Imperial College London

Highlights from 2021 AASLD meeting

Rob Goldin

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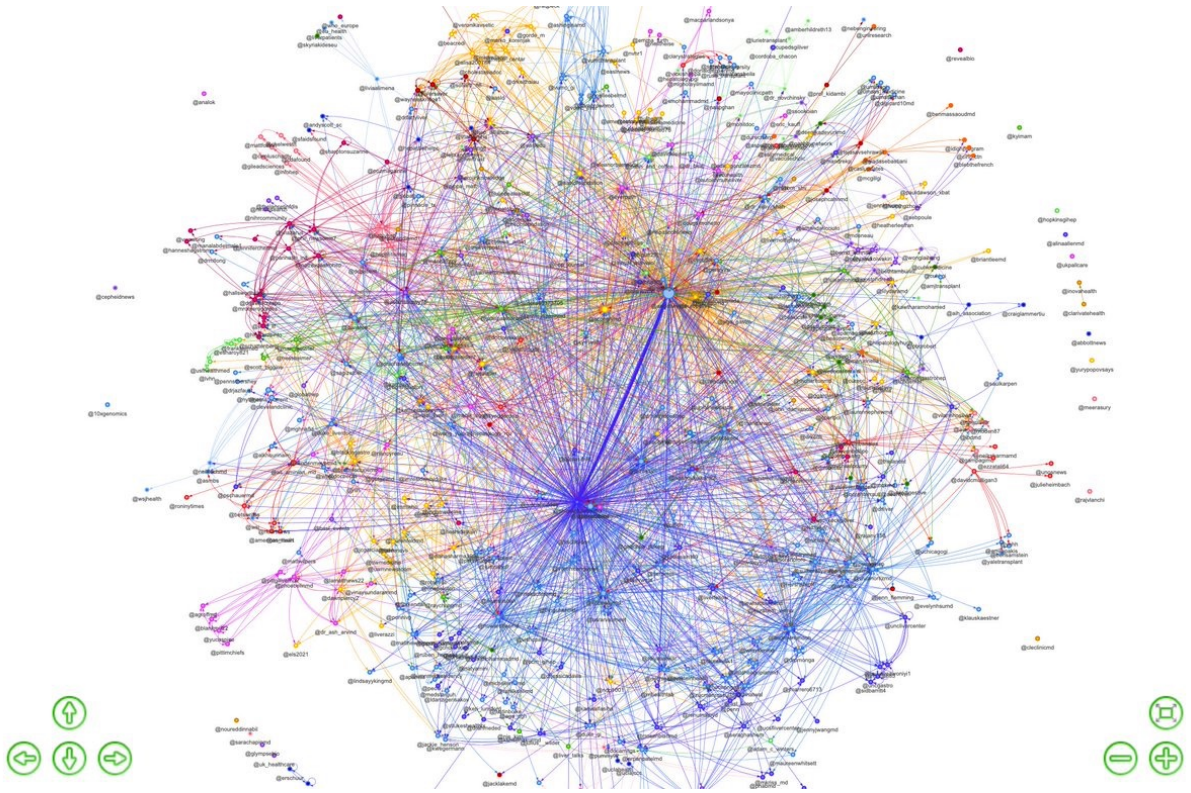
Social Media Network for the Meeting



The #LiverMtg21 Influencers

Top 10 Influential


@AASLDtweets 100


@AtoosaRabiee 74


@LizzieAbyMD 64


@HowardTLeeMD 61


@jturnesv 58


@AndrewMMoon 54


@rabataller 54


@sconglymd 50


@ebtapper 48


@AASLDFoundation 48

Prolific Tweeters


@EuropeLiver 366


@ShimaghavimiMD 350


@HowardTLeeMD 144


@liverpath 143


@AtoosaRabiee 139


@jturnesv 125


@sconglymd 102


@JCabezasGlez 102


@AASLDPresident 99


@DrJHK 89

Highest Impressions


@wedocaresaudi 5.4M


@EuropeLiver 2.8M


@NeilFlochMD 1.6M


@drmoutaz 1.5M


@AASLDtweets 1.5M


@LancetGastroHep 964.2K


@ShimaghavimiMD 878.2K


@LizHIVHep 846.2K


@AtoosaRabiee 628.8K


@ebtapper 568.2K

The Numbers

25.943M Impressions

5,990 Tweets

1,323 Participants

50 Avg Tweets/Hour

5 Avg Tweets/Participant

Tweet

Twitter data from the #LiverMtg21 hashtag from Thu, November 11th 2021, 6:00AM to Tue, November 16th 2021, 6:00AM (Europe/Madrid) – Symplur.

symplur

Liver Biopsy

684 ENDOSCOPIC ULTRASOUND-GUIDED LIVER BIOPSY IS COMPARABLE TO PERCUTANEOUS LIVER BIOPSY

- Primary outcome was to compare the rates of adequacy of

sample defined as presence of ≥11 complete portal tracts

and >15mm in length

- A final pathological diagnosis was reached in all subjects in both groups.
- The rate of adequate sample was higher in the PCTLB however it was not statistically significant (55.6% vs 75%, p=0.1).
- The mean of total portal tracts obtained via PCT-LB was higher compared to EUS-LB (12.5 vs 18.9, p=0.009).
- However, there was no difference in the mean maximum length of biopsy specimen (19.4mm vs 19.6mm, p=0.93).

ENDOSCOPIC ULTRASOUND-GUIDED LIVER BIOPSY IS COMPARABLE TO PERCUTANEOUS LIVER BIOPSY: A RANDOMIZED CLINICAL TRIAL

Table 1: Study Outcomes

	EUS-guided liver biopsy (36 subjects)	Percutaneous liver biopsy (44 subjects)	p value
Mean age in years (SD)	53.4 (13.7)	51.8 (13.8)	0.61
Gender [Female]	26 (72%)	27 (61%)	0.34
Maximum length of biopsy specimen (mm)			
Mean (SD)	19.5 (5.8)	19.6 (5.7)	0.93
Number of complete portal tracts			
Mean (SD)	12.5 (10.6)	18.9 (10.5)	0.009
0 – 4	5	4	
5 – 10	11	7	
>11	20 (55.6%)	33 (75%)	0.1
Mean Pain Score (VAS) 24-48 hours post procedure (SD)	2.5 (2.1)	4.5 (2.1)	0.0001
Mean length of hospital visit in hours (SD)	2.2 (1.6)	4.02 (1.6)	0.0001

SD: Standard deviation; VAS: Visual Analog Scale

692 ENDOSCOPIC ULTRASOUND GUIDED LIVER BIOPSY: LEFT LOBE IS EQUAL TO RIGHT LOBE FOR DIAGNOSIS

- Endoscopic-ultrasound guided liver biopsy (EUS-LB) is a newer modality of taking liver biopsy under direct supervision and sedation.
- The measure of agreement Kappa between left and right lobe was 0.462 (p=0.0001).
- Similarly when the left lobe pathological diagnosis was compared with the final combined diagnosis, agreement was seen in 45/50 (90%) of cases (Kappa 0.474, p=0.0001).

612 CLINICAL UTILITY OF LIVER BIOPSY

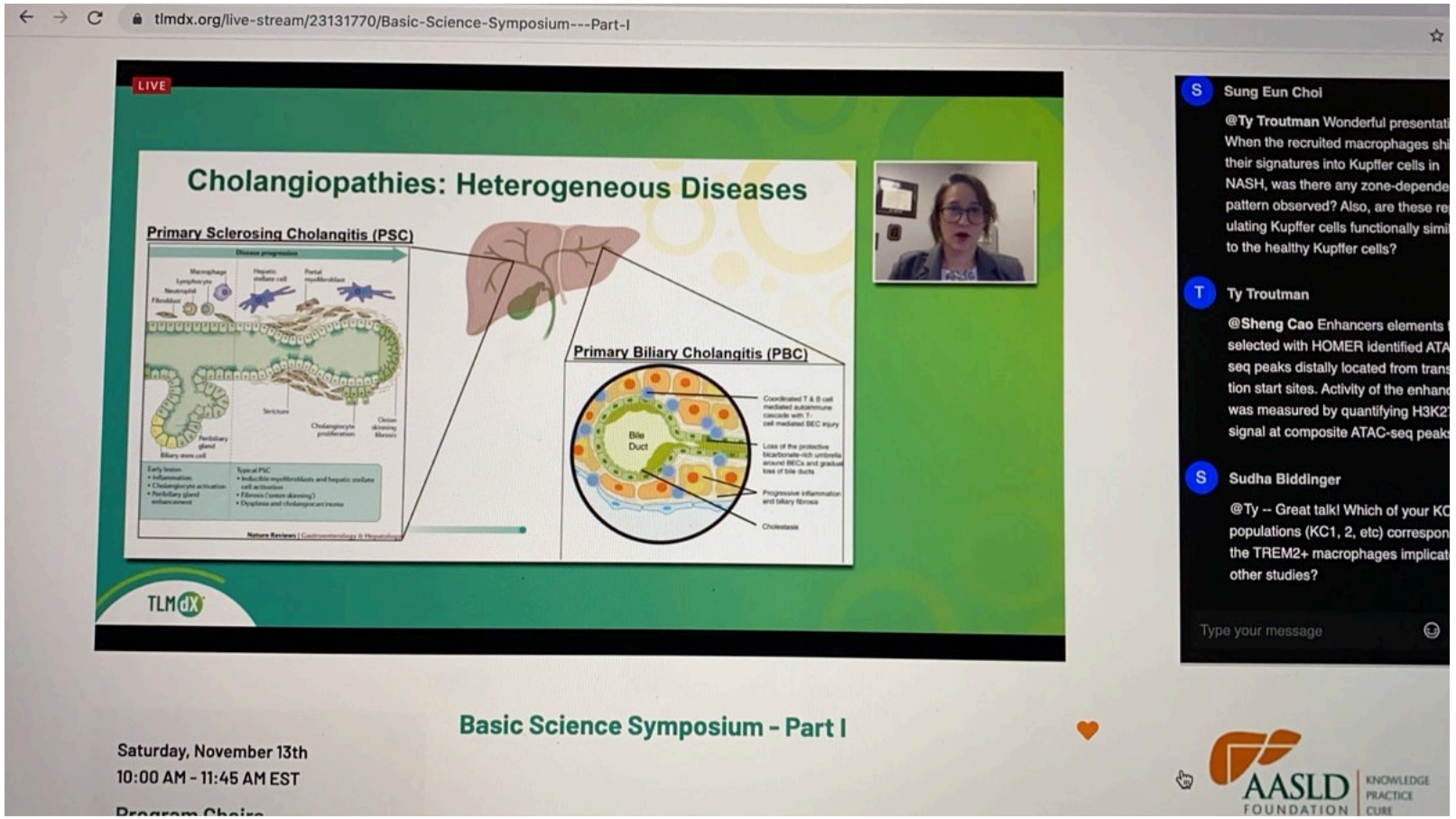
We performed a prospective questionnaire survey study to assess

1. how accurately providers predicted pre-biopsy diagnosis and severity of liver disease, and
2. to determine how histopathology findings might alter would alter the physician's management plan.

612 CLINICAL UTILITY OF LIVER BIOPSY

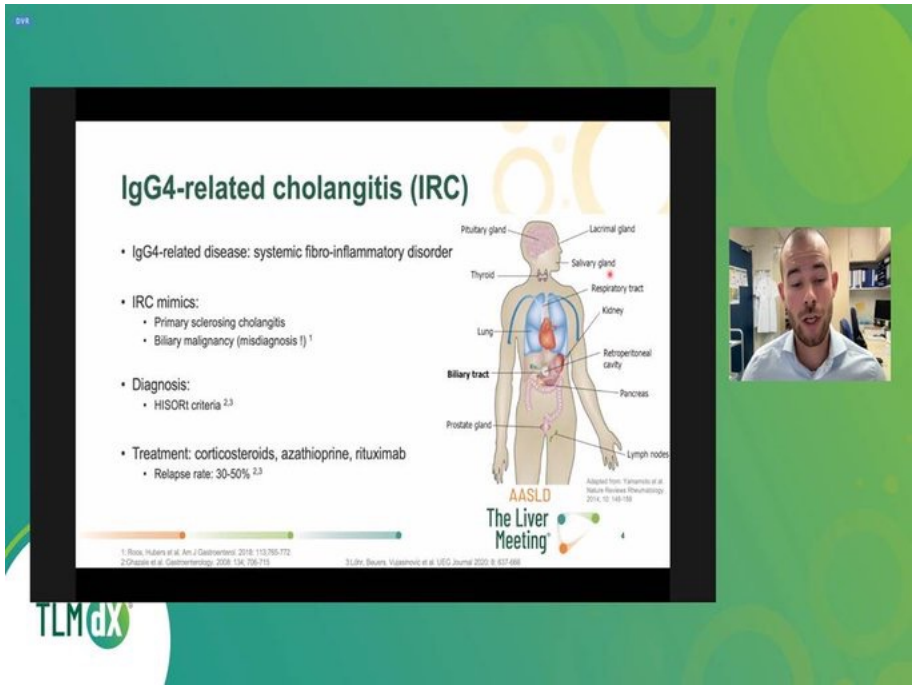
- Well-trained specialists can predict the underlying hepatic pathological abnormality and liver disease stage (fibrosis) with a reasonably high degree of accuracy (63% and 68%, respectively).
- A total of 106 diagnoses (in 81 patient) were suspected
- The most common prebiopsy clinical diagnoses were autoimmune hepatitis and alcoholic liver disease (ALD).
- The most common histological diagnoses were ALD and transplant rejection.
- However, histopathological tissue assessment identifies unsuspected diagnoses in at least one-third of patients, and histologic findings play an important role in management.

Biliary tract diseases



IgG4-RD

- The role of anti-annexin 11 antibodies in the pathogenesis from the disease of IgG4-RD.
- These antibodies may lead to rise in pH of biliary contents resulting in the inflammation seen.


IgG4-related cholangitis (IRC)
• IgG4-related disease: systemic fibro-inflammatory disorder
• IRC mimics:
• Primary sclerosing cholangitis
• Biliary malignancy (misdiagnosis !) [1]
• Diagnosis:
• HISORt criteria [2,3]
• Treatment: corticosteroids, azathioprine, rituximab
• Relapse rate: 30-50% [2,3]
Pituitary gland
Lacrimal gland
Salivary gland
Thyroid
Respiratory tract
Kidney
Lung
Retroperitoneal cavity
Biliary tract
Pancreas
Prostate gland
Lymph nodes
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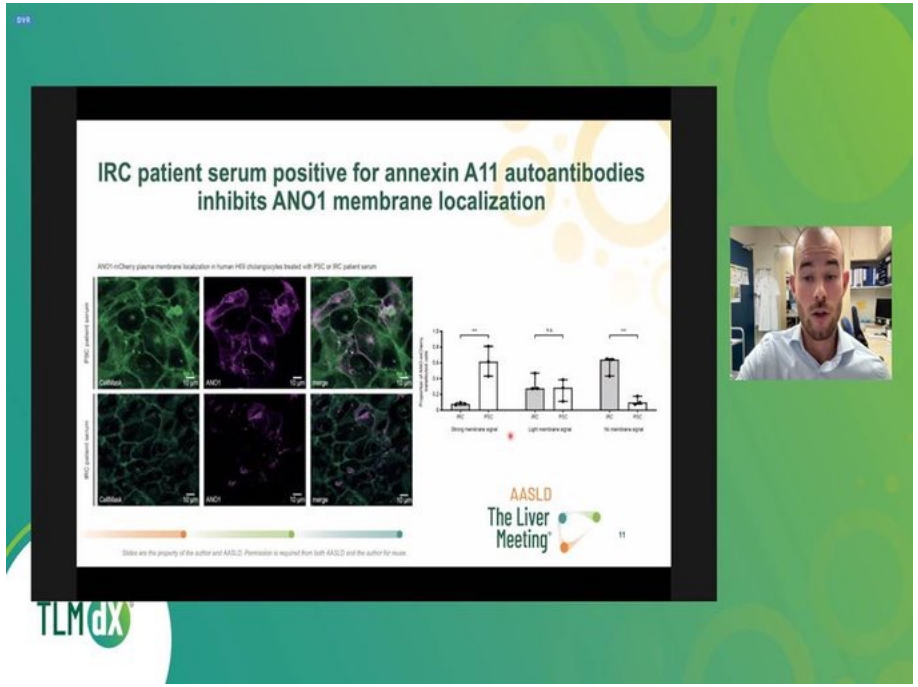
IRC patient serum positive for annexin A11 autoantibodies inhibits ANO1 membrane localization
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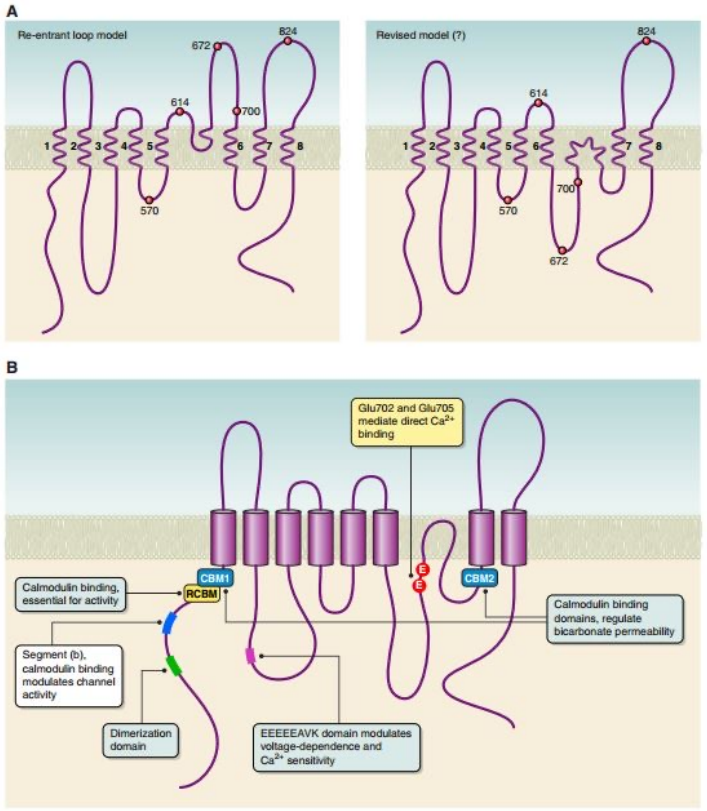
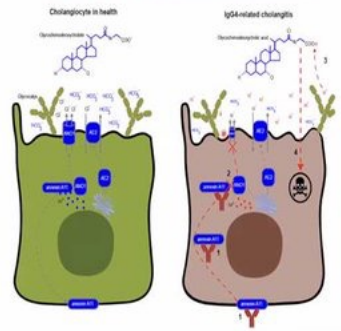
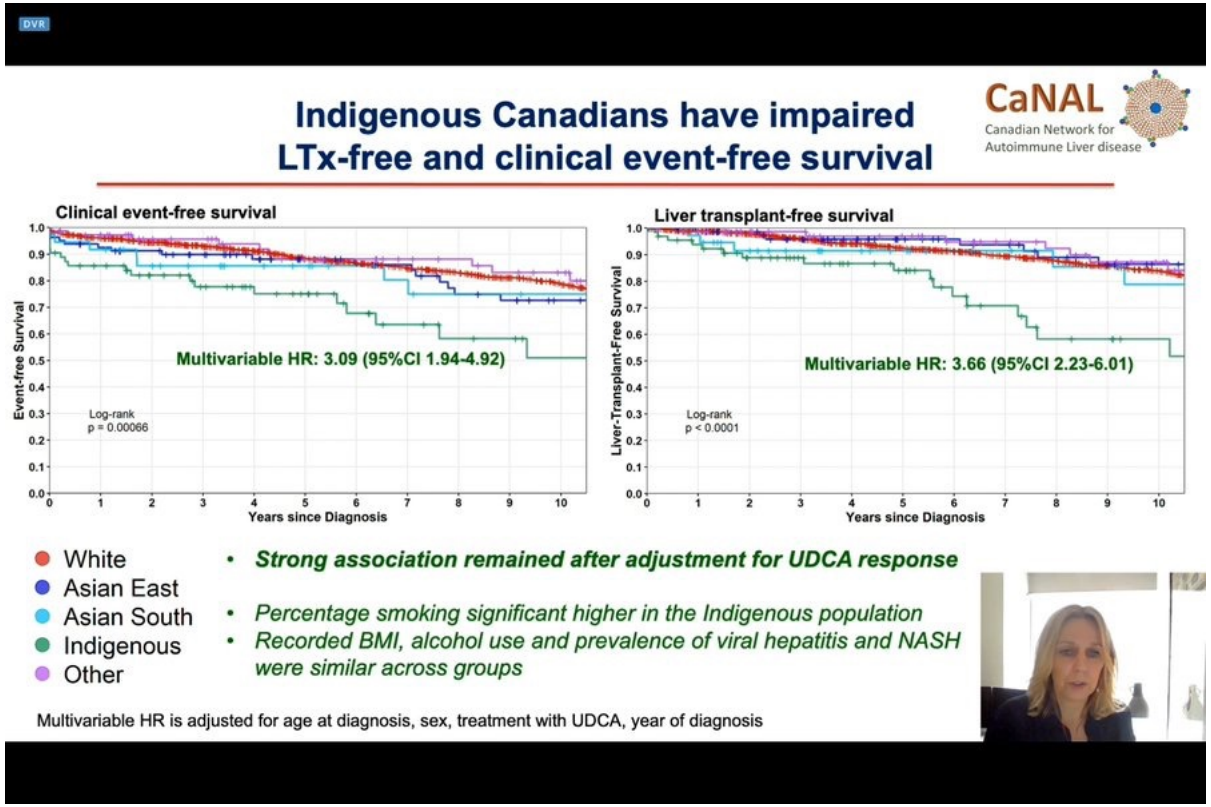
Anoctamin 1 (ANO1)



Annexin A11 autoantibodies in IRC may destabilize the biliary bicarbonate umbrella



PBC in Indigenous Canadians



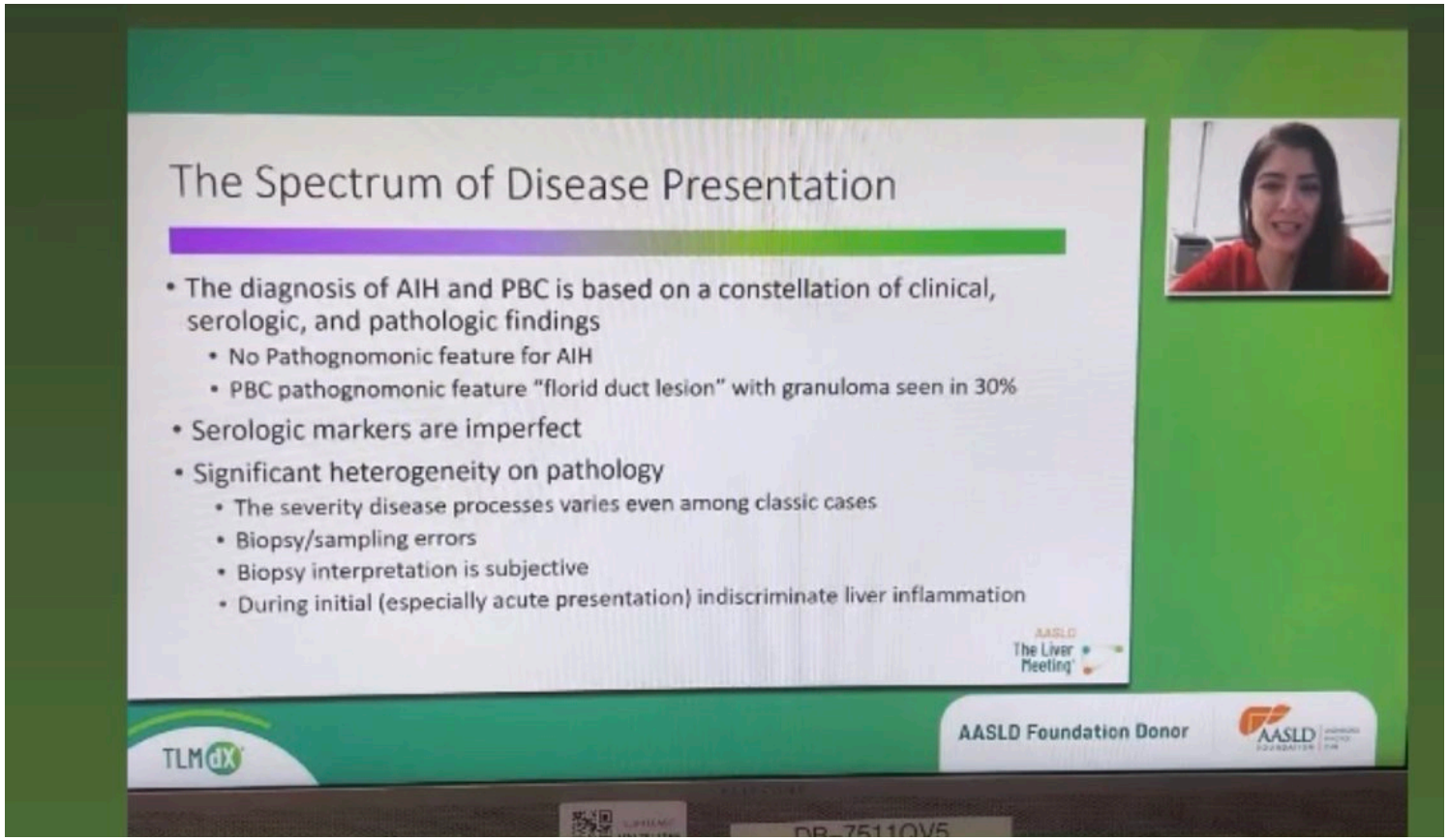
PBC in Indigenous Canadians

Conclusion

CaNAL
Canadian Network for Autoimmune Liver disease

- Indigenous population with PBC has an impaired event-free survival and liver-transplant-free survival compared to the overall PBC population in Canada
- Indigenous Canadians present with advanced biochemical profile (ALP, bilirubin and Globe Score) which sustained over time
- Indigenous Canadians have lower self-reported QoL. Impairment in majority of PBC-40 domains (fatigue, symptoms, cognitive and emotional)

AIH and PBC


The Spectrum of Disease Presentation
• The diagnosis of AIH and PBC is based on a constellation of clinical, serologic, and pathologic findings
• No Pathognomonic feature for AIH
• PBC pathognomonic feature "florid duct lesion" with granuloma seen in 30%
• Serologic markers are imperfect
• Significant heterogeneity on pathology
• The severity disease processes varies even among classic cases
• Biopsy/sampling errors
• Biopsy interpretation is subjective
• During initial (especially acute presentation) indiscriminate liver inflammation
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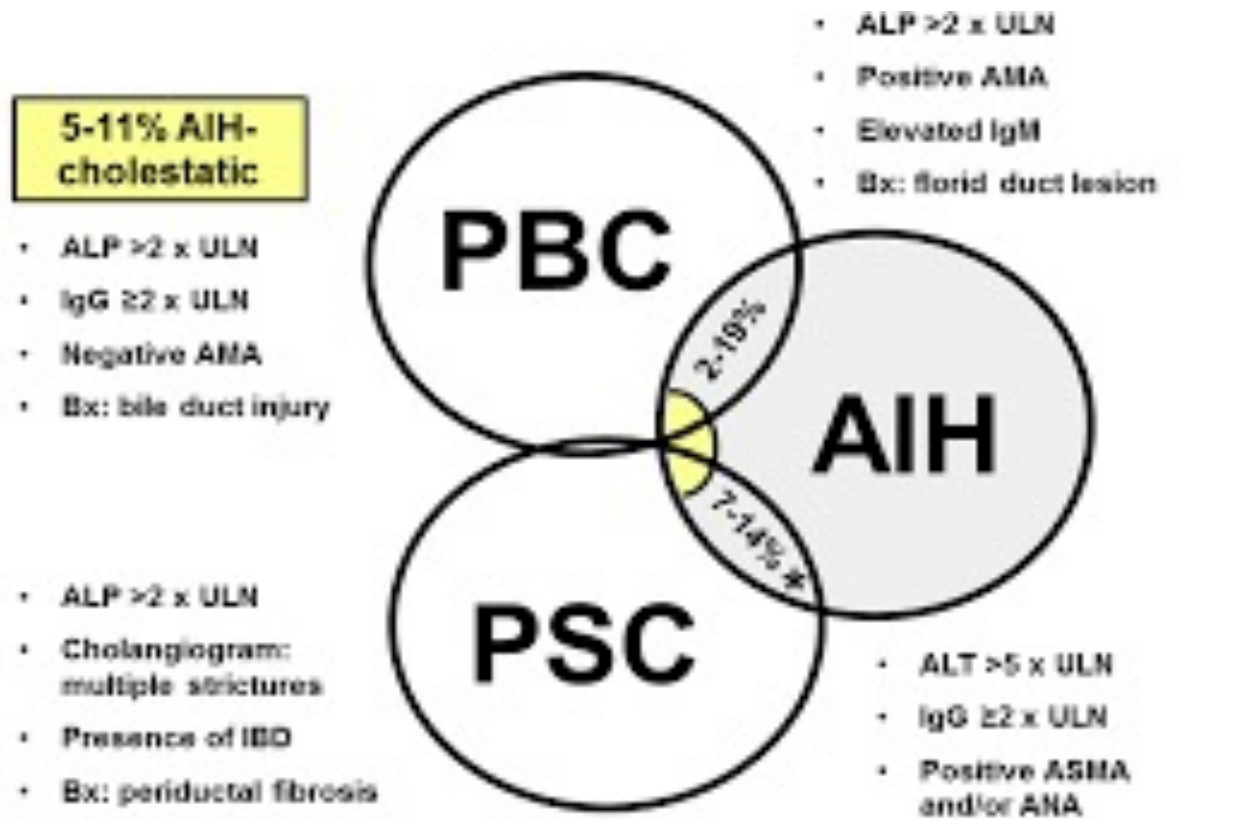


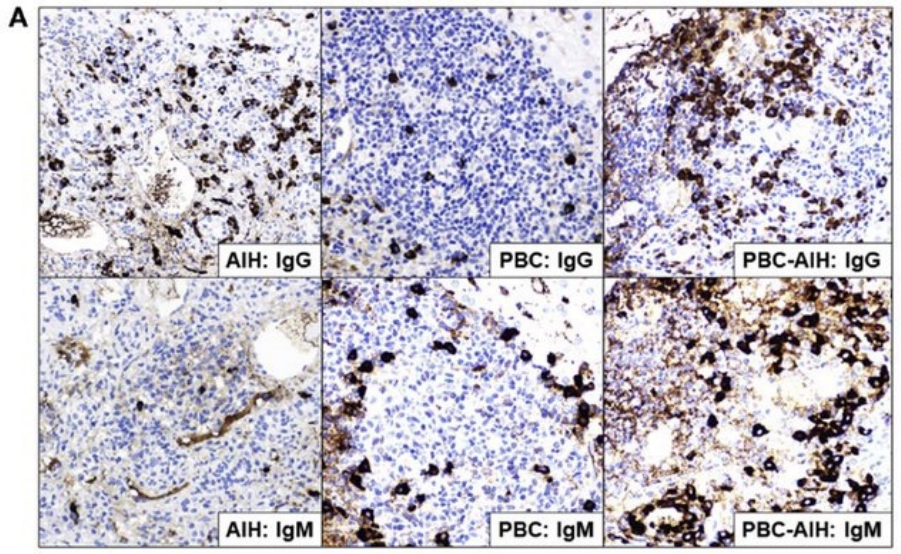
*Up to 40% in AIH patients with IBD

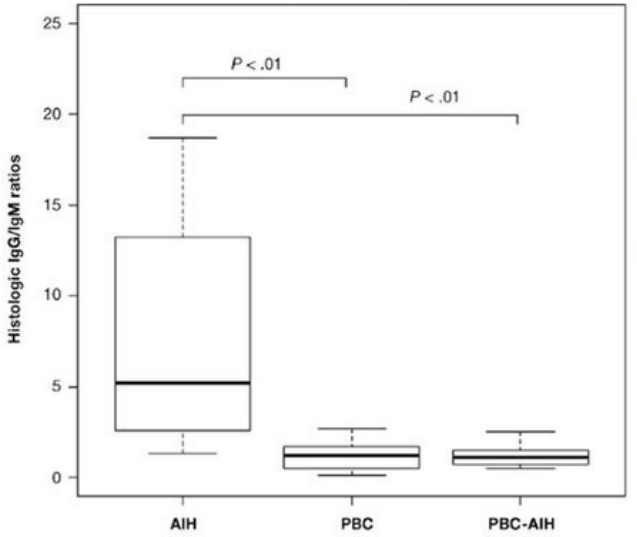
PBC and AI Hepatitis

- Many similarities in histologic, biochemical and serologic presentations of AIH and PBC
- Moderately severe interface hepatitis is seen in PBC and is an independent predictor of fibrosis progression
- Lymphocytic cholangitis and even ductopaenia can be seen in AIH

Immune phenotype of plasma cell and the ratio of IgG+/IgM+ on biopsy suggests PBC-AIH variants more closely resemble PBC.

Immunostains for IgG and IgM





Lee, BT et al CGH 2021;19:397-399

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PBC AI Overlap

Latinx/Hispanic PBC pts present more with AIH features, have poor response to TX and worse outcomes.

DEEP LEARNING MODEL FOR STAGING AND GRADING AUTOIMMUNE HEPATITIS FROM HISTOLOGY

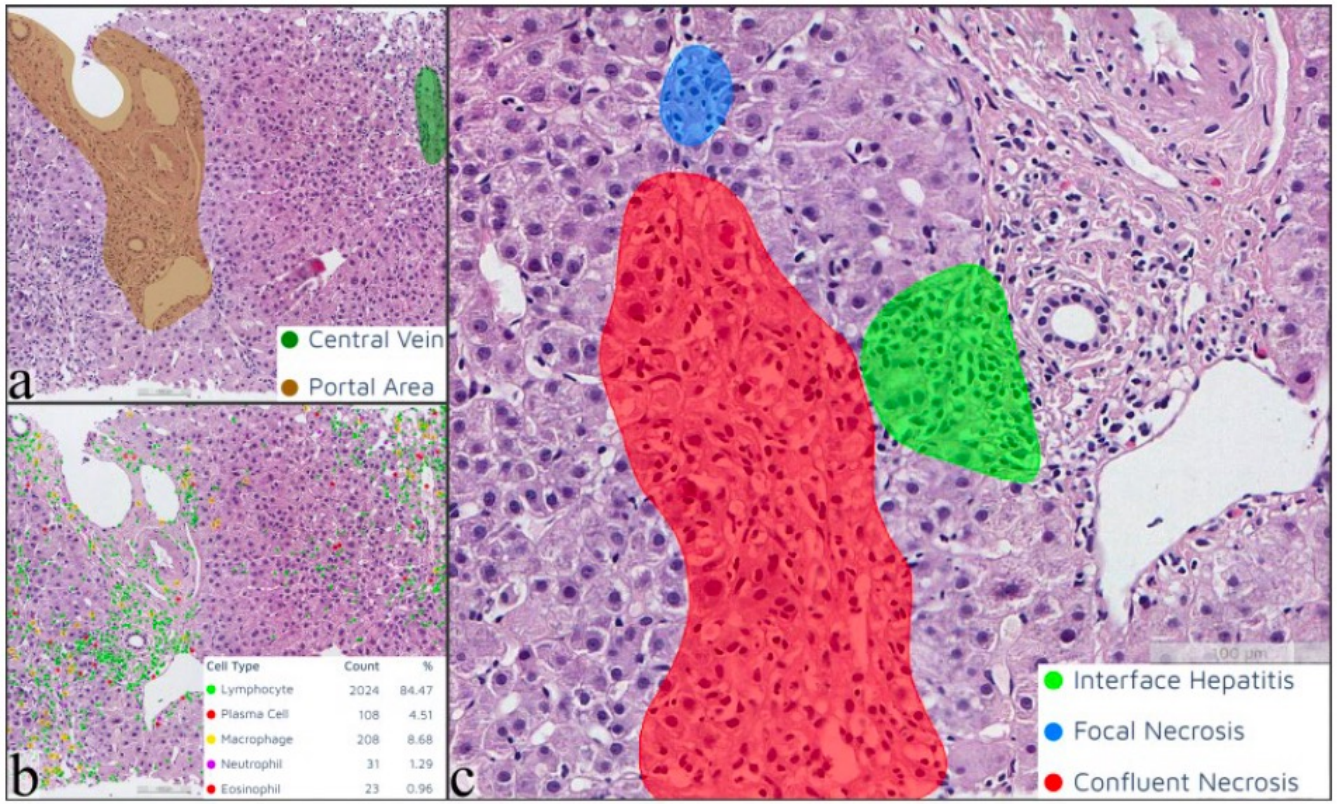


Fig: AI predictions on AIH patient biopsy: (a)liver structures, (b)immune cells and counts, and (c) hepatitis lesions including interface hepatitis, focal necrosis and confluent necrosis.

Fatty liver disease

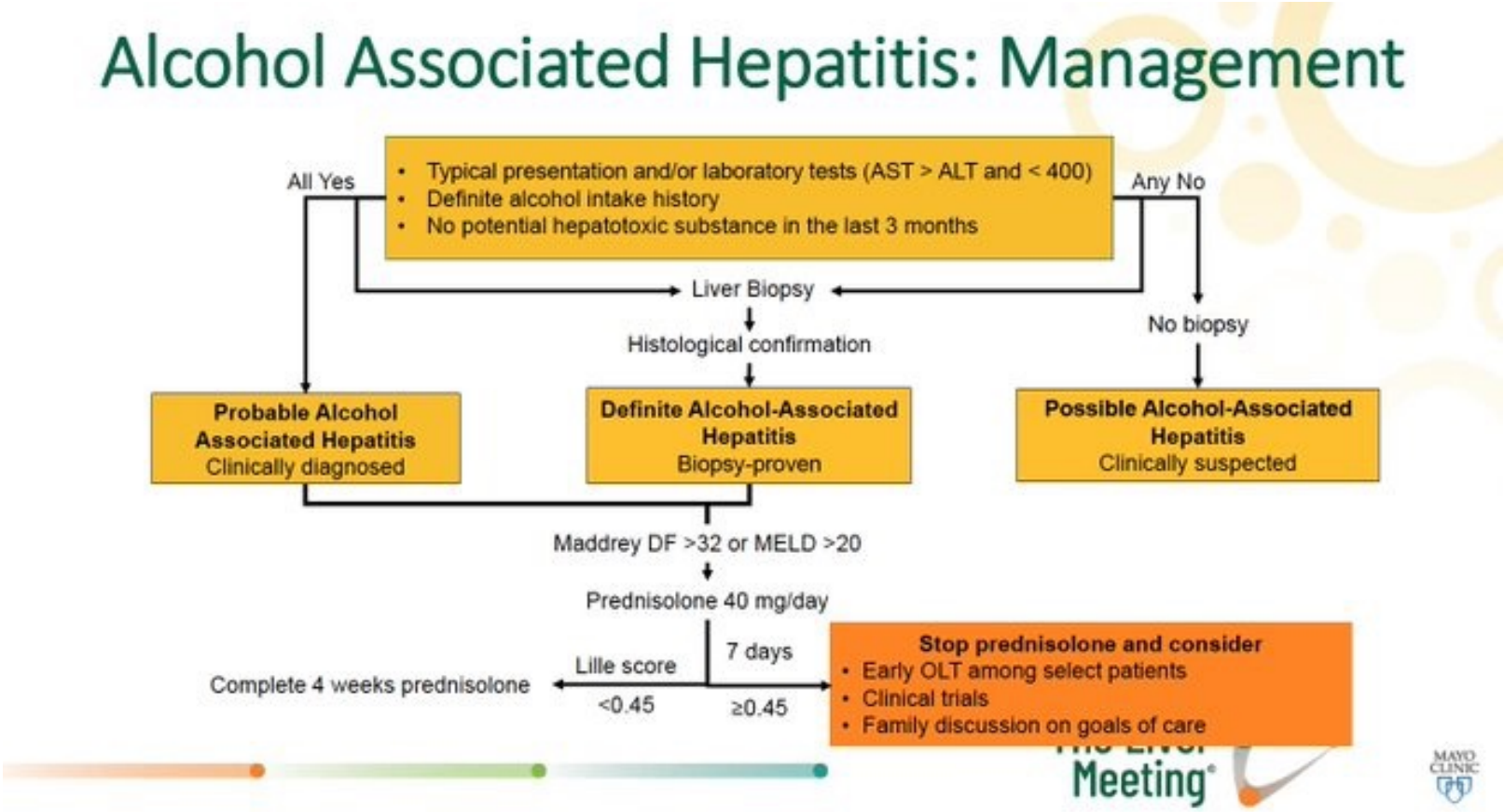
NASH: Fibrosis scores and Treatment

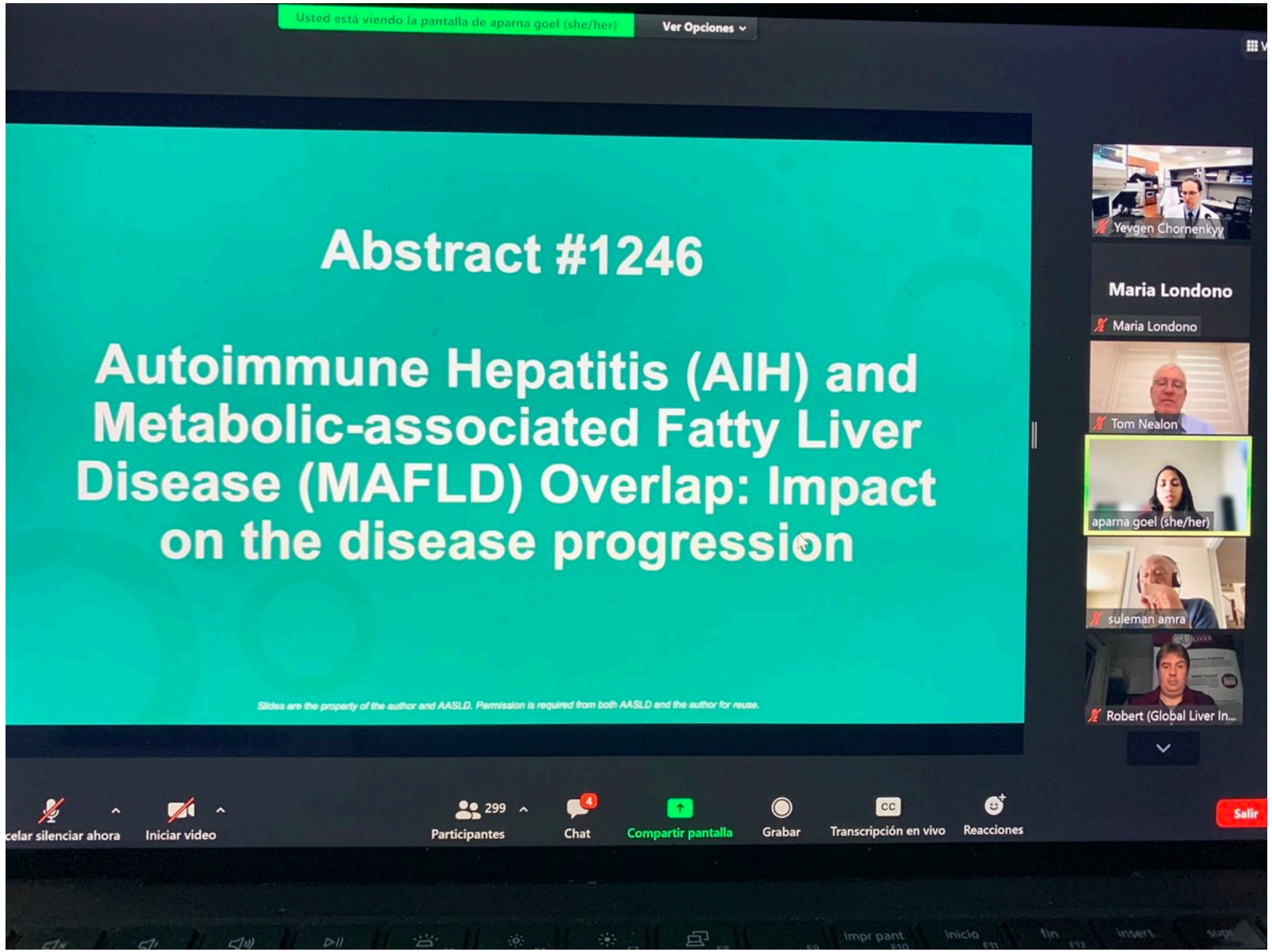
	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Footnotes:

1. Patients with F4 or cirrhosis (based on biopsy, LSM values based on vibration controlled transient elastography (VCTE, FibroScan®) or > 5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM > 20 kPa or platelet count of < 150,000/mm^3.
2. All patients require regular physical activity, healthy diet, avoid excess alcohol intake.
3. Weight loss recommended for cardiometabolic benefit and reversal of steatosis. Greater weight loss is often associated with more benefit, such as reversal of steatohepatitis (usually with weight loss ≥7%) or fibrosis (usually with weight loss ≥10%).
4. Individualize based on further work-up and efforts to confirm the diagnosis of NASH. A liver biopsy provides helpful information and should be considered for cases where there is a diagnostic doubt such as patients with indeterminate, unreliable, or conflicting non-invasive assessments or as part of phase 2 or 3 clinical trials.
5. No pharmacological agent is FDA-approved for the treatment of NASH. Patients with T2DM may benefit from some diabetes medications, such as pioglitazone [80, 81, 86, 87, 88] and some GLP-1 RAs [84, 85] that have reported histological improvement in RCTs in patients with NASH, either with or without diabetes. Among GLP-1 RAs, semaglutide has the strongest evidence of liver histological benefit [85].
6. Vitamin E improves steatohepatitis in patients with NASH without diabetes [80], with less evidence in patients with T2D [81].
7. Pharmacotherapy in patients with NASH cirrhosis is very limited and should be avoided until more data become available.
8. Statins can be used safely in patients with steatohepatitis and liver fibrosis; to be avoided in decompensated cirrhosis.

Management of Alcohol Associated Hepatitis




Usted está viendo la pantalla de aparna goel (she/her)
Ver Opciones
Abstract #1246
Autoimmune Hepatitis (AIH) and Metabolic-associated Fatty Liver Disease (MAFLD) Overlap: Impact on the disease progression
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Yevgen Chornenkyy
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Tom Nealon
aparna goel (she/her)
suleman amra
Robert (Global Liver In...
celar silenciar ahora
Iniciar video
299
Participantes
Chat
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Grabar
Transcripción en vivo
Reacciones
Salir

- Approximately 20% of patients with AIH have features of MAFLD.

- However, the prevalence of AIH-related features in patients with MAFLD, and the impact of AIH/MAFLD overlap in the progression of both diseases are unknown.

- Cohort 1 included 150 patients with AIH. The presence of steatosis and/or steatohepatitis was analyzed at baseline biopsy.

- Cohort 2 included 109 patients with biopsy proven MAFLD. Autoantibodies (>1:40), IgG levels, and AIH histological features (interface hepatitis and moderate-severe portal inflammation) were analyzed at diagnosis

- The prevalence of AIH/MAFLD ranged between 7% and 11%.
- In patients with AIH, the presence of diabetes and metabolic syndrome was associated with higher risk of developing cirrhosis.
- In patients with MAFLD, the existence of AIH features was associated with more advanced fibrosis at diagnosis.

Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a (Swedish) nationwide cohort

- All NAFLD histological stages were associated with significantly increased overall mortality, and this risk increased progressively with worsening NAFLD histology.
- Most of this excess mortality was from extrahepatic cancer and cirrhosis, while in contrast, the contributions of cardiovascular disease and HCC were modest.

TABLE 3. Reporting Recommendations for NAFLD and NASH

- Evaluate the biopsy for the pattern of fatty liver injury and the presence or absence of other liver diseases (biliary tract disease, autoimmune or viral hepatitis, alpha-1-antitrypsin deficiency, hemochromatosis, granulomatous disease, vascular liver disease).
- The diagnostic line should incorporate both the overall pattern of injury (e.g., fatty liver or steatohepatitis) along with an assessment of the severity of the key features (see table below).
- Etiology (e.g., metabolic syndrome, alcohol, drugs) may be added if known from clinical history.
- Concurrent injury from another etiology may be added if known, or recognized by histology.
- It is optional to add semiquantitative scores if there is agreement between the pathologist and the hepatologist as to when to report such scores. Note that all such systems either split the evaluation of lobular inflammation from portal inflammation or score only lobular inflammation. Lobular inflammation is the only inflammation component added to composite scores (such as the NAS or the SAF). The scoring reference should always be cited, and the descriptive terms in the diagnostic line may be based on the scores.

DVR

Human ASH has larger lipid droplets which predominantly affect the periportal zone as compared to NASH controls

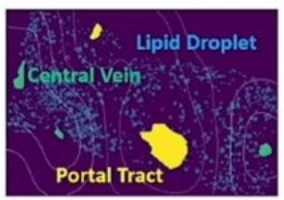
1. ASH subjects (n=11)
2. NASH controls (n=10)

Manual Annotation of Central Vein, Portal Tract and Lipid Droplets

Training the machine learning algorithm

Precise lipid droplet data:
1. Location
2. Size

A



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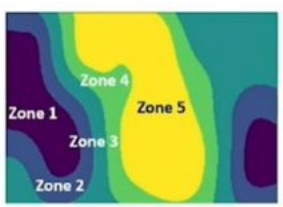

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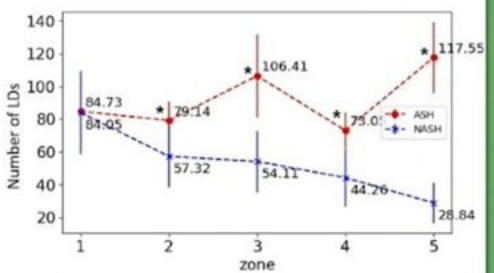

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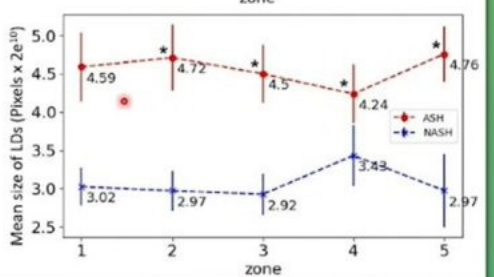

TLM dX

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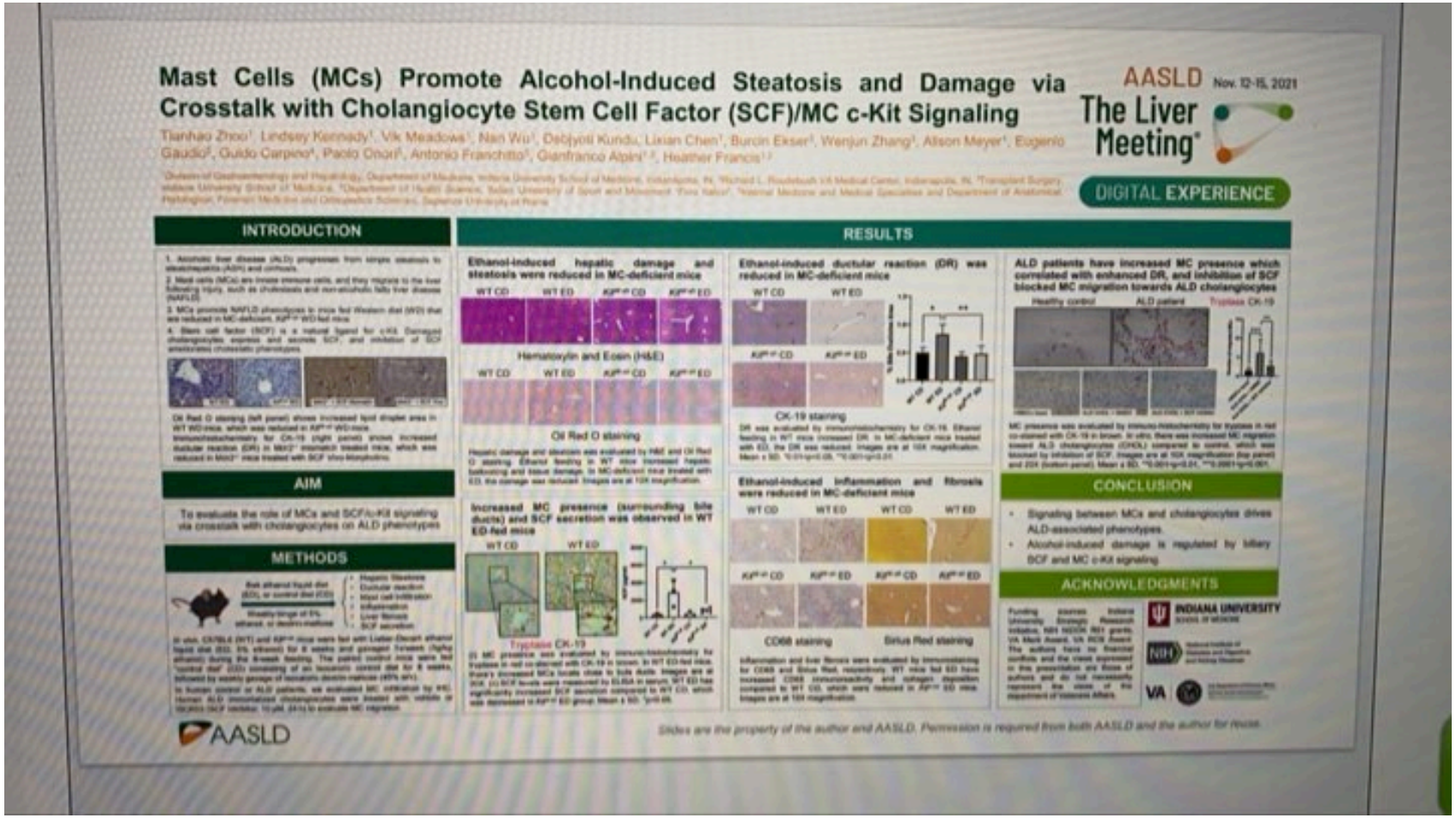
Mast cells and fatty change in alcoholics



Mast Cells (MCs) Promote Alcohol-Induced Steatosis and Damage via Crosstalk with Cholangiocyte Stem Cell Factor (SCF)/MC c-Kit Signaling

AASLD Nov. 12-15, 2021
The Liver Meeting
DIGITAL EXPERIENCE

Tianhao Zhou, Lindsey Kennedy, Vik Meadows, Nan Wu, Debjyoti Kundu, Lixian Chen, Burcin Ekser, Wenjun Zhang, Alison Meyer, Eugenio Gaudio, Guido Carpino, Paolo Onori, Antonio Franchitto, Gianfranco Alpini, Heather Francis

INTRODUCTION

AIM

To evaluate the role of MCs and SCF/c-Kit signaling via crosstalk with cholangiocytes on ALD phenotypes

METHODS

RESULTS

Ethanol-induced hepatic damage and steatosis were reduced in MC-deficient mice

Hematoxylin and Eosin (H&E)

Oil Red O staining

Ethanol-induced ductular reaction (DR) was reduced in MC-deficient mice

CK-19 staining

Increased MC presence (surrounding bile ducts) and SCF secretion was observed in WT ED-fed mice

Tryptase CK-19

Ethanol-induced inflammation and fibrosis were reduced in MC-deficient mice

CD68 staining

Sirius Red staining

ALD patients have increased MC presence which correlated with enhanced DR, and inhibition of SCF blocked MC migration towards ALD cholangiocytes

Healthy control

ALD patient

Tryptase CK-19

CONCLUSION

- Signaling between MCs and cholangiocytes drives ALD-associated phenotypes.
- Alcohol-induced damage is regulated by biliary SCF and MC c-Kit signaling.

ACKNOWLEDGMENTS

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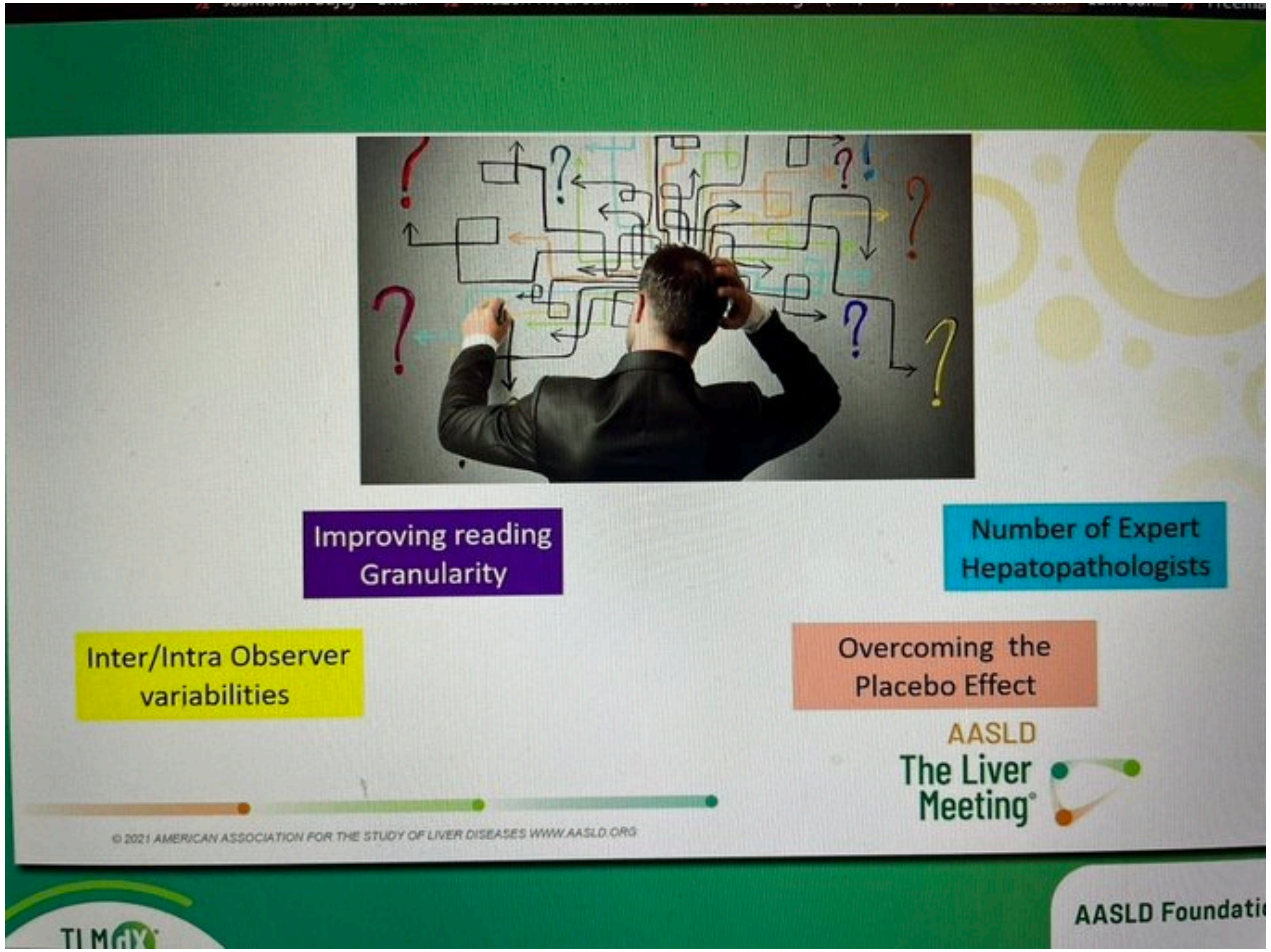
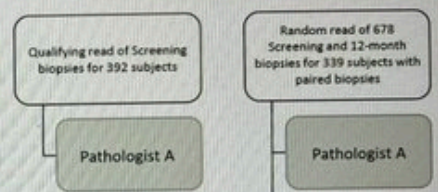
Pathology in clinical trials of NASH



Suboptimal Reliability of Liver Biopsy In Identifying Fibrotic NASH for RCTs

- 339 patients had paired biopsies from the EMMINENCE study (MSDC-0602K).
- Pathologist A's scores for the screening biopsies were systematically lower when read mixed randomly among follow-up biopsies → low intra-reader kappa coefficient.
- Study histologic eligibility criteria were met for 77% (A re-read), 69% (B), and 77.3% (C) → low inter-reader kappa.
- All 3 pathologists agreed on eligibility criteria in only 53.7% → 46.3% of patients did not meet histologic inclusion criteria by at least 1 of the 3 pathologists.



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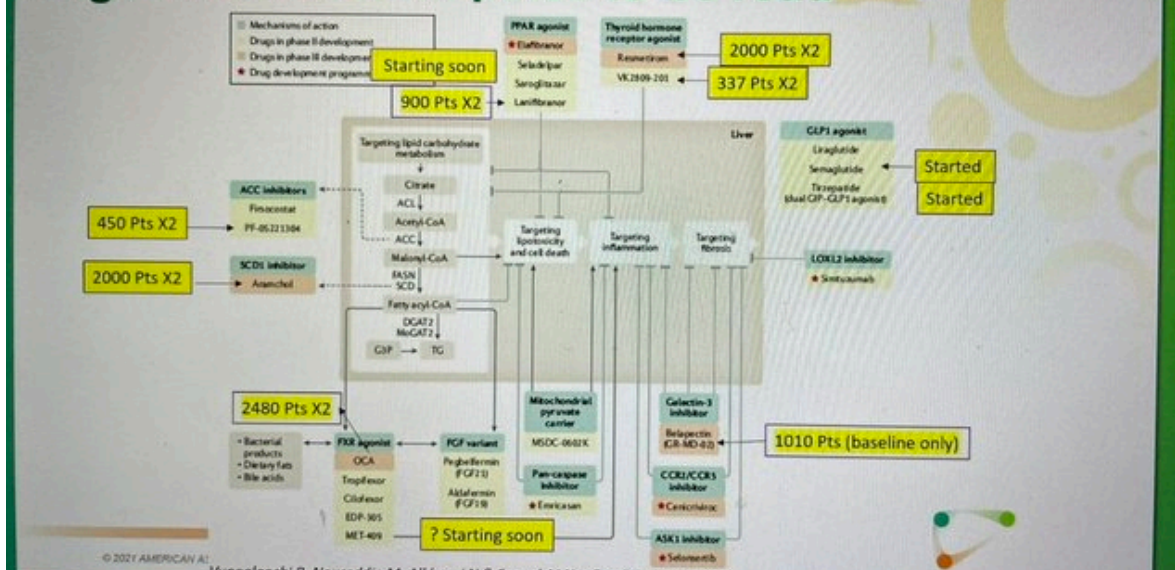
Davison BA, et al. J Hepatol. 2020.

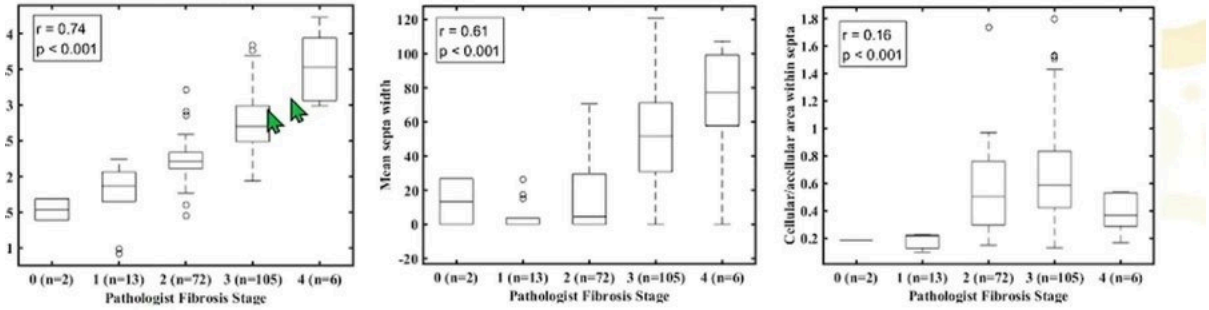
Huge number of biopsies to be read



Vuppalanchi R, Noureddin M, Alkhouri N & Sanyal AJ Nat Rev Gastro Hep 2021

qFibr*osis*

Concordance of these parameters with NASH-CRN



qFibrosis is NASH-CRN based AI, correlates well with NASH-CRN

Septa width is only applicable in mid-late stage fibrosis where septa are observed

Cellular/acellular feature only applicable in mid stage fibrosis as septa are typically very thin in late stage fibrosis

qFibrosis parameters such as StrLengthPTAgg, #IntersectionPT also show the same trend in tracking fibrosis changes by NASH-CRN

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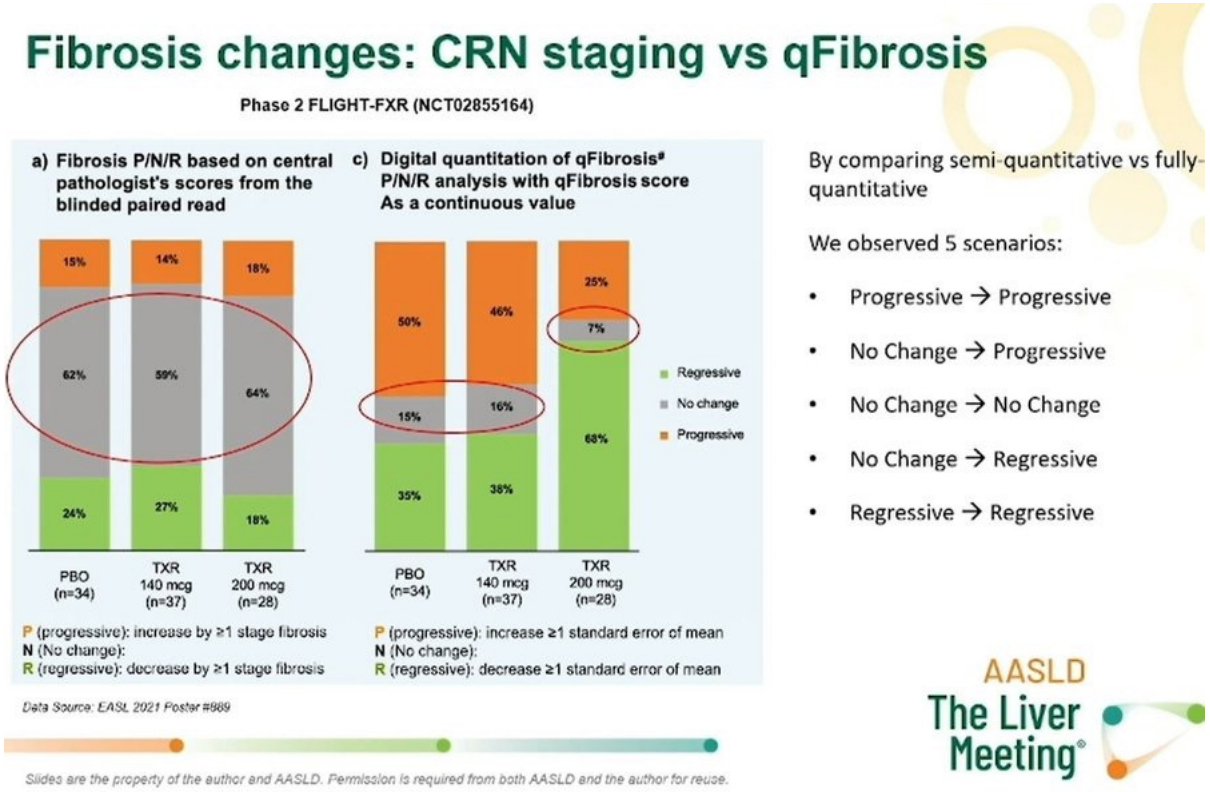

By comparing semi-quantitative vs fully-quantitative

We observed 5 scenarios:

- Progressive → Progressive
- No Change → Progressive
- No Change → No Change
- No Change → Regressive
- Regressive → Regressive

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Liver cancer

HCC in NAFLD

Summary of Results

- The cumulative incidence of HCC was **2.1%** among 47,165 NAFLD patients with mean 3.5 years of follow up
- **14.2%** of NAFLD-HCC patients had no diagnosis of cirrhosis
- The annual incidence rates of HCC in NAFLD patients was:
  - **2.36% with cirrhosis** and **0.11%, without cirrhosis**
  - NAFLD-cirrhosis patients were **32.7 times** (95% CI 24.1 – 44.4) more likely to develop HCC than those without cirrhosis and FIB-4 <1.30.
- Among NAFLD patients without cirrhosis, the annual incidence rates were:
  - **0.28% with FIB-4>2.67** and **0.07% with FIB-4 <1.30**
- Noncirrhotic NAFLD-HCC patients, compared with NAFLD without HCC, were more likely to have **lower** BMI, albumin, serum iron, and **higher** alkaline phosphatase and platelet count.

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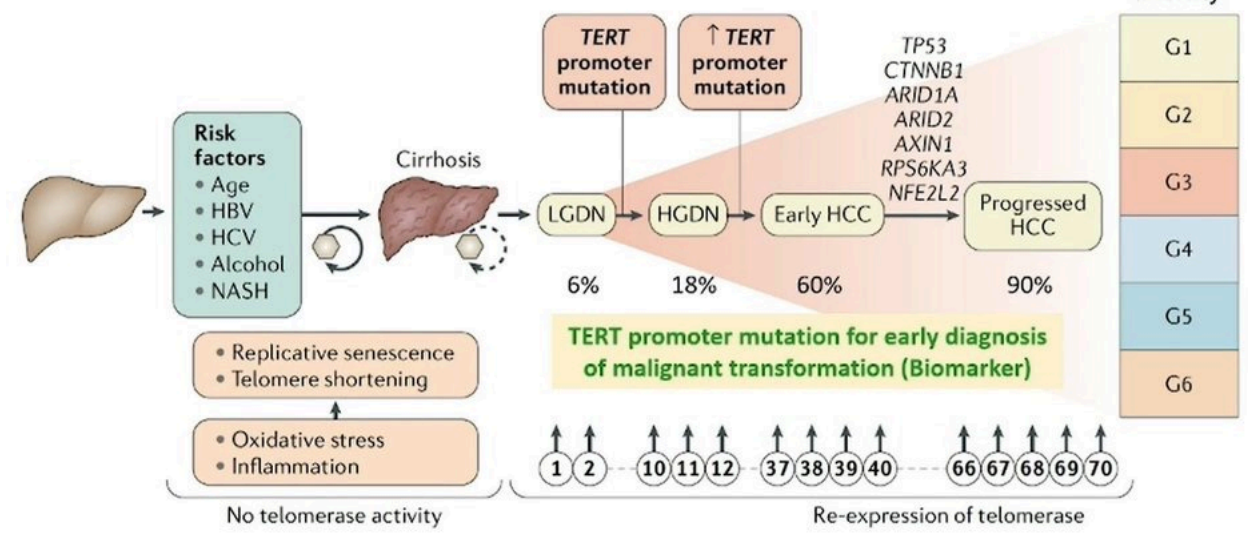
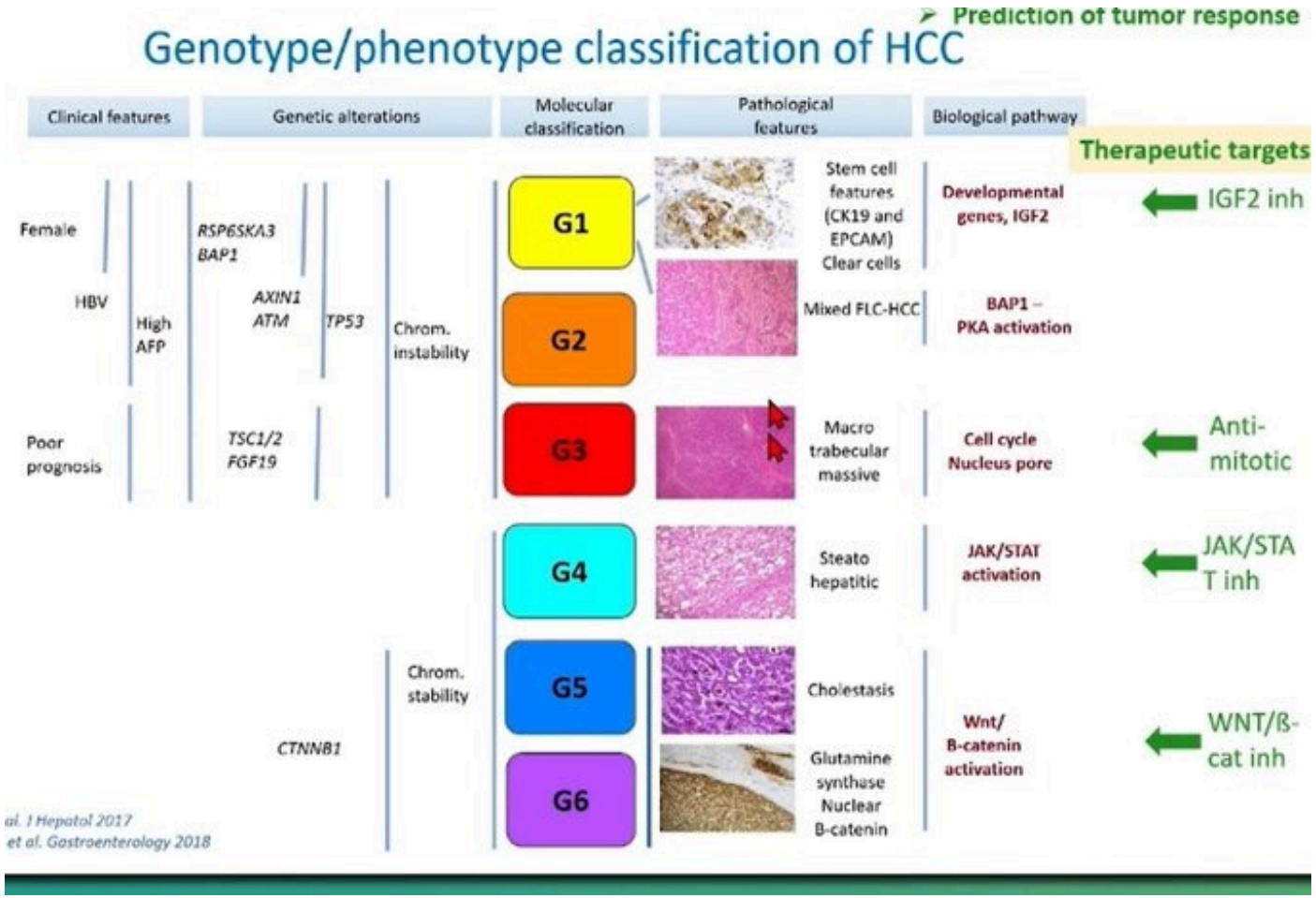
➢ Refine diagnosis

Telomerase reactivation the earliest recurrent genomic event in liver carcinogenesis



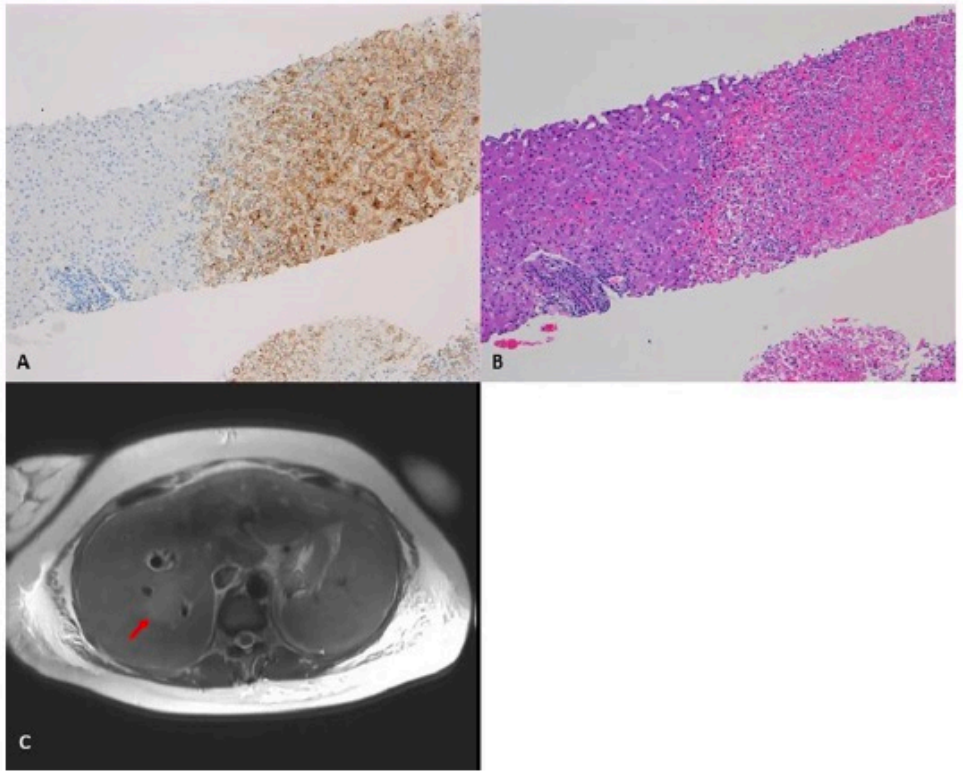
Nault et al, Nature Reviews Gastroenterology & Hepatology, 2019


Prediction of tumor response
Genotype/phenotype classification of HCC
Clinical features
Genetic alterations
Molecular classification
Pathological features
Biological pathway
Therapeutic targets
Female
HBV
High AFP
Poor prognosis
RSP6SKA3
BAP1
AXIN1
ATM
TP53
TSC1/2
FGF19
CTNNB1
Chrom. instability
Chrom. stability
G1
G2
G3
G4
G5
G6
Stem cell features (CK19 and EPCAM) Clear cells
Mixed FLC-HCC
Macro trabecular massive
Steato hepatitic
Cholestasis
Glutamine synthase Nuclear B-catenin
Developmental genes, IGF2
BAP1 – PKA activation
Cell cycle Nucleus pore
JAK/STAT activation
Wnt/ B-catenin activation
IGF2 inh
Anti-mitotic
JAK/STAT inh
WNT/ß-cat inh
al. J Hepatol 2017
et al. Gastroenterology 2018

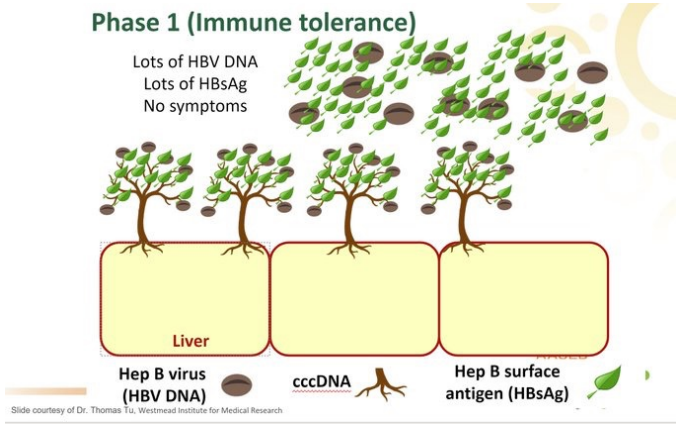
Infectious diseases

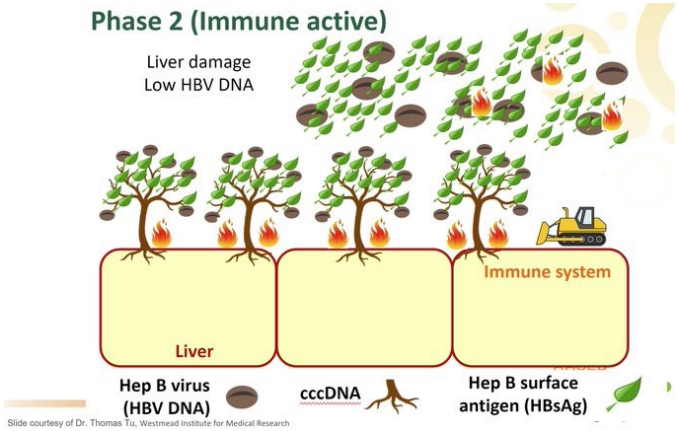
689 DISSEMINATED HERPES SIMPLEX VIRUS PRESENTING INSIDIOUSLY AS ACUTE HEPATITIS IN PREGNANCY

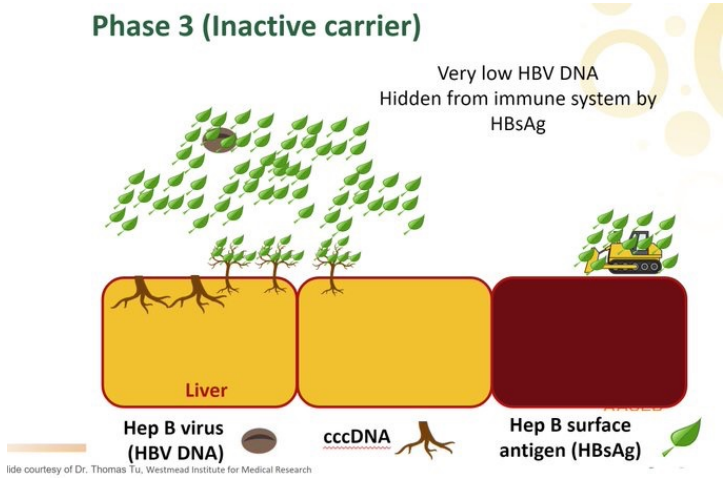
HSV shows a non-zonal necrosis pattern and typical HSV viral inclusions.

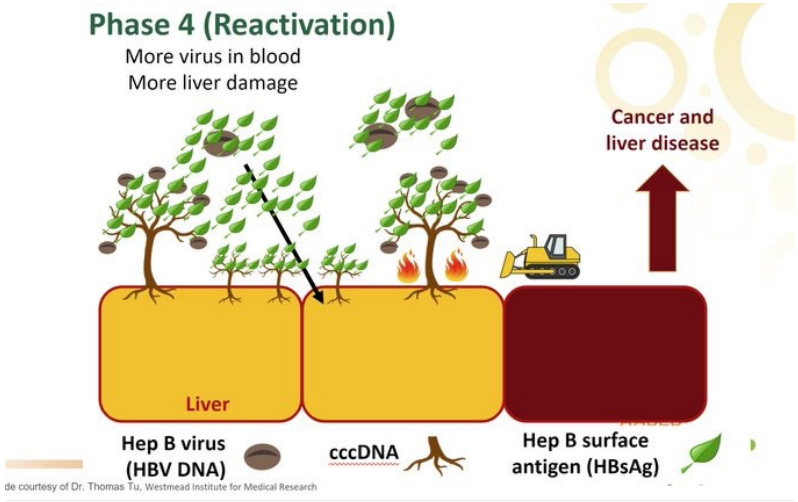


Natural History of HBV Infection









Covid 1

Impact of COVID-19 on the liver

- Increased ALT, AST (AST>ALT), alk phos, GGT – most resolve
- Elevations in liver tests associated with more severe disease – most but not in all studies
- ALI and ALF with COVID19 alone is rare
- Problems from delays in care – HCC surveillance or treatment, antiviral therapy, impact on liver transplant candidacy and transplant
- Cholangiopathy may occur in those with severe COVID19 disease, usually after recovery from initial infection

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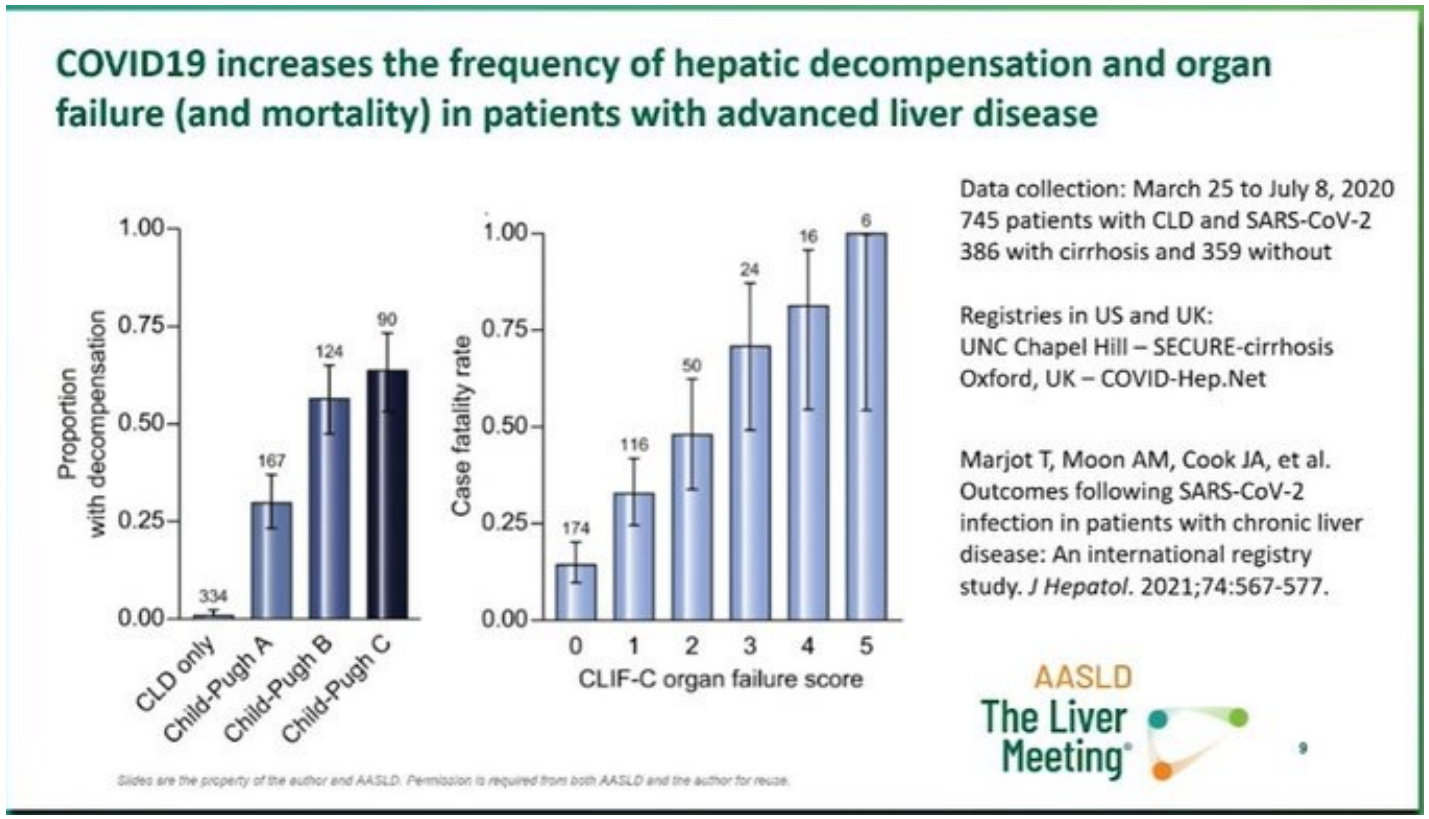
Obese patients with NASH have increased hepatic expression of SARS-CoV-2 critical entry points

- In summary, our results indicate that in the livers of obese patients, SARS-CoV-2 entry factors are differently affected by T2D and NAFLD. While obese women with T2D have unexpectedly lower levels of *ACE2* and *TMPRSS2* than obese normoglycemic women, obese patients with NASH show markedly higher expression of these genes, suggesting that advanced stages of NAFLD might predispose individuals to COVID-19.

Covid 2


COVID19 increases the frequency of hepatic decompensation and organ failure (and mortality) in patients with advanced liver disease
Proportion with decompensation
1.00
0.75
0.50
0.25
0.00
334
167
124
90
CLD only
Child-Pugh A
Child-Pugh B
Child-Pugh C
Case fatality rate
1.00
0.75
0.50
0.25
0.00
174
116
50
24
16
6
0
1
2
3
4
5
CLIF-C organ failure score
Data collection: March 25 to July 8, 2020
745 patients with CLD and SARS-CoV-2
386 with cirrhosis and 359 without
Registries in US and UK:
UNC Chapel Hill – SECURE-cirrhosis
Oxford, UK – COVID-Hep.Net
Marjot T, Moon AM, Cook JA, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. J Hepatol. 2021;74:567-577.
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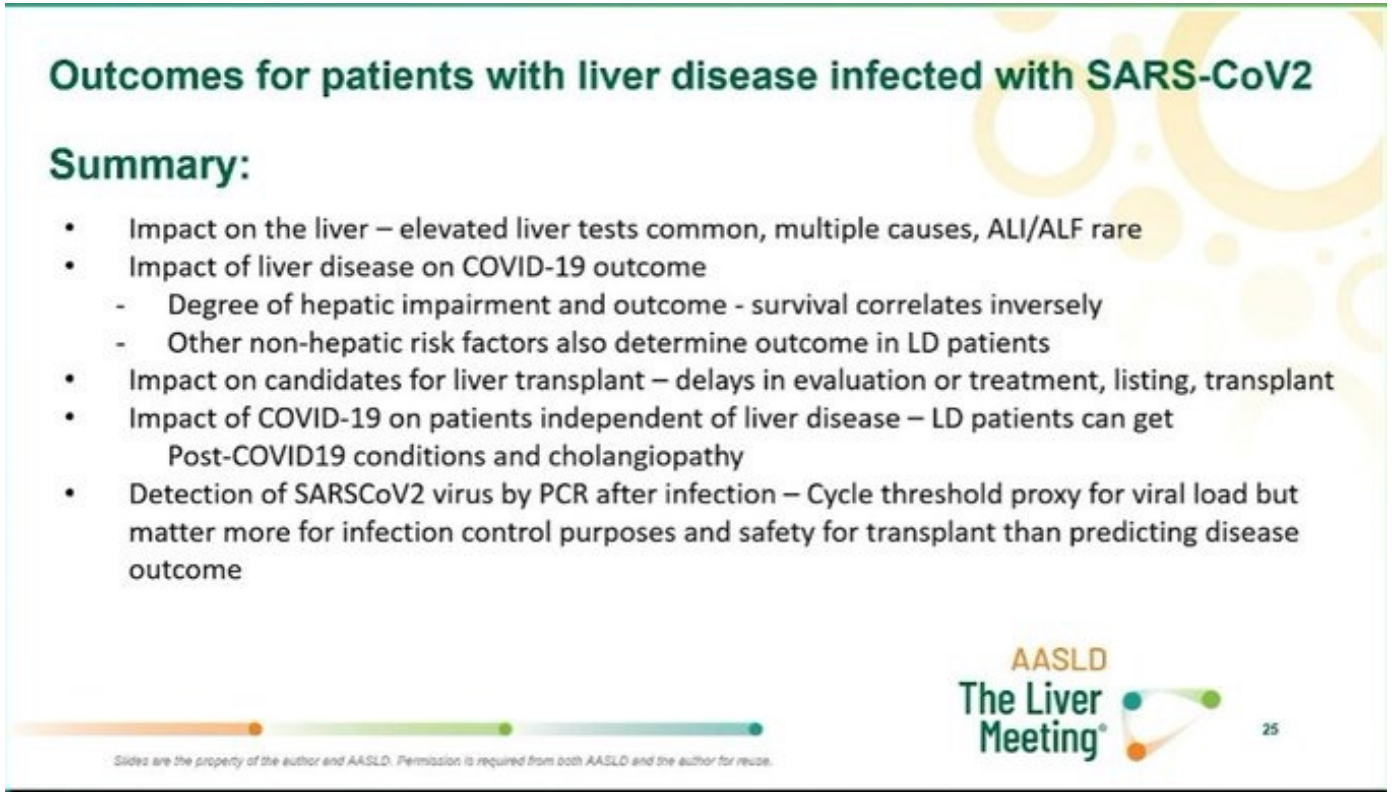
Covid 4


Outcomes for patients with liver disease infected with SARS-CoV2
Summary:
• Impact on the liver – elevated liver tests common, multiple causes, ALI/ALF rare
• Impact of liver disease on COVID-19 outcome
- Degree of hepatic impairment and outcome - survival correlates inversely
- Other non-hepatic risk factors also determine outcome in LD patients
• Impact on candidates for liver transplant – delays in evaluation or treatment, listing, transplant
• Impact of COVID-19 on patients independent of liver disease – LD patients can get Post-COVID19 conditions and cholangiopathy
• Detection of SARSCoV2 virus by PCR after infection – Cycle threshold proxy for viral load but matter more for infection control purposes and safety for transplant than predicting disease outcome
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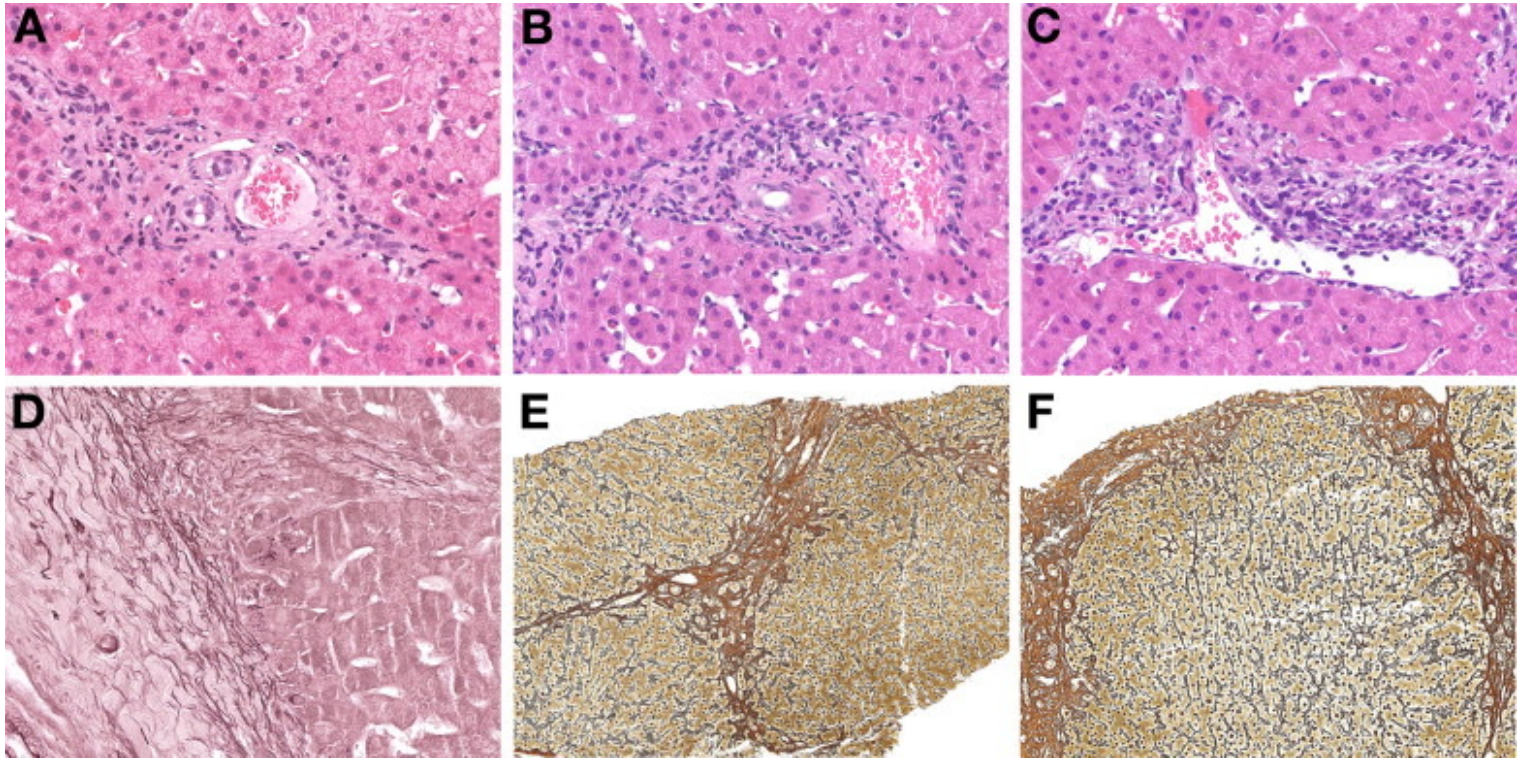
536 KETAMINE IS A RISK FACTOR FOR JAUNDICE IN COVID-19 PATIENTS

- The guidelines for maintenance sedation of patients with ARDS include ketamine as a second-line agent.
- was associated with jaundice in this cohort.
- The relationship between ketamine and Covid-19 cholangitis should be investigated.

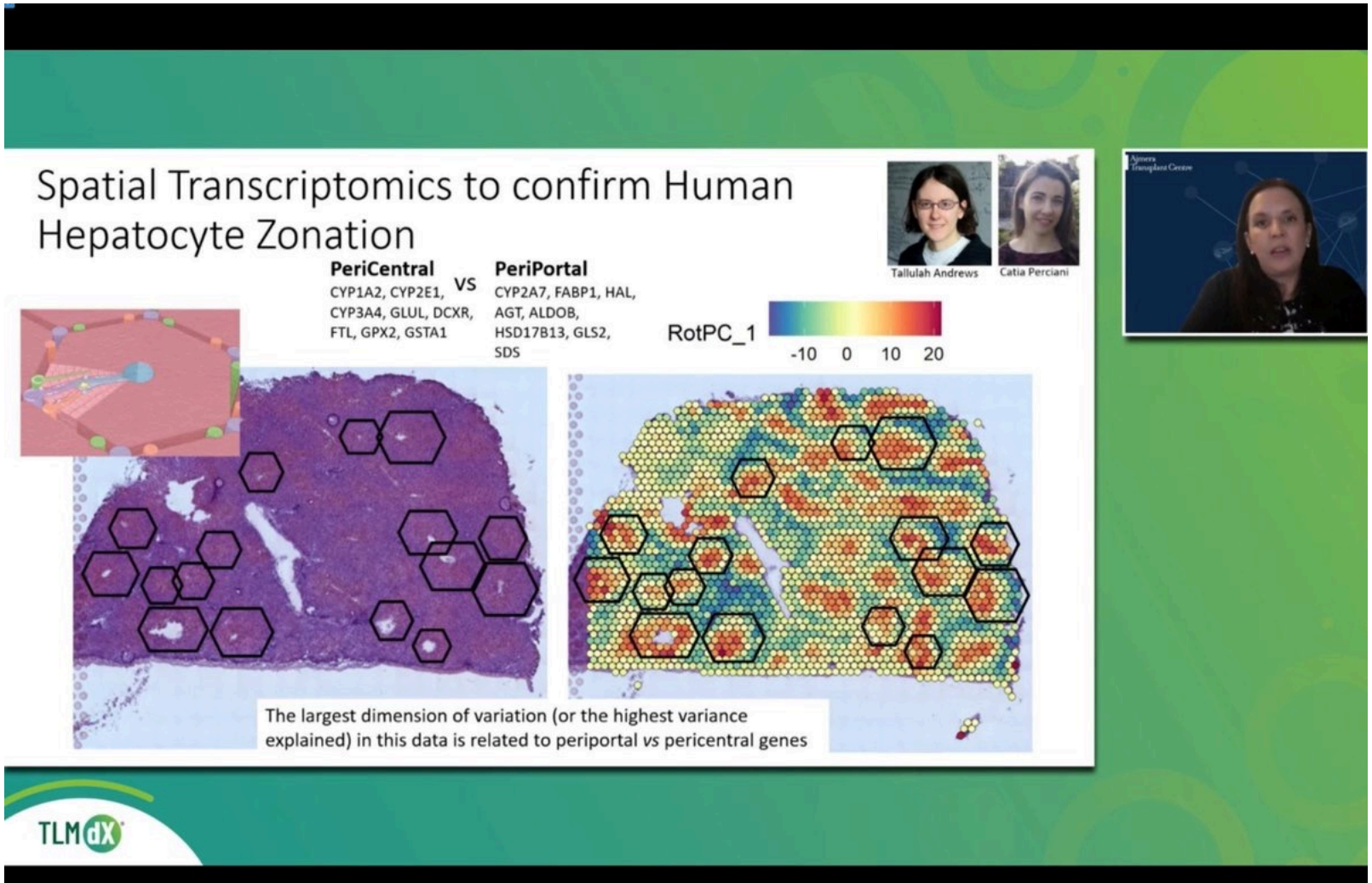
Intravenous ketamine and progressive cholangiopathy in COVID-19 patients. J Hepatol. 2021;74(5):1243-4. .

Katamine induced bile duct damage

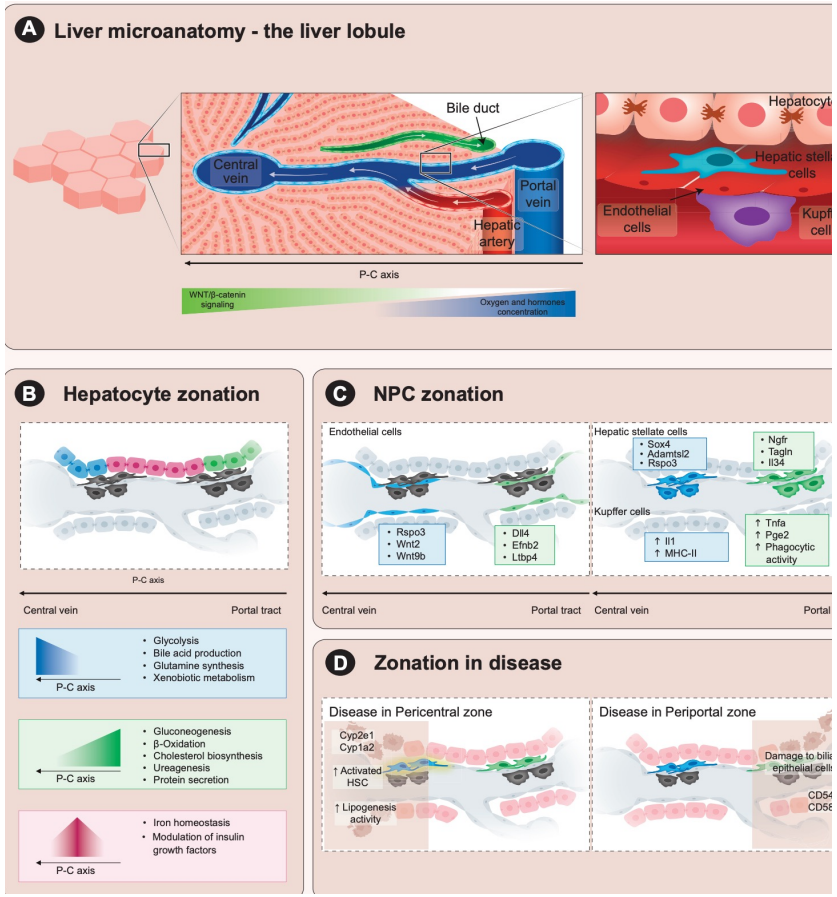


Basic Science

Spatial Transcriptomics and Liver Zonation

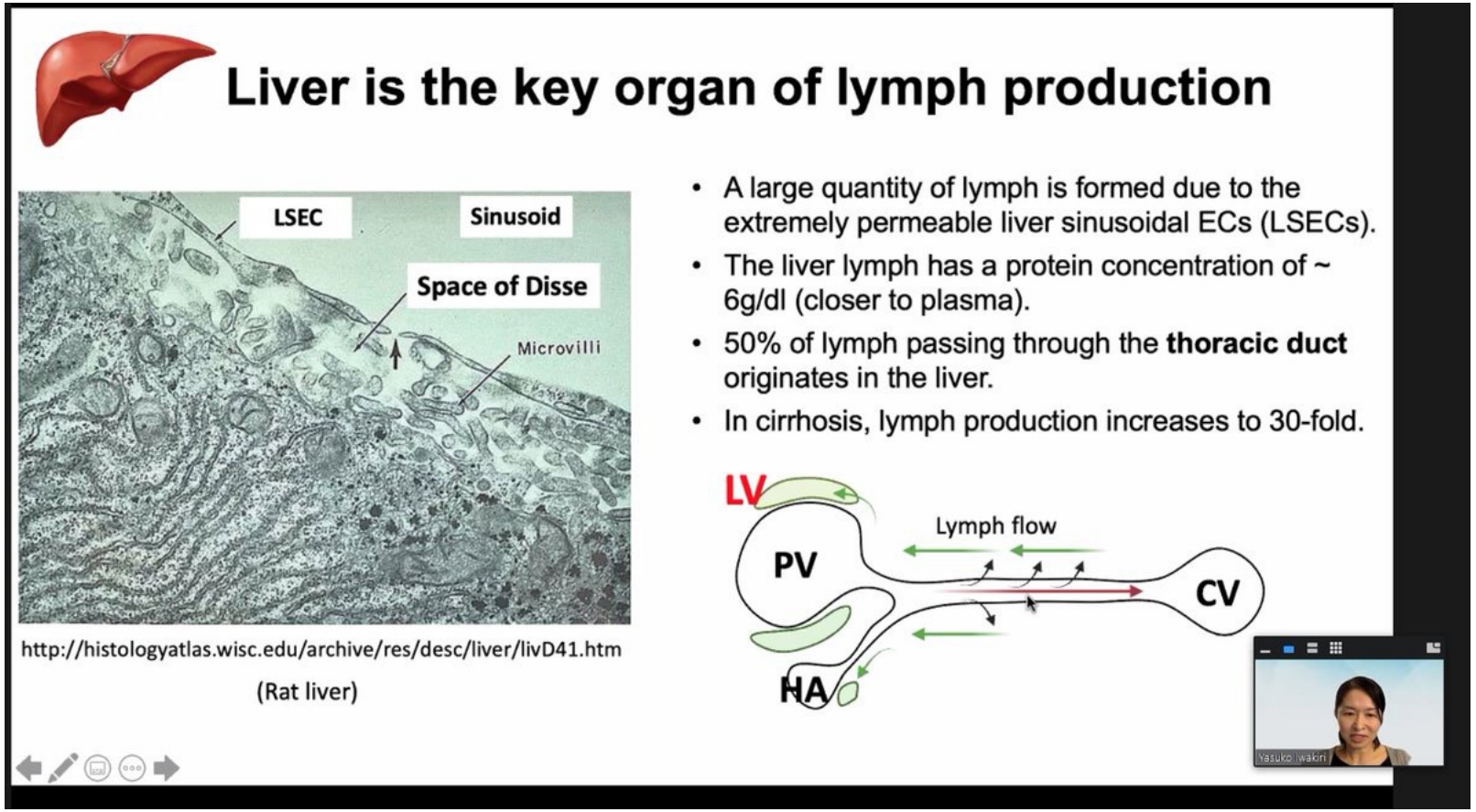


The molecular and histopathologic variability across liver zonation in patients with alcohol-related liver disease

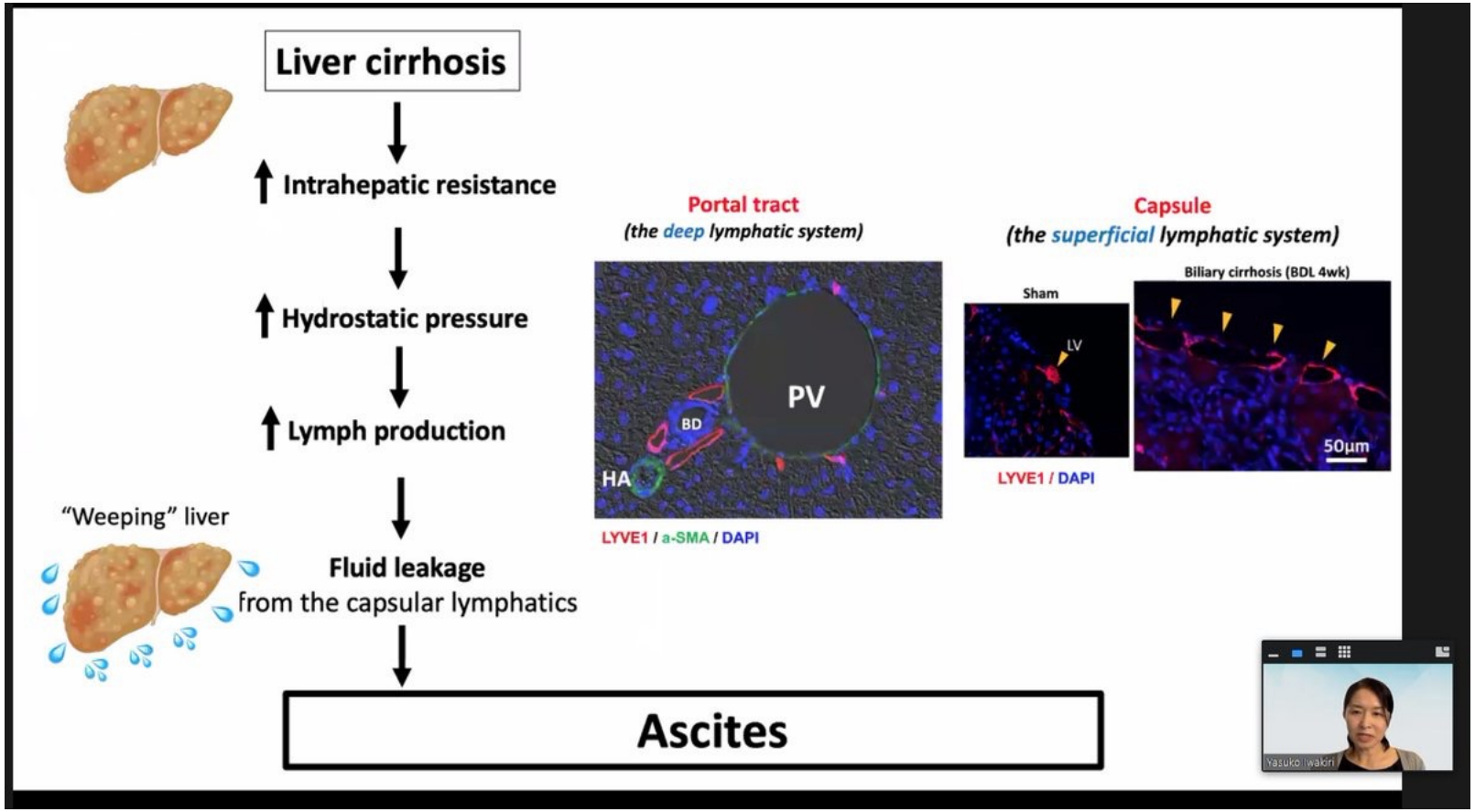


https://doi.org/10.1016/j.jhep.2020.09.003

Liver lymphatics



Liver lymphatics



566 GENOMIC ANALYSIS ENHANCES CLINICAL CARE OF ADULTS WITH UNEXPLAINED LIVER DISEASE

- Whole exome sequencing on 46 patients with unexplained liver disease despite comprehensive workup.
- Found diagnoses in 22% (including JAG1, ABCB4, ABCB11, LIPE, SMAD4)!
- More likely to find if <40years and with extrahepatic manifestations.
- Resulted in management management change in 60%.

Tertiary Lymphoid Tissue

Tertiary Lymphoid Tissue

- Tertiary lymphoid tissues are a normal component of the healthy lung tissue of certain species like rabbits, but they are not a constitutive feature of the healthy human or mouse lungs.
- In humans, they are inducible ectopic lymphoid tissues that develop at sites of chronic inflammation, autoimmune disease, cancer or an allograft.
- As with lymph nodes, they initiate adaptive immune responses and coordinate local tissue immunity.

Tertary Lymphoid Tissue

Tertiary lymphoid organs share many features with secondary lymphoid organs, such as the presence of T and B cell compartmentalization into:

- T cell zones and B cell follicles,
- chemokines that mediate the compartmentalization,
- antigen-presenting cells,
- lymphatic sinuses
- high endothelial venules
- follicular dendritic cells and
- fibroblastic reticular cells

Tertiary Lymphoid Structures

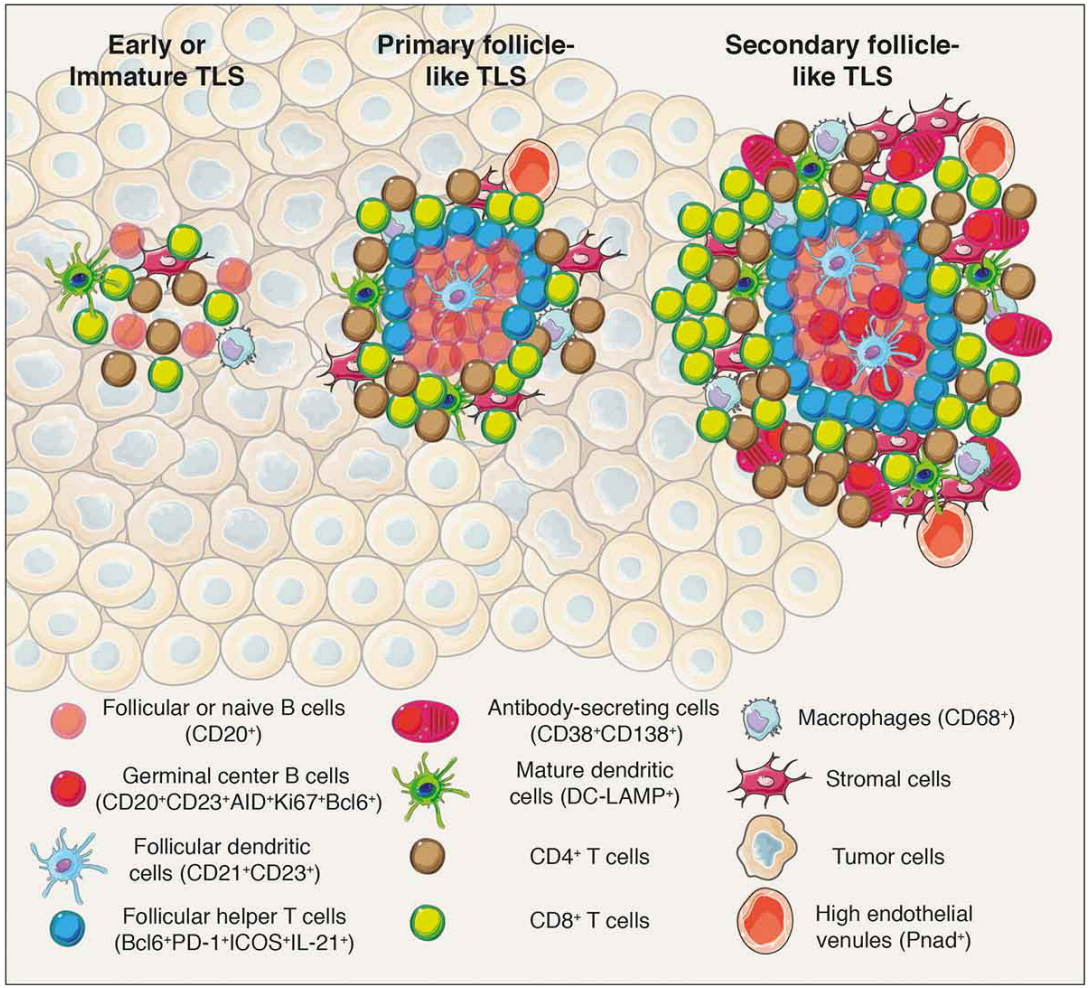
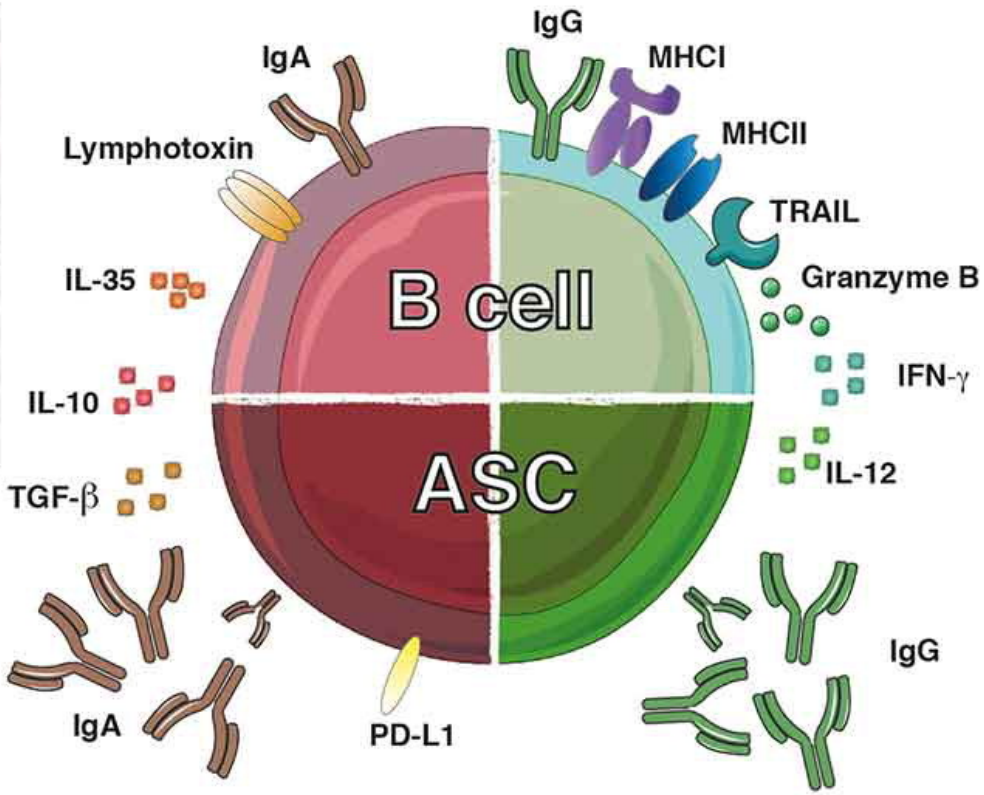


Figure 2

Effects of Tertiary Lymphoid Follicles on Tumours

Pro-tumoral effects

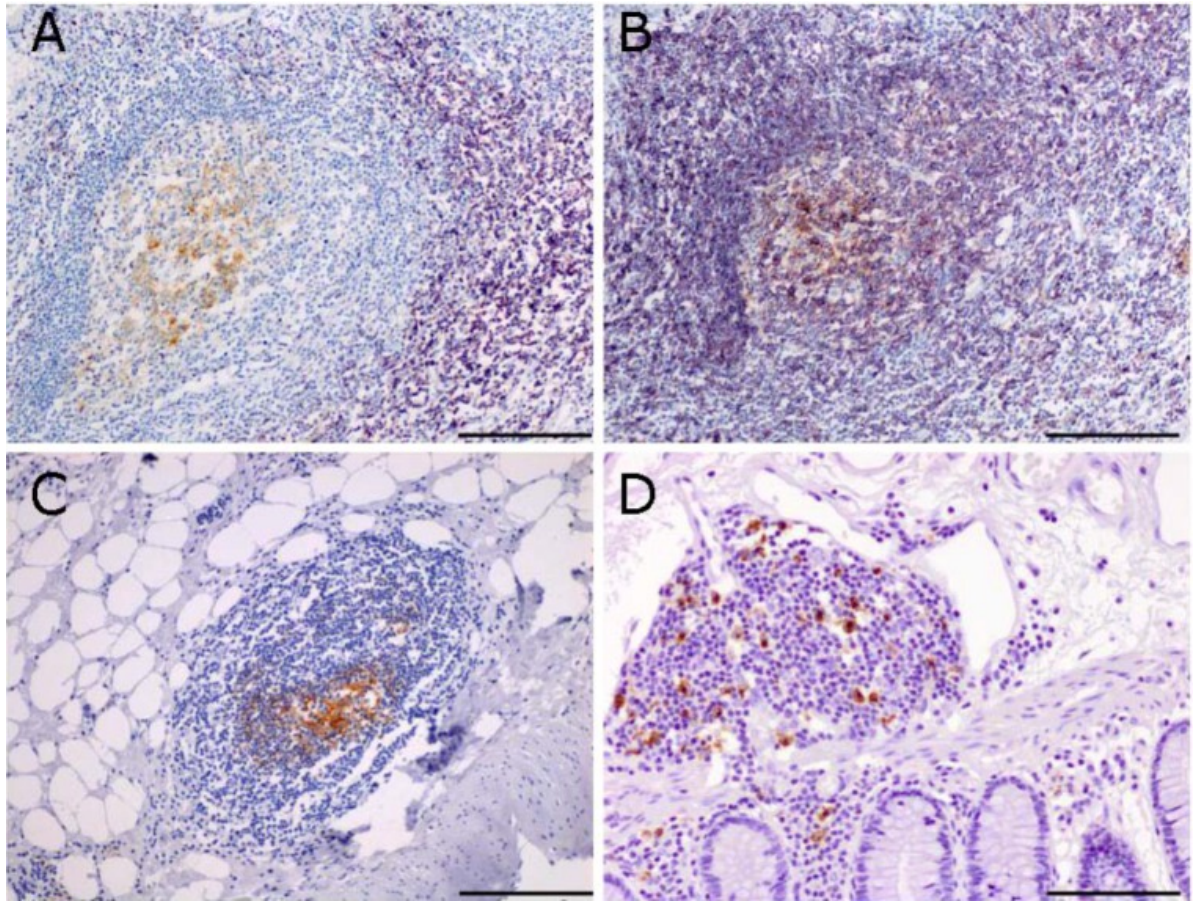
~ IL-10, TGF-β: suppressive cell differentiation (Treg, M2 macrophage, MDSC)
~ IL-10, IL-35, PD-L1: CTL inhibition
~ Lymphotoxin: tumor survival



Anti-tumoral effects

~ MHC I & II: antigen presentation
~ TRAIL, Granzyme B: cytotoxicity
~ IFN-γ, IL-12: effector cell differentiation and maturation (Th1, CTL, NK, M1 macrophage)
~ IgG1 secretion & binding to FcγR:
* ADCC
* phagocytosis
* antigen uptake
* complement cytotoxicity

Tertiary lymphoid follicles: Immunohistochemistry



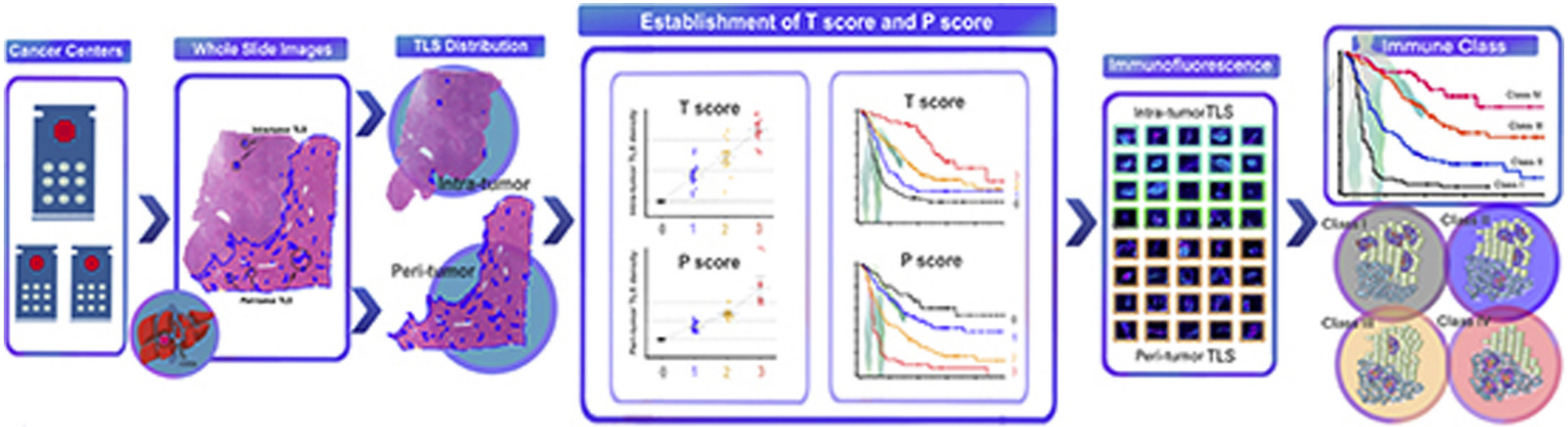
T cells (purple, A) and CD20+ B cells (purple, B) surround CD21+ follicular dendritic cells (brown, A–C).
Mature dendritic cells are also present, as evidenced by DC-LAMP staining (D).

Distribution and density of tertiary lymphoid structures predict clinical outcome in intrahepatic cholangiocarcinoma

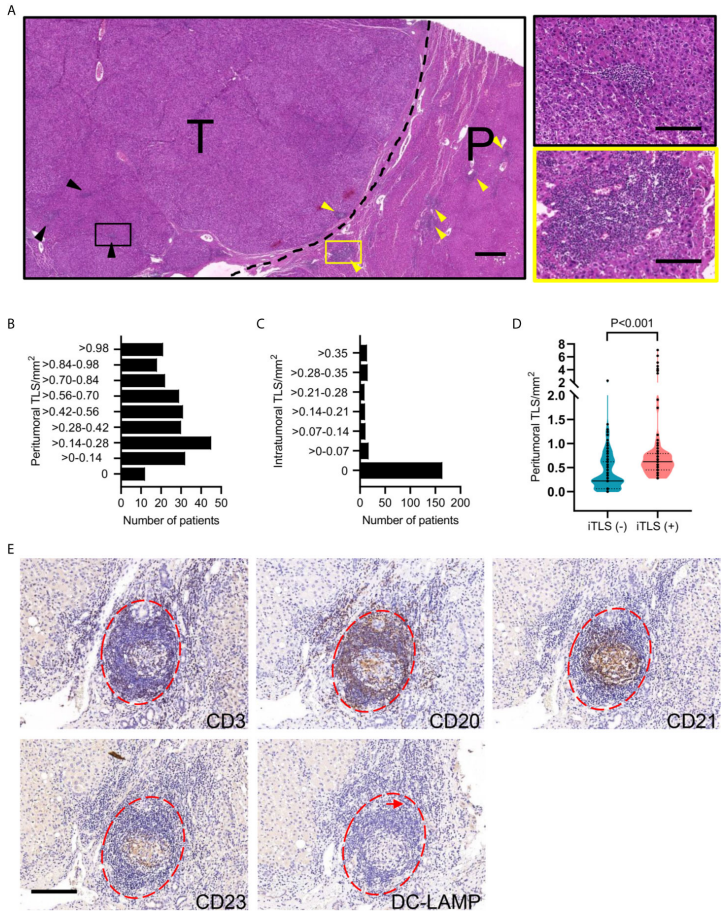
1.Tertiary lymphoid structures within (better) and outside (worse) tumour region have opposite prognostic impacts on patients with intrahepatic cholangiocarcinoma

2.The heterogeneous distribution of Tfh and Treg cells within distinct Tertiary Lymphoid Structures might be determinant of their functional state.

The geographic integration of TLSs stratified intrahepatic cholangiocarcinomas into four immune subclasses with distinct clinical outcomes.

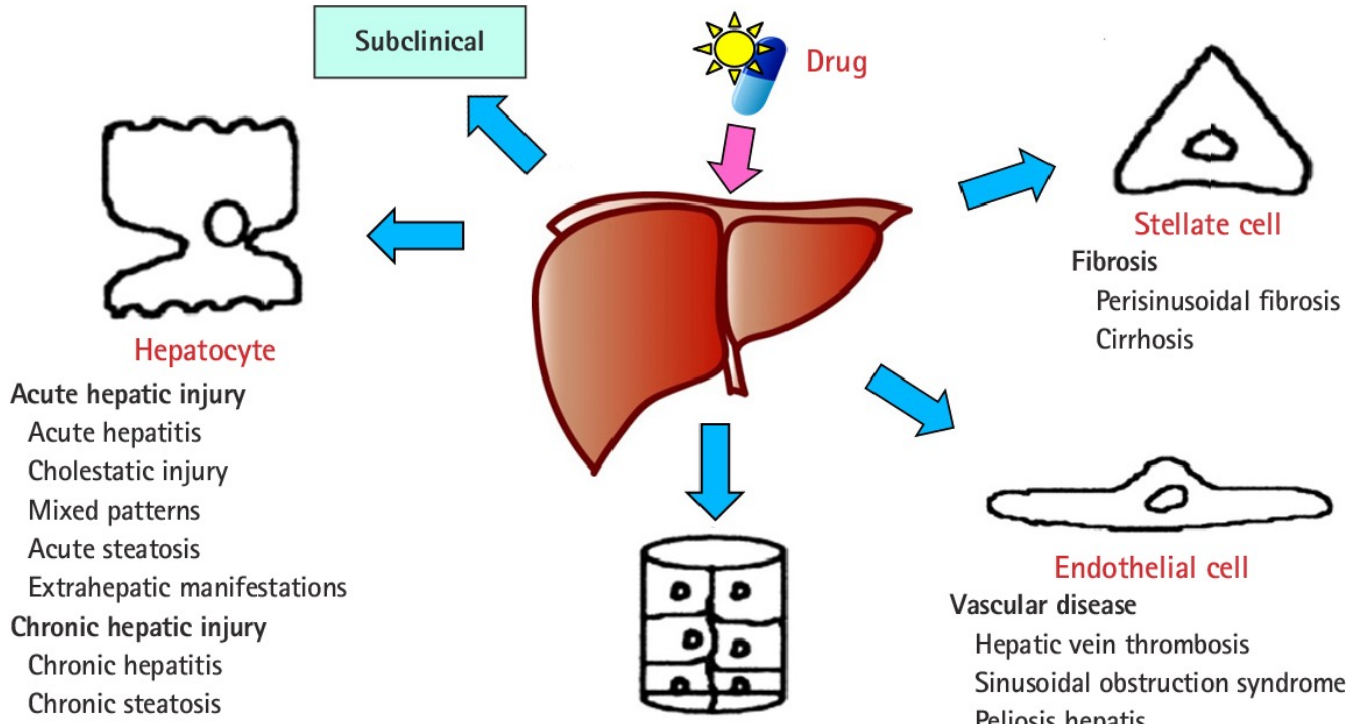


Peritumoral Tertiary Lymphoid Structures Correlate With Protective Immunity and Improved Prognosis in Patients With Hepatocellular Carcinoma



https://doi.org/10.3389/fimmu.2021.648812

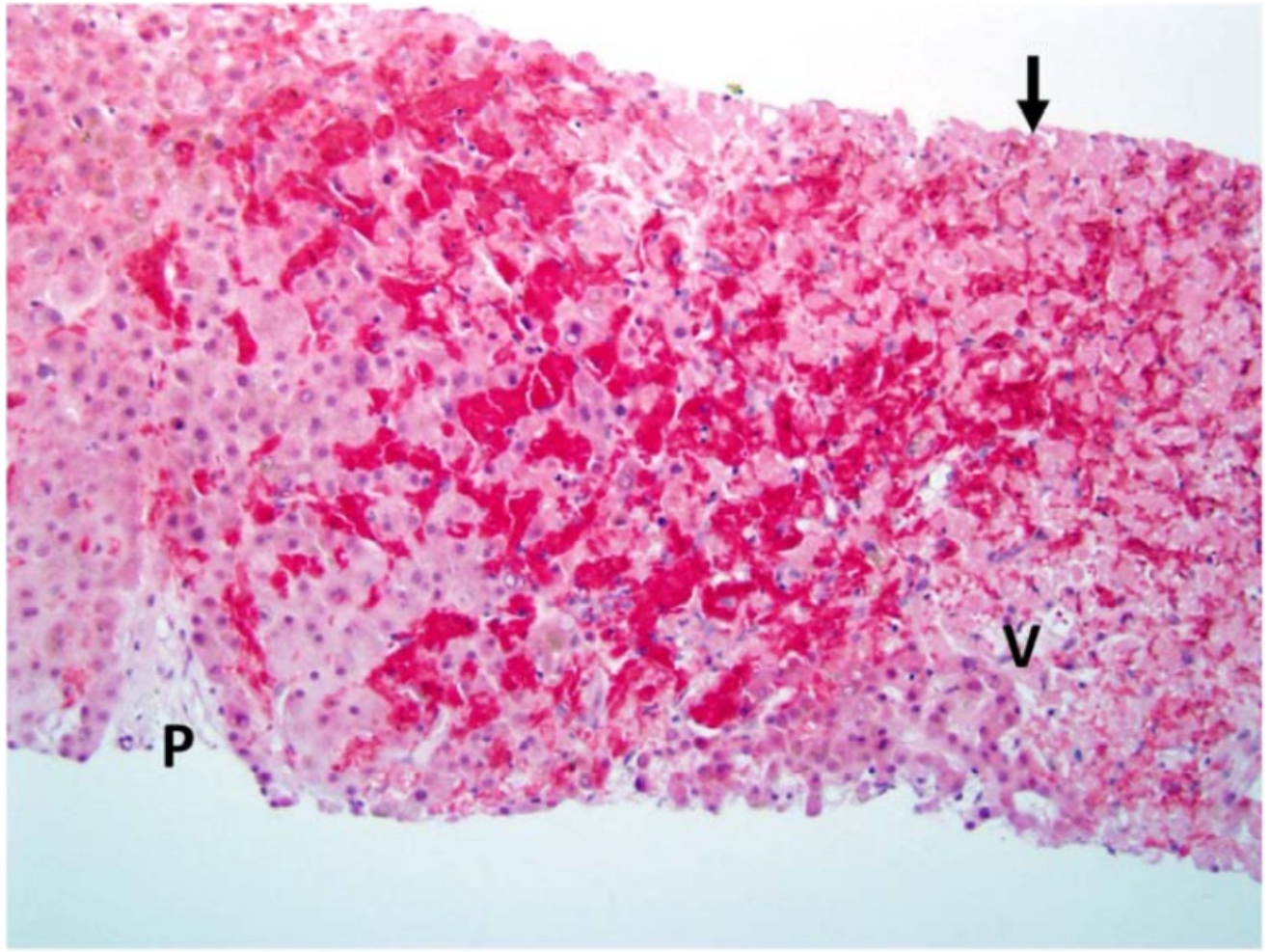
Drug-induced Vascular Diseqse



Drug-induced Vascular Disease

- Drug-induced vascular injury can affect different vascular structures of the liver, from the sinusoids to the large hepatic veins and hence.
- These include sinusoidal obstruction syndrome, nodular regenerative hyperplasia and peliosis hepatis.
- Budd-Chiari Syndrome, associated, with the contraceptive pill is now rare

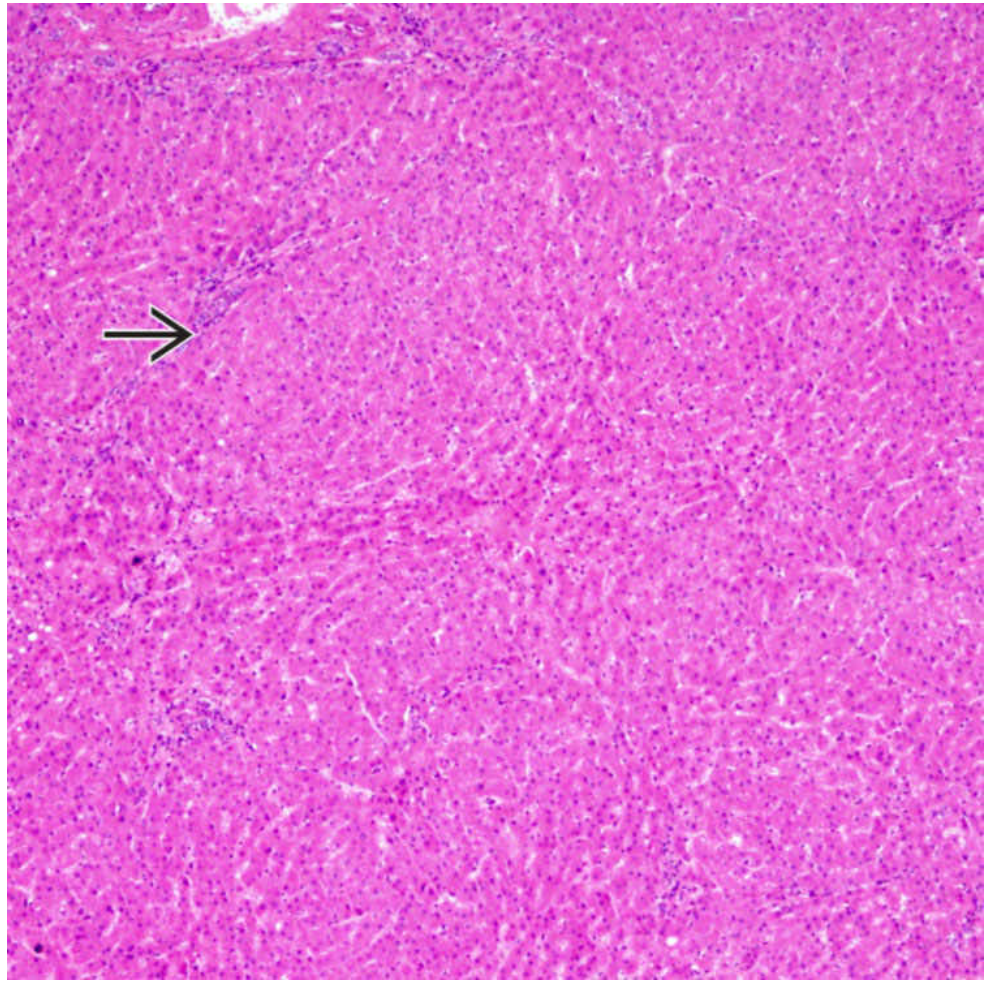
Sinusoidal obstruction syndrome (veno-occulsive

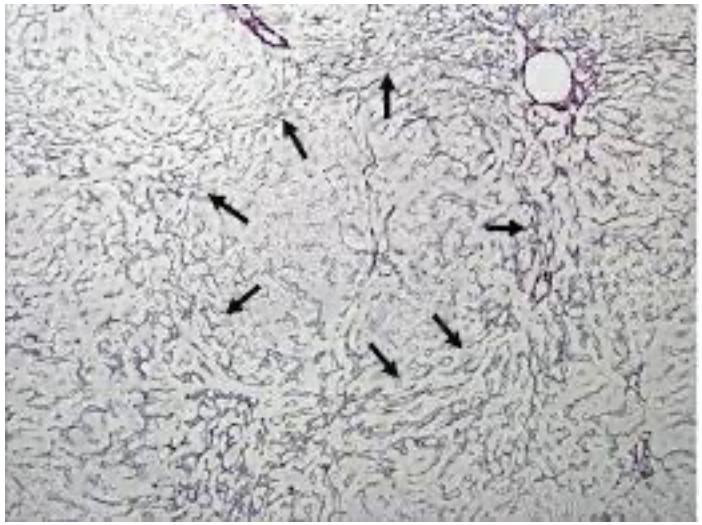


- Sinusoidal obstruction syndrome has also been reported as a complication of the cyclophosphamide-containing myeloablative regimens used in preparation for bone marrow transplantation[
- A number of other drugs have been associated with SOS including long-term use of thiopurines, such as azathioprine, mercaptopurine and thioguanine, dacarbazine, and gemtuzumab.
- However, in the subacute and chronic forms of SOS secondary to prolonged intake of herbal teas (containing pyrrolidizidine alkaloids) or long-term use of thioguanines, progressive fibrosis and cirrhosis may ensue

- Ninety percent of patients receiving oxaliplatin-based therapy developed parenchymal heterogeneity on abdominal CT scans, which was absent pre-treatment and was used as a surrogate of vascular changes.
- These changes were reversed in 68% of patients in 1 year, but imaging findings of portal hypertension persisted and progressed until the last follow-up in 1.4% of patients
- In a retrospective analysis of resected liver specimens from patients in 2 prospective non-randomised trials (5-fluorouracil/oxaliplatin ± bevacizumab) it was evident that bevacizumab protected against the development of SOS via an unknown mechanism.

Nodular regenerative hyperplasia





Nodular Regenerative Hyperplasia

- azathioprine (as a result of active metabolite 6-thioguanine)
- oxaliplatin, and
- chlorambucil

Various non–drug-related disease states

Peliois (Bacillary Peliosis)