Progression to Cirrhosis – considerations in operationalizing the endpoint

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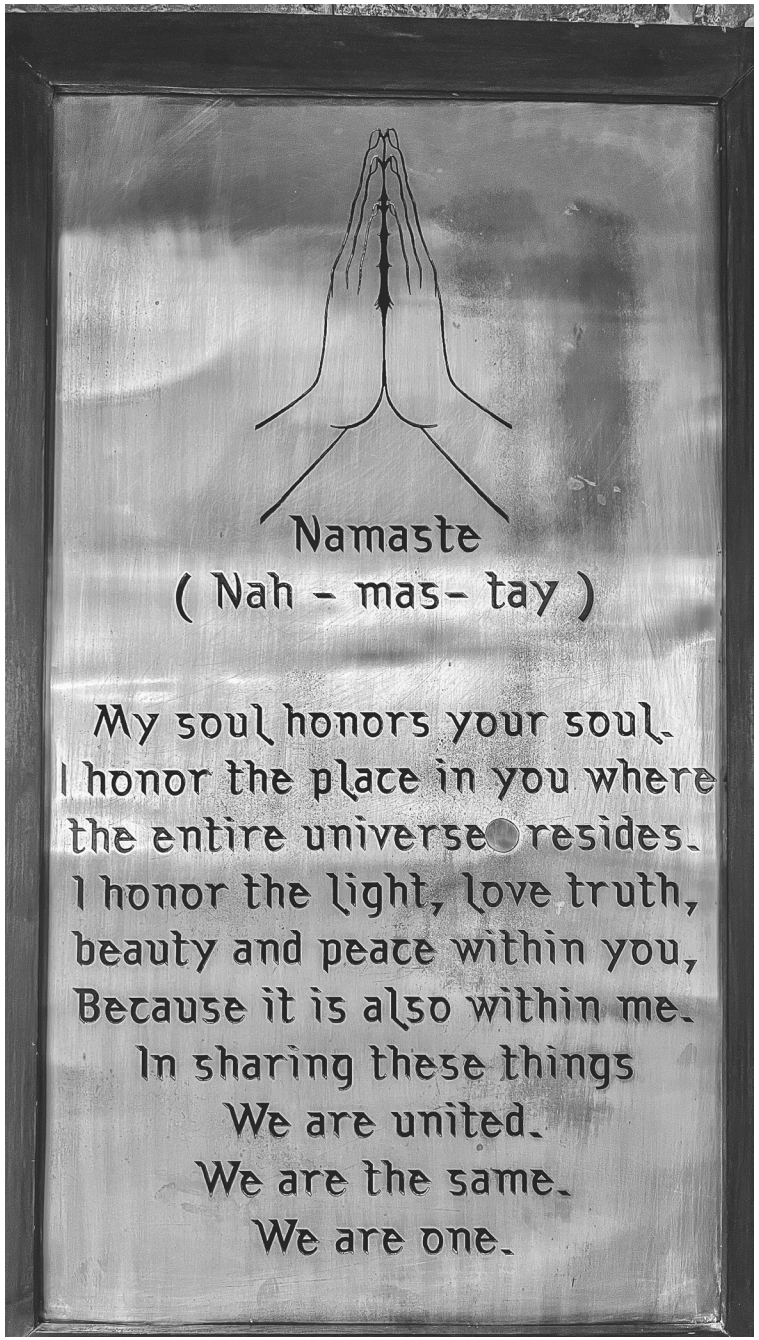

UNASHAMED LIVER LOVER

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

- Ownership interests: Durect, Tiziana, Genfit, Exhalenz, Northsea, Rivus, Inversago
- 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, Histoindex, Path AI, Takeda
- Grant support to school: Gilead, Intercept, Novartis, Novo Nordisk, Inventiva, Eli Lilly, Genentech, Boehringer Ingelhiem, Bristol Myers Squibb

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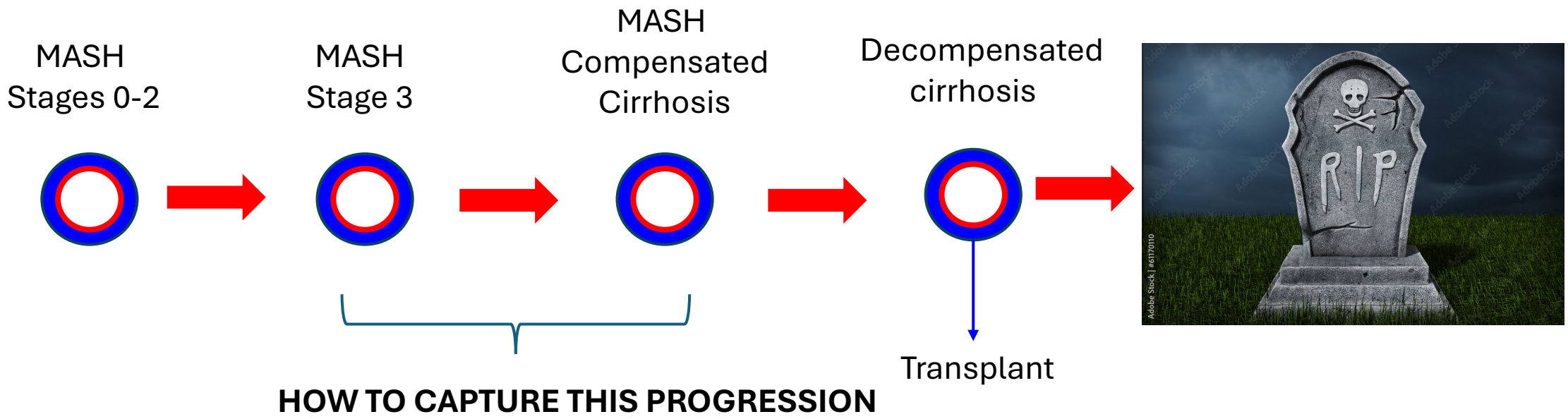
The MASH journey



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".

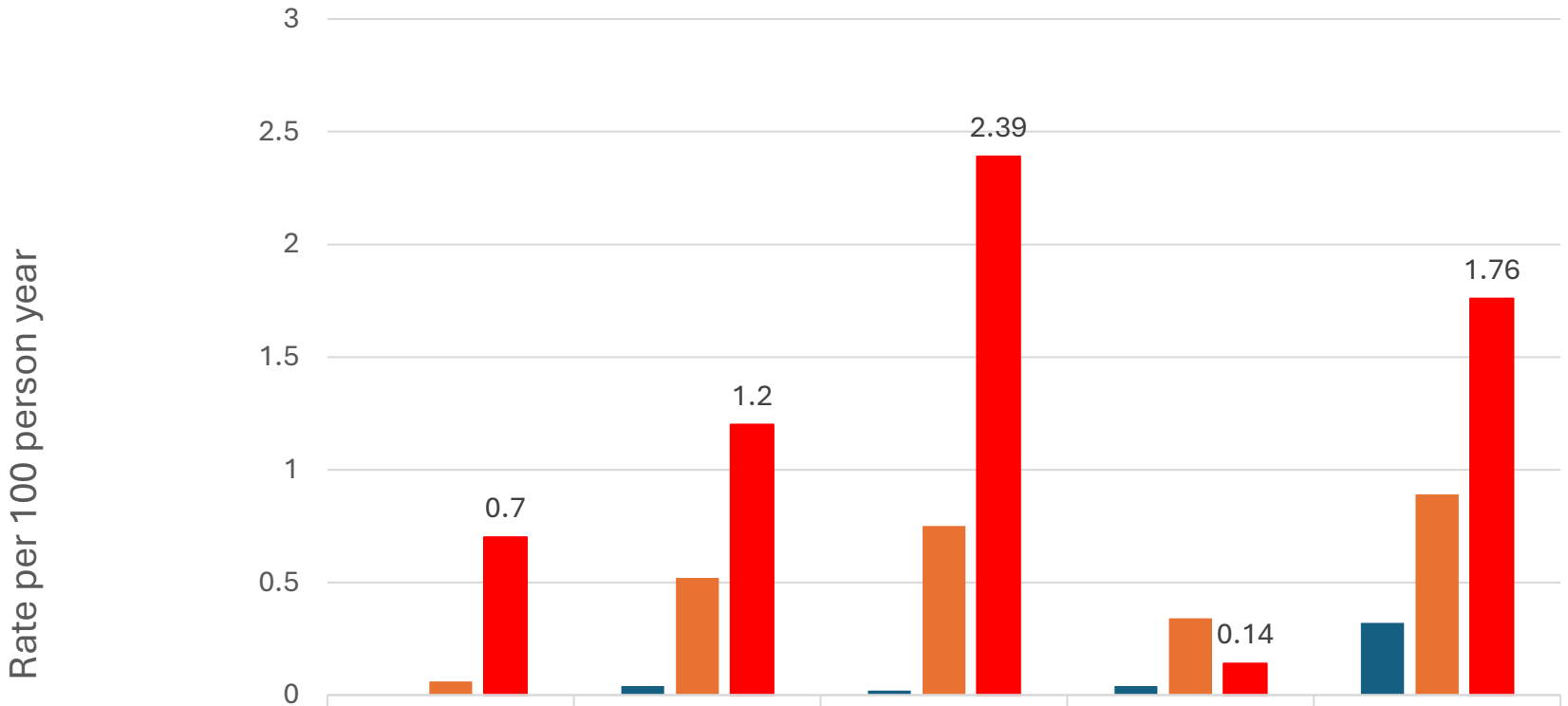
Anthony et al, Bull WHO, 1977; 55:521-540

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

Liver Forum approach for sub-stratification of compensated cirrhosis

	Stratum A	Stratum B	Stratum C
High Evidence Tier			
Portal pressure related measurements			
HVPG (mm Hg)[&1-3]	~ 5	6-10	> 10
Varices [1, 4]	Absent	Absent	Present*
Ascites [1-3]	Absent	Absent	Seen on Imaging only or recompensated
Hepatic encephalopathy [1-3]	Absent	Absent	Absent-Minimal and recompensated
Platelets count (10^9/L)** [1-3, 5]	≥ 150,000	<150,000	<150,000
Histology Related Measures			
?Ishak Fibrosis stage	5	5-6	6
NAS score	≥3 or 4	≥3 or 4	None (cryptogenic)
Function related measurements			
Child-Pugh Score [2, 3, 6]	CTP-5	CTP-5	CTP-6
MELD [2, 3, 6, 7]	<10	10-12	>12*
Albumin (gm/dl) [2, 3, 6, 7]	> 3.5	2.8-3.5	≤2.8
Bilirubin (mg/dl) [2, 3, 6, 7]	< 1.3 mg/dL	1.3-2 mg/dL	>2 mg/dL
INR [2, 3, 6, 7]	<1.2	>1.2	>1.2
Good Evidence Tier			
Portal Pressure or/And Fibrosis (stiffens) related measurements			
VCTE[~8, 9]	14-20	21-25	> 25
MRE[10-14]	4.3-6.5 kPa	5-6.5 kPa	>6.5 kPa
Liver cT1[15]	825 – 875	>875	>875
ELF[16, 17]	<9.8	9.8-11.29	≥11.3
FIB-4[17]	1.3-2.67[#]	>2.67-3.25[#]	>3.25
Function related measurements			
Liver Frailty Index[18, 19]	<3.2	3.2-4.3	≥4.4

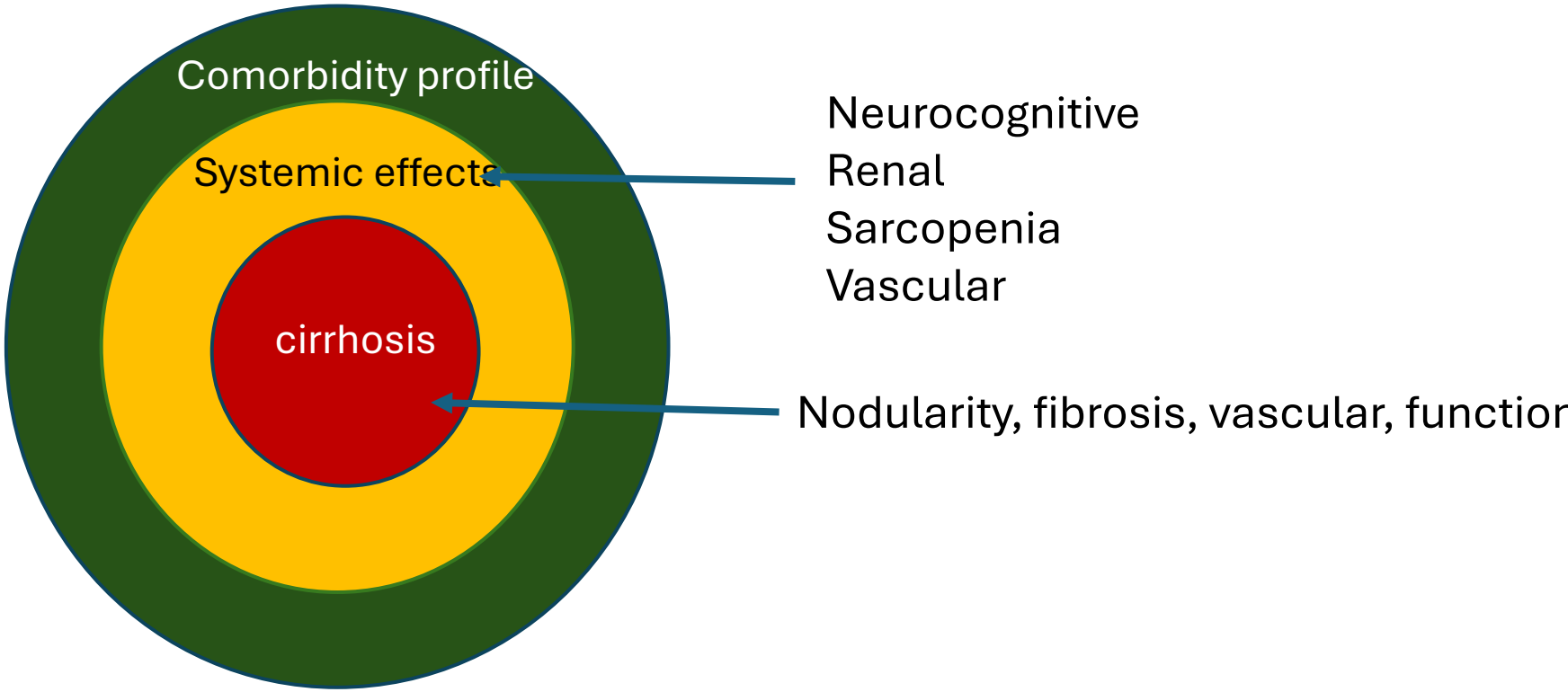
Liver Related Events in Adults with MASH



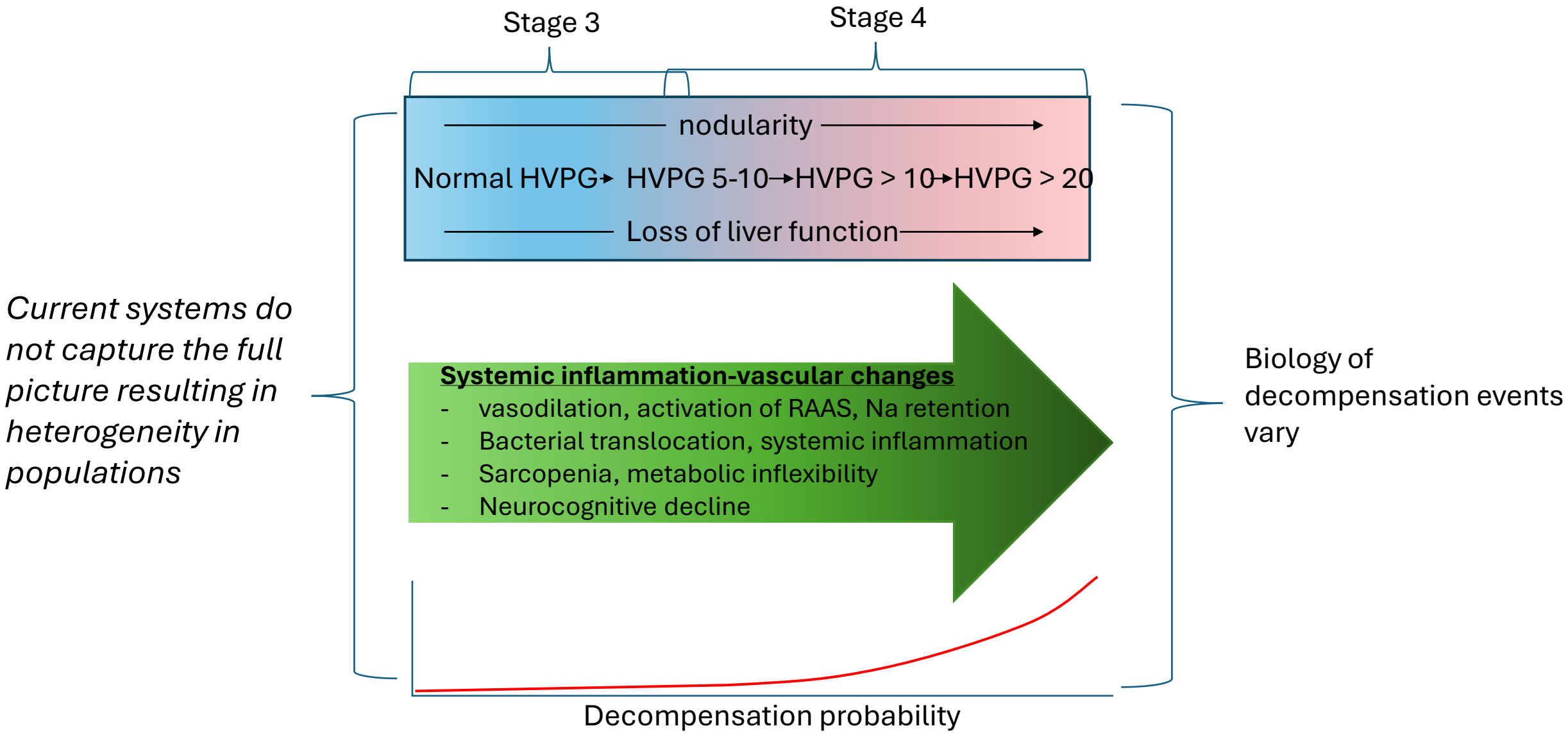
	Variceal Bleeding	Ascites	Encephalopathy	Hepatocellular Carcinoma	Death from any cause
F0 to F2, N=1237	0	0.04	0.02	0.04	0.32
F3 (Bridging), N=369	0.06	0.52	0.75	0.34	0.89
F4 (Cirrhosis)	0.7	1.2	2.39	0.14	1.76

Sanyal AJ, et al. N Engl J Med 2021; 385:1559-1569

Mechanisms by which cirrhosis affects how a patient “feels, functions and survives”



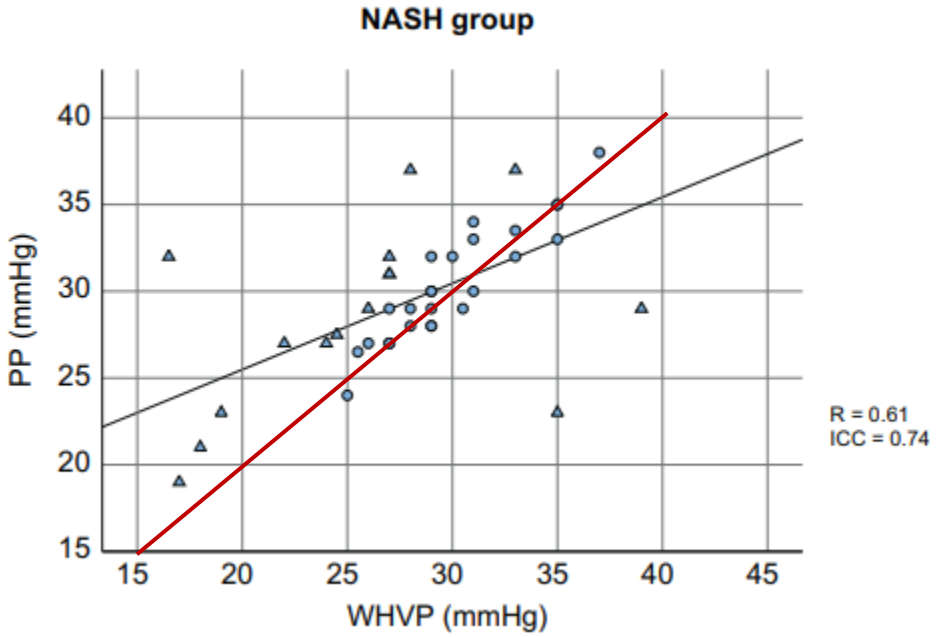
Tipping point hypothesis

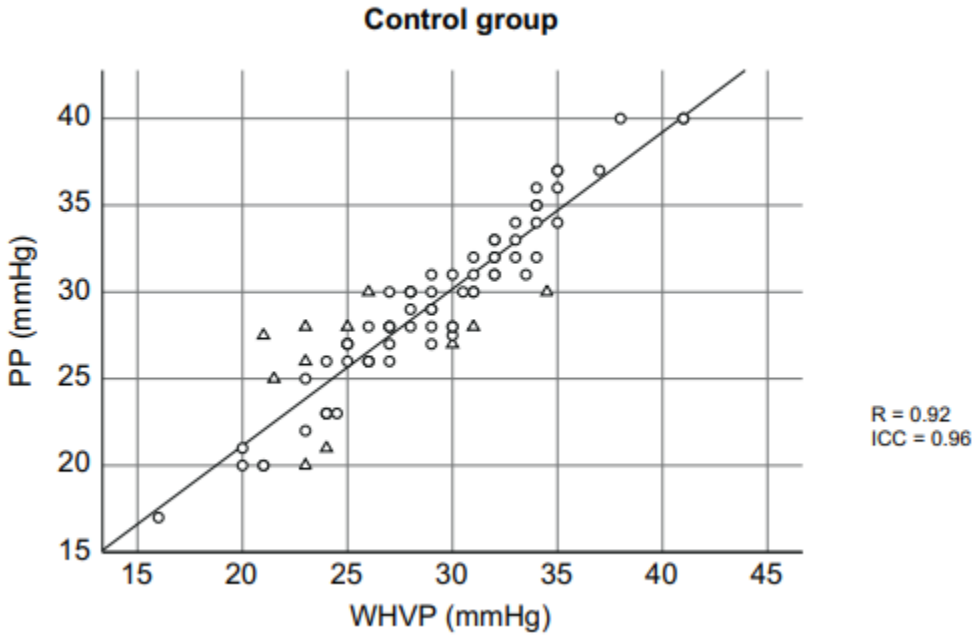


Current systems do not capture the full picture resulting in heterogeneity in populations

Biology of decompensation events vary

MASH has a pre-sinusoidal component to portal hypertension

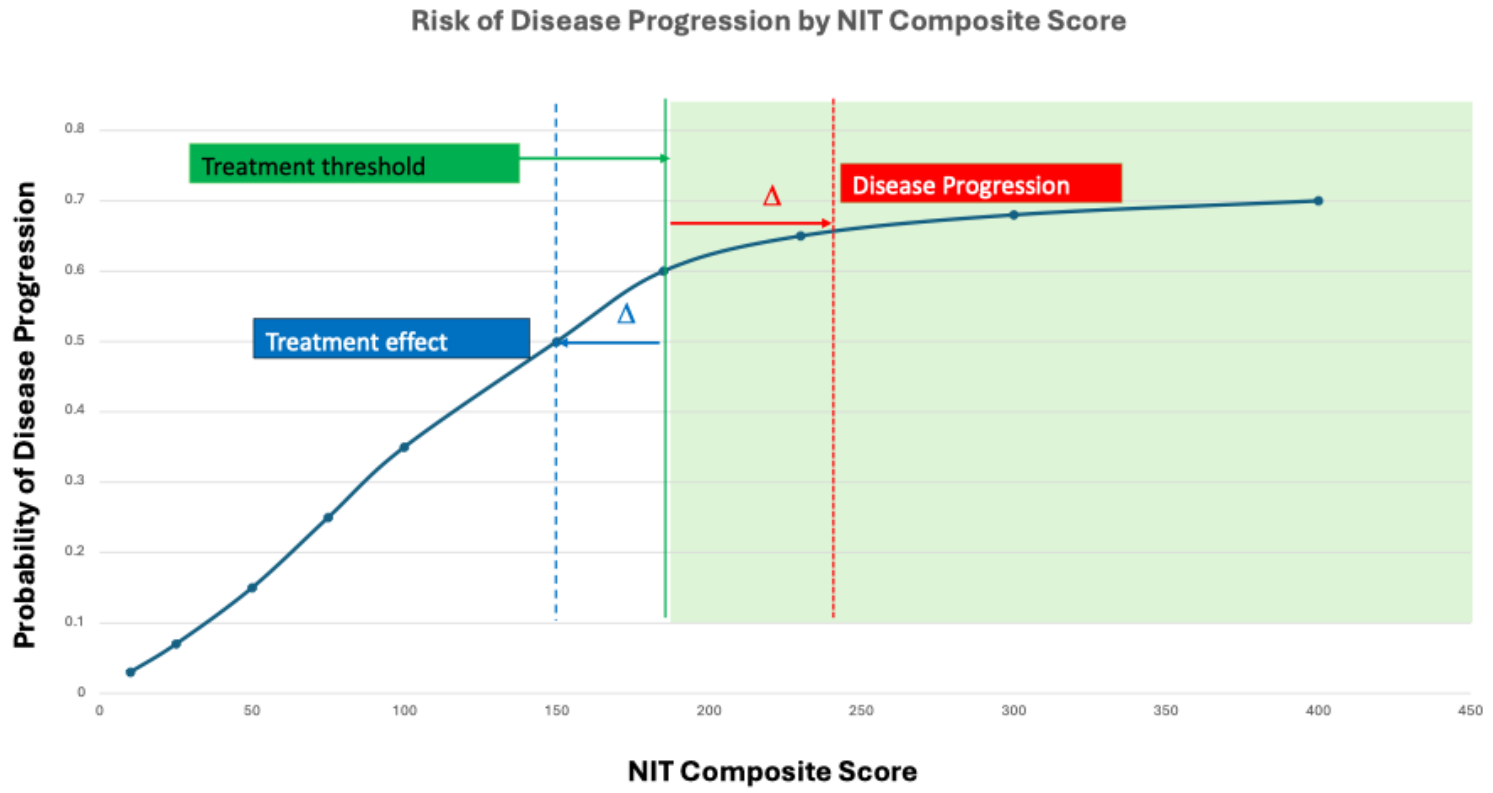




Ferrusquía-Acosta, J et al. Journal of Hepatology 2021 vol. 74 j 811–818

Hypothetical model of NIT trajectory related to disease progression

NIT changes in absence of treatment (red Δ) predicts increased probability of disease progression, while treatment induced changes in NIT (blue Δ) associated with a reduction in disease progression

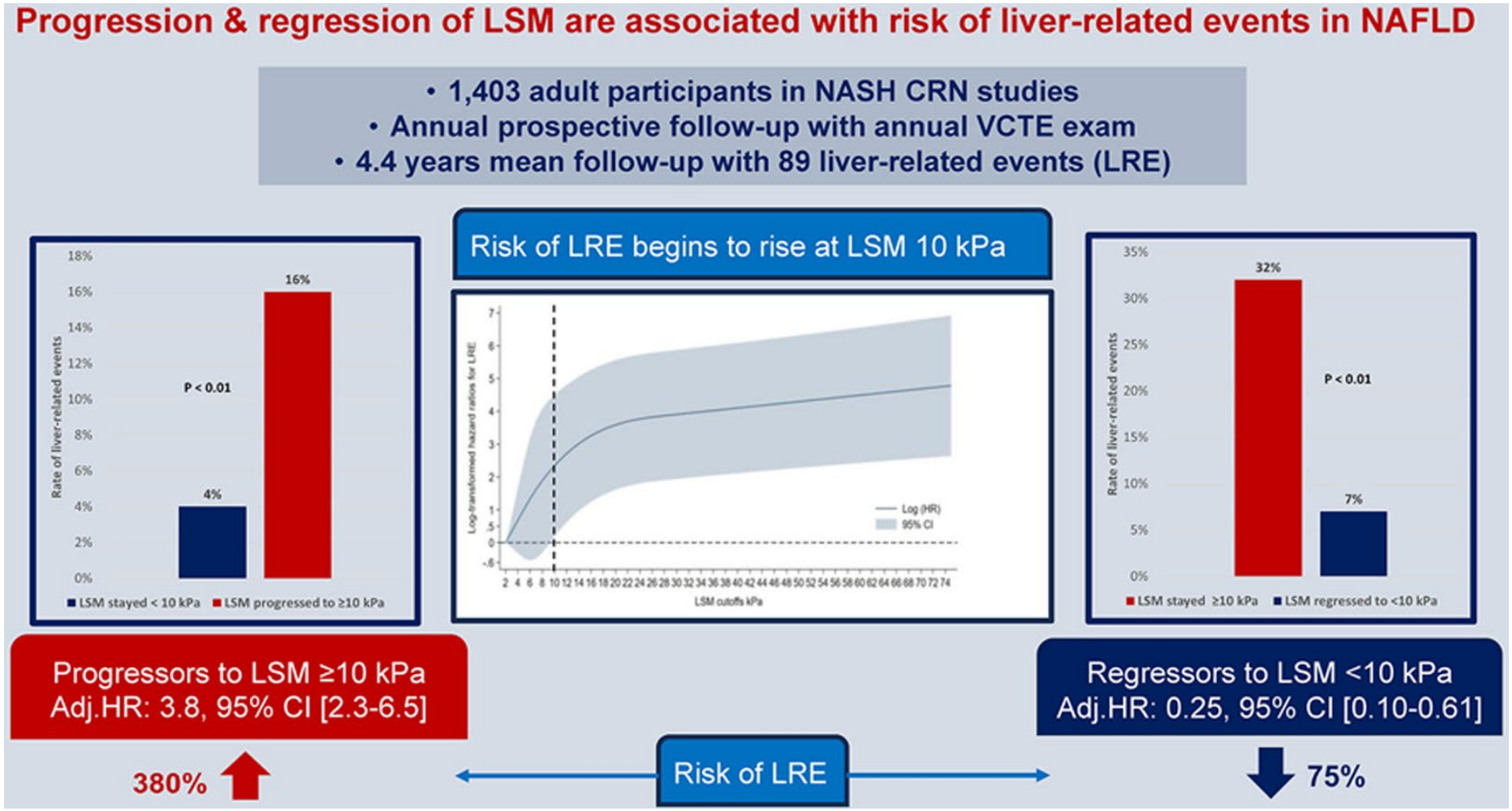


How to define cirrhosis to validate the endpoint?

- Histology
- Is a non-invasive profile or **<u>linkage to outcomes</u>** acceptable?
- Sensitivity vs Specificity?

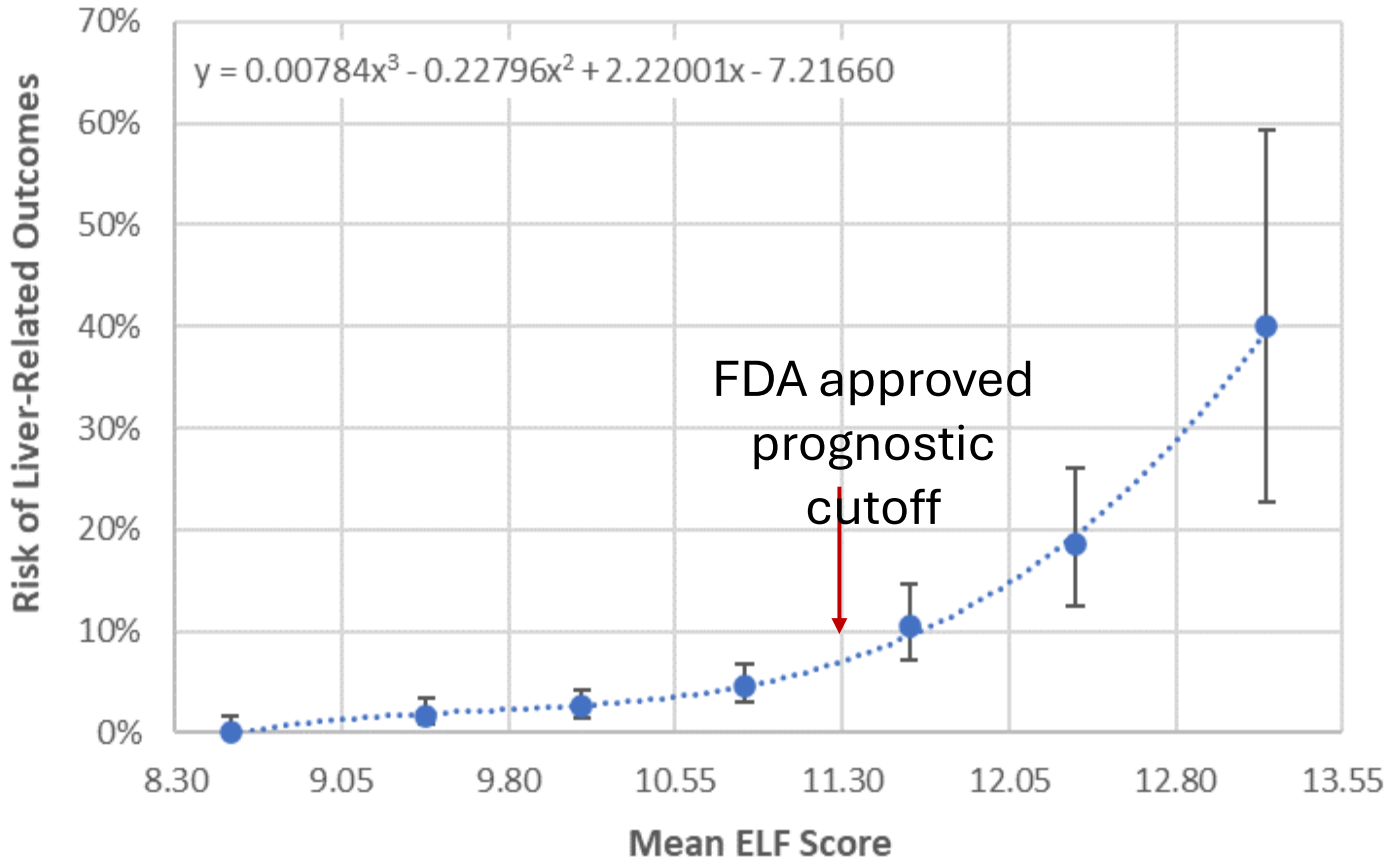
LSM does however provide prognostic information

Most patients will have a LSM between 10-20 Kpa at beginning of trial



Gawrieh, S. et al. Increases and decreases in liver stiffness measurements are independently associated with the risk of liver-related events in NAFLD Journal of Hepatology, 2024

ELF scores are linked to outcome risk



Gee et al, AASLD 2024

Benefit assessment needs re-calibration using patient centered approaches

- Subpart H phase 3 trial endpoint
  - Improvement in activity
  - Improvement in fibrosis
  - Improvement in cardiovascular risk profile
  - Changes in eGFR
  - Improvement in glycemic indices
  - Safety endpoints

- Post subpart H phase 4 endpoint
  - Progression to cirrhosis
  - Decompensation (ascites, encephalopathy, variceal hemorrhage)
  - Rise in MELD score from < 12 to 15 or higher
  - Death
  - Again- cardiac, renal, glycemic, cancer related endpoints are not part of the equation despite strong data that the biology of these diseases are linked to NAFLD and contribute to overall threat to life

A proposal for developing a NIT based approach that will become a validated endpoint reflecting progression to cirrhosis

Characteristics that change	Measures with large bodies of data to support Prognostic and disease monitoring COUs	Potential additional approaches- need more data
Fibrosis	• Histology • NIT reflective largely of fibro-inflammation (LSM, ELF etc.)	• Hot and cold fibrosis related endotypes
Structure	-	• nodularity
Vascular	• HVPG	• Collaterals-EUS based measures • Spleen size/pulsatility • Spleen stiffness
Functional	• Synthetic dysfunction • MELD	• Breath tests • Gadoxetate clearance
Non-hepatic	-	• Minimal Hepatic encephalopathy

NIT based progression to cirrhosis can be captured operationally

- **NITs to be used for progression to cirrhosis must be scalable and feasible (access- affordability-practicality) for wide spread implementation**
- **Ability of NITS to capture progression to cirrhosis:**
  - Capture disease elements central to its biology that is targeted by therapeutics
  - Broad concordance with histological progression
  - Progression criteria will capture worsened outcome profile
  - Sensitivity to change

Thank you for your attention