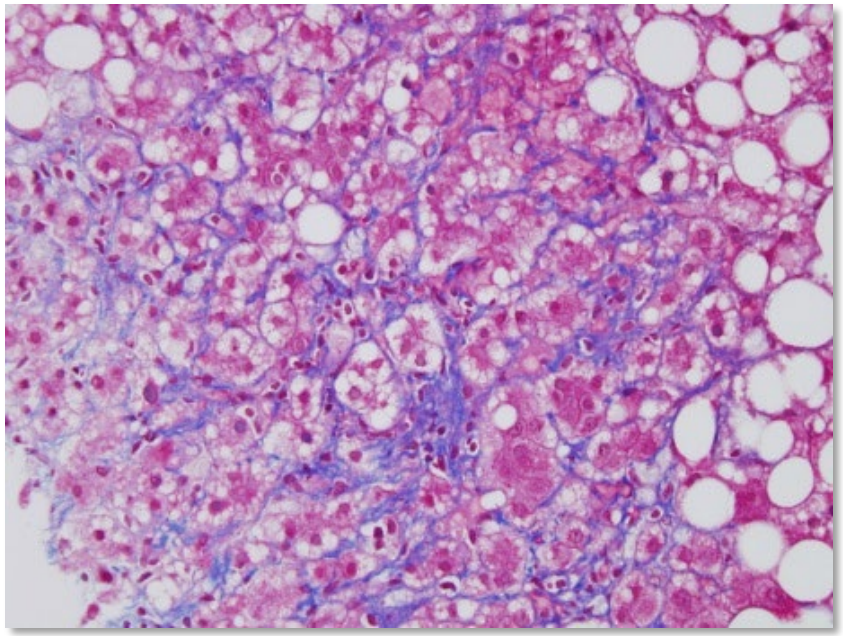
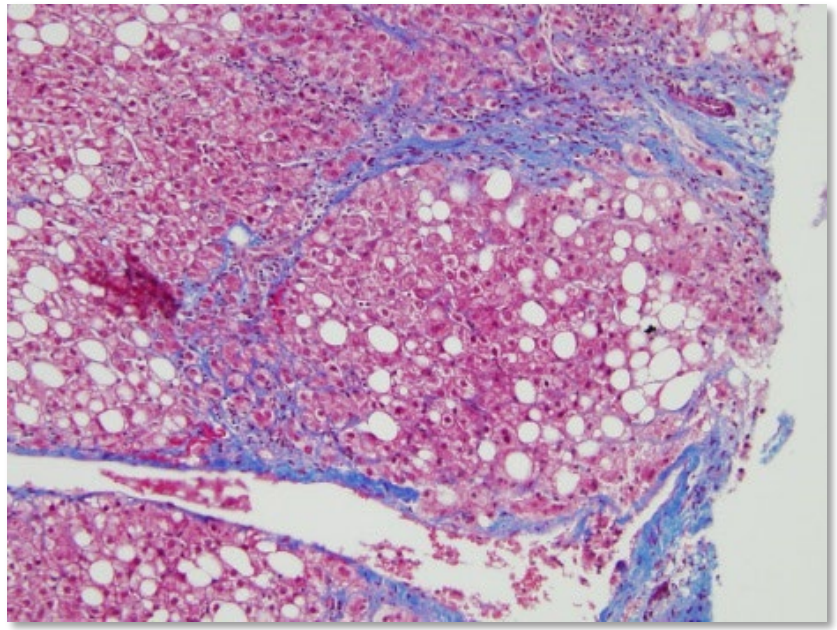
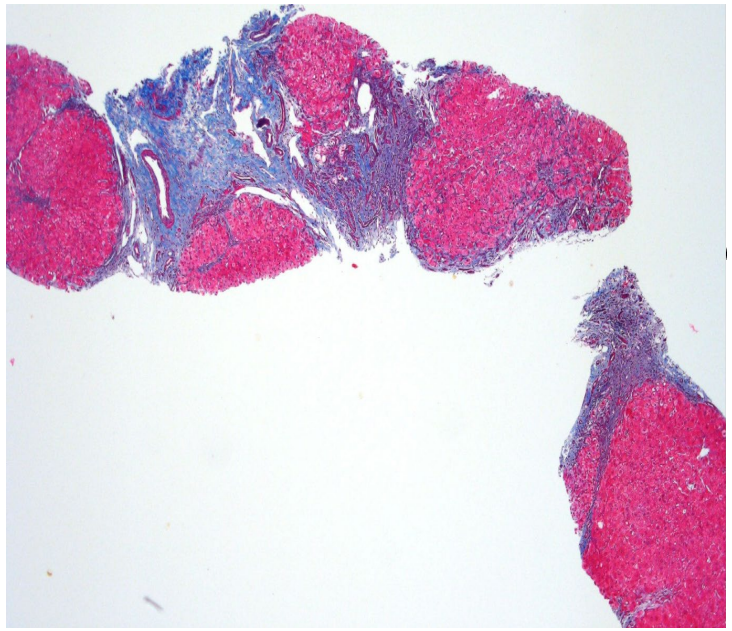
NASH cirrhosis- the challenges of diagnosis, prognosis and treatment







Arun J. Sanyal MBBS, MD

Z Reno Vlahcevic Professor of Medicine

Director, The Stravitz-Sanyal Institute for Liver Disease and Metabolic Health

Virginia Commonwealth University School of Medicine

Richmond, VA

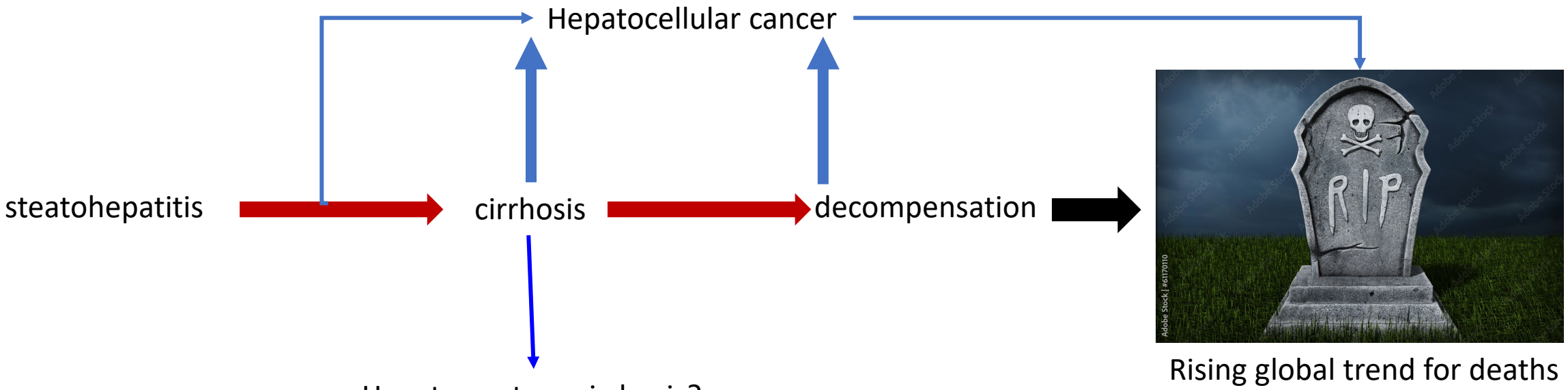
Disclosures

[Arun J. Sanyal]

I disclose the following financial relationship(s) with a commercial interest:

- Ownership interests: Durect, Tiziana, Genfit, Exhalenz
- Consultant: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Merck, Pfizer, Boehringer Ingelhiem, Bristol Myers Squibb, Eli Lilly, Genentech, Amgen, Alnylam, Regeneron, Thera Technologies, Madrigal, Salix, Malinckrodt, Gatehouse, Rivus, Siemens, Lipocine, 89 Bio, Astra Zeneca, Akero, Foresite, Mitopower, Takeda, Ursobio, Histoindex, Path AI,
- Grant support to school: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Eli Lilly, Genentech, Boehringer Ingelhiem, Bristol Myers Squibb

NASH cirrhosis- the problem at hand!



Rising global trend for deaths

What is cirrhosis?

cirrhosis is defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.

- **Features of cirrhosis:**
  - Parenchymal nodules separated by fibrous septa
  - Differences in liver cell size and appearance
  - Fibrous septa with abnormal lobular architecture
  - Altered architecture and vascular relationships without septum formation (thrombosis, recanalization of veins)

"The precise point at which pre-cirrhotic changes become established cirrhosis cannot always be determined".

Anthony et al, Bull WHO, 1977; 55:521-540

- Sufficient confidence that core elements are found:
  - Liver structure- nodules
  - Fibrosis- severity and distribution
  - Function- synthetic
  - Vascular changes- collaterals, portal hypertensic

- Changes are not uniform
- Evolves in both directions
- Unitary term implying one way evolution is not data supported

Capturing the 4 pillars of cirrhosis in a clinical trial

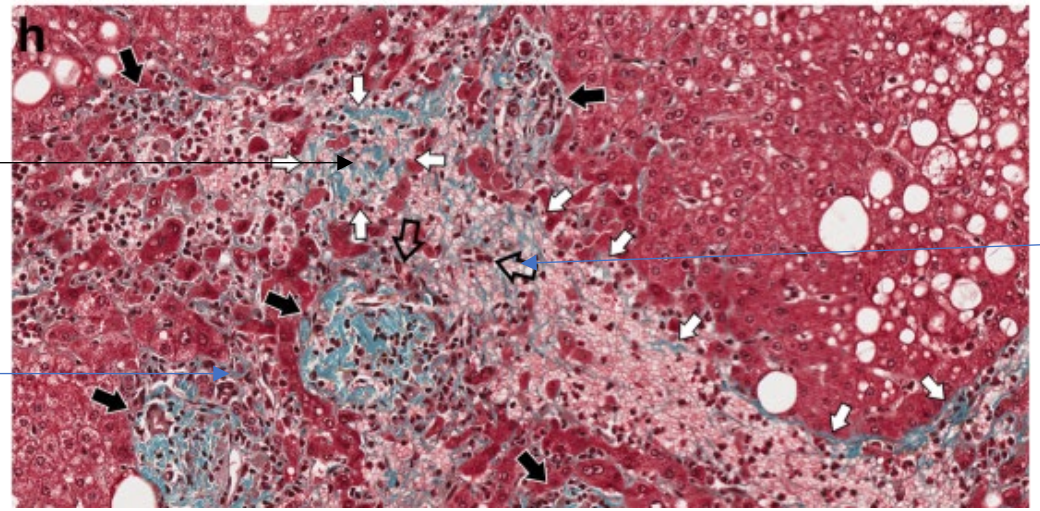
Nodularity	Imaging- Ultrasound, CT scan or MRI- surface of liver Volume of liver
Capturing fibrosis as a continuum	- Liver Stiffness - Blood based biomarkers (FIB-4, ADAPT, ELF etc.) - If histology used, use a quantitative fibrosis score
Portal hypertension	- HVPG - Collaterals on imaging - Spleen stiffness
Liver injury and function	- Conventional - Quantitative LFTs- HepQuant, Gadotexate Clearance

Is this sufficient? What are we missing

Parenchymal extinction in NASH progression

Occluded hepatic vein

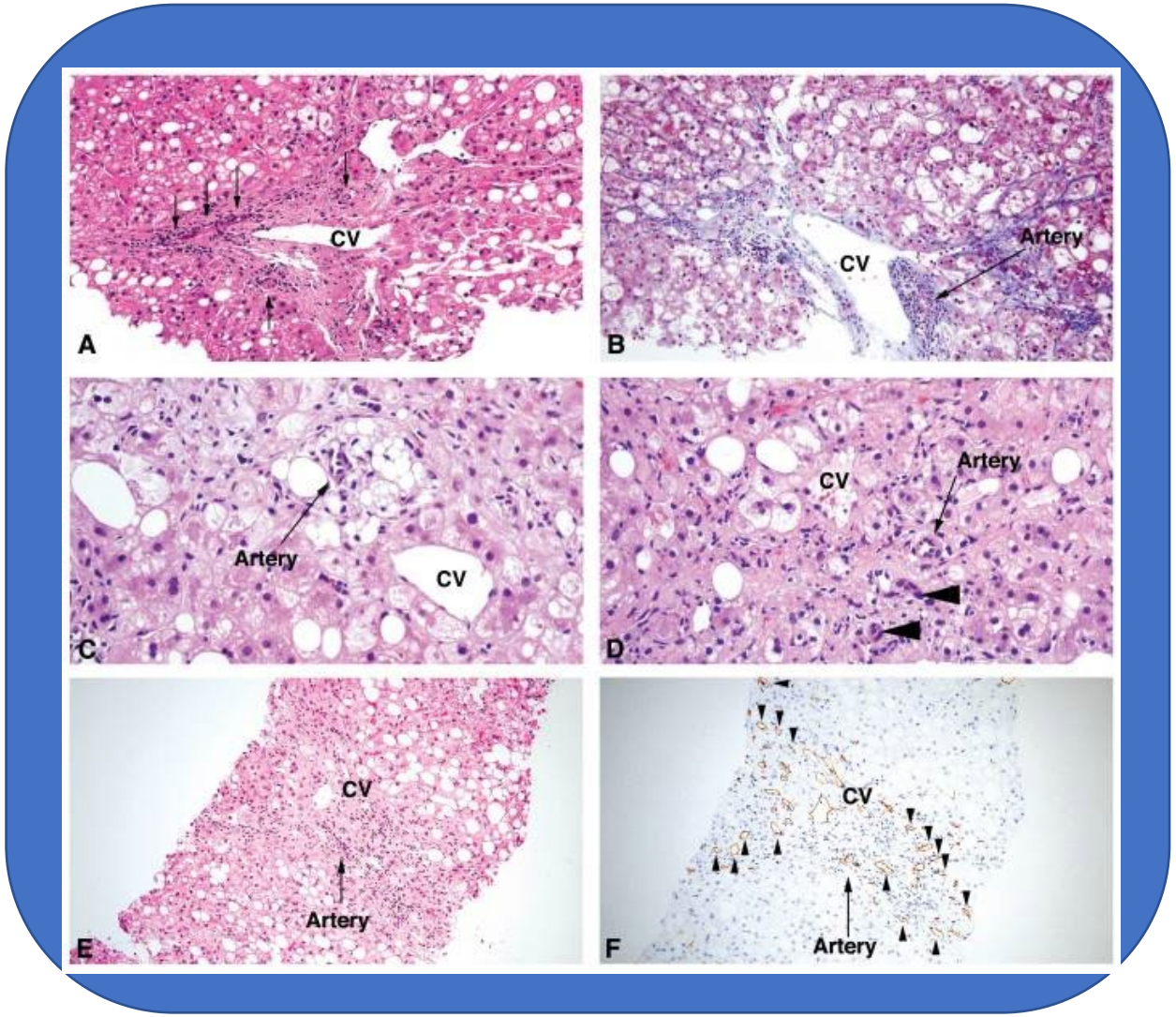
Parenchymal extinction
And portal area

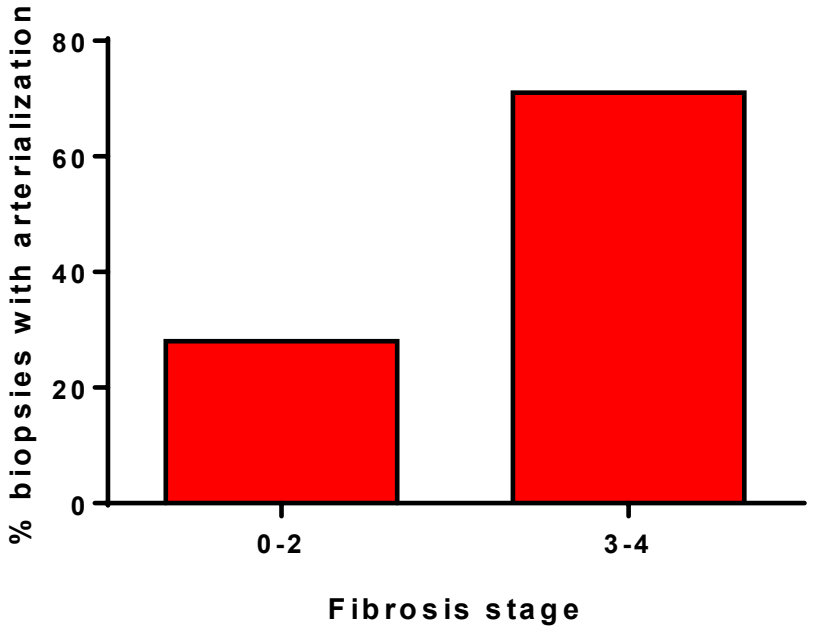


Arterio-venous channels
(open arrows)

Wanless I. Curr Hepatol Rep, 2020; 19:40-53

Centrizonal arterialization as a feature of advanced NASH



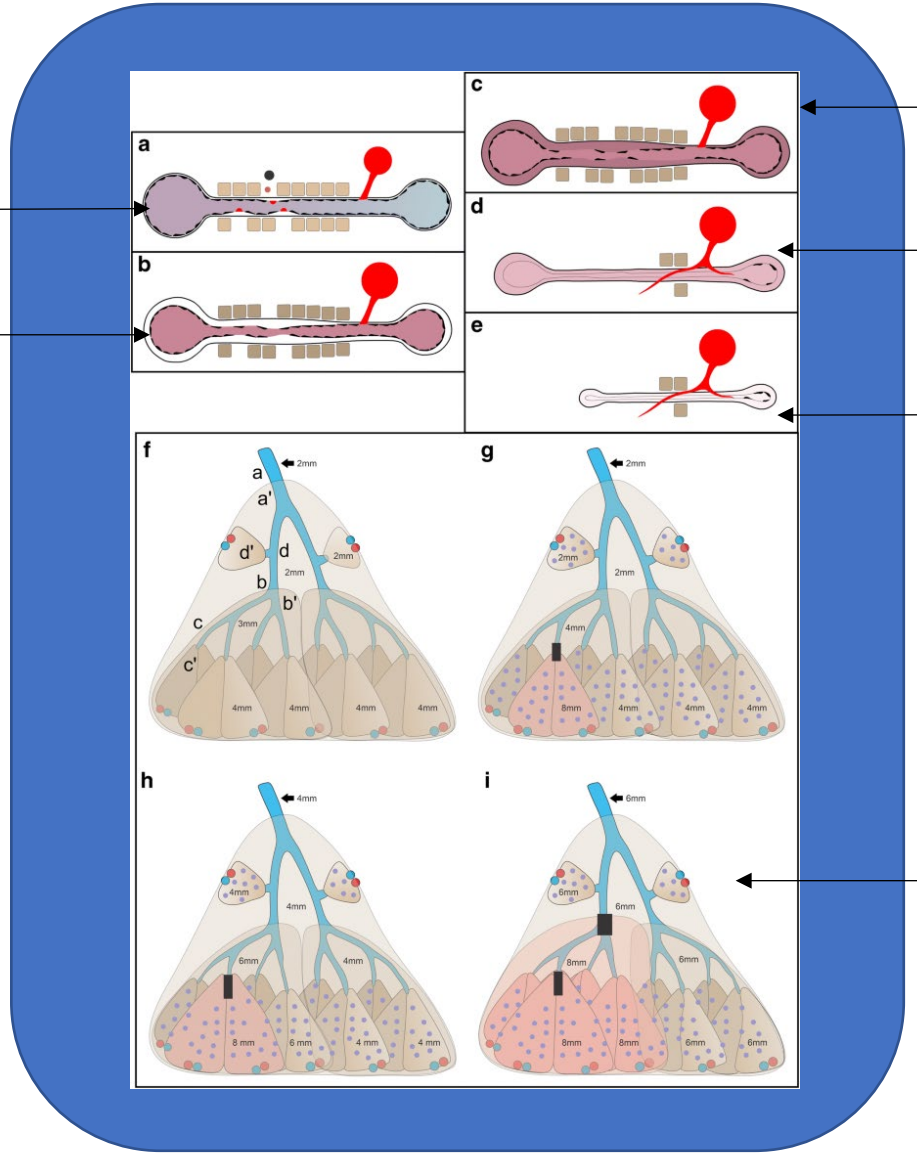


Gill et al, Am J Surg Pathol, 2011: 35:1400-4

Nested cone architecture of venous drainage and implications of venous occlusion

hepatocyte injury with adjacent endothelial reaction and injury

Subendothelial edema and luminal impingement



Arterial hyperemia and local compartment syndrome

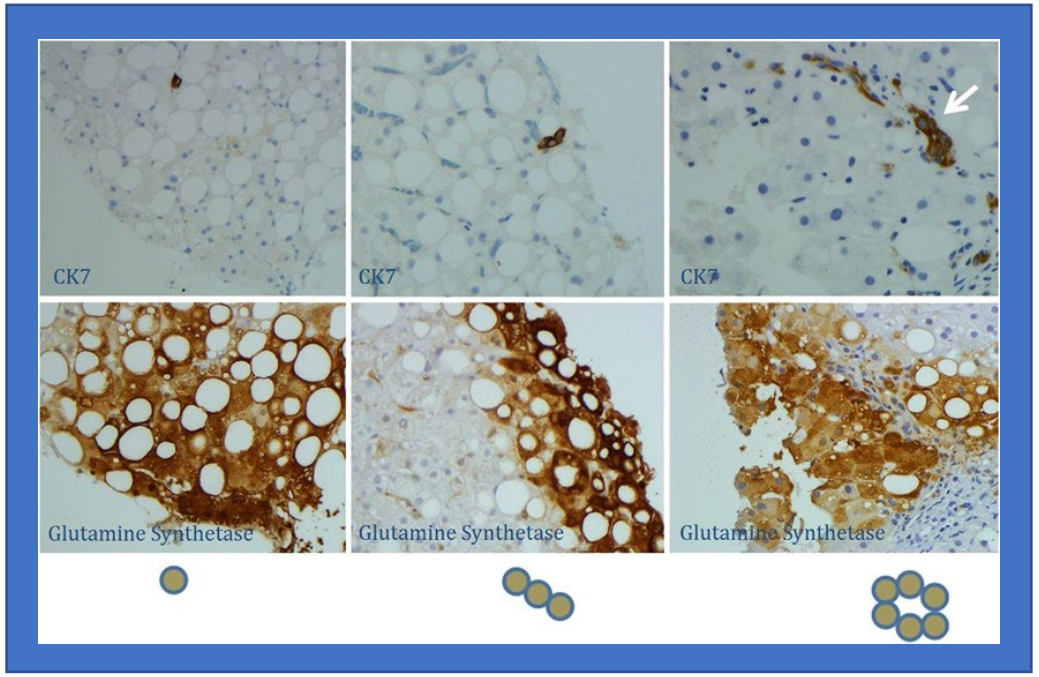
Arterial branch has grown in to sinusoid and vents blood in to portal vein (open PEL)

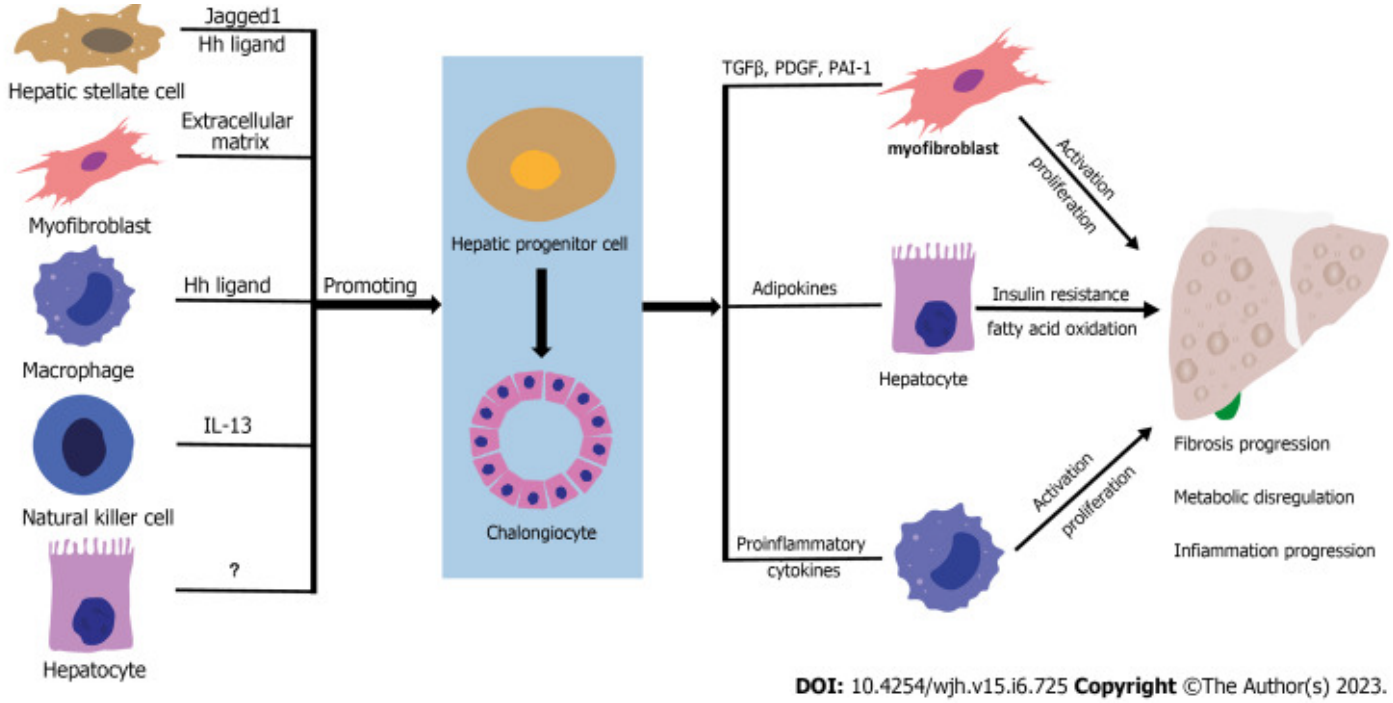
With complete decompression, HV and PV are approximated (closed PEL)

Venous drainage is based on tissue cones with little cross cone-drainage

Wanless I. Curr Hepatol Rep, 2020; 19:40-53

Ductular reaction and its role in disease progression

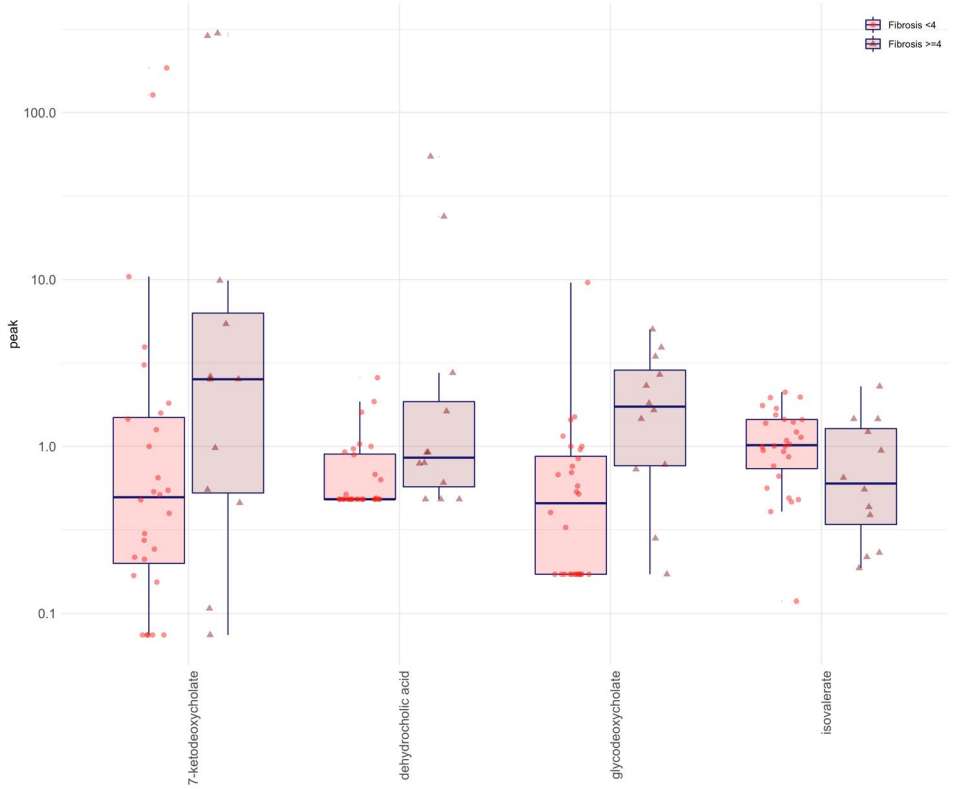


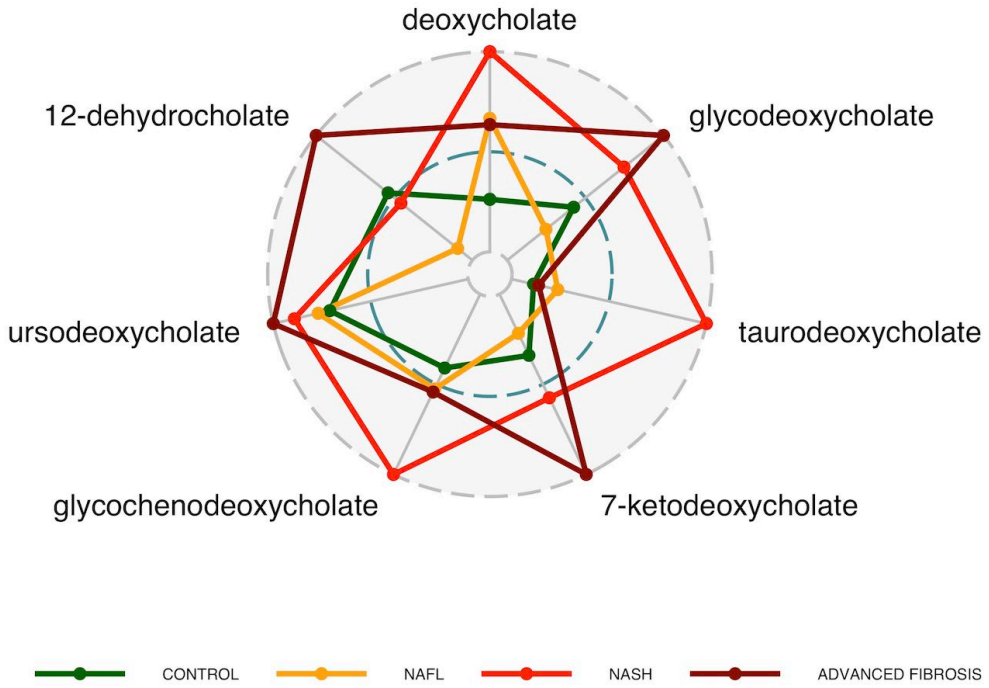


DOI: 10.4254/wjh.v15.i6.725 **Copyright** ©The Author(s) 2023.

Zhao et al, Mod Pathol, 2018; 31:150-159
He et al, World J Hepatol, 2023, 15:725-740

Deoxycholic derivatives are increased with increasing fibrosis





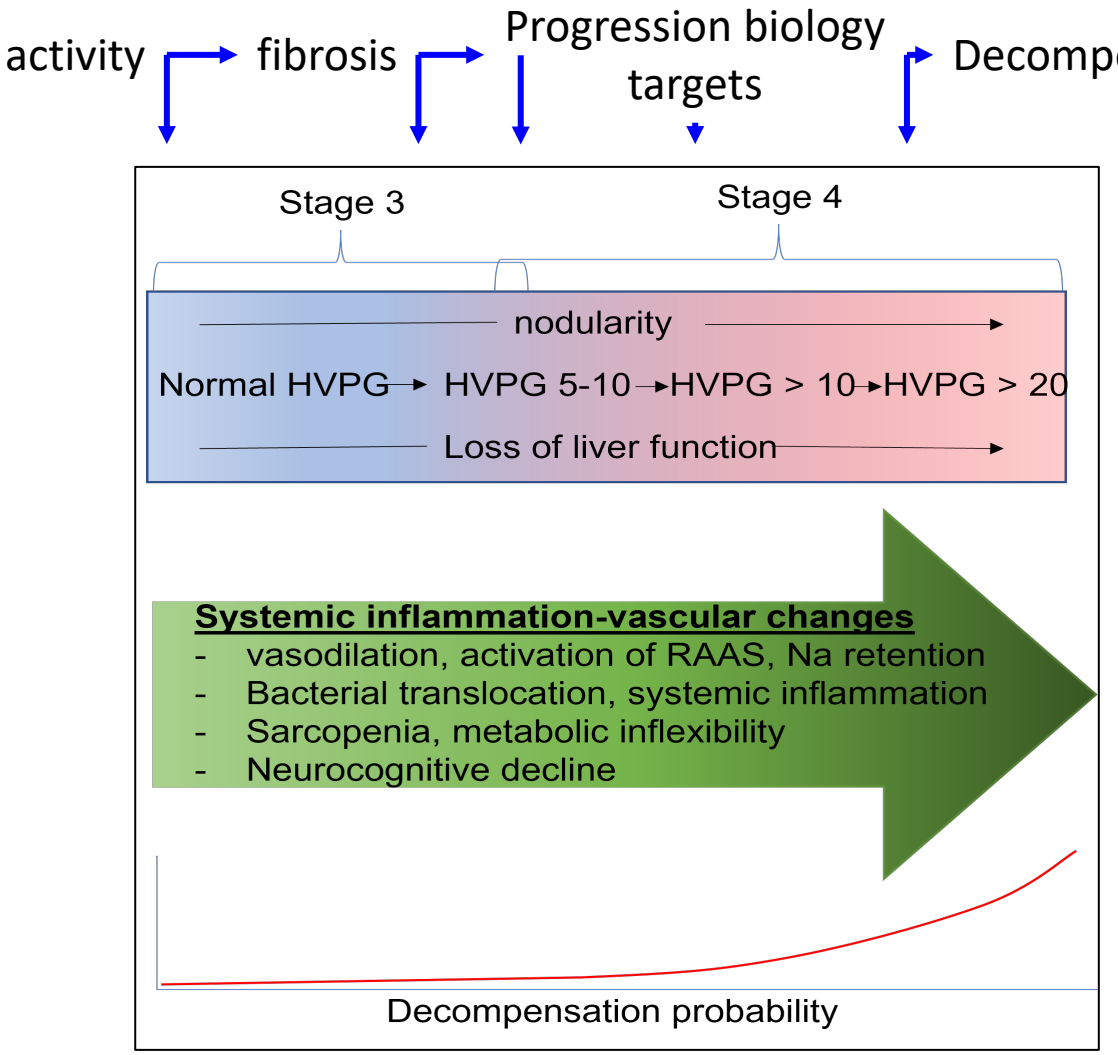
Smirnova et al, Hepatology 2022; 76:1811-1824

A simple focus on fibrosis may not be sufficient

Early stages → Advanced Fibrosis → Decompensation

- Matrix biology
- Vascular biology
- Cholestasis related mechanisms
- Impact on hepatic functioning mass
- Region-specific fibrogenic drivers
- Regenerative biology
- Microenvironmental factors

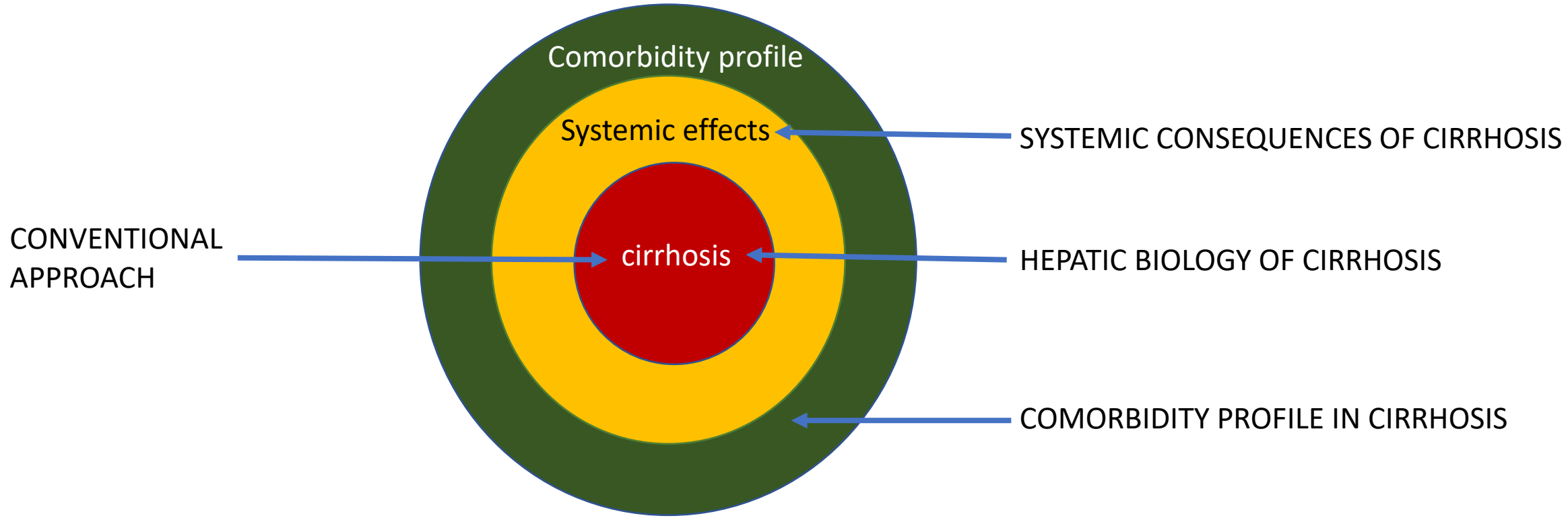
Paradigm 1: instead of progression to cirrhosis capture progression to tipping point when clinical risk increases to some threshold value



Needs:

- *Measures of nodularity, fibrosis, portal hypertension, liver function*
- *Additional factors*
- *Linkage of these to clinical outcomes*
- *More holistic models that capture the point in advanced fibrosis when outcome risk exceeds a pre-specified threshold*

Paradigm 2: Conventional approaches fail to take in to account the systemic consequences and comorbidity profile of patients with cirrhosis due to MASH



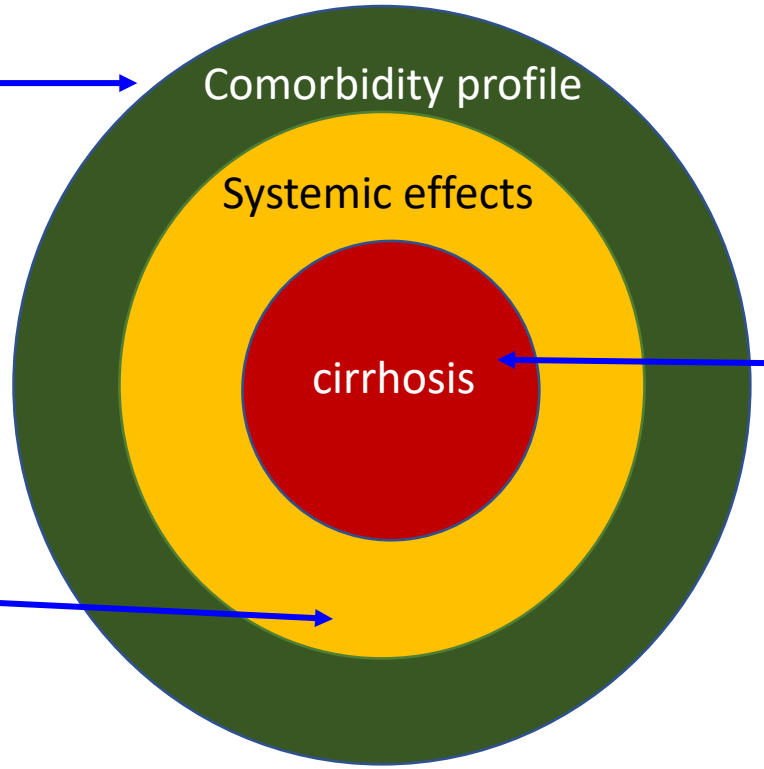
Expansion from the 4 pillars of cirrhosis to a comprehensive assessment of cirrhosis

Nodularity	Imaging- Ultrasound, CT scan or MRI- surface of liver Volume of liver
Capturing fibrosis as a continuum	- Liver Stiffness - Blood based biomarkers (FIB-4, ADAPT, ELF etc.) - If histology used, use a quantitative fibrosis score
Portal hypertension	- HVPG - Collaterals on imaging - Spleen stiffness
Liver injury and function	- Conventional - Quantitative LFTs- HepQuant, Gadotexate Clearance
Vascular changes	- Perfusion heterogeneity
Clinical	- Stroop test, dynamic markers of Na retention

There is room for further innovation in endpoint construction

Together, they impair how a patient feels, function and survives

Comorbidity related outcomes
- Cardiovascular
  - CAD, CVD, PVD
  - Diastolic dysfunction
  - arrhythmias
- Renal



Design should:
- Integrate outcomes
- Address competing threats to provide overall benefit to patient

Liver-impairment related outcomes
- Loss of liver function
- Hepatocellular cancer

Systemic effects related outcomes
- Variceal hemorrhage
- Ascites (SBP, AKI-HRS etc.)
- Neurocognitive decline
  - HE
  - Dementia
  - Vascular
- Infections

Thank you for your attention

VCU Stravitz-Sanyal Institute for
Liver Disease and Metabolic Health
School of Medicine

Implications of the status quo inclusive of recommendations of the international pathology consensus

	Pathology assessment	Trial Assessment
Etiology	Noureddin et al, Gastroenterology, 2020; 159:422-427	
Staging		
Advanced (stages 3-4)	Stages 3 and 4 with substages	Histologically need to show progression or regression Problems with ordinal staging
Advanced with regression	Features of regressive septae	Not well established in MASH trial space. Needs further validation
End-stage	Thick septae with well defined nodules	Need ways to quantitate these. Septal thickness has been linked to portal hypertension and outcomes risk