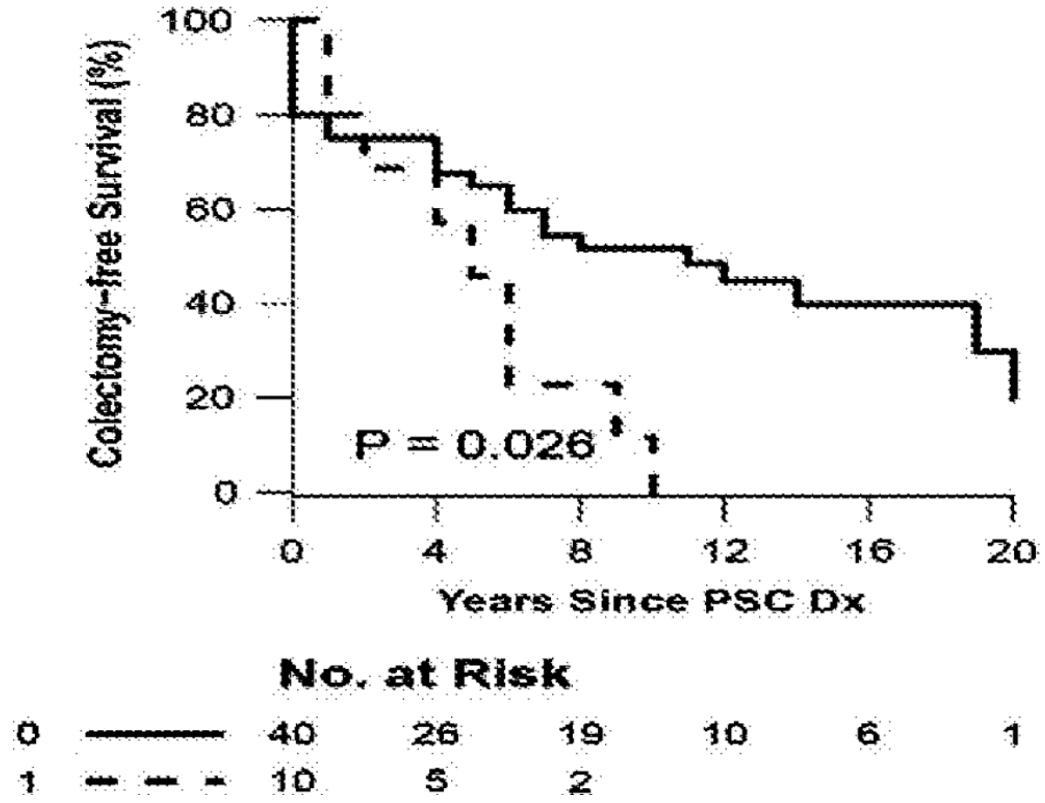
- Azathioprine
- Budesonide
- Docosahexaenoic acid
- Methotrexate
- Metronidazole
- Minocycline
- Mycophenolate mofetil
- Nicotine
- Pentoxifylline
- Pirfenodone
- Prednisolone
- Tacrolimus
- Vancomycin

Natural History “PSC” & IgG4



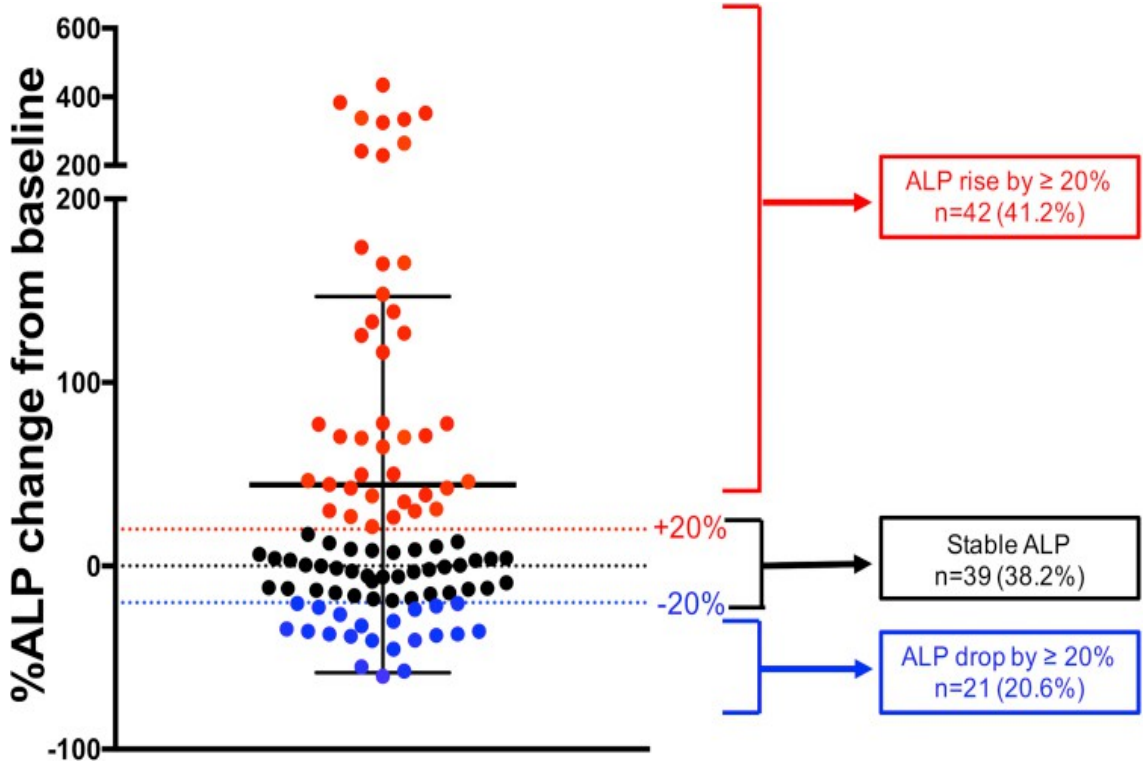
Mendes F, Jorgensen R, Keach J, et al. Elevated Serum IgG4 Concentration in Patients with Primary Sclerosing Cholangitis. Am J Gastroenterol 2006;101:2070-75

Elevated IgG4 level is associated with reduced colectomy-free survival in patients with PSC/UC

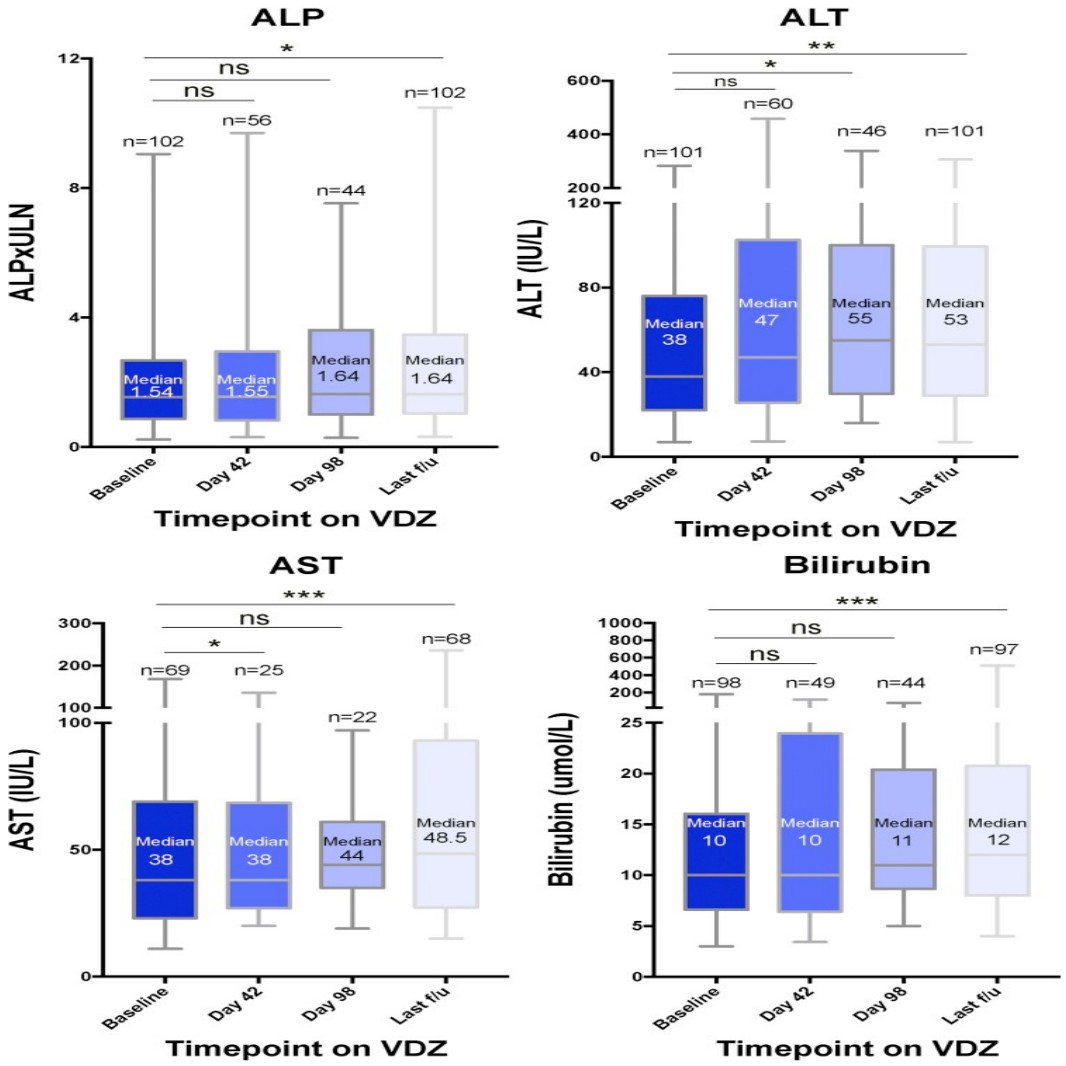


Navaneethan U, Venkatesh PGK, Choudhary M, et al. Elevated immunoglobulin G4 level is associated with reduced colectromy-free survival in patients with primary sclerosing cholangitis and ulcerative colitis. Journal of Crohn's and Colitis. 2013; 7: e35 –e41.

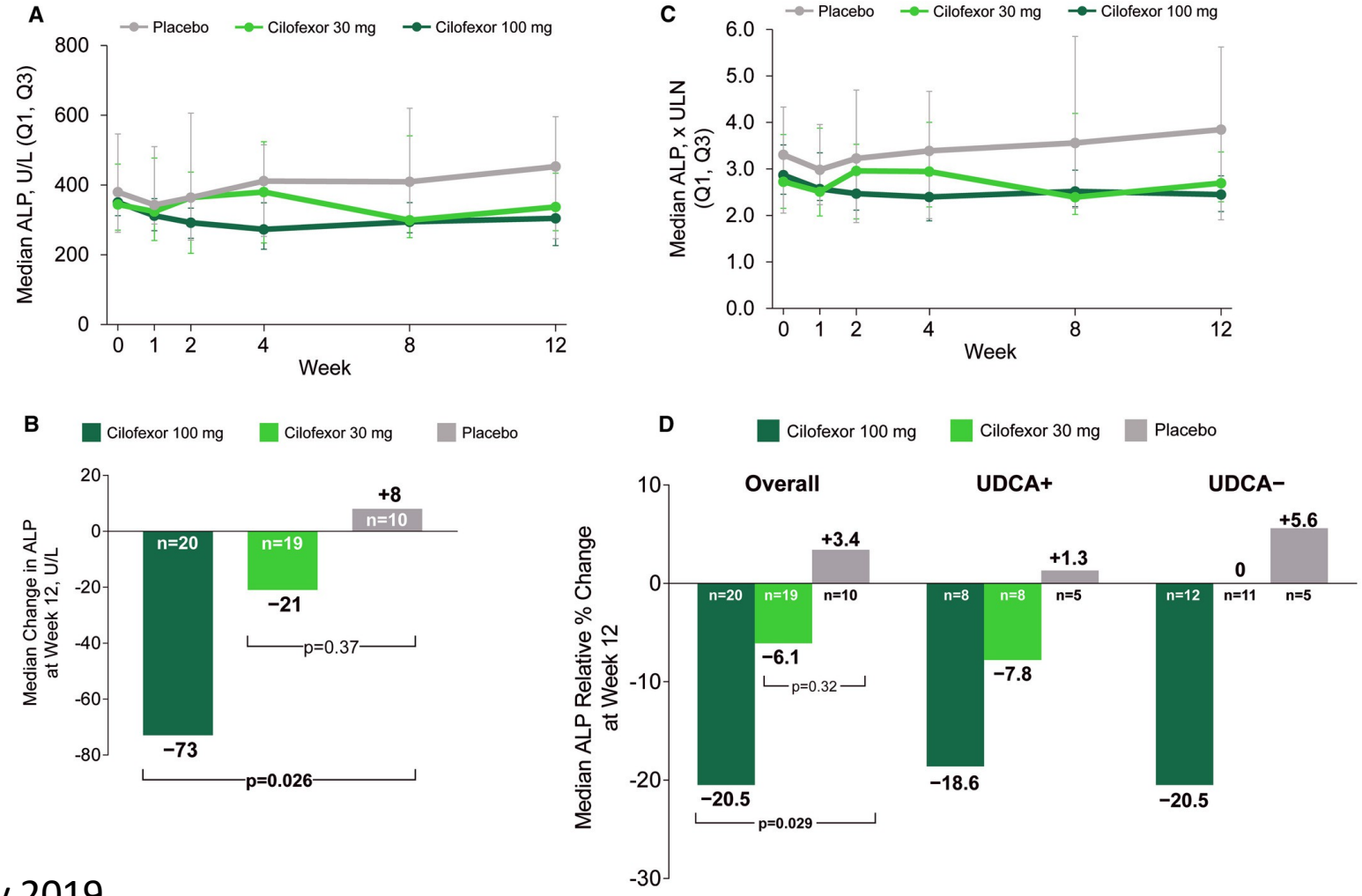
Effects of Vedolizumab in Patients With Primary Sclerosing Cholangitis and Inflammatory Bowel Diseases



CGH 2020



Cilofexor Improves Markers of Cholestasis and Liver Injury in Primary Sclerosing Cholangitis

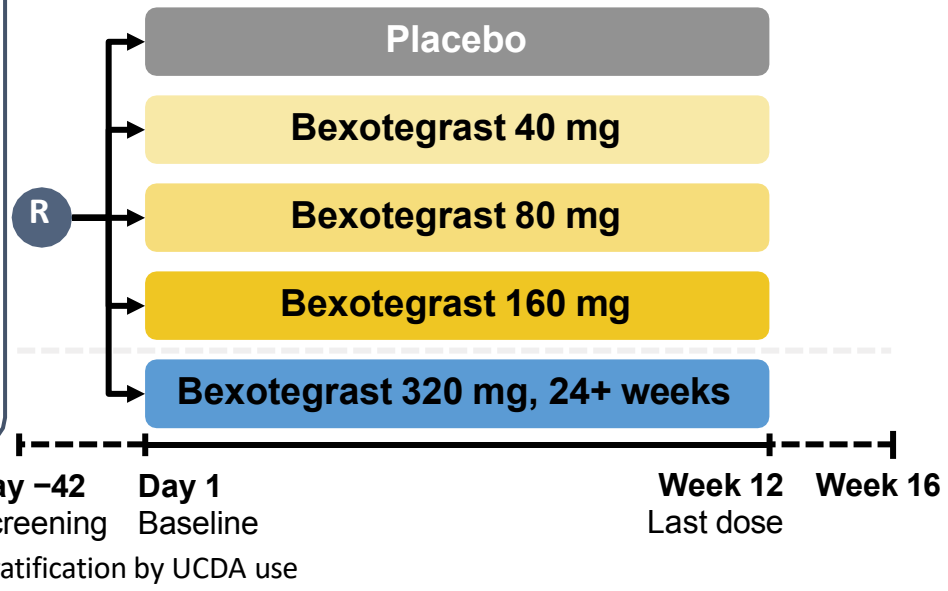


Hepatology 2019

Oral αvβ6/αVβ1 integrin inhibition in PSC: 12-week interim safety and efficacy analysis of INTEGRIS-PSC, a Phase 2a trial of bexotegrast

Key eligibility criteria
Large duct PSC
Suspected mod to sev liver fibrosis, plus ≥1 of:
- ELF ≥7.7
- TE ≥8 to ≤14.4 kPa
- MR elastography ≥2.4 to ≤4.9 kPa
- Biopsy showing fibrosis w/o cirrhosis

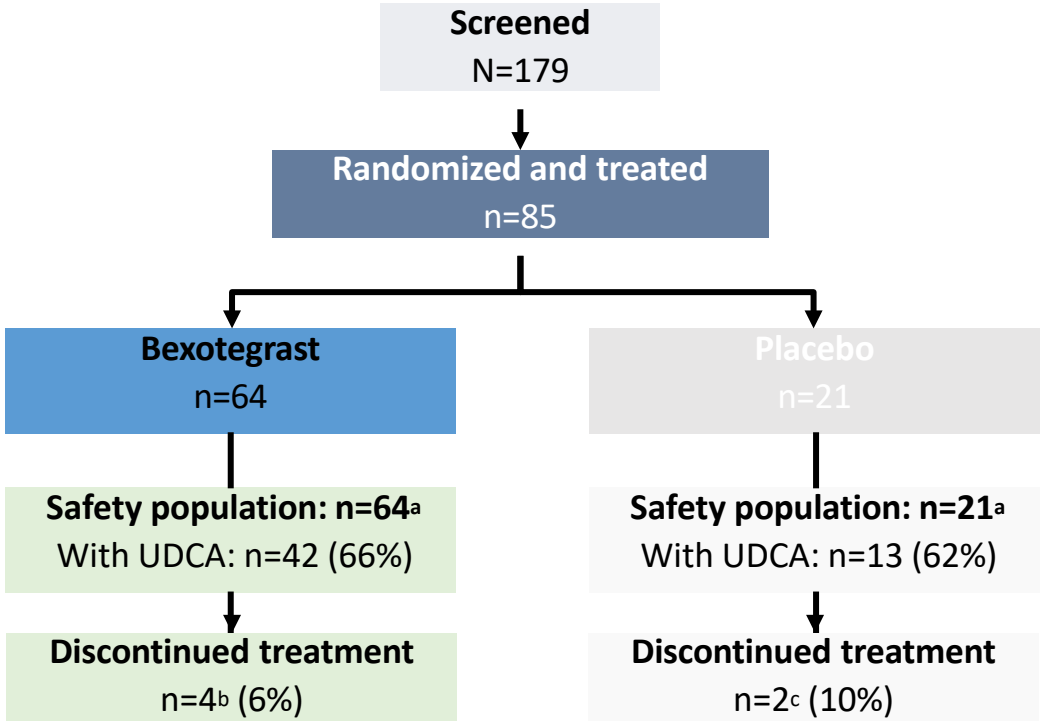
UDCA dose up to <25 mg/kg/day



Primary and secondary endpoints
- Safety and tolerability
- PK

Exploratory endpoints
- Change in ELF score, PRO-C3, ALP, itch NRS
- Change in gadoxefate-enhanced MR parameters (sub-study)

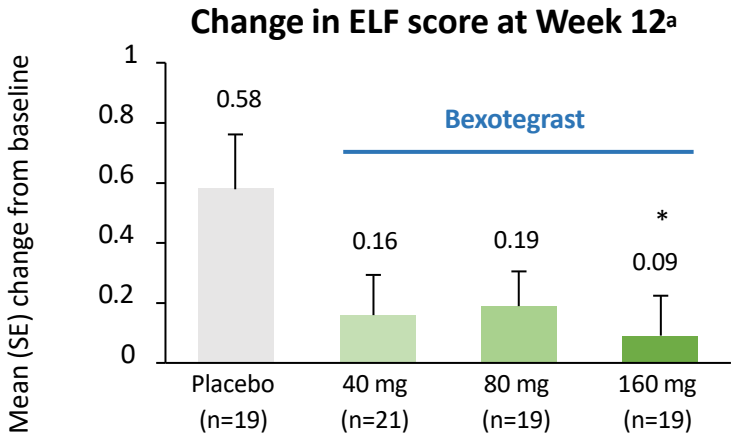
Patient disposition

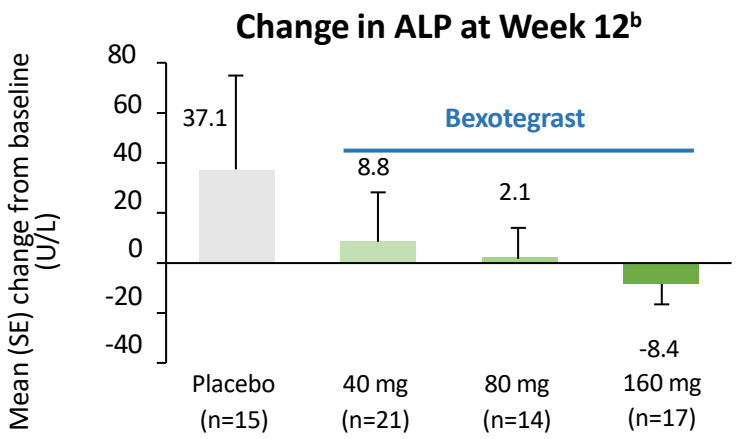


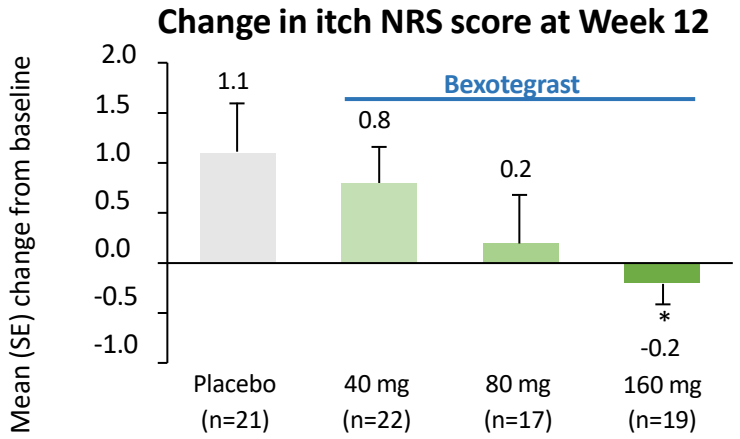
[a]Safety population is the key population for both analysis of safety and efficacy; [b]Adverse event (n=3; 40 mg, 80 mg, 160 mg), protocol deviation (n=1; 40 mg); [c]Adverse event (n=2)

Hirschfield GM, et al. AASLD 2023. Oral presentation #5008. Sponsored by Pliant Therapeutics

Oral αvβ6/αVβ1 integrin inhibition in PSC: 12-week interim safety and efficacy analysis of INTEGRIS-PSC, a Phase 2a trial of bexotegrast







Safety

n (%)	Placebo (n=21)	Bexotegrast			
		40 mg (n=24)	80 mg (n=20)	160 mg (n=20)	All (n=64)
TEAE	16 (76.2)	10 (41.7)	16 (80.0)	15 (75.0)	41 (64.1)
Related to study drug	7 (33.3)	1 (4.2)	6 (30.0)	4 (20.0)	11 (17.2)
Serious TEAE	0	1 (4.2)	1 (5.0)	0	2 (3.1)
Related to study drug	0	0	0	0	0
Frequent TEAEs (n≥3 in one arm)					
Pruritus	5 (23.8)	2 (8.3)	4 (20.0)	3 (15.0)	9 (14.1)
Fatigue	2 (9.5)	3 (12.5)	2 (10.0)	4 (20.0)	9 (14.1)
Headache	4 (19.0)	1 (4.2)	2 (10.0)	3 (15.0)	6 (9.4)
Nausea	0	1 (4.2)	2 (10.0)	3 (15.0)	6 (9.4)
COVID-19	3 (14.3)	2 (8.3)	1 (5.0)	0	3 (4.7)
Frequent bowel movements	3 (14.3)	0	3 (15.0)	0	3 (4.7)
Cholangitis	3 (14.3)	0	1 (5.0)	1 (5.0)	2 (3.1)

- Treatment with bexotegrast appeared to stabilize disease in patients with PSC compared with placebo
- Longer term follow-up is appropriate to determine if this means an antifibrotic effect

*P<0.05 vs placebo. [a]Patients had baseline ELF >7.7 (moderate to severe liver fibrosis); [b]Patients had baseline ALP >ULN

Hirschfield GM, et al. AASLD 2023. Oral presentation #5008. Sponsored by Pliant Therapeutics

PSC: Conclusions

- Pathogenesis complex
- Standard dose UDCA ineffective
- High-Dose (28-30 mg/kg) contraindicated
- Alkaline Phosphatase may be a biomarker
- Nonabsorbable antibiotics inconclusive
- Immunosuppression ineffective
- Combination therapies may be needed
- Personalized medicine may bring hope