2020 Annual Update in Medical Hepatology

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Latest Advances in Autoimmune & Cholestatic Liver Disease

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Cholestasis

- Greek in origin
- Means bile stoppage
- In its most overt form it presents as jaundice
- In early stages, cholestatic diseases lead to a preferential increase in the cholestatic liver enzymes: AP and GGTP

Differential of Cholestatic Injury
Biliary obstruction (stones, strictures, cysts, malignancy)
Infiltrative Diseases (Amyloid, Sarcoid, Malignancy, esp: Lymphoma)
Drug (Amox/Clav); TPN
Outflow (Right sided heart failure, Budd Chiari)
Sepsis
Cystic Fibrosis
Cholestatic Hepatitis (HBV/HCV)
Rejection; GVHD
Autoimmune Cholangitis
ICP, BRIC, PFIC
Secondary sclerosing diseases
Paraneoplastic
Idiopathic

Primary Biliary Cholangitis
&
Primary Sclerosing Cholangitis

I. Primary Biliary Cholangitis

formerly known as Primary Biliary Cirrhosis (2015)

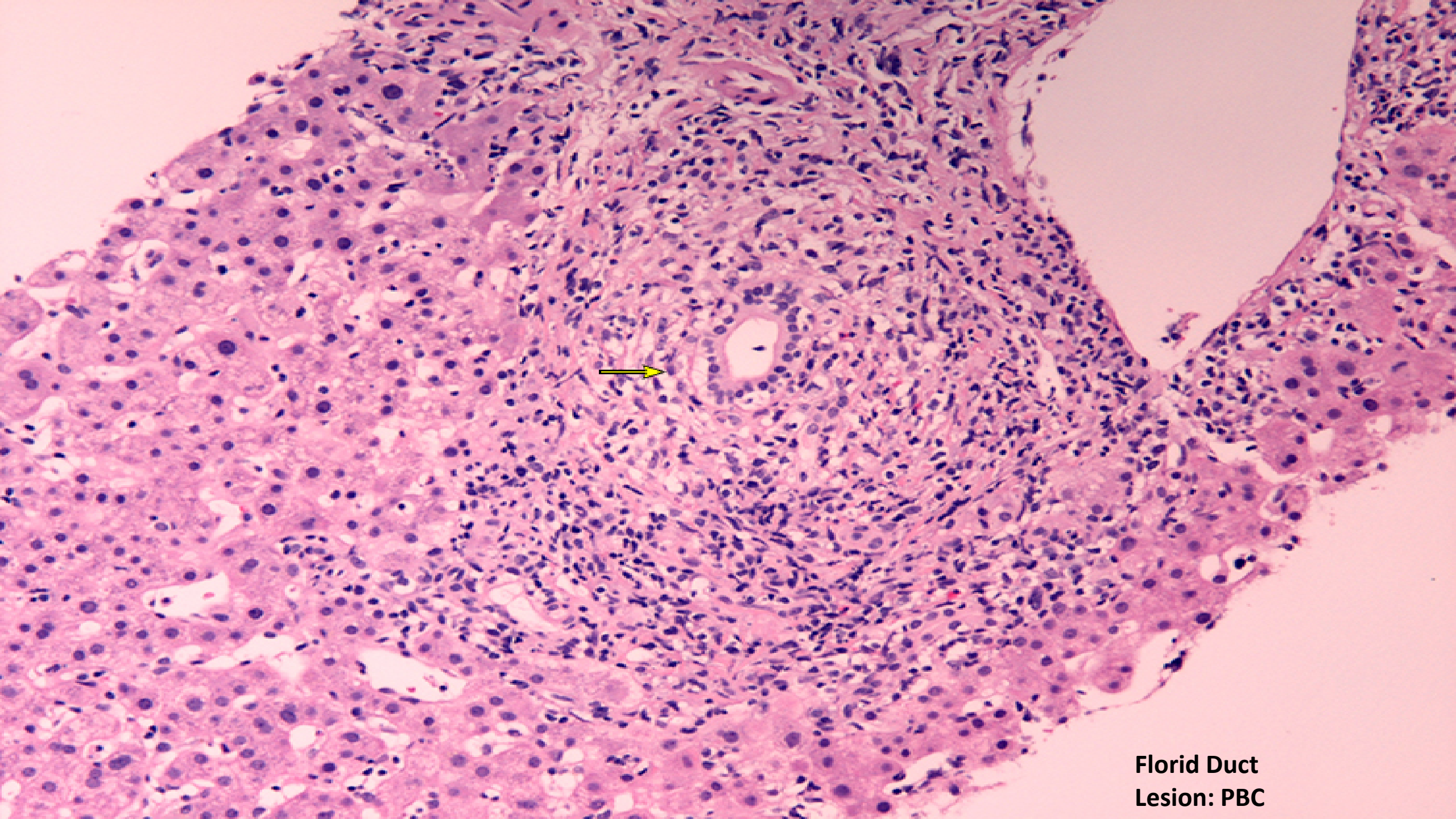
- Chronic liver disease resulting from progressive immunologic destruction of the small intralobular bile ducts that may result in cirrhosis and liver failure
- 90% of patients are female
- Diagnosis typically made $4^{th}/5^{th}$ decades of life
- Fatigue, itching (pruritus), abdominal discomfort
  - 50% of pts are asymptomatic

PBC diagnosis: 2 of the following 3

- Elevation in LFTs – specifically AP/GGTP (cholestatic enzymes)
- Antimitochondrial antibodies (AMA) are the serologic hallmark; present in 95% of patients
- Liver biopsy classically shows ‘florid duct lesion’

PBC

- PBC used to be one of the more common indications for liver transplant
- But since the approval of UDCA, the prognosis of pts with PBC (diagnosed before onset of cirrhosis) is quite good


Florid Duct
Lesion: PBC

- Papers all published in (relatively) high IF journals
- All within the last calendar year

- Abstracts from AASLD 2020

1. Changes in Disease Characteristics of PBC.

Takamura et al. Hepatol Res. October 2020.

- 508 patients from 1982 to 2016; Japanese cohort
- Divided into decade cohorts
- Male to female ratio increased from 6% to 25%
- Median age in females increased from 54 to 60 years
- UDCA response rate towards end of study period: 78%
- Ten-year survival rates increased

2. Liver Stiffness Measured by MR or Transient Elastography is an Independent Predictor of Outcomes Among Patients with PBC

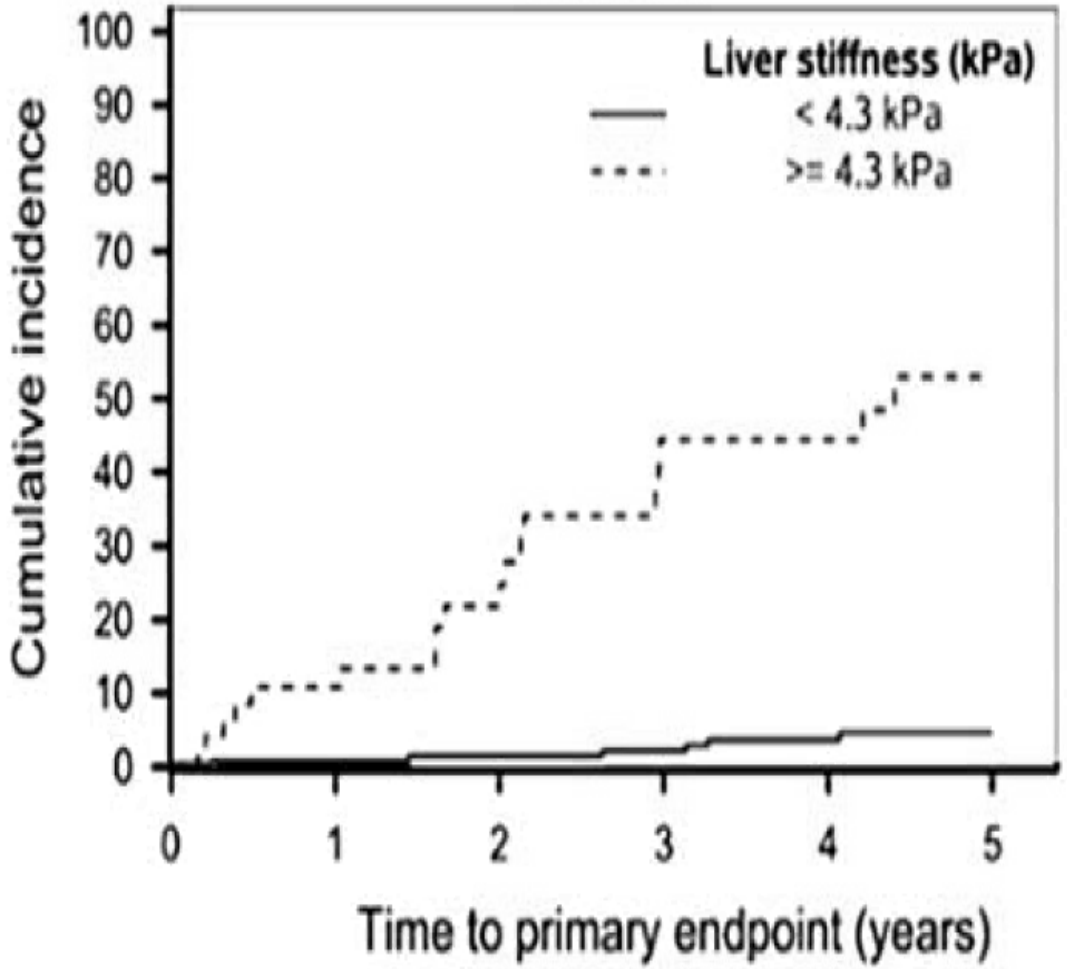
Osman et al. J Clin Gastroenterol. Sept 2020.

- 538 consecutive patients with PBC at 3 MAYO Centers
- TE: 286, MRE 332
- ~ 33% of patients underwent concomitant biopsy
- Optimal threshold for stage F4: kPa of **14.4** for TE and 4.60 for MRE (AUC .90)
- Threshold to predict hepatic decompensation (variceal bleed, ascites, PSE) 10.2 for TE and 4.3 for MR
  - Secondary endpoint: hepatic decompensation, LT , HCC or death

B

Magnetic resonance elastography

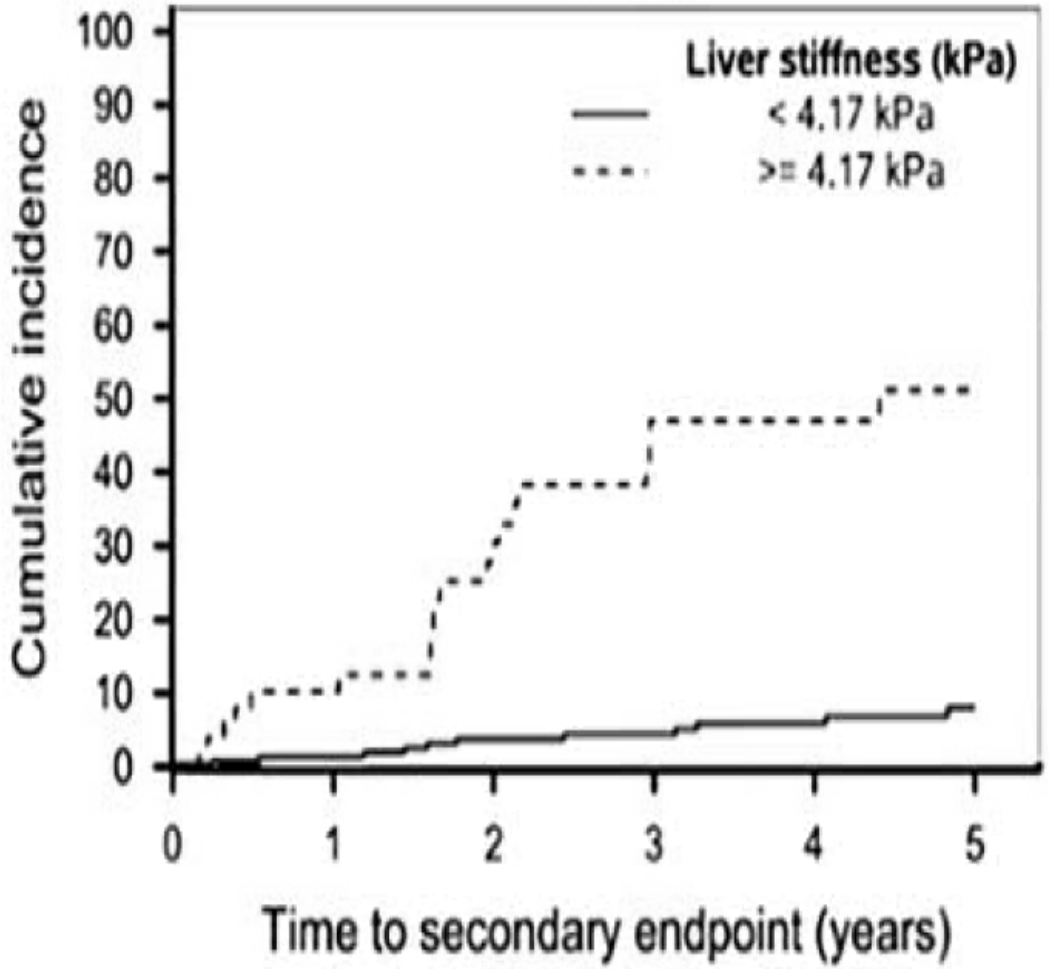
‡ n=293



Patients-at-Risk

< 4.3 kPa	240	192	158	134	104	73
>= 4.3 kPa	53	35	26	16	14	9

¶ n=290



Patients-at-Risk

< 4.17 kPa	231	186	155	131	102	71
>= 4.17 kPa	59	39	28	18	15	11

Elastography and PBC (cont).

- Features of portal hypertension were seen in a fair number of patients with liver biopsy: F2 and F3 fibrosis
  - Spleen size at 11cm was considered PHTN
- Likely pre-sinusoidal component of PBC
  - (as opposed to sampling error as PHTN was seen in a fair number of non cirrhotic PBC patients on elastography)
- Elastography results may help dictate the need for surveillance EGD

3. A Placebo-Controlled Randomized Trial of Budesonide for PBC Following an Insufficient Response to UDCA.

Hirschfield et al. J Hepatol September 2020.

- 62 patients with biopsy proven PBC who had persistent AP (> 1.5x ULN) elevation after six months of weight-based UDCA
- Randomized to budesonide 9mg/day or placebo x 36 months with UDCA maintained

PBC Patients with:
- histologically confirmed inflammatory activity (Ishak-score)
- inadequate response to UDCA (ALP > 1.5 x ULN)
- no liver cirrhosis

9 mg Budesonide + 12-16 mg/kg UDCA N = 40

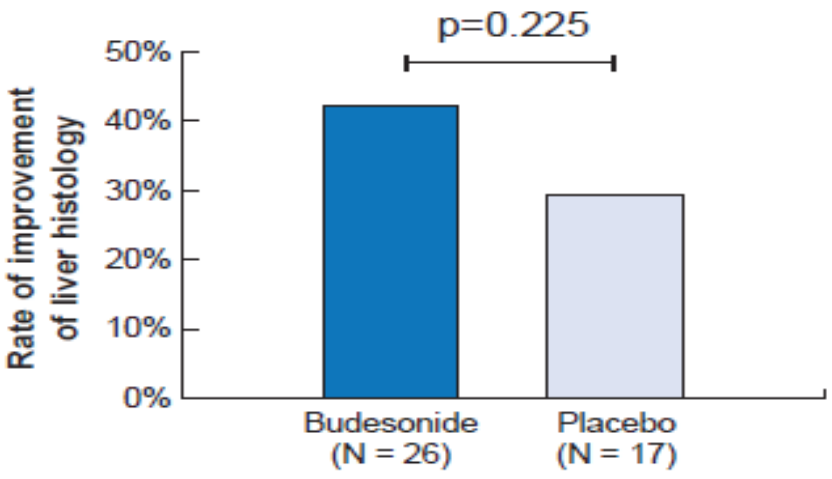
Placebo + 12-16 mg/kg UDCA N = 22

36 months

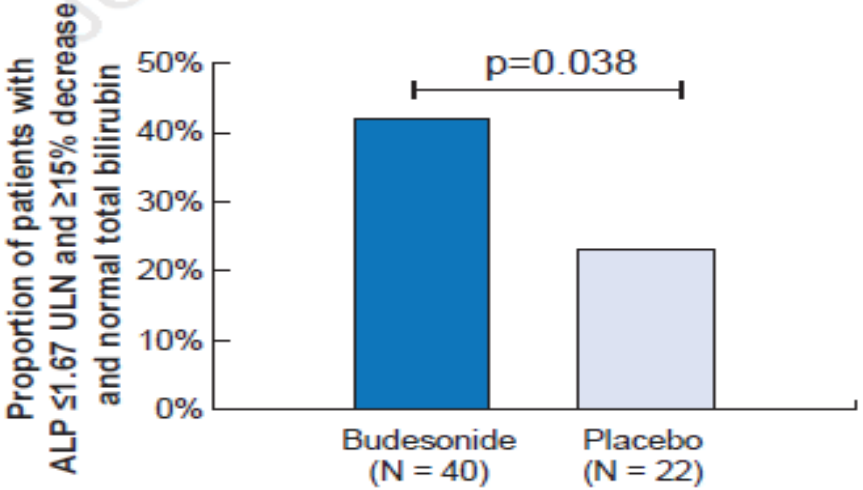
No difference in serious adverse events: budesonide and placebo group

Would need to be cautious with bone health

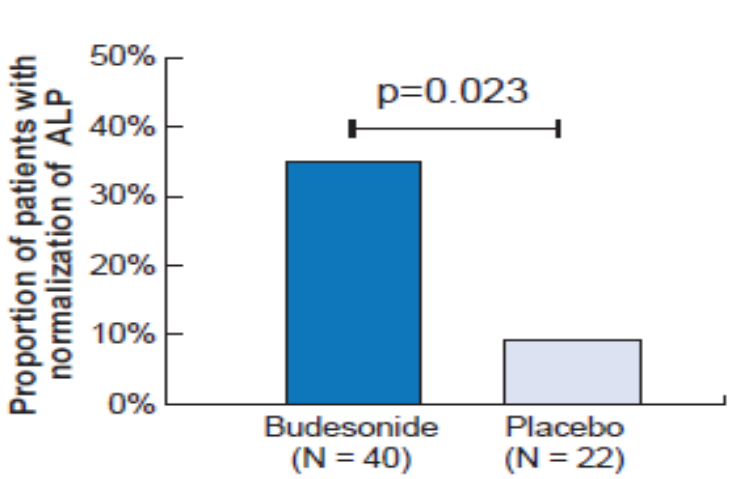
Liver Histology (Paired Biopsies)



ALP ≤1.67 ULN + ≥15% Decrease + and Normal Total Bilirubin



Normalisation of Alkaline Phosphatase



4. Extrahepatic Autoimmune Diseases in PBC: Prevalence and Significance for Clinical Presentation and Disease Outcome.

Efe et al. J Gastroenterol Hepatol. August 2020.

- Prevalence and clinical significance of extrahepatic autoimmune diseases (EHAIDs) have not been evaluated in a large cohort of PBC patients
- 1554 patients with PBC from 20 international centers
- 35 different EHAID were diagnosed in 440 patients with PBC: 28%
- Autoimmune thyroid disease: 10.5%

Table 1 Extrahepatic autoimmune diseases among 1554 primary biliary cholangitis patients

Concurrent extrahepatic autoimmune diseases	Patients, *n* (%) Total: 440 (28.3)
Endocrine diseases	166 (10.7)
Hashimoto's thyroiditis	141 (9.1)
Grave's disease	24 (1.5)
Addison disease	1 (0.1)
Rheumatologic disorders	264 (17)
Sjögren disease	130 (8.3)
Systemic sclerosis	46 (2.9)
Rheumatoid arthritis	42 (2.7)
Systemic lupus erythematosus	26 (1.7)
Mixt/undifferentiated connective tissue disease	6 (0.4)
Temporal arteritis	4 (0.3)
Polyarteritis nodosa	3 (0.2)
Ankylosing spondylitis	3 (0.2)
Anti-phospholipid syndrome	1 (0.1)
Dermatomyositis	1 (0.1)
Polymyositis	1 (0.1)
Granulomatosis with polyangiitis	1 (0.1)
Gastrointestinal disorders	47 (3)
Celiac disease	26 (1.7)
Ulcerative colitis	10 (0.6)
Crohn's disease	9 (0.6)
Collagenous colitis	1 (0.1)
Autoimmune gastritis	1 (0.1)
Dermatological diseases	35 (2.3)
Psoriasis	23 (1.5)
Vitiligo	5 (0.4)
Lichen sclerosus	2 (0.1)
Chronic urticaria	2 (0.1)
Lichen planus	1 (0.1)
Bullous Pemphigoid	1 (0.1)
Pemphigus vulgaris	1 (0.1)
Lung diseases	4 (0.3)
Sarcoidosis	4 (0.3)
Neurological diseases	8 (0.5)
Multiple sclerosis	6 (0.4)
Myasthenia gravis	2 (0.1)
Hematological disorders	10 (0.6)
Idiopathic thrombocytopenic purpura	4 (0.3)
Pernicious anemia	3 (0.2)
Autoimmune hemolytic anemia	3 (0.2)
Renal disease	2 (0.1)
IgA nephropathy	1 (0.1)
Membranous nephropathy	1 (0.1)

5. Incidence of HCC in PBC: A Systemic Review and Meta-Analysis.

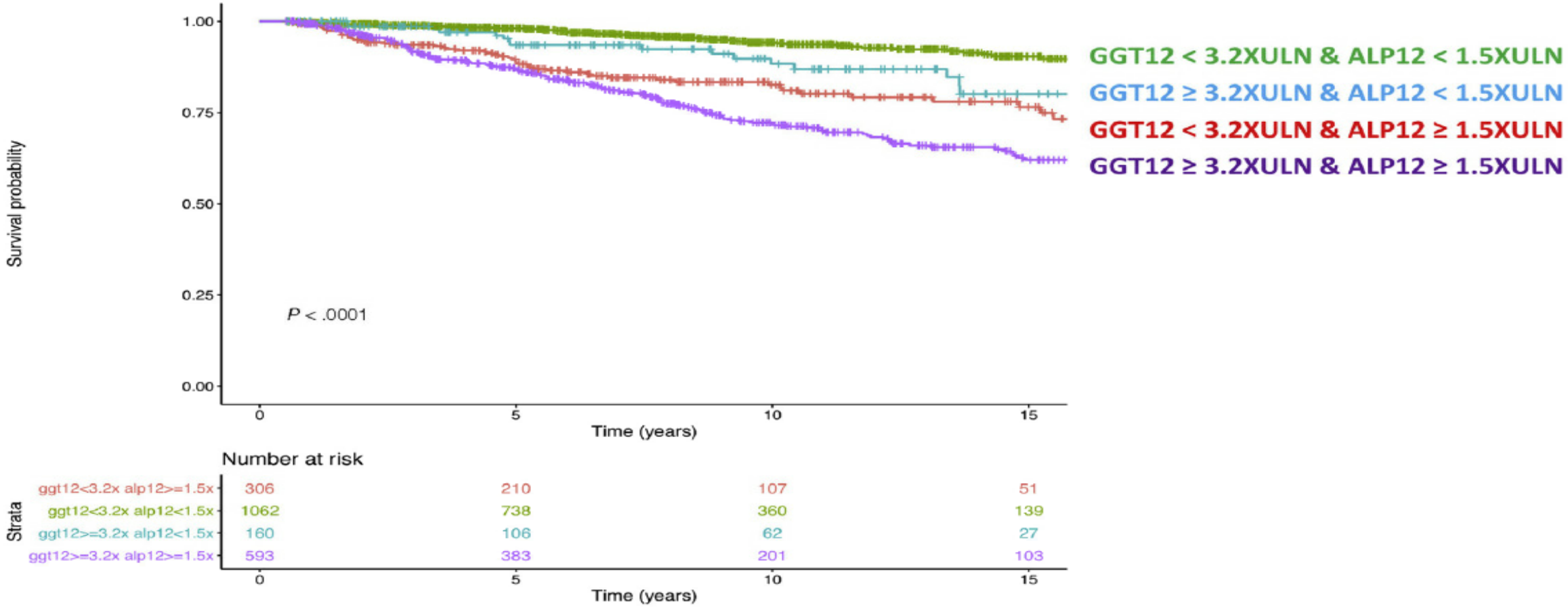
Natarajan et al. DDS July 2020.

- 29 studies: 22,615 patients
- Incidence of HCC in patients with PBC cirrhosis was 15.7 per 1000 patient-years; roughly 1% per year
  - HBV Cirrhosis: 9-54 per 1000 person years
  - HCV Cirrhosis: 37-71 per 1000 person years
- Cirrhosis is the strongest risk factor
- Male gender is also a risk factor
  - 9.82 per 1000 person-years versus 3.82 in females

6. Measurement of GGT to Determine Risk of LT or Death in Patients with PBC.

Gerussi et al. Clin Gastroenterol Hepatol. August 2020.

- GGT is a serum marker of cholestasis
  - More specific for biliary disease (when compared to ALP)
- Global PBC Study Group, comprising 14 centers in Europe and North America
- 2129 patients
- 91% female, mean diagnosis 53 years of age
- Serum level of GGT at 12 months after treatment higher than 3 fold ULN (despite ALP lower than 1.5 fold ULN) portended increase risk of death or LT



	Group 1	Group 2	Group 3
Group 1	/	0.006	1e-10
Group 2	0.006	/	0.12
Group 4	<2e-16	0.006	0.009

Figure 4. Transplant-free survival of patients with GGT levels <3.2 × ULN versus ≥3.2 × ULN at 12-month follow-up in patients with ALP levels <1.5 × ULN and those with ≥1.5 × ULN. Pairwise comparisons among survival rates of the 4 groups have been estimated by log-rank test with Benjamini-Hochberg adjustment for multiplicity. Groups are defined as follows: Group 1 (*green*), GGT at 12 months <3.2 × ULN and ALP at 12 months <1.5 × ULN; Group 2 (*blue*), GGT at 12 months ≥3.2 × ULN and ALP at 12 months <1.5 × ULN; Group 3 (*red*), GGT at 12 months <3.2 × ULN and ALP at 12 months ≥1.5 × ULN; Group 4 (*purple*), GGT at 12 months ≥3.2 × ULN and ALP at 12 months ≥1.5 × ULN. ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; NS, not significant; ULN, upper limit of normal.

7. Gender and Racial Differences in Hospitalizations for PBC in the USA.

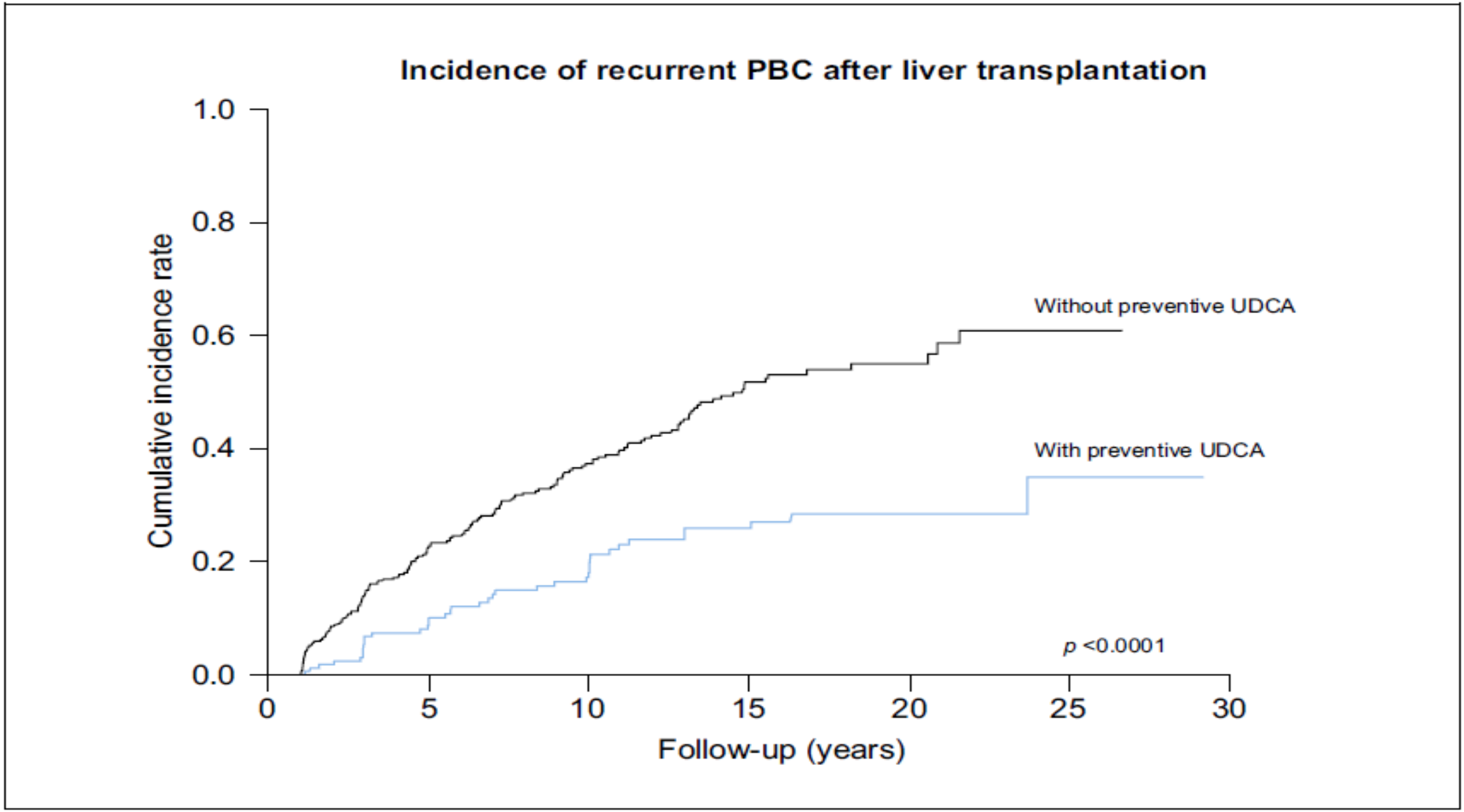
Adejumo et al. DDS June 2020.

- National Inpatient Sample (NIS) 2007 to 2014
- 8460 PBC hospitalizations
  - 17% Hispanic
  - 6% Black
- Compared to Whites, PBC hospitalization rate was 12% higher among Hispanics (RR: 1.12), 53% lower in Blacks (RR 0.47)
- Rate was higher among females compared to males (RR 4.02)
- Despite less hospitalization, blacks had higher mortality

8. Long-term Impact of Preventative UDCA Therapy After Transplantation for PBC

Corpechot et al. J Hepatol. September 2020.

- Recurrence of PBC after LT is frequent and can impair graft and patient survival
- 780 patients transplanted for PBC between 1983-2017
  - followed for median of 11 years
- Of them 190 received preventative UDCA (10-15mg/kg/day).
- Preventative UDCA was associated with reduced risk of PBC recurrence (HR 0.41), graft loss (HR 0.33), liver related death (HR 0.46) and all cause death (HR 0.69).
- UDCA led to a survival gain of 2.26 years over a period of 20 years. Exposure to cyclosporine (rather thank FK) had a complementary protective effect


Incidence of recurrent PBC after liver transplantation
Cumulative incidence rate
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
Follow-up (years)
Without preventive UDCA
With preventive UDCA
p <0.0001

9. Elevated Neutrophil/Lymphocyte Ratio (NLR) One year post diagnosis is associated with decreased LTx free survival in PBC.

Aziz et al. Canada ABSTRACT AASLD 2020

- Lymphopenia as measured by neutrophil/lymphocyte ratio has been linked with diminished survival in patients with AI diseases and several liver disorders
- 531 PBC patients from Canadian registry
- Mean f/u of 8 years
- Elevated NLR at one year was associated with increased HR 1.08 ($p<0.001$).
- Optimal cut-off was 1.9

10. At least four studies looking at long term efficacy in OCA; real word data

- Largest study published by Gish et al. Loma Lynda University.
- 319 patients with PBC treated with OBA
- 84% received UDCA during baseline
- Mean f/u was 12 months
- At baseline AP 293
- Proportion of patients with biochemical response was 55%-70% (depending on Toronto or Paris classification).
- This study did not discuss discontinuation for pruritus: other studies suggested ~ 15% of patients

Other Abstracts:

- Intrepid Study: EDP-305
  - a non bile acid Farnesoid X Receptor agonist showed numerically higher response rates compared to placebo with robust reduction in markers of liver injury. Pruritus was frequent leading to drug discontinuation (especially at higher dose).
- Several studies: real world evidence suggests that a fair number of patients with PBC are undertreated (when using normalization of AP as therapy).
  - IE treat with UDCA but if not near normal, we need to do better about OCA?

Quick mentions from Late breakers

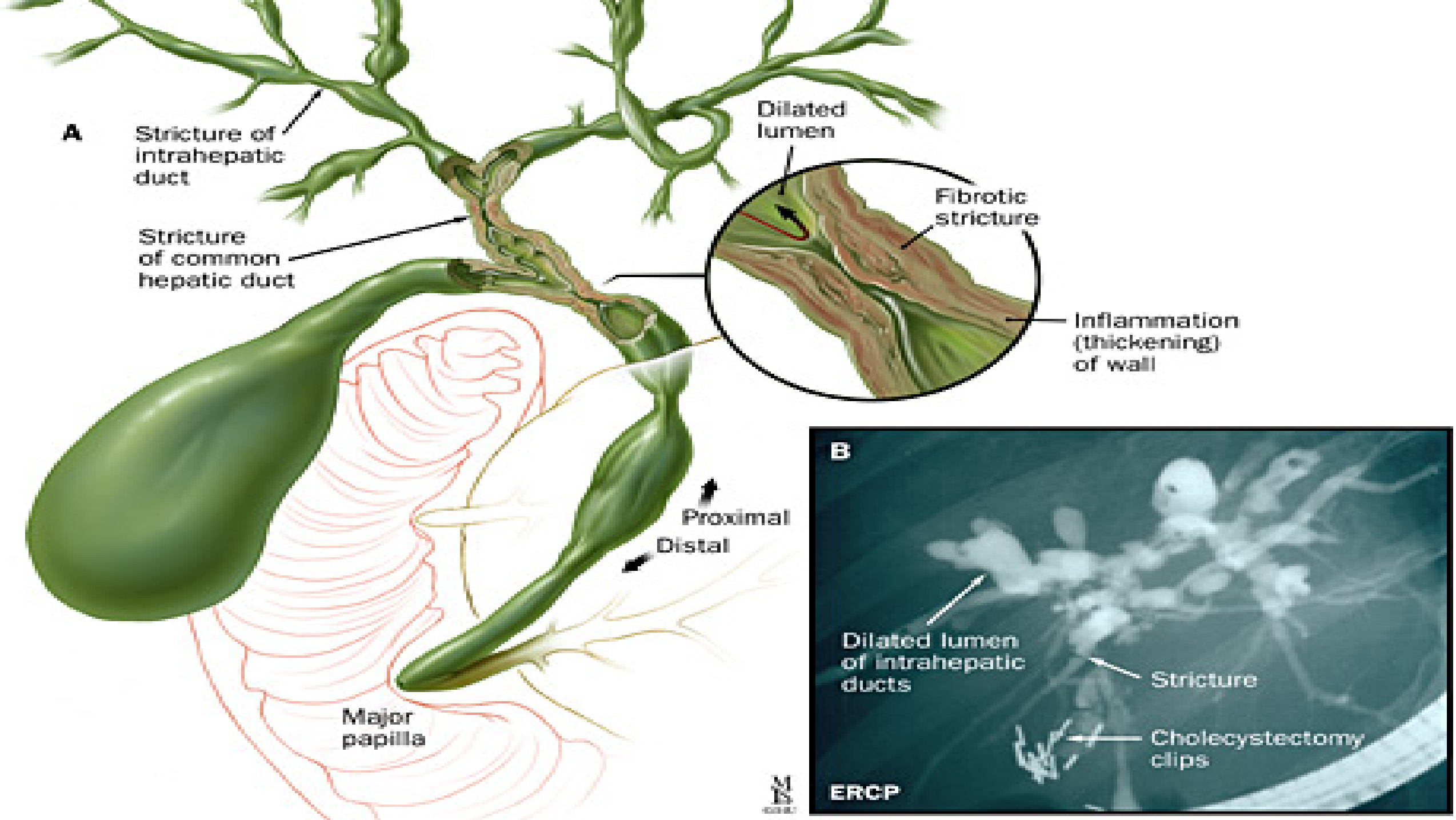
- Phase 2 study looking at Saroglitazar Magnesium. Vuppalanchi et al. PPAR agonist with dual agonistic properties (α/Y).
  - 37 patients with PBC. 16 week course resulted in sustained improvement compared to placebo with good safety profile. Phase 3 study is planned.
- Phase 3 study of Seladelpar in patients with PBC. Hirschfield et al. A selective PPAR-delta agonist.
  - PBC patients who were intolerant to UDCA or NR to AP. 265 patients with PBC. 10/5mg doses for 3 months. Randomized Placebo Controlled.
  - 10mg dose had rapid and significant improvement in cholestasis, inflammation and pruritus. Safe and well tolerated.

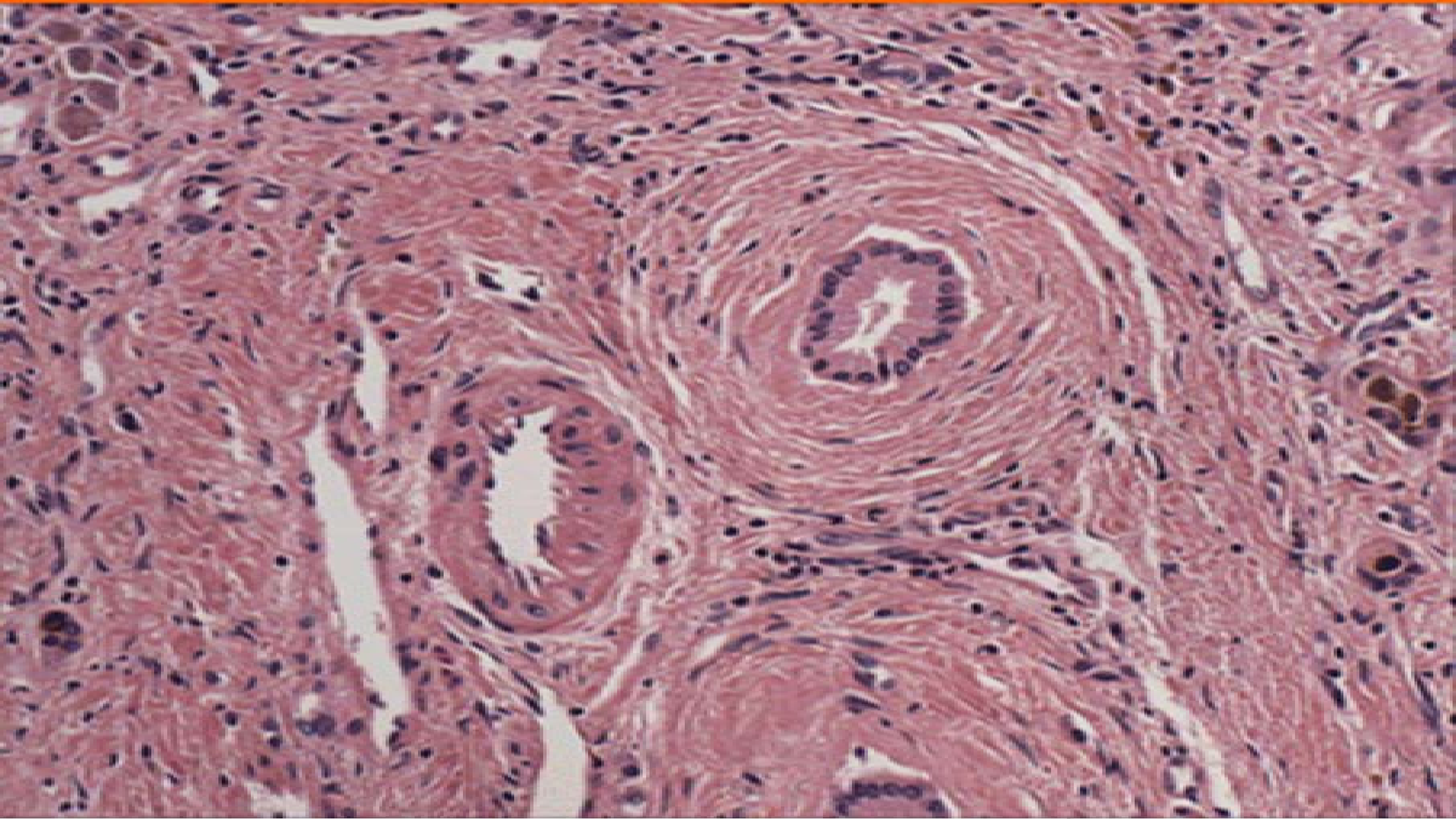
II. Primary Sclerosing Cholangitis

- Chronic progressive disorder of unknown etiology (?Immune mediated) that is characterized by inflammation, fibrosis, and stricturing of medium size and large ducts in the intrahepatic and extrahepatic biliary tree
- Dx made on cholangiogram
  - MRCP > ERCP
- 40K cases in US
- 70% are male; average age dx 40
- ~ 80% of patients have concomitant IBD (UC)
  - Increased risk of colon cancer

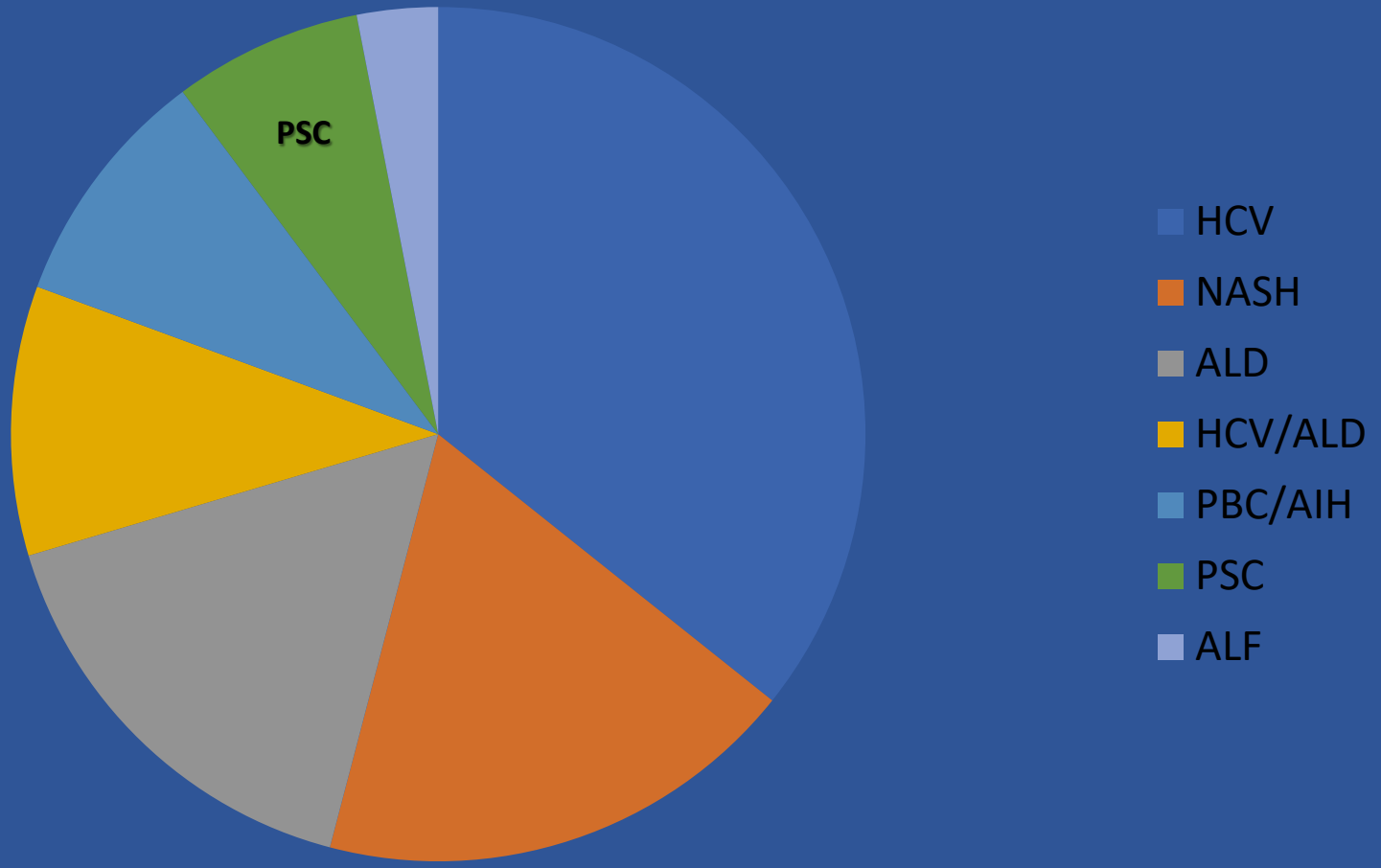
PSC

- Increased risk of cholangiocarcinoma
- Increased risk of GB cancer
- No proven medical treatment
- Literature suggests that up to 50% of patients will require OLTx at 15 years


A
Stricture of intrahepatic duct
Stricture of common hepatic duct
Dilated lumen
Fibrotic stricture
Inflammation (thickening) of wall
Proximal
Distal
Major papilla
B
Dilated lumen of intrahepatic ducts
Stricture
Cholecystectomy clips
ERCP



Liver Transplants US Last Decade



1. Fecal Microbiota Transplantation in Patients with PSC: A Pilot Clinical Trial.

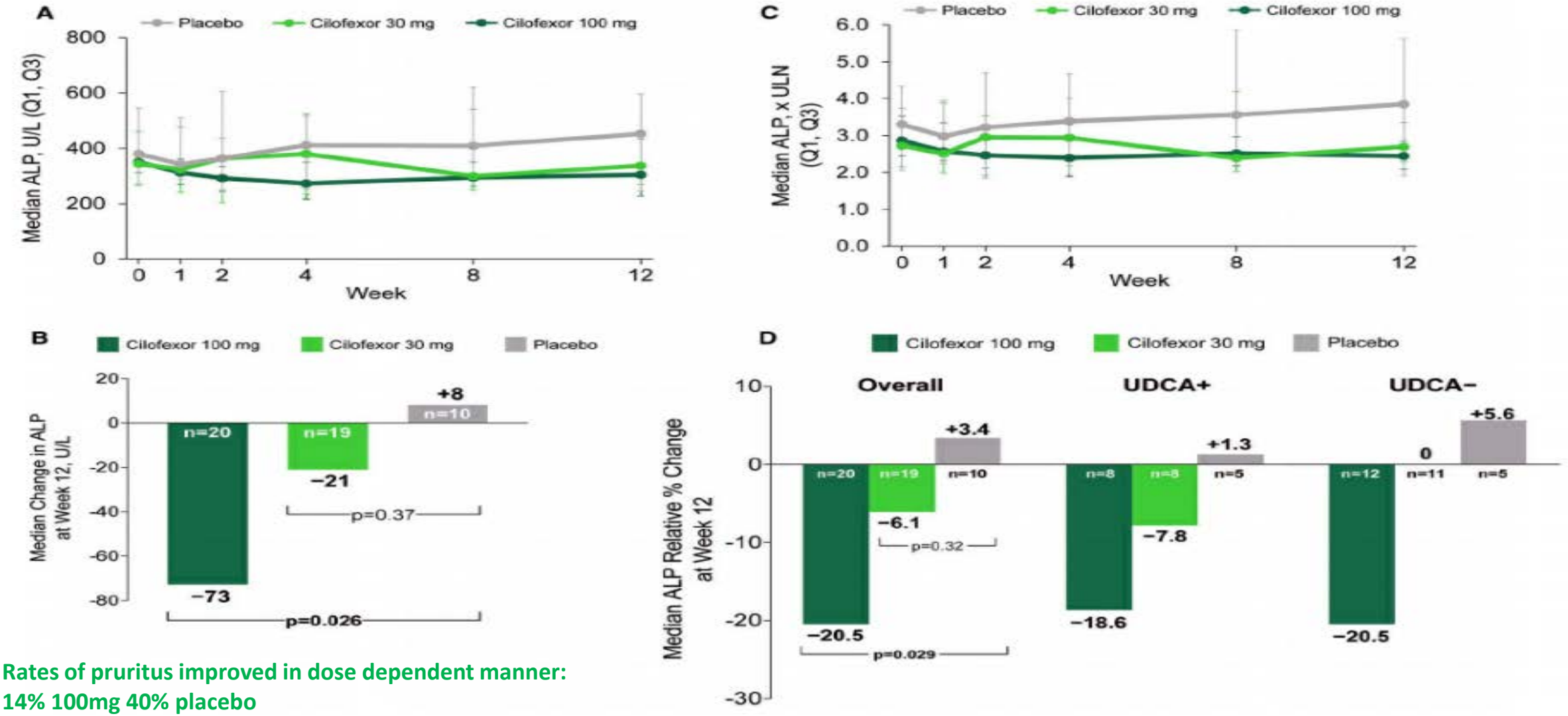
Allegretti, et al. Am J Gastroenterol July 2019

- PSC has no effective medical therapy
- A perturbation of the gut microbiota has been described in association with PSC
- Open label pilot study. PSC with IBD and elevated AP > 1.5x ULN
  - Not on UDCA at time of FMT
- Single FMT by colonoscopy
- 10 patients (9 had UC, 1 Crohns). Mean baseline AP 489
- No adverse events
- 30% experienced a > 50% decrease in AP

2. FXR receptor agonist Cilofexor Improves Markers of Cholestasis and Liver Injury in patients with PSC.

Trauner et al. Hepatology September 2019.

- Phase II double blind, placebo-controlled study
- Evaluating cilofexor a non-steroidal FXR agonist in non cirrhotic large duct PSC
  - 100mg, 30mg or placebo
- 52 patients were randomized
- Median age 43, 58% male and 60% with IBD and 46% on UDCA
- Baseline AP 348



Rates of pruritus improved in dose dependent manner:
14% 100mg 40% placebo

FIG. 1. Cilofexor improves serum ALP in patients with PSC. (A) Median (IQR) serum ALP between baseline and week 12 of the double-blind phase of the study. (B) Median absolute change in serum ALP from baseline to week 12 of therapy. *P* values versus placebo are according to Wilcoxon rank-sum test. (C) Median (IQR) change in serum ALP relative to the ULN between baseline and week 12 of therapy. (D) Median relative (percentage) change in serum ALP from baseline to week 12 of therapy (overall and according to UDCA treatment). *P* values versus placebo are according to Wilcoxon rank-sum test.


FDA
APPROVED

Hepatology 2009

AUTOIMMUNE, CHOLESTATIC AND BILIARY DISEASE

High-Dose Ursodeoxycholic Acid for the Treatment of Primary Sclerosing Cholangitis

Keith D. Lindor,[1] Kris V. Kowdley,[2] Velimir A. C. Luketic,[3] M. Edwyn Harrison,[4] Timothy McCashland,[5] Alex S. Befeler,[6] Denise Harnois,[7] Roberta Jorgensen,[1] Jan Petz,[1] Jill Keach,[1] Jody Mooney,[2] Carol Sargeant,[3] Tamara Bernard,[5] Debra King,[6] Ellen Miceli,[7] Jeff Schmoll,[8] Tanya Hoskin,[8] Prabin Thapa,[8] and Felicity Enders[8]

150 patients, Randomized, double-blinded, placebo controlled

Table 4. Development of Primary Endpoints

Primary Endpoints	UDCA	Placebo
Death	5	3
Liver transplantation	11	5
Minimal listing criteria for liver transplantation	13	10
Development of cirrhosis	6	4
Esophageal and/or gastric varices	15	5
Cholangiocarcinoma	2	2
Total endpoints	52	29
Number of patients reaching a primary endpoint	30	19
Number of patients reaching death, orthotopic liver transplantation, minimal criteria listing	22	15

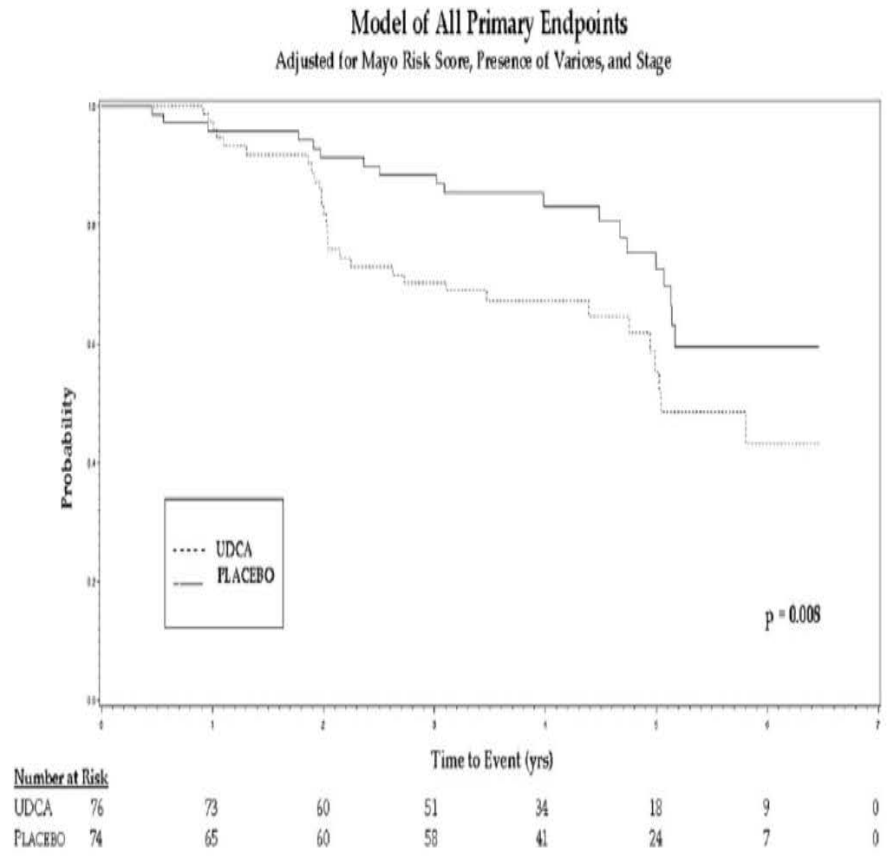


Fig. 2. Kaplain-Meier curve for time until reaching primary endpoints.

Recommendations:

AASLD: 2010

28. In adult patients with PSC, we recommend against the use of UDCA as medical therapy (1A).

MEDICAL TREATMENT

AGA 2017

At this time, there is no established medical treatment for patients with PSC.

Recommendation

1. Ursodeoxycholic acid (UDCA) in doses >28 mg/kg/day should not be used for the management of patients with PSC. (Strong recommendation and high quality of evidence) (42)

Recommendation 5: We recommend that UDCA is not used for the routine treatment of newly diagnosed PSC (*strength of recommendation: STRONG; quality of evidence: GOOD*). For patients already established on UDCA therapy, there may be evidence of harm in patients taking high dose UDCA 28–30 mg/kg/day (*strength of recommendation: WEAK; quality of evidence: LOW*). BRITISH: 2019

EASL: 2017 PSC Review

There is presently no medical therapy proven to delay the development of liver cirrhosis in patients with PSC. There has been extensive debate as to the efficacy of UDCA,[56,57] leading to inconsistent prescription practices around the world. Whilst high-dose UDCA (28–30 mg/kg/day) is likely to be harmful,[157] there is insufficient evidence to argue for or against prescription of low-dose (13–15 mg/kg/day) UDCA.[223] In some centres, a six month trial period of low-dose (13–15 mg/kg/day) UDCA prescription is utilised, whereby a decrease in ALP levels is used as the basis for potential long-term prescription.[224] Immunosuppression may be effica-

Key point

Ursodeoxycholic acid has a positive impact on surrogate markers for PSC activity and is widely prescribed for treatment of PSC, but should not be used at high doses.

3. UDCA Treatment and Long-Term Outcome and Bile Duct Cancer in PSC.

Arizumi et al. Japan. ORAL ABSTRACT AASLD 2020

- 435 patients with PSC
- Very well-maintained database 2012-2015
- 58% male, median age 46
- Mean f/u 5 years
- UDCA given to 86%
  - Details on dose not provided (presumably not high dose)
- MV analysis demonstrated UDCA Rx was associated with improvement in LT free survival HR 0.467
- AND decrease in biliary tract cancer HR 0.324


LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED

4. Systemic Review with Meta-Analysis: Risk Factors for Recurrent PSC after LT.

Steenstraten et al. Ailment Pharmacol Ther. May 2019

- 21 studies were reviewed; 14 included in the meta-analysis
- 2159 patients who underwent LT for PSC
  - 70% male
  - Age range 31-49 years
- Recurrence was 17.7%
- Factors contributing to increased risk of recurrent PSC:
  - Colectomy before LT was protective: HR 0.65
  - Cholangiocarcinoma pre-LT increased risk: HR 2.42
  - IBD: HR 1.73
  - Older donor age HR 1.24
  - ACR HR 1.94

5. Good Long-Term Outcomes in Patients with PSC Undergoing LDLT.

Choudhary et al. J Clin Exp Hepatol Sept-Oct 2020.

- Delhi, India
- 32 patients with PSC underwent LT (of 2268 LTs from August 2004 to July 2018)
- Mean MELD at time of lT was 19
- 25% had UC
- Almost all underwent hepatico-J
- Recurrence was seen in 20% at mean f/u of 5 years
- Five patients died at f/u 4 sepsis, 1 recurrent PSC

6. PSC with Isolated Intrahepatic Disease is Associated with Better Prognosis than PSC with Intra and Extra Hepatic Disease.

Are et al. Indiana. AASLD ABSTRACT 2020

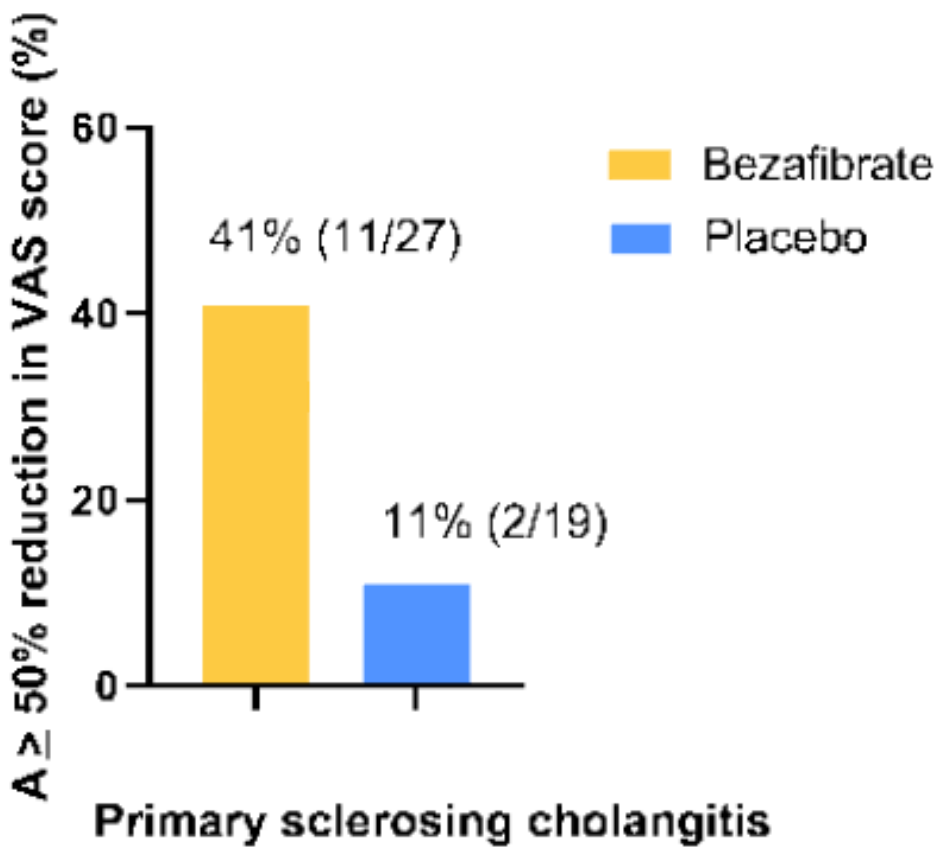
- Radiology group 1988-2019
- 440 patients
- 111 had disease isolated to intra-hepatics
- 329 had extrahepatic (with or without intra-hepatics)
- Isolated intrahepatic PSC had lower incidence of cholangitis 19% vs 34% and
- Lower incidence of cholangiocarcinoma .9% versus 7%
- Isolated intrahepatic had lower risk of LT and death
- Isolated intrahepatic PSC can be considered as a favorable sub type of large duct PSC

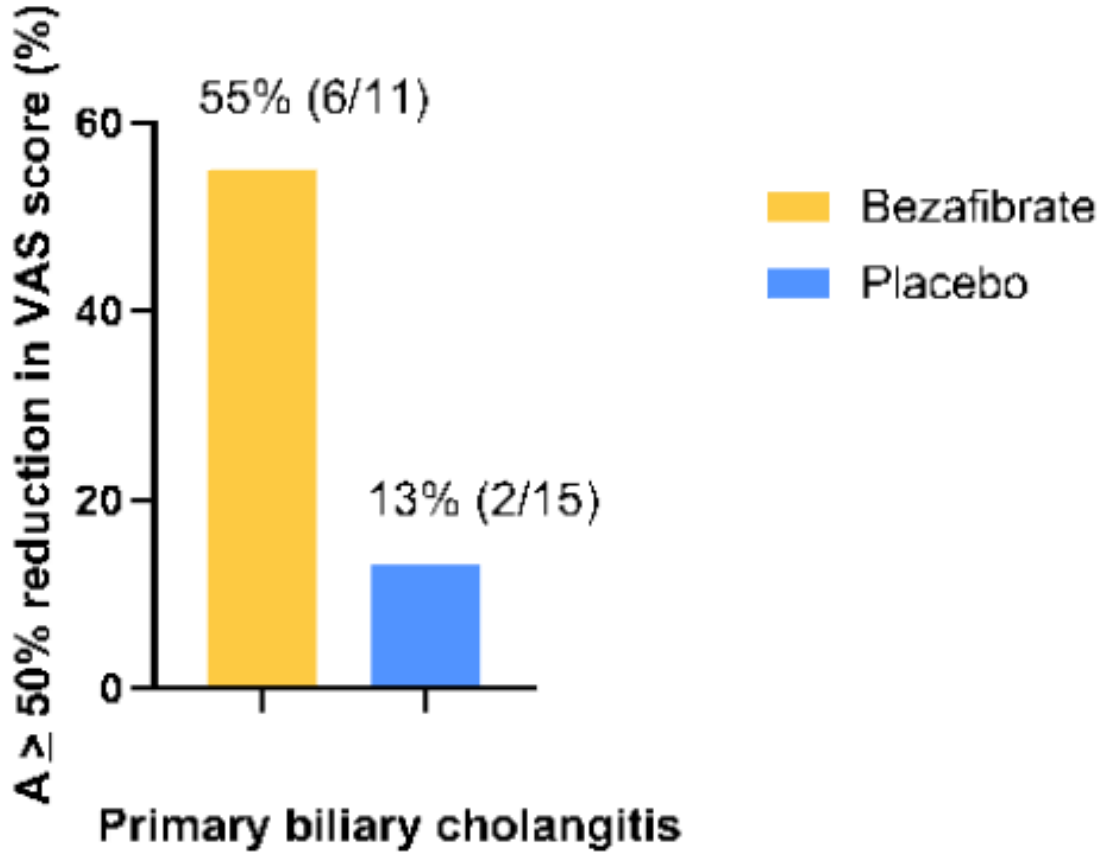
7. Fibrates for Itch (FITCH) in Fibrosing Cholangiopathies.

Vries et al. Gastro October 2020. Cholestasis Working Group; Netherlands

- Pruritus significantly impairs quality of life in patients with cholestatic disease
- Bezafibrate: a broad peroxisome proliferator-activated receptor (PPAR) agonist
  - Not available in US; fenofibrate is off label
- Double blind, randomized, placebo-controlled
- PSC, PBC or secondary sclerosing cholangitis (SSC)
- Patients with moderate/severe pruritus
- 400mg bezafibrate or placebo x 21 days

Result: bezafibrate led to a 45% reduction in pruritus (versus 11% in placebo); in addition 35% improvement in AP



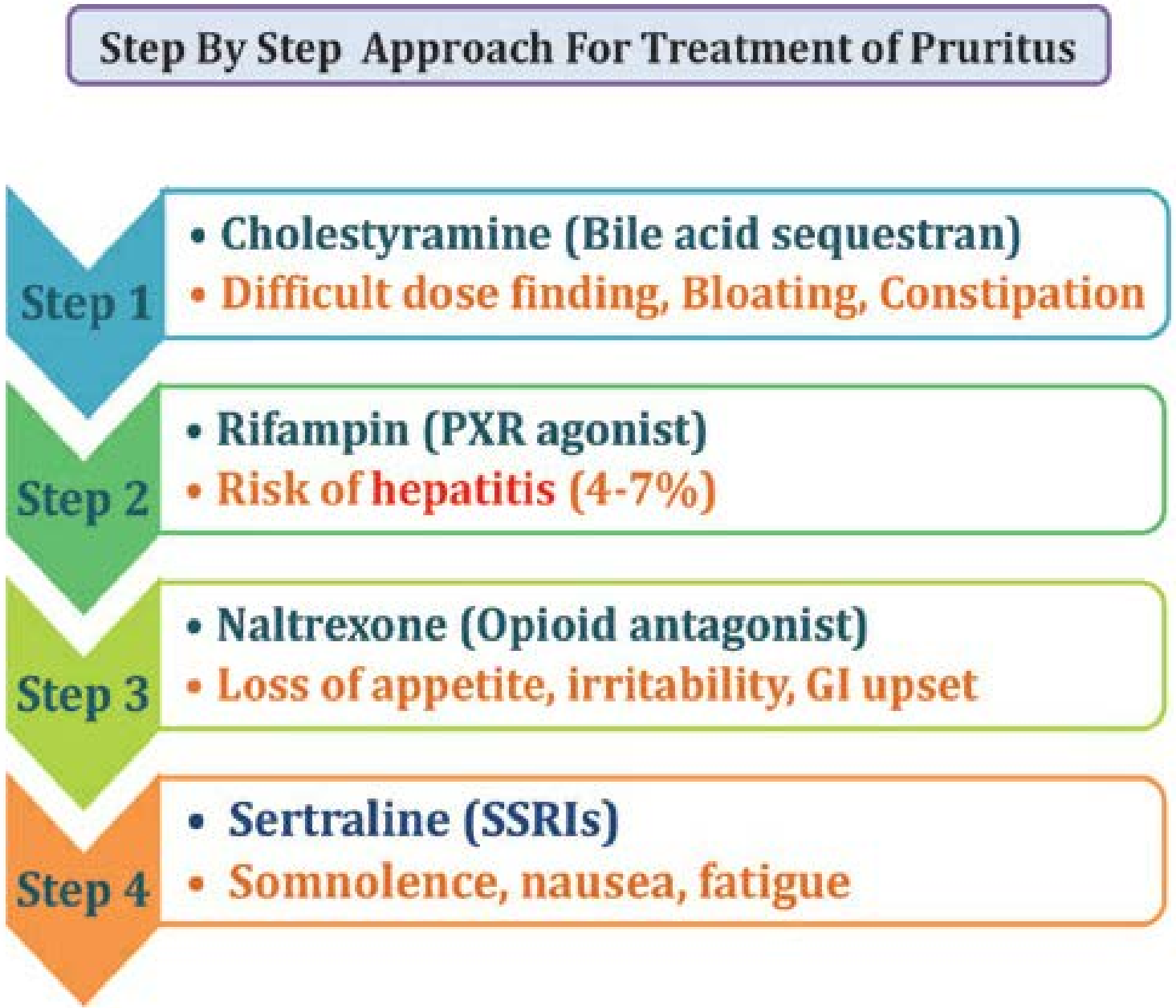


8. Comparison of Sertraline with Rifampin in the Treatment of Cholestatic Pruritus: A Randomized Clinical Trial.

Ataei, et al. Rev Recent Clin Trials.

- Single, blinded randomized clinical trial of 36 patients of PSC and PBC divided into two groups
- Sertraline 100mg/day
- Rifampin 300mg/day
- 4 weeks
- Pruritus improved equally in both groups, but sertraline had less adverse effects on liver enzymes

Graphical Abstract:



Late Breaking Abstract AASLD 2020

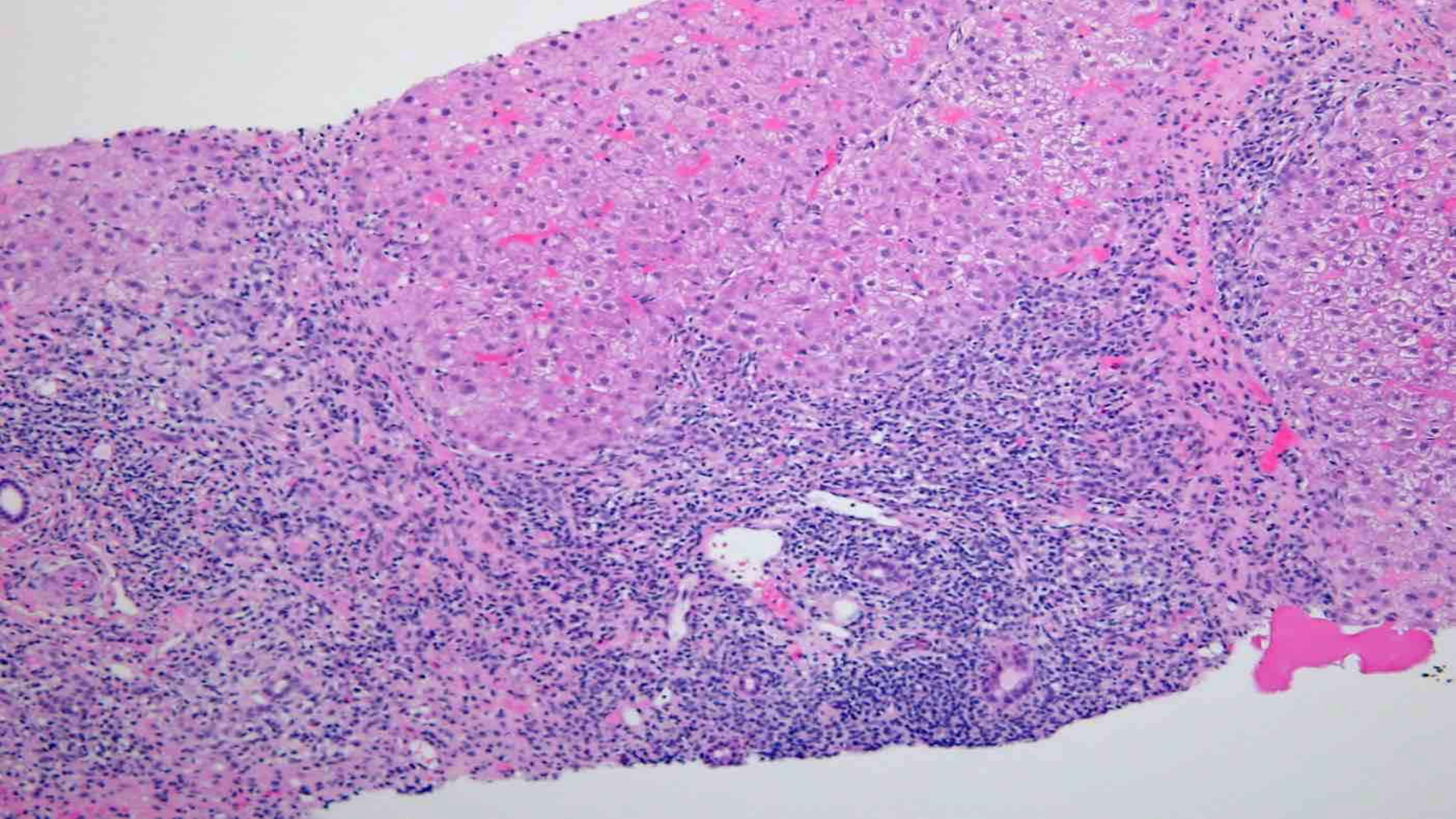
- Glimmer Trial: Levy et al. Randomized Double Blind Placebo Controlled Study evaluating Linerixibat: an ileal bile acid transport inhibitor.
- 147 patients with PBC and at least moderate itching. 12 weeks BID Linerixibat demonstrated rapid and significant improvement in itch and quality of life
  - High placebo response was observed

Two late breakers looking at cholestatic injury in COVID-19 patients (Faruqui et al; Park S).

- Rare: between two studies total of 13 patients with predominantly cholestatic injury
- Patients were very ill: ARDS, MV, ECMO, Sepsis, DVT etc…
- Mean AP 1789, TBr 12
- 8/14 patients imaging findings of large duct disease (beaded appearance)
- One report of vanishing bile duct syndrome – leading to a transplant evaluation.
- Hypothesis is that this is more of a secondary sclerosing phenomenon ischemia, thrombus, drug etc…as opposed to direct viral injury

Autoimmune Hepatitis

- Chronic, inflammatory disease of the liver
- Characterized by circulating autoantibodies and elevated serum globulin levels.
  - Diagnosis remains one of histology
- The disease may start as acute hepatitis and progress to chronic liver disease and cirrhosis.
- Occurs predominantly in women.
- Classically presents with predominant hepatocellular injury
- And is usually exquisitely response to corticosteroid therapy



1. Epidemiology of AIH in the US; A Population Based National Study.

Tunio et al. J Clin Gastroenterol. October 2020.

- April 2014-April 2019 using a commercial database integrated from 26 major health care systems
- 11, 600 patients with AIH

TABLE 1. Demographic Characteristics of AIH

Demographics	AIH Cases [n (%)]
Overall (n)	11,600
Gender	
Male	2300 (20)
Female	9300 (80)
Age group (y)	
Children (< 18)	130 (1)
Adults (18-65)	6630 (57)
Elderly (> 65)	4880 (42)
Race	
White	8720 (75)
African American	1320 (13)
Asian	270 (2)
Hispanic	160 (1)

AIH indicates autoimmune hepatitis.

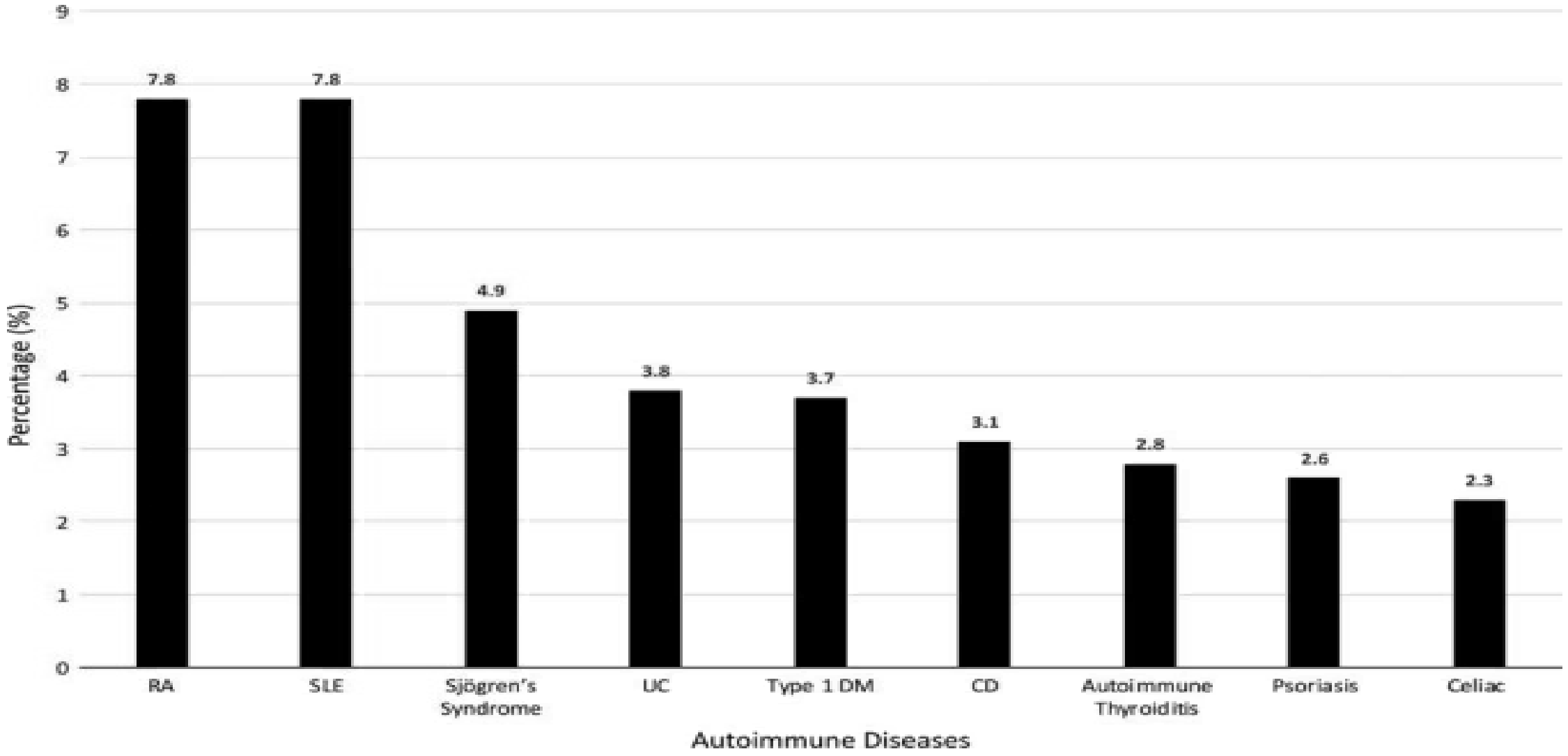


FIGURE 4. Percentage of patients with autoimmune hepatitis and other autoimmune diseases. CD indicates Crohn's disease; DM, diabetes mellitus; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UC, ulcerative colitis.

2. Increased Mortality in AIH: Nationwide Population Cohort Study with Histopathology.

Sharma et al. Clin Gastroenterol Hepatol. October 2020.

- Swedish cohort utilizing all 28 pathology departments in Sweden
- > 6000 patients with AIH with nearly 20 year follow up
  - Matched to 28, 146 in the general population
- Increase risk of death in entire population
- Cirrhosis and PHTN: HR 7.55
- Cirrhosis on biopsy: HR 4.55
- Non cirrhotic fibrosis HR 2.68
- Inflammation with no fibrosis HR 2.18
- Conclusion: AIH carries a 2 fold increased risk of death most of these are liver related, however there was an increased risk in cardiovascular disease (HR 1.27) and extrahepatic malignancy (HR 1.69).

3. Systemic Review: Diagnostic Accuracy of Non-Invasive Tests for Staging Liver Fibrosis in AIH.

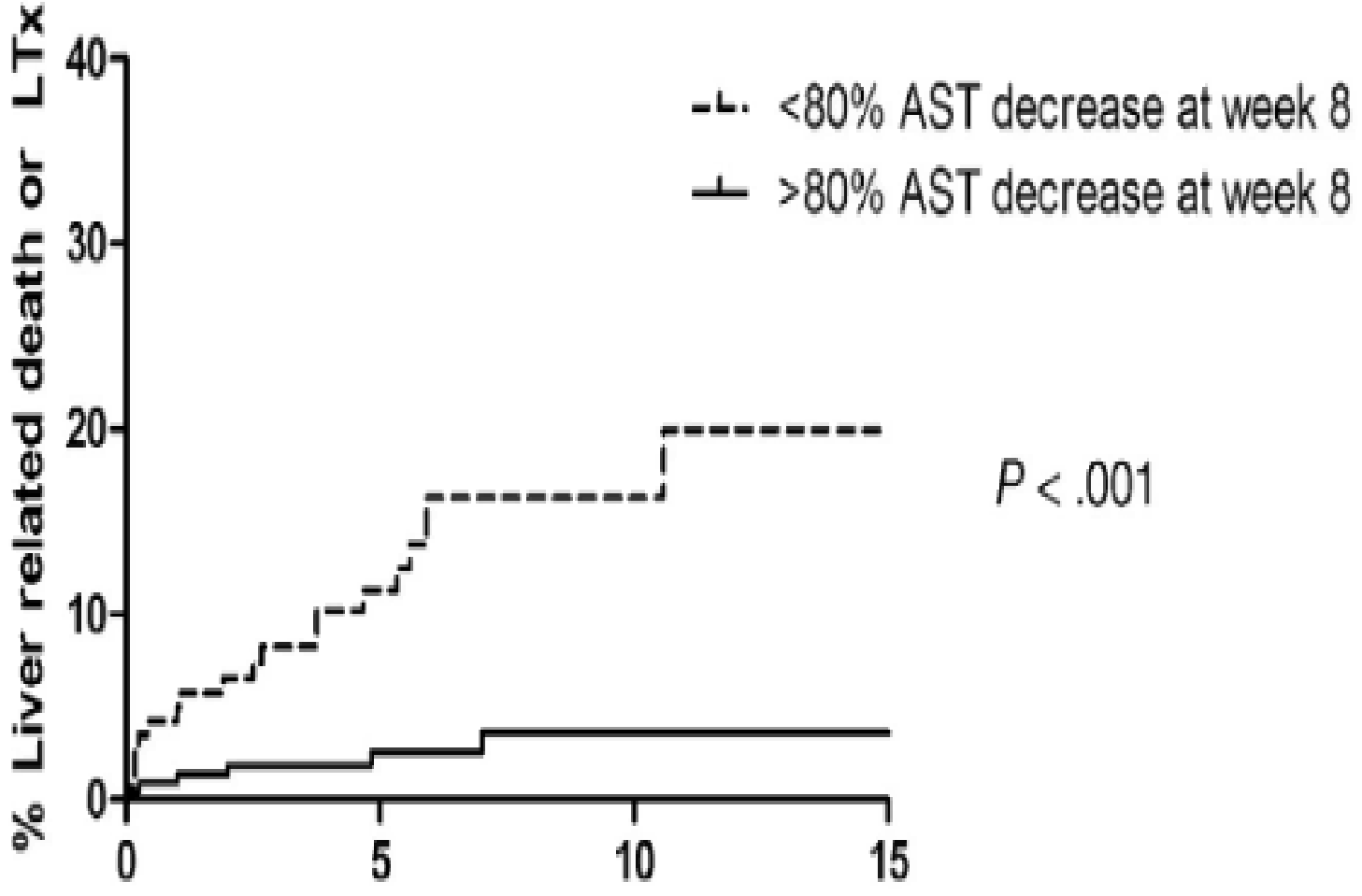
Wu et al. Hepatol Int. January 2019.

- 16 studies
- 861 patients
- AST/Platelet Ratio Index (APRI), Fibrosis-4 Index (FIB-4), AST/ALT ratio and transient elastography (TE)
- *All versus liver biopsy*
- TE had good performance for fibrosis staging AUROC 0.90 and was extremely superior to APRI and FIB-4 which was considered poor.

4. Rapid Response to Treatment of AIH Associated with Remission at 6 and 12 Months.

Clin Gastroenterol Hepatol. Pape, et al June 2020.

- Retrospective cohort study
- > 700 patients collected from 7 European countries
- A decrease of more than 80% in level of AST after 8 weeks was associated with optimal normalization
- Rapid responder: > 80% normalization at 8 weeks had a lower risk of live related death or transplantation; HR 0.18



Number at risk:

<80% AST decrease	143	77	29	8
>80% AST decrease	224	132	49	13

Figure 1. Kaplan-Meier curve of liver-related death or transplantation over time in the discovery cohort. Patients with an AST decrease of ≥80% are compared with patients with an AST decrease <80% (log-rank $P < .001$). LTx, liver transplantation.

5. Cannabidiol Consumption and Perceived Impact of Extrahepatic Symptoms in Patients with AIH.

Mathur et al. DDS January 2020.

- Survey conducted via *Facebook* AIH community (2600 individuals)
- 371 patients responded; mean age 49, 32% reported advanced fibrosis
- 91% women, 89% Caucasian and 89% North America
- 25% of respondents used CBD
- Main indications: pain, sleep and fatigue
- Improvement reported in 82%, 87% and 61%

6. New AIH AASLD Guidelines. Published Hepatology December 2019.

Mack et al (Senior Author: Czaja)

- What's new since 2010:
- Histological features of NALFD are present in up to 30% of patients with AIH; concurrent NAFLD may influence response
- Diagnostic scoring systems should be used only to support clinical judgement
- Elastography may be used to assess the stages of hepatic fibrosis non-invasively
- Testing TPMT activity prior to AZA treatment is encouraged

AASLD Guidelines 2019

- AZA can be continued throughout pregnancy. MMF is contraindicated in pregnancy
- Liver tissue examination prior to drug withdrawal in individuals with ≥ 2 years of biochemical remission is preferred but not mandatory in adults
- MMF and TAC can be use as 2nd line agents who have failed first line therapy
- Patients with acute severe AIH should receive steroids followed by LT if no improvement within two weeks
- Glucocorticoids can be discontinued after LT and patients monitored for recurrence of AIH

7. Increased Post-Transplant Mortality for AIH Compared to PBC/PSC.

Lee et al. J Clin Gastroenterol. August 2020.

- UNOS database study

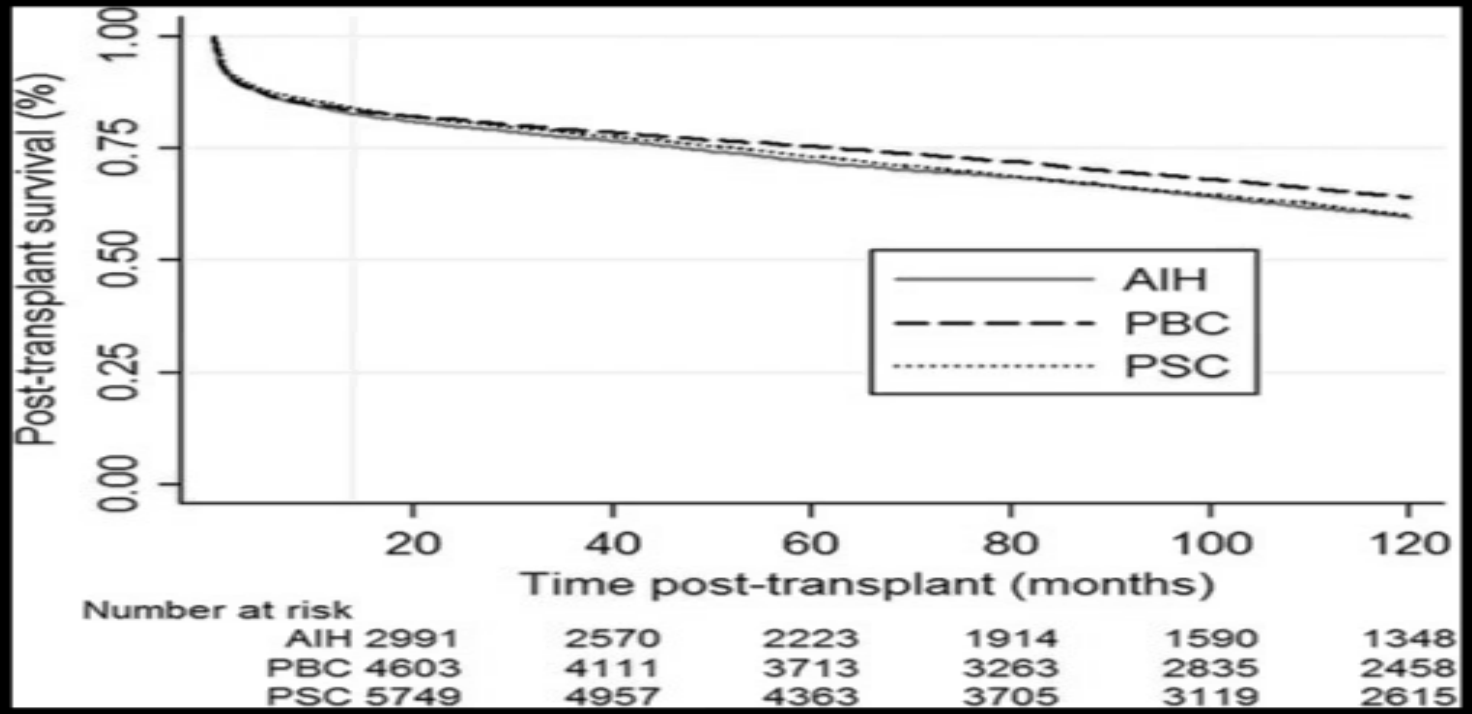


FIGURE 1

Kaplan-Meier curves comparing graft survival (composite of posttransplant death and retransplant) by autoimmune etiology. One-year graft survival was 82.2% survival for AIH, 83.2% for PBC, and 84% for PSC. Differences between the groups continue to widen with 5-year graft survival of 70.9% for AIH, 74.4% for PBC, and 72.5% for PSC and 10-year graft survival of 56.3% for AIH, 63% for PBC, and 59.1% for PSC. AIH indicates autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

Source

Increased Posttransplant Mortality for Autoimmune Hepatitis Compared With Other Autoimmune Liver Diseases

Journal of Clinical Gastroenterology54(7):648-654, August 2020.

8. Long-term Survival After LT for AIH: European LT Registry.

Heinemann et al. Liver Transpl. July 2020.

- 1998-2017
- 2515 patients undergoing LT for AIH
- 79% 5 year, 70% 10 year and 60% 15 year patient survival. Similar to alcohol but worse than PBC and PSC
- Infections post LT in AIH group were significantly higher especially fungal infections (HR 3.38)

9. Two Oral AASLD Abstracts on AIH and Pregnancy:

(El- Jamaly et al and Wang et al).

- 641 patients with AIH Australia
- Noted a significant increase in likelihood of diabetes compared to controls OR 5.68
- Premature births: OR 2.73
- Small gestational age: OR 2.47
- Low birth weight: 2.47

- 935 patients with AIH USA
- Increase in gestational DM: 17% vs 8.7% (OR 2.2)
- HTN complications: 8.6% vs 4.4% (OR 2.4)
- Higher pre-term birth: 8.6% vs 4.6% (OR 2.0)

- No increased risk however in maternal/fetal death

TEN TAKE HOME POINTS:

Ten Take Home Points

- 1. UDCA leads to response in ~ 2/3rd of patients with PBC
  - Goal is to (near) normalize AP
  - OCA has good long term, real life results; fibrates also seems to have a role
  - Newer PPAR agonists are coming
- 2. Consider bezafibrate and sertraline as safe options for pruritus PBC/PSC patients
  - Linerixbat shows early promising results
- 3. Elastography is accurate in PBC and AIH and may help in predicting clinical outcomes
- 4. HCC surveillance should be recommended in PBC/AIH patients with cirrhosis
- 5. GGT and NLR at one year may help to determine high risk PBC patients
- 6. UDCA ‘prophylaxis’ should be SOC in all PBC patients post LT

Ten Take Home Points

- 7. There is no FDA approved treatment for PSC
  - UDCA should not be used at high doses (28-30mg/kg). It remains unclear whether there is a lower dose of UDCA which may provide benefit (understanding most guidelines recommend against its use)
  - Fecal Microbiota, Cilofexor show some promise in PSC patients
  - PSC is in desperate need for research, trials and therapy
- 8. Isolated intrahepatic disease is associated with better prognosis in PSC
- 9. Concomitant AI disease are not uncommon in AIH/cholestatic diseases
- 10. AIH increases overall mortality
  - Post LT mortality is higher in AIH versus PBC/PSC
    - Do we need to re-consider standard IS regimen in patients transplanted for AIH?
  - AIH does have negative impact on pregnancy