Prognostic Value of NITs

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BEST U.S.News & WORLD REPORT RANKINGS

#5 in GI and GI surgery

HRI

Disclosures

- Principal Investigator for a Drug Study: Allergan, Akero, BMS, Gilead, Galectin, Genfit, GSK, Conatus, Corcept, Enanta, Madrigal, Novartis, Novo Nordisk, Shire, Takeda, Terns, Viking and Zydus
- Advisory Board: : Altimmune, BI, Cytodyn, Corcept, 89BIO, GSK, Madrigal, Merck, Novo Nordisk, Northsea therapeutics, Terns and Takeda
- Stockholder: Rivus Pharma, CIMA, Cytodyn, and ChronWell
- Associate Editor: Clinical Gastroenterology
- and Hepatology

Objectives

- #1 To discuss The Evidence behind NITs and their prediction of Major Adverse Liver Outcomes (MALO)
  - Problems with Biopsy
  - Prediction of MALO
  - How can I translate this into phase 3 clinical trials
- #2 At-Risk MASH (pre-cirrhosis) tests and their prediction of outcome

Why We Need This ASAP?

- MASLD is one of the most common chronic diseases
  - E.g., in comparison to T2DM, CKD, Obesity, Heart Failure….All have approved meds
  - None of them use invasive assessment in their RCT
- Epidemic: Leading cause of liver transplant and growing
- Screening failure rate ~>70%
  - >>>Biopsy issues
  - Many patients are left out while they have a real disease
- Patients, sponsors, researchers and investors frustration
- First drug is approved while other trials are ongoing

Why We Need This ASAP?

- First drug is approved while other trials are ongoing
  - Patient withdrawal because they want the new drug
  - FDA approved medicine without biopsy while phase 3 RCTs are placebo controlled with Bx
  - GLP-1s or duals are now commercially available
    - Supply issues but!!
      - Compounding: They are becoming as popular as having an iPhone
      - Boutique beauty shops run by NP/PAs

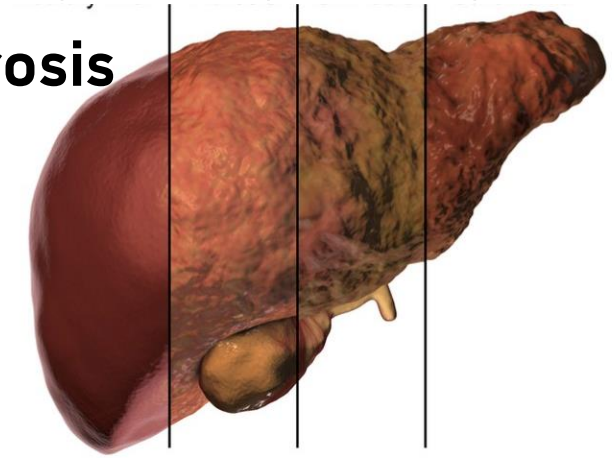
What do I need to Replace those?

- 1- Addressing the areas mentioned earlier
  - Fibrosis (Stiffness and serum biomarkers)
  - <ASH resolution (Steatosis +Inflammation+ Ballooning)
- 2- Evidence:
  - As good as biopsy or better
  - Prediction of MALO
- 3- Better Quality Data

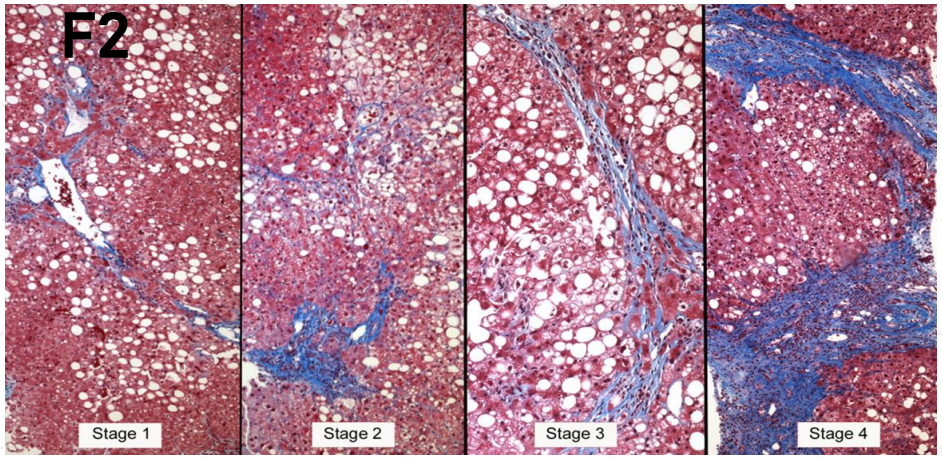
Objective:

To discuss Serum NITs in MASH In A Relation to Outcomes

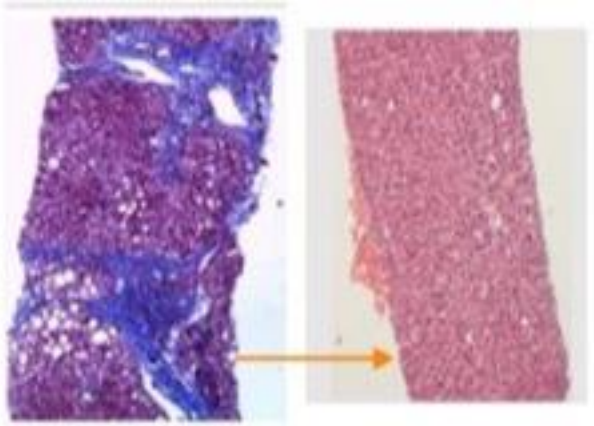
Fibrosis

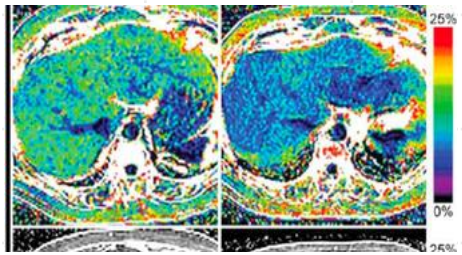


MASH with NAS ≥ 4 + ≥ F2

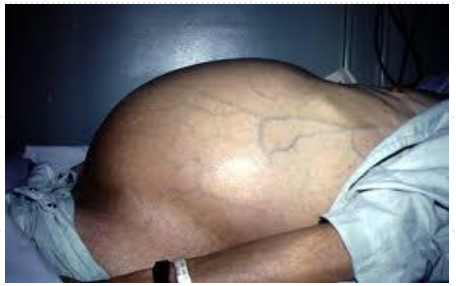


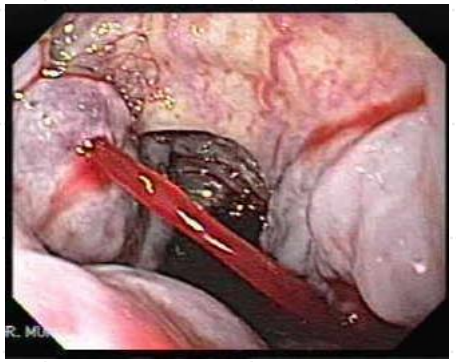
Monitoring Response to Therapy



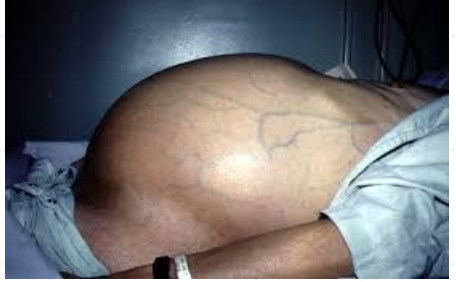


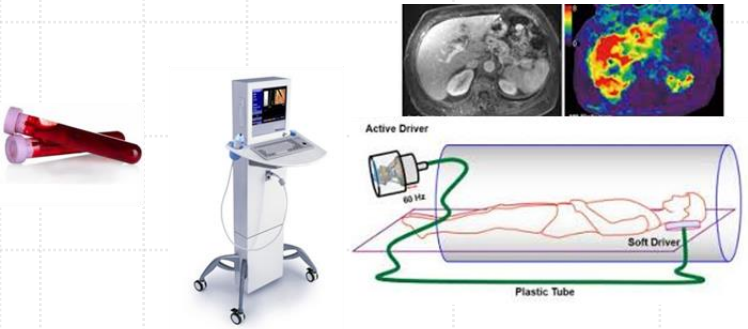
Major Clinical Liver Events (MALO)



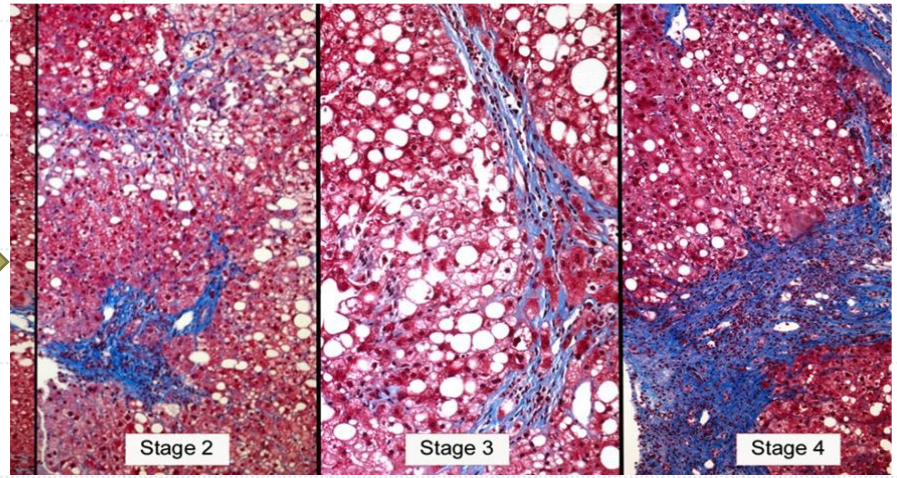


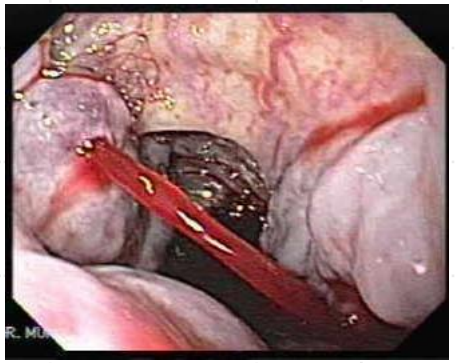
Noninvasive Biomarkers as Surrogates to Histology: Where we Started





Non-invasive Biomarkers

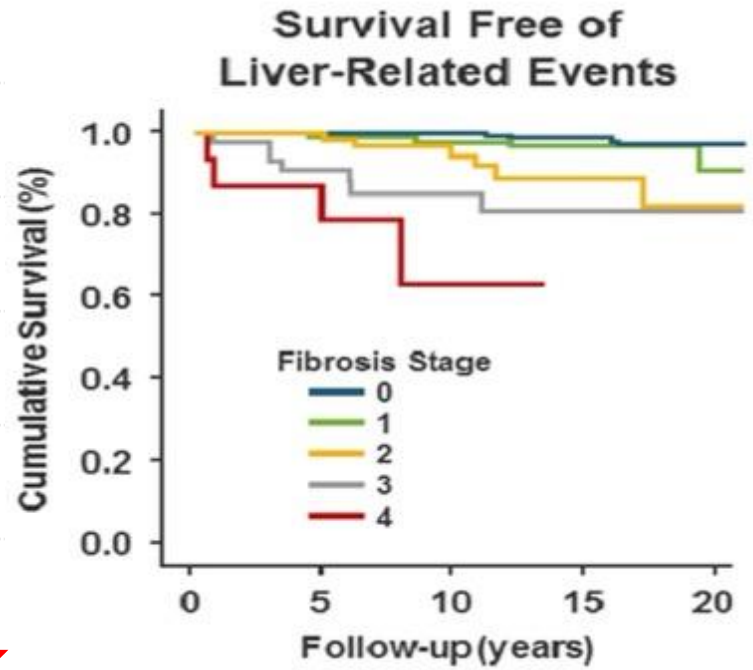




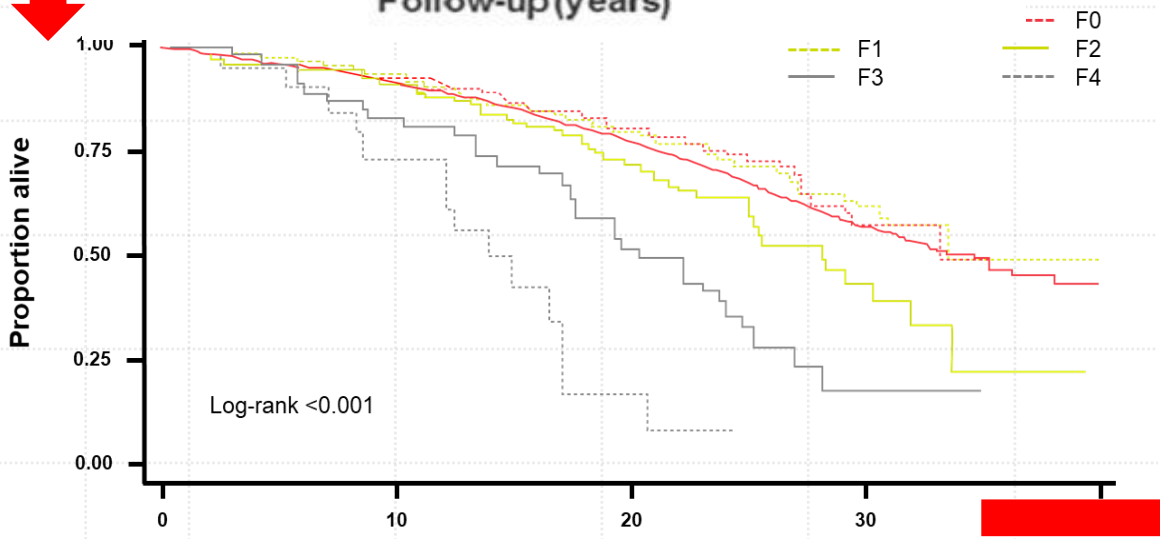
? NASH Resolution
Fibrosis Improvement

Surrogate → Surrogate → Outcome

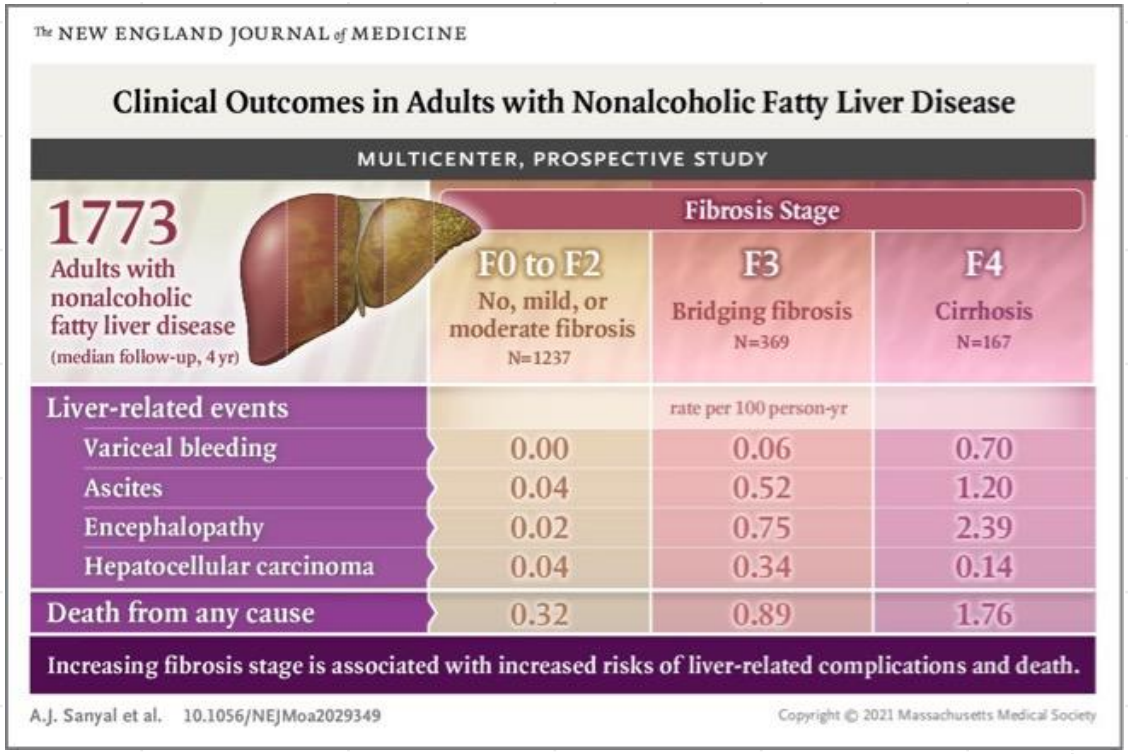
Fibrosis Improvement Over the Years



Agulo; Gastro 2015



Adapted from Hagström H et al. *J Hepatol* 2017;67:1265 –1273



The NEW ENGLAND JOURNAL of MEDICINE

Clinical Outcomes in Adults with Nonalcoholic Fatty Liver Disease

MULTICENTER, PROSPECTIVE STUDY

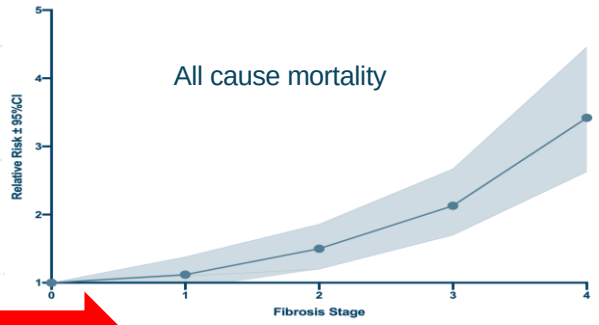
1773 Adults with nonalcoholic fatty liver disease (median follow-up, 4 yr)

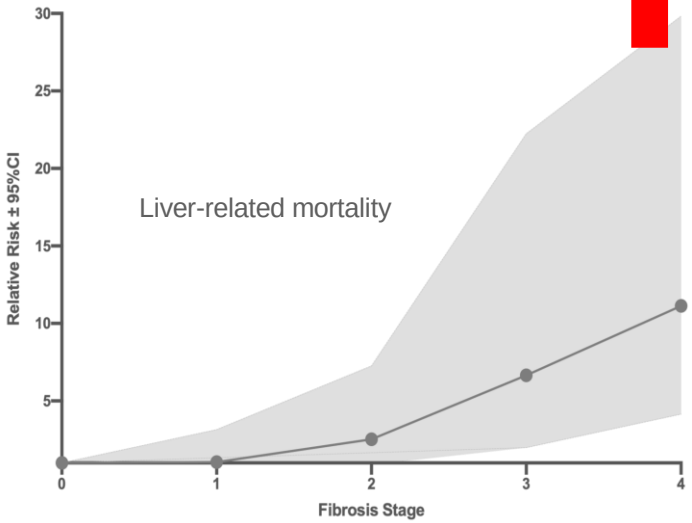
	Fibrosis Stage		
	F0 to F2 No, mild, or moderate fibrosis N=1237	F3 Bridging fibrosis N=369	F4 Cirrhosis N=167
Liver-related events		rate per 100 person-yr	
Variceal bleeding	0.00	0.06	0.70
Ascites	0.04	0.52	1.20
Encephalopathy	0.02	0.75	2.39
Hepatocellular carcinoma	0.04	0.34	0.14
Death from any cause	0.32	0.89	1.76

Increasing fibrosis stage is associated with increased risks of liver-related complications and death.

A.J. Sanyal et al. 10.1056/NEJMoa2029349

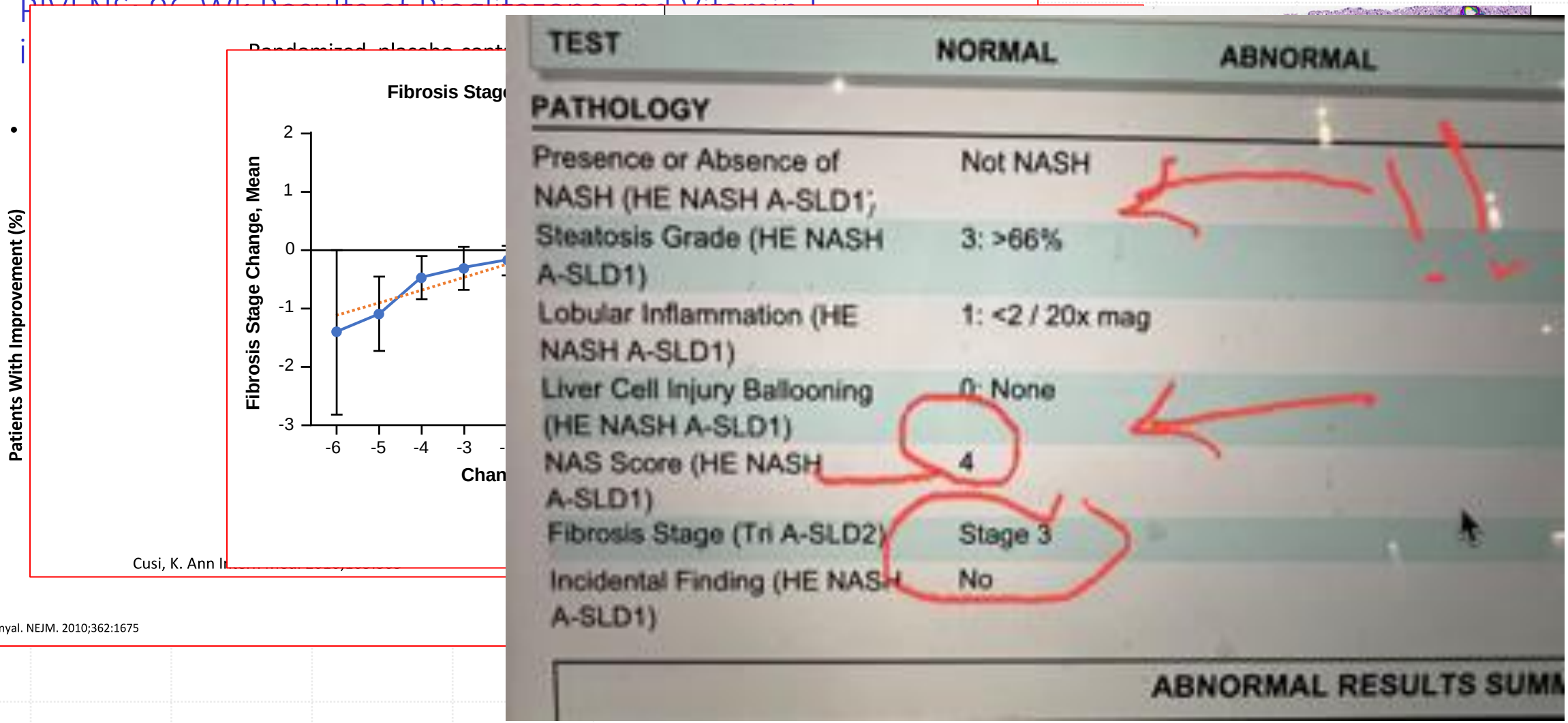
- Systematic review and meta-analysis of 13 studies 4,428 NAFLD patients (2,875 with histological NASH).





Taylor RS, et al. *Gastroenterol*. 2020;158:1611-25.

NASH Resolution Over the Years



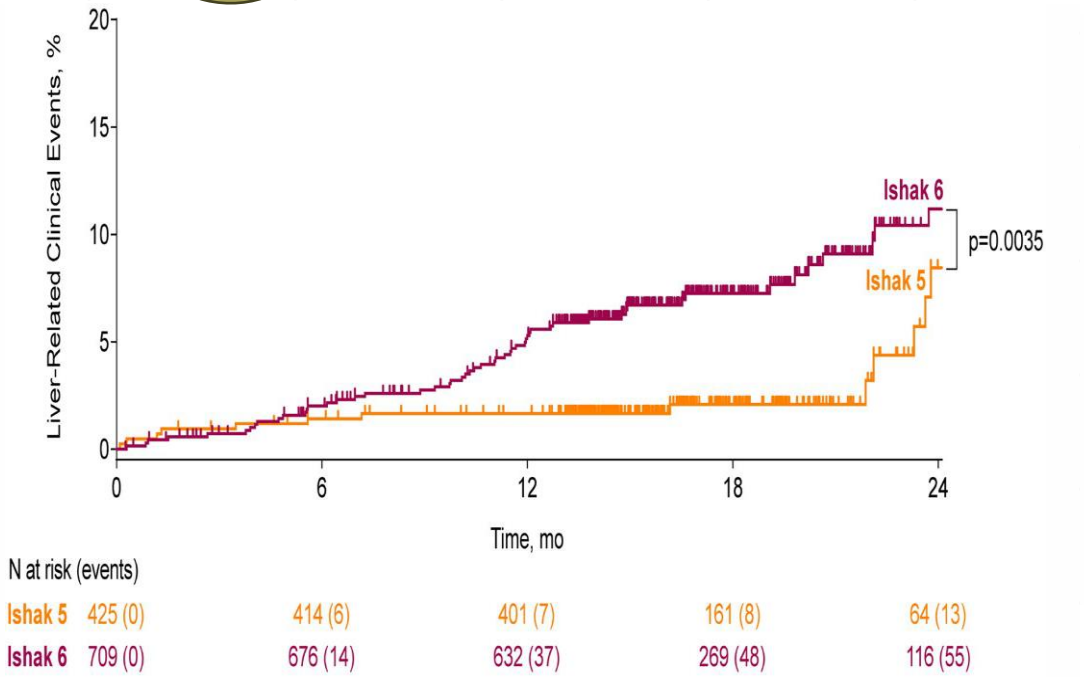
Sanyal. NEJM. 2010;362:1675

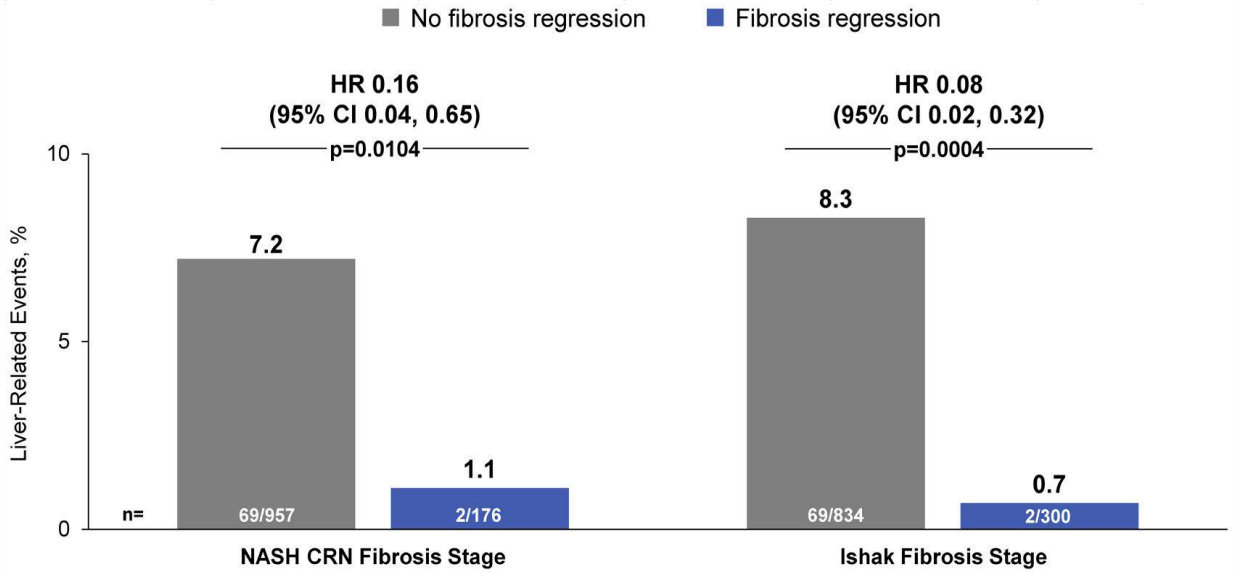
Brunt et al; J Hep 2022

Cirrhosis regression is associated with improved clinical outcomes in patients with MASH

Evidence in Histology

- **Recent**
- **NASH Resolution: No evidence**

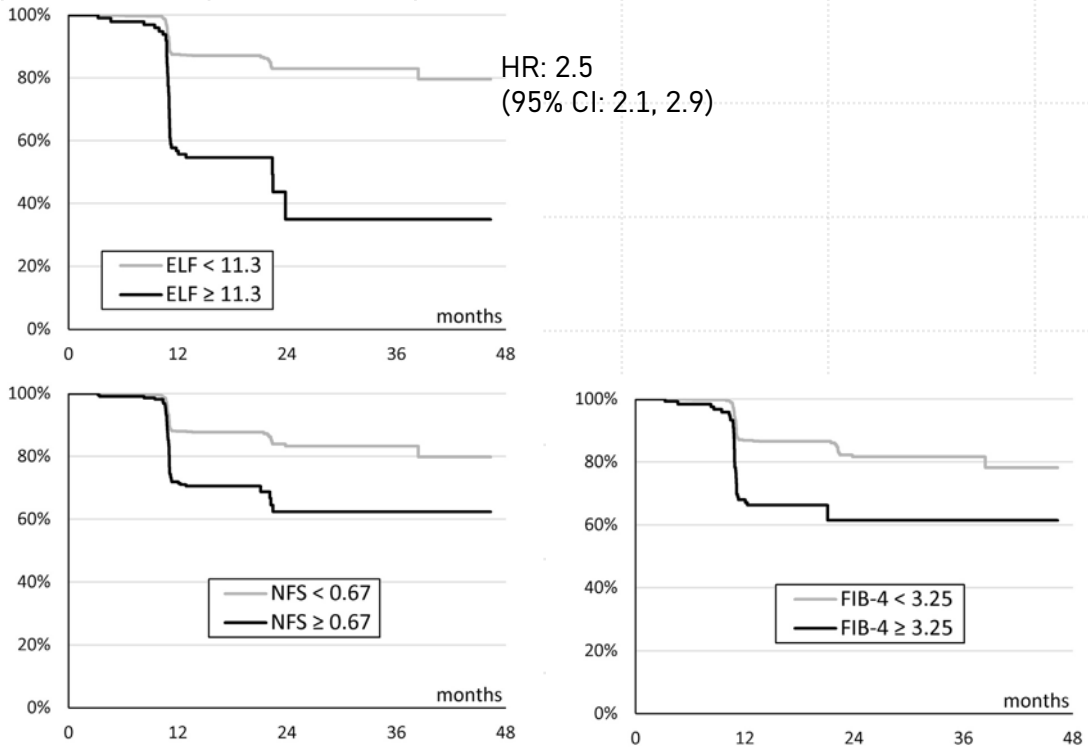




Sanyal et al; Hepatology 2021

NITs as Predictors of Clinical Outcomes (Baseline)

Kaplan-Meier curve for event-free survival of clinical events stratified by blood biomarker/score
(n=1021 NASH with ≥F3,
median follow-up period: 16 months)



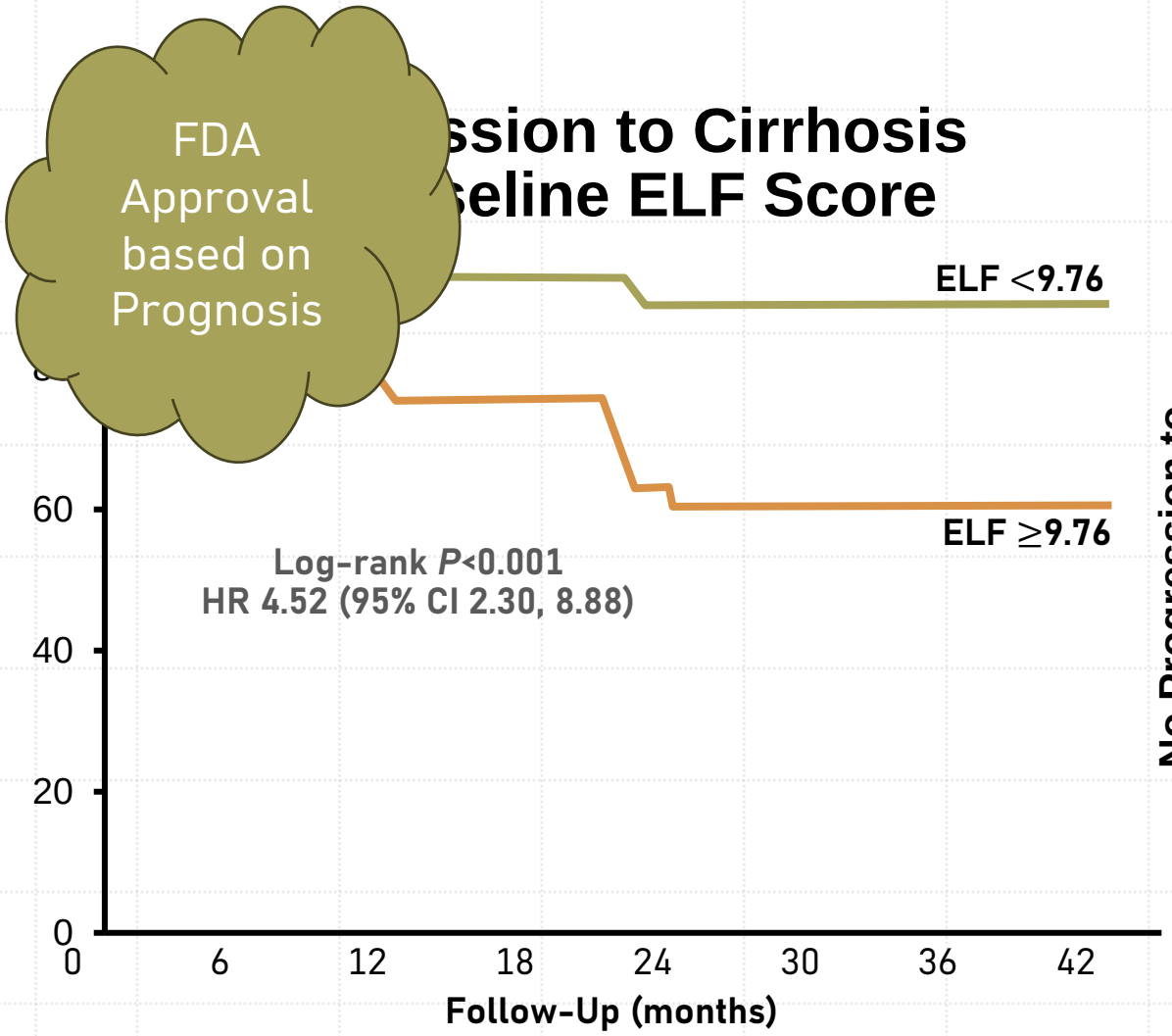
Biomarker	Sens	Spec	PPV	NPV	HR (95% CI)
ELF ≥ 11.3	0.28	0.94	0.48	0.87	2.5 (2.1, 2.9)
NFS ≥ 0.67	0.59	0.76	0.16	0.96	1.8 (1.6, 2.1)
FIB-4 ≥ 3.25	0.59	0.76	0.16	0.96	1.5 (1.4, 1.6)
VCTE ≥ 13.5 kpa	0.59	0.76	0.16	0.96	1.1 (1.1, 1.1)

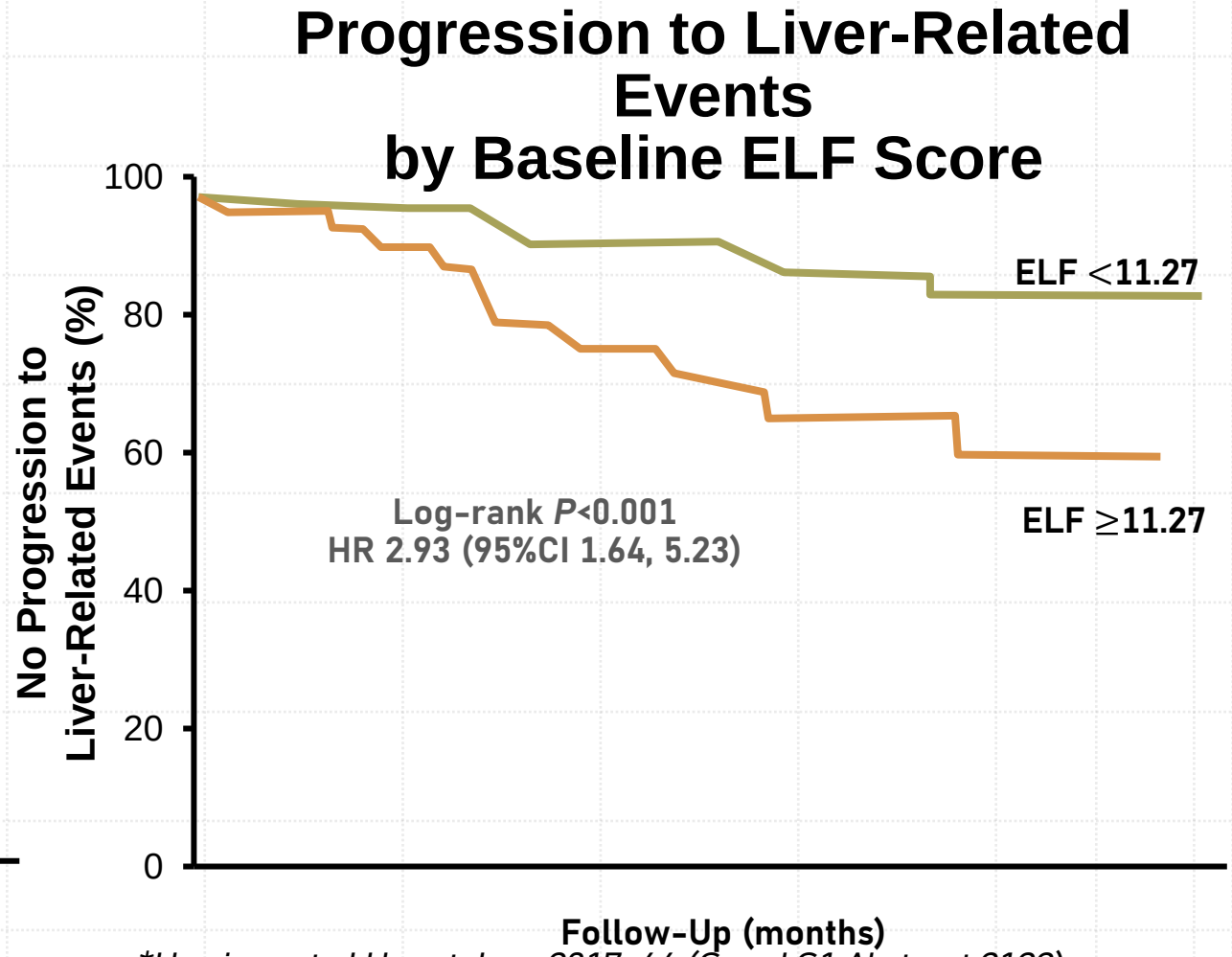
Advanced fibrosis - NAS ≥4 and F ≥3 , **CC** - compensated cirrhosis; **HR**- Hazard ratio Adjusted for Age, Sex, Race, Type 2 Diabetes, BMI, and Baseline NAFLD fibrosis score
PPV -Positive predictive value, **NPV** - Negative predictive value, *n~ 612.

Younossi et al., (2021) Gastroenterology,

ELF Predicts Progression to Cirrhosis and Clinical Events

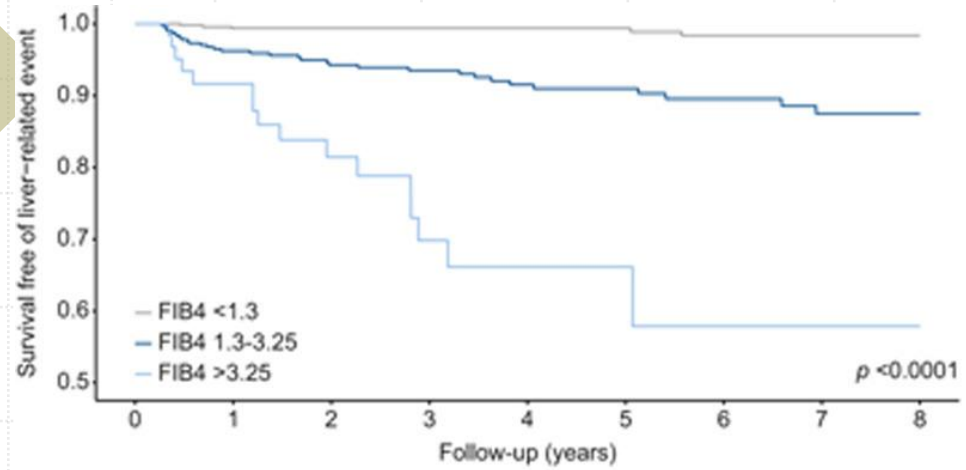
FDA Approval based on Prognosis

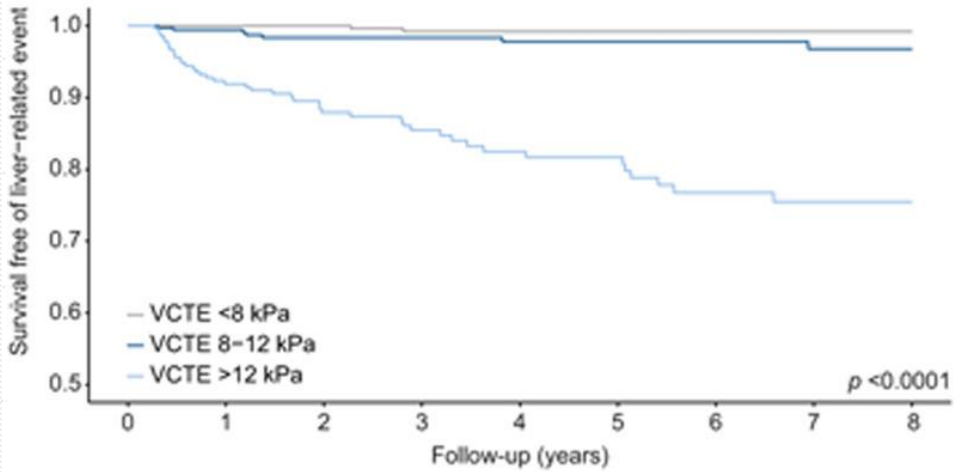


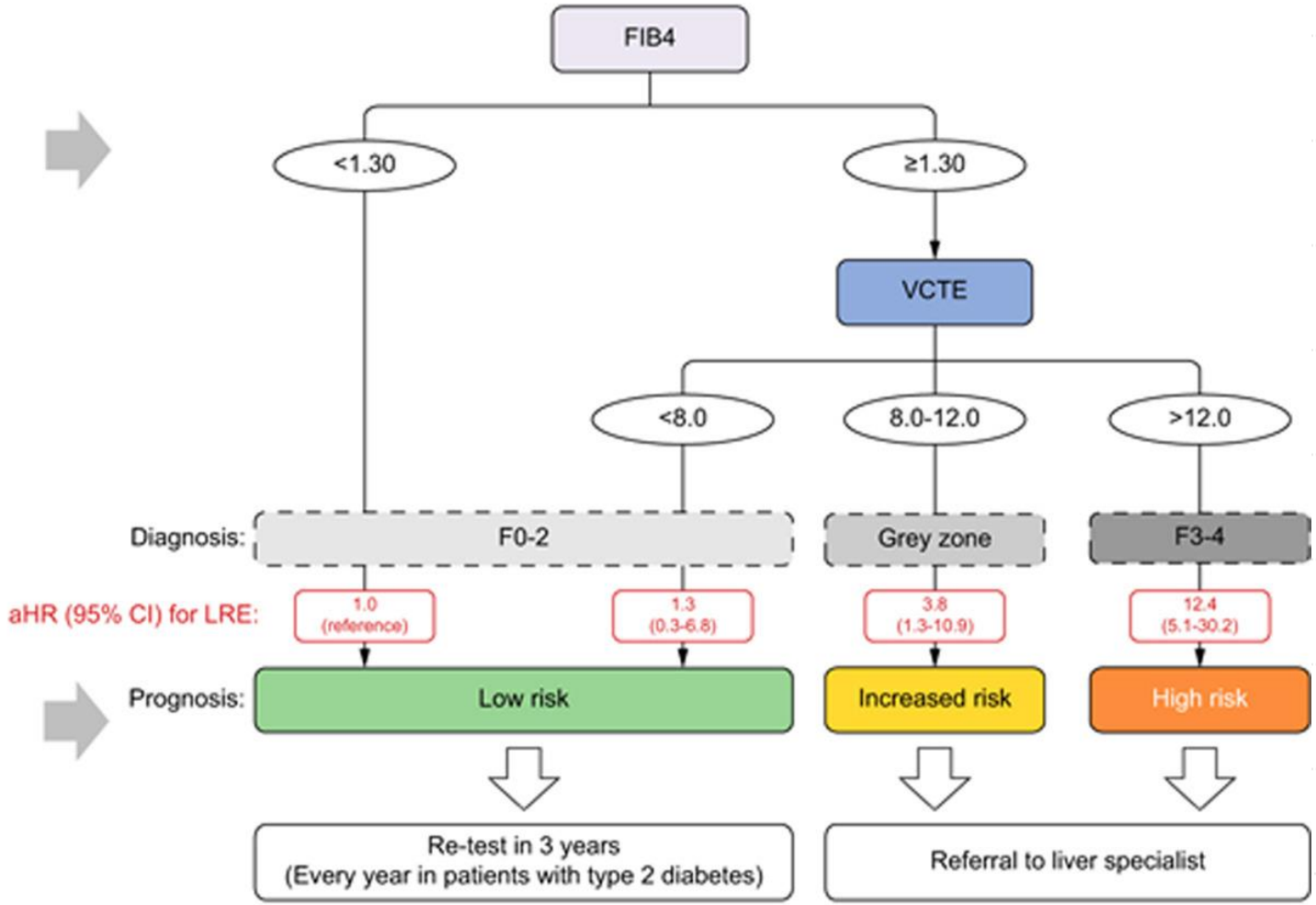


*Harrison et al Hepatology 2017; 66 (Suppl S1 Abstract 2122)
*Simtuzumab trial
* Galectin Trial

VCTE Predicts Clinical Events



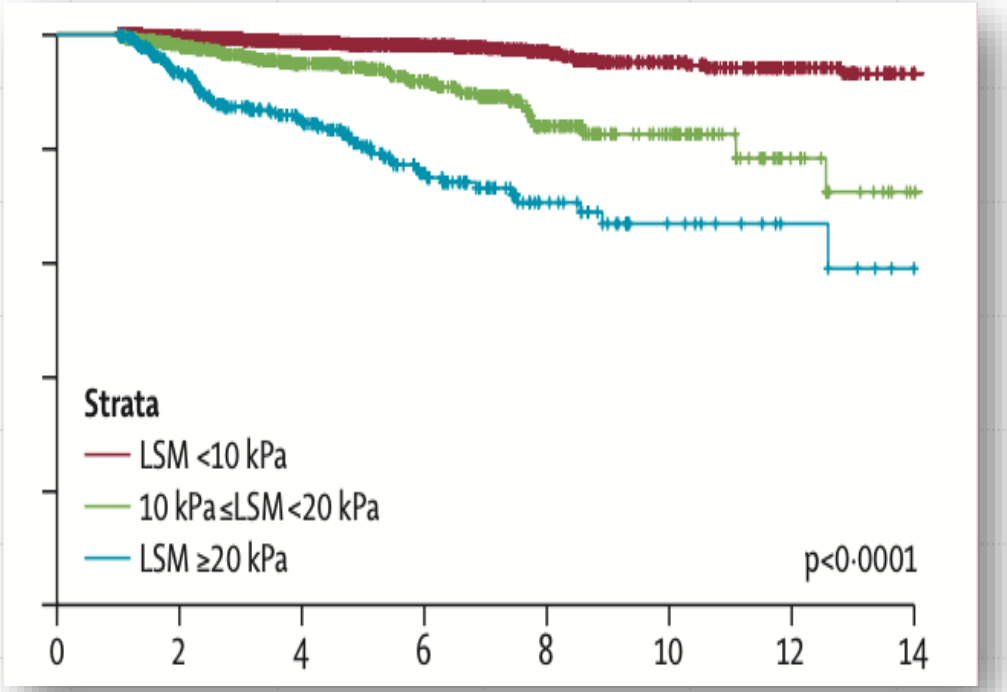




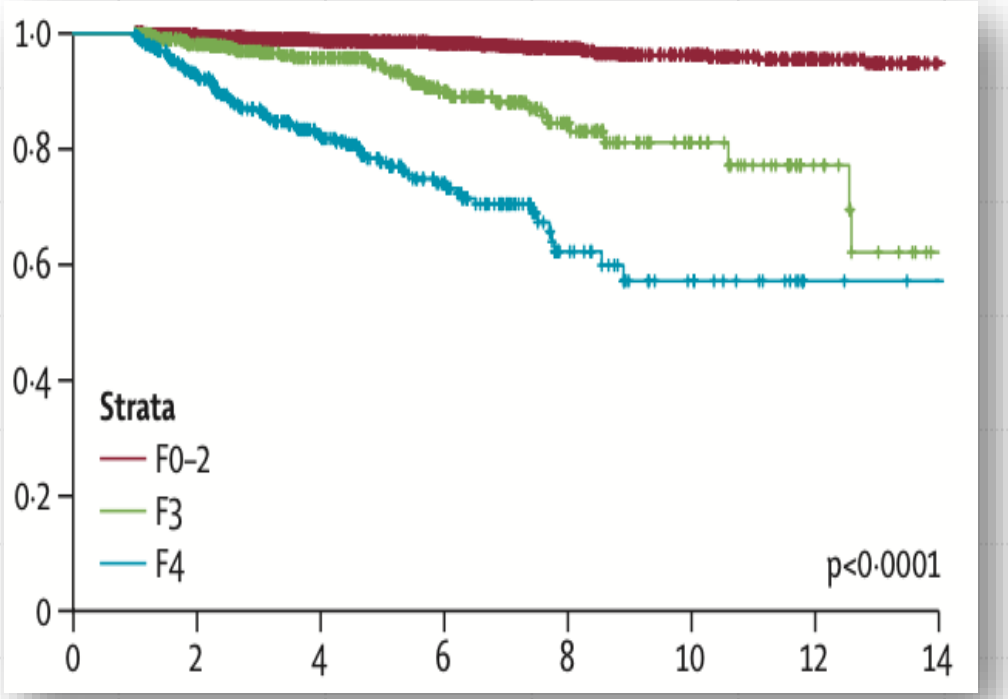
Bousier J et al J Hep 2022

Baseline LSM (VCTE) Predicts Clinical Outcomes as well as liver biopsy in NAFLD

Baseline LSM



Liver biopsy



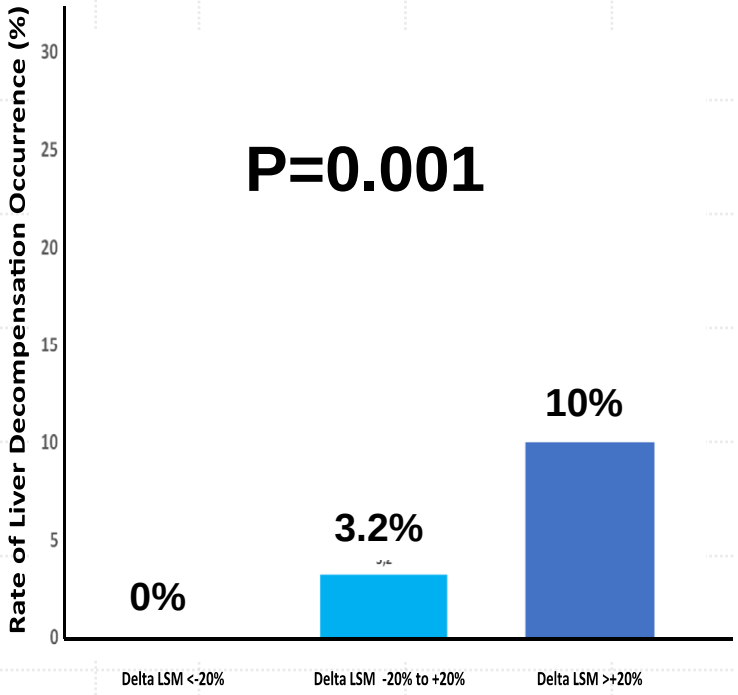
IPD Meta-analysis N= 25 studies ; N= 2518 NAFLD patients; median f-up 57 mo

Courtesy of L. Castera

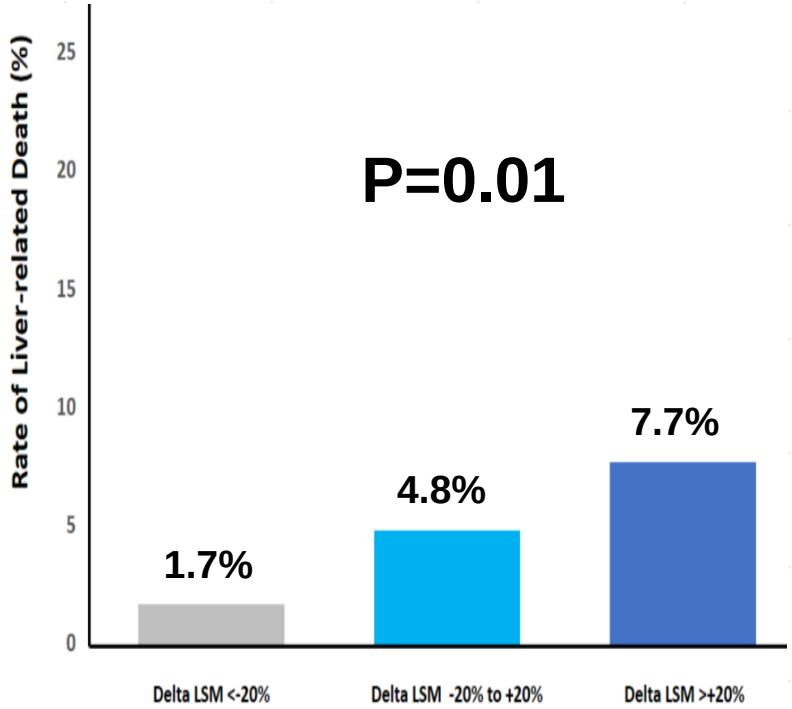
Mozes FE et al. Lancet GH 2023; 8: 704-13

Changes (>20%) in LSM (VCTE) Predict Outcomes in F3-F4

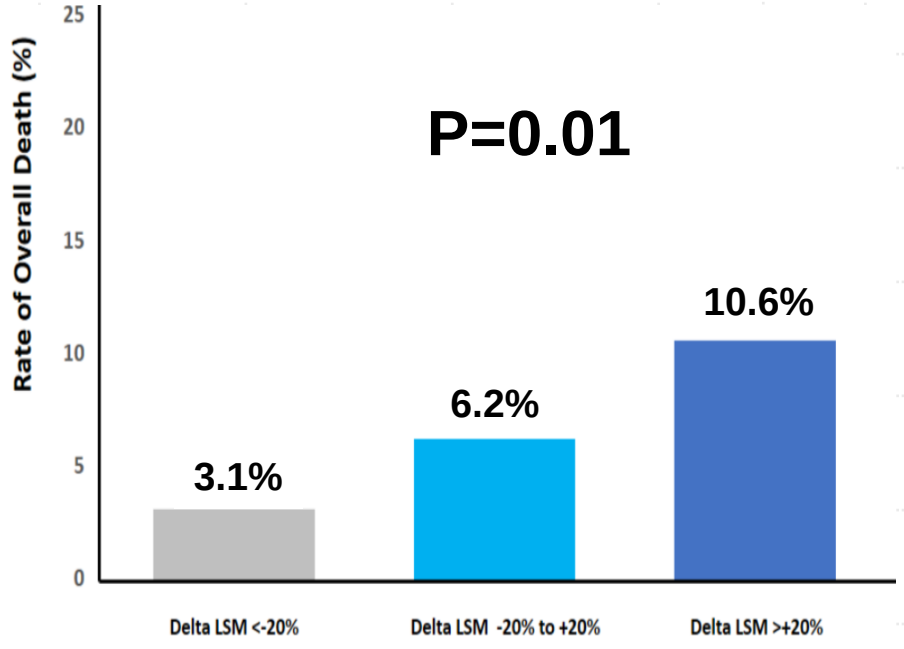
Liver-related events



Liver-related mortality



Overall mortality



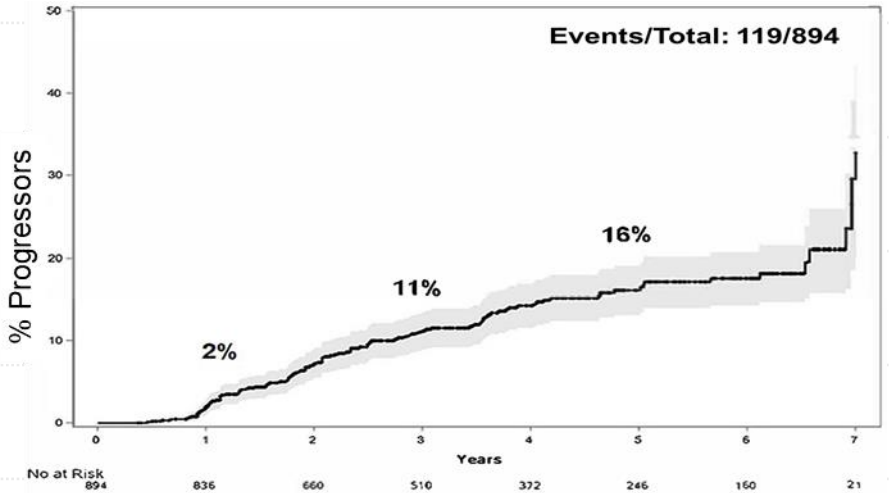
N= 563 NAFLD patients with LSM >10 kPa and repeated LSM; median f-up 35 months

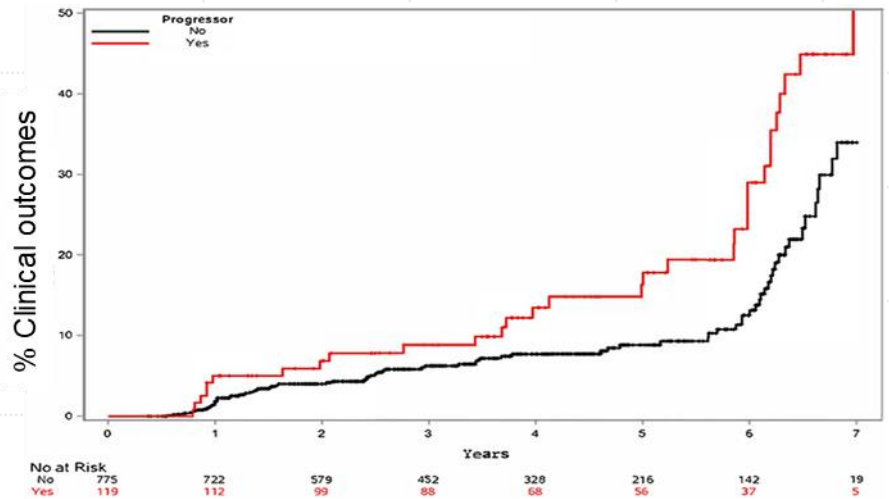
Courtesy of L. Castera

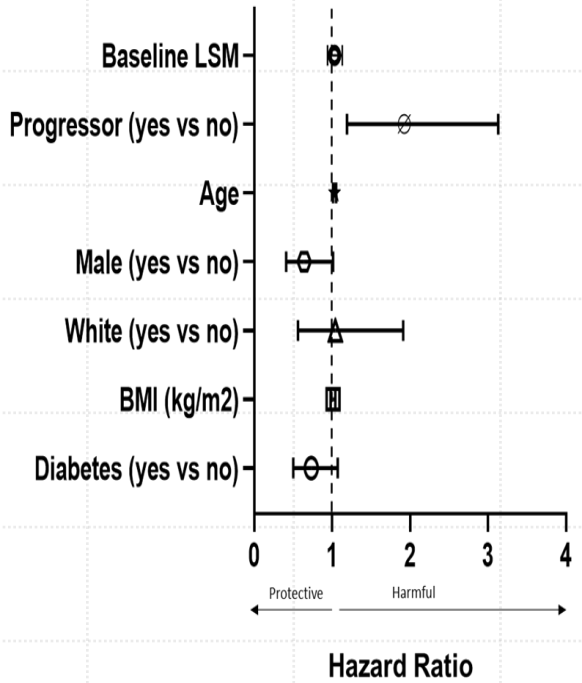
Petta et al. Clinical Gastroenterol Hepatol 2021; 19:806-15

Increase in LSM is independently associated with poor clinical outcomes in NAFLD

- 894 participants with the entire NAFLD spectrum from NASH CRN with prospective protocolized follow up
- Progression= reaching LSM >14.9 kPa in those baseline LSM < 12.1 kPa







	Events	Hazard Ratio (95% CI)	P value [1]
Baseline LSM		1.03 (0.94-1.13)	0.53
Progressor (yes vs no)	31/119	**1.93 (1.19-3.13)**	**<0.01**
Age		**1.03 (1.01-1.05)**	**<0.01**
Male (yes vs no)	26/330	0.64 (0.41-1.01)	0.056
White (yes vs no)	97/721	1.04 (0.56-1.91)	0.91
BMI (kg/m2)		1.01 (0.95-1.04)	0.51
Diabetes (yes vs no)	53/427	0.73 (0.50-1.07)	0.11

[1] Covariate Wald p-value

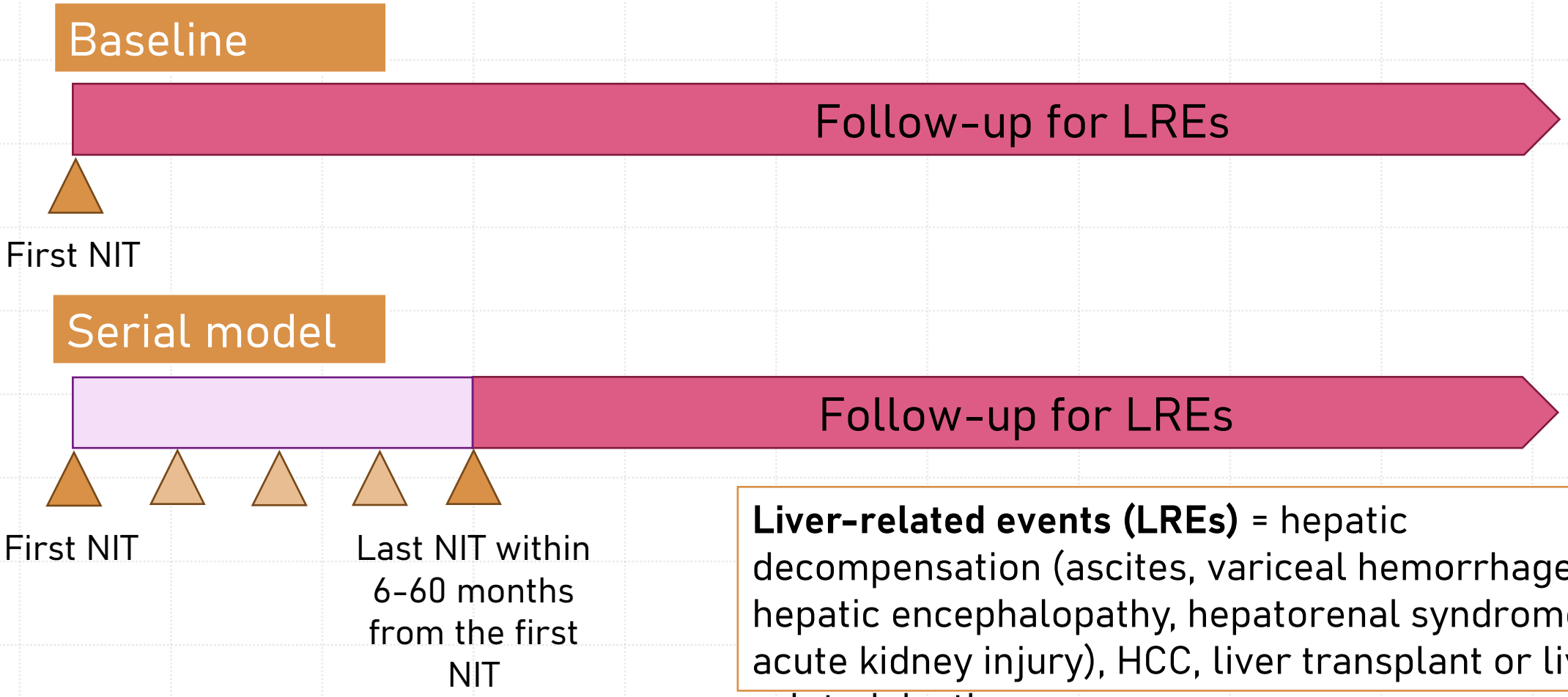
Gawrieh s et al. Abstract #72, The Liver Meeting 2022, Washington, DC

Serial vibration controlled transient elastography-based Agile scores predict liver-related events in metabolic dysfunction-associated steatotic liver disease – a multicenter cohort study of 16,603 patients

Huapeng Lin, Hye Won Lee, Terry Yip, Emmanuel Tsochatzis, Salvatore Petta, Elisabetta Bugianesi, Masato Yoneda, Ming Hua Zheng, Hannes Hagstrom, Jerome Boursier, Jose Luis Calleja, Geoerge Goh, Wah Kheong Chan, Manuel Romero-Gomez, Arun Sanyal, Victor de Ledinghen, Philip Newsome, Jaian-Gao Fan, Laurent Castera, Michelle Lai, Stephen Harrison, Celine Fournier-Poizat, Grace Wong, Grazia Pennisi, Angelo Armandi, Atsushi Nakajima, Wen-Yue Liu, Ying Shang, Marc de Saint-Loup, Elba Llop, Kevin Kim Jun The, Carmen Lara-Romero, Amon Asgahrpour, Sara Mahgoub, Mandy Chan, Clemence Canivet, Rocio Gallego-Duran, Seung Up Kim, Vincent Wong

Courtesy of Vincent Wong

Study design



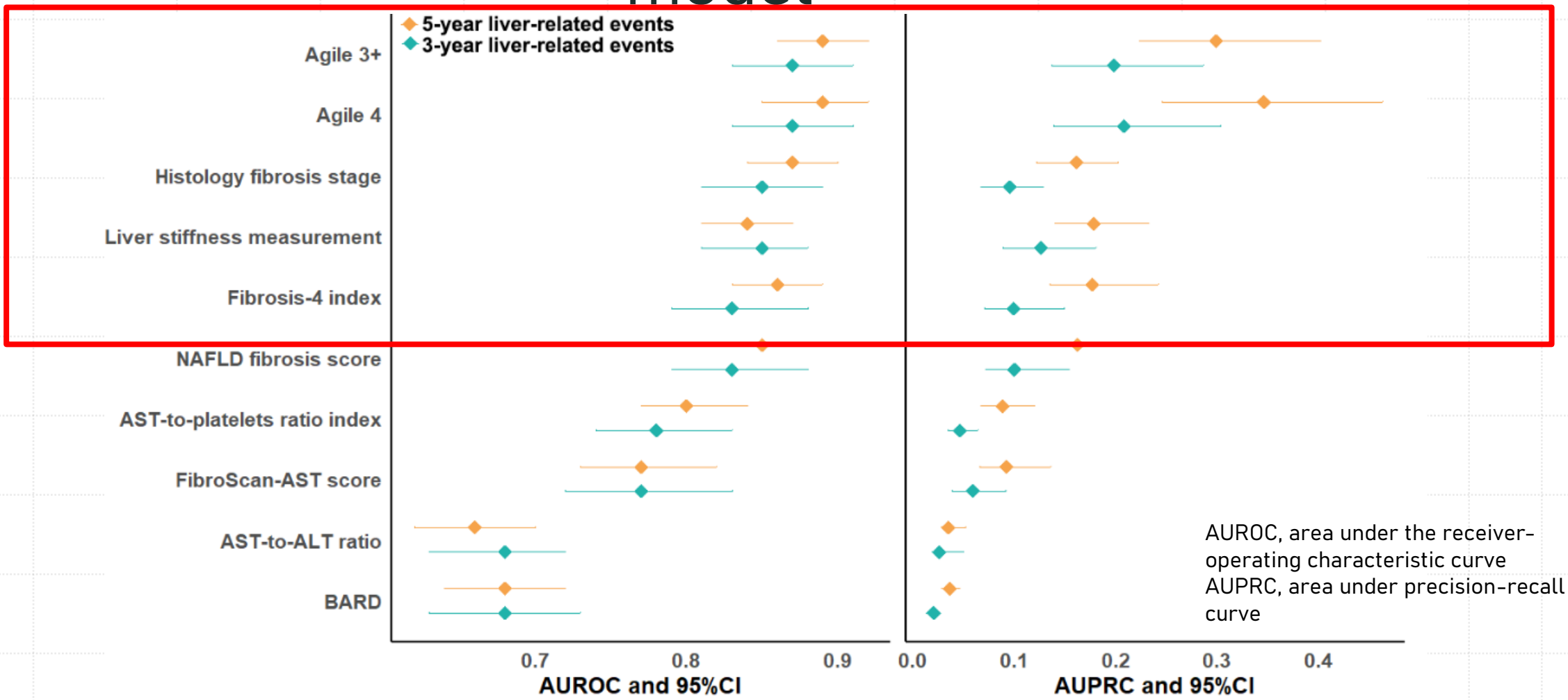
Liver-related events (LREs) = hepatic decompensation (ascites, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome-acute kidney injury), HCC, liver transplant or liver-related death

Courtesy of Vincent Wong

Liver-related events at a median follow-up of 52 months

Liver-related events	N
Hepatocellular carcinoma	139
Hepatic decompensation	209
Ascites	134
Spontaneous bacterial peritonitis	16
Variceal hemorrhage	69
Hepatic encephalopathy	53
Hepatorenal syndrome	9
Liver transplantation	15
Liver-related death	65
Total	**316**

Prognostic performance of NITs in the baseline model



AUROC, area under the receiver-operating characteristic curve
AUPRC, area under precision-recall curve

Percentage change of Agile 3+ and LREs

Baseline	Percentage change	% of patients	LRE per 1000 person-years
Low risk	>20% reduction	20.2	0.7
	Stable	16.8	0.5
	>20% increase	38.5	0.8
Intermediate risk	>20% reduction	3.9	1.1
	Stable	4.2	2.7
	>20% increase	2.4	3.2
High risk	>20% reduction	3.0	2.6
	Stable	10.2	28.2
	>20% increase	0.5	37.4

What magnitude of LSM (VCTE) Decline is Relevant ?

20%

Petta et al. CGH 2021

de Franchis et al. J Hepatol 2022

Courtesy of L. Castera

25%

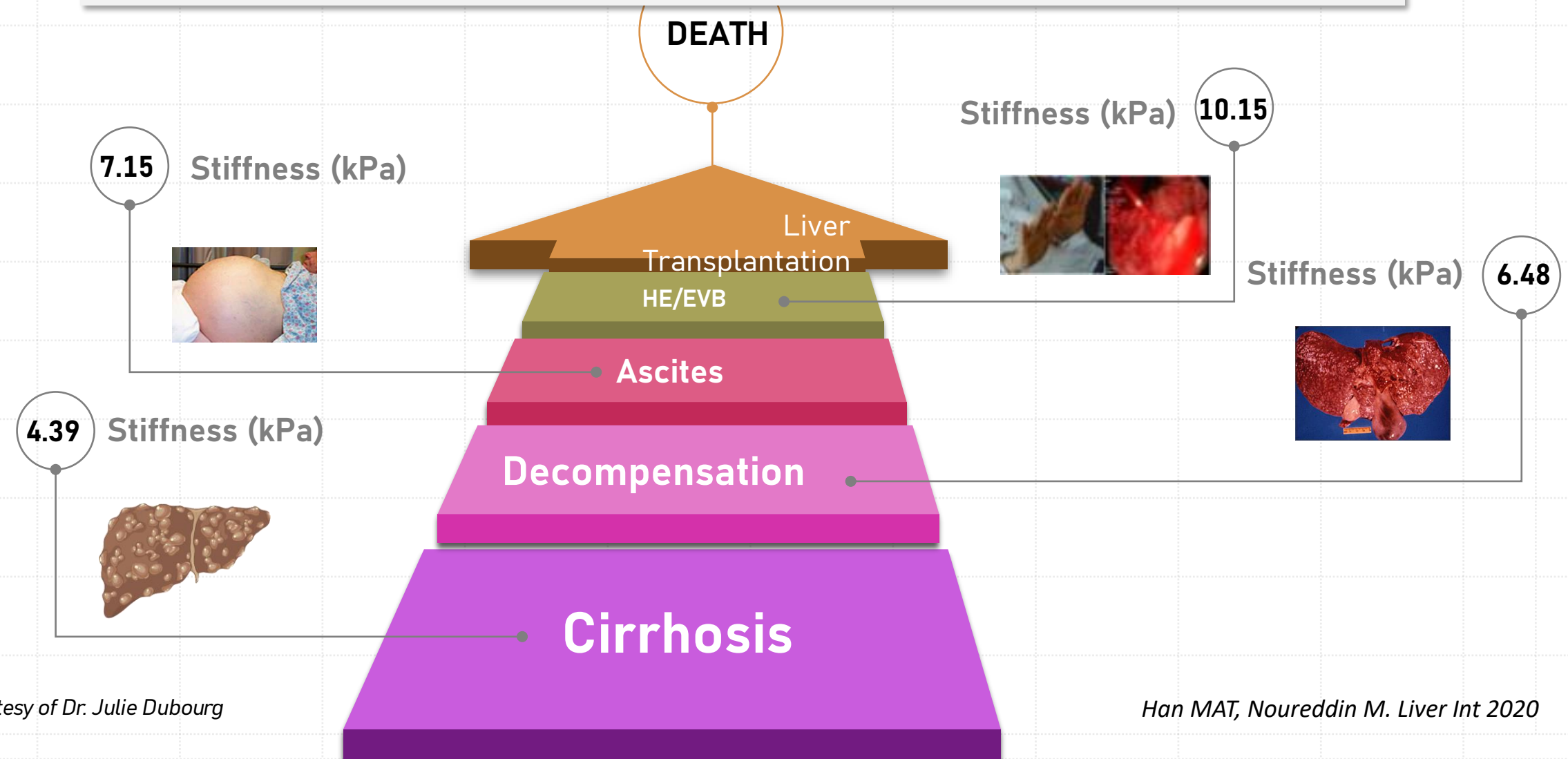
Harrison et al. J Hepatol 2020

30%?

Aim Conservatively

MRE Predicts Liver Outcomes

Odds of Decompensation increase as liver stiffness increase (OR 3.28)



Slide courtesy of Dr. Julie Dubourg

Han MAT, Noureddin M. Liver Int 2020

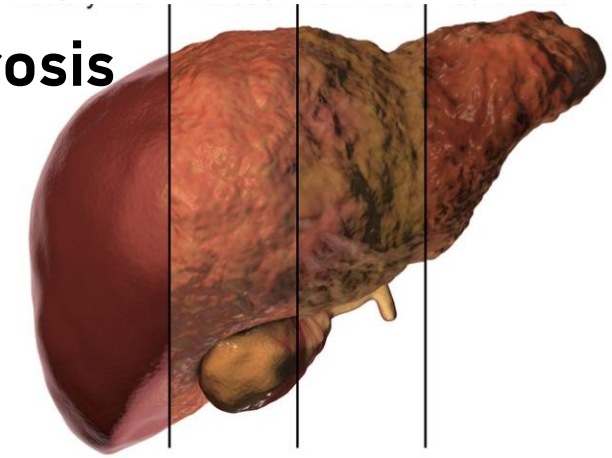
Diagnosis/Staging

Monitoring Response to Therapy

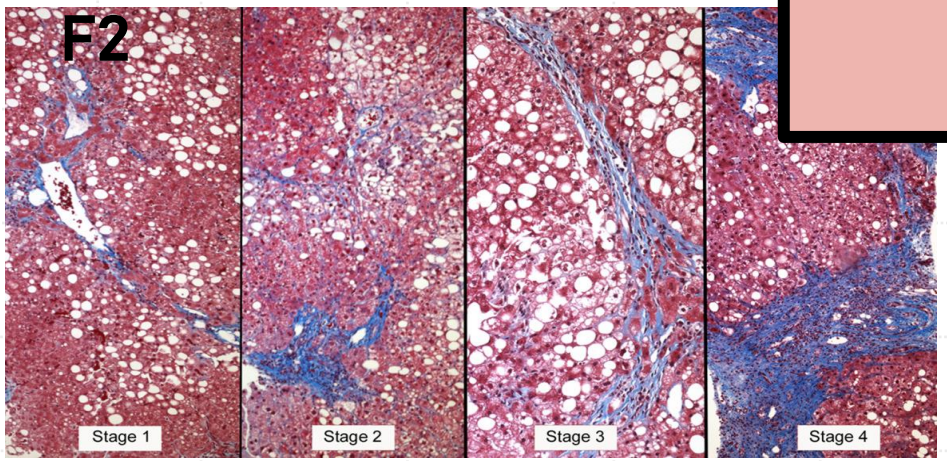
Predicting Outcome

NITs Reasonably Likely to Predict Outcomes

Fibrosis

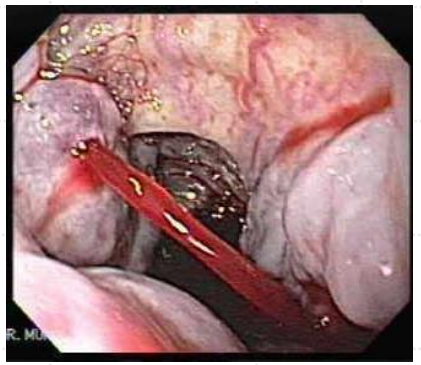


MASH with NAS ≥ 4 + ≥ F2



Let's Backpaddle

Major Clinical Liver E
(MALO)

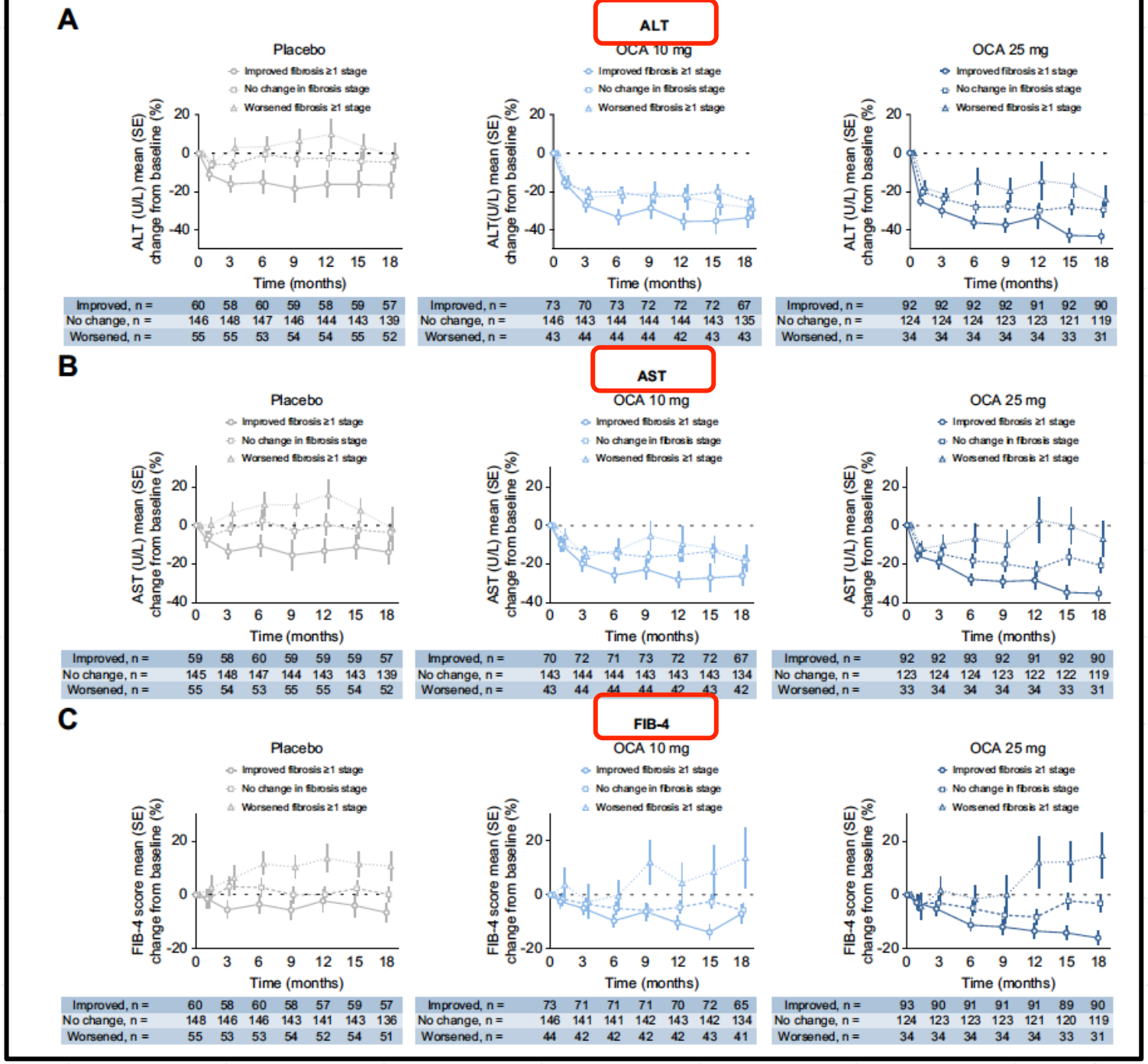


Longitudinal Assessment of NITs from the REGENERATE study

Patients with ≥-stage fibrosis improvement had the greatest improvement in NITs, while patients with ≥1-stage fibrosis worsening typically showed no NIT improvement.

AUROC values for each of these were suggestive of only weak association

NIT improvements observed in REGENERATE are associated with fibrosis improvement at Month 18, individual NIT changes are not likely to be effective univariate clinical predictors of fibrosis improvement by Month 18.



Rinella et al; J Hep 2022

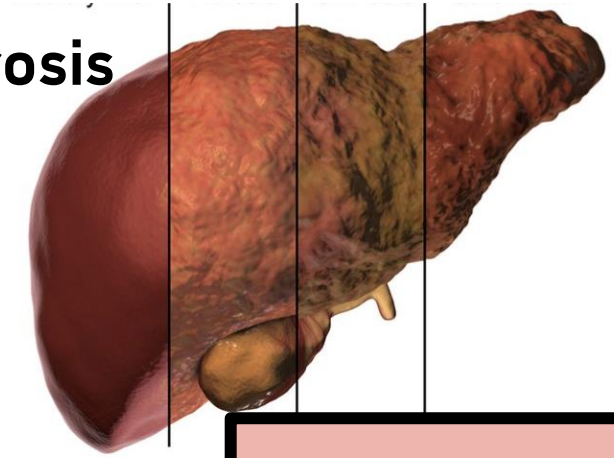
Diagnosis/Staging

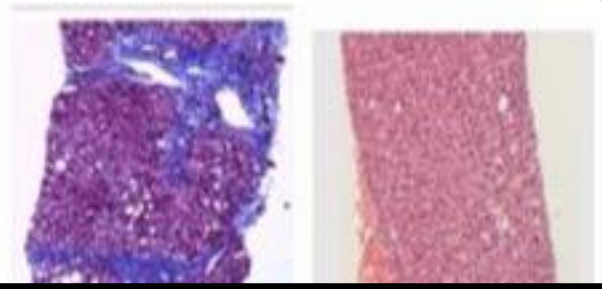
Monitoring Response to Therapy

Predicting Outcome

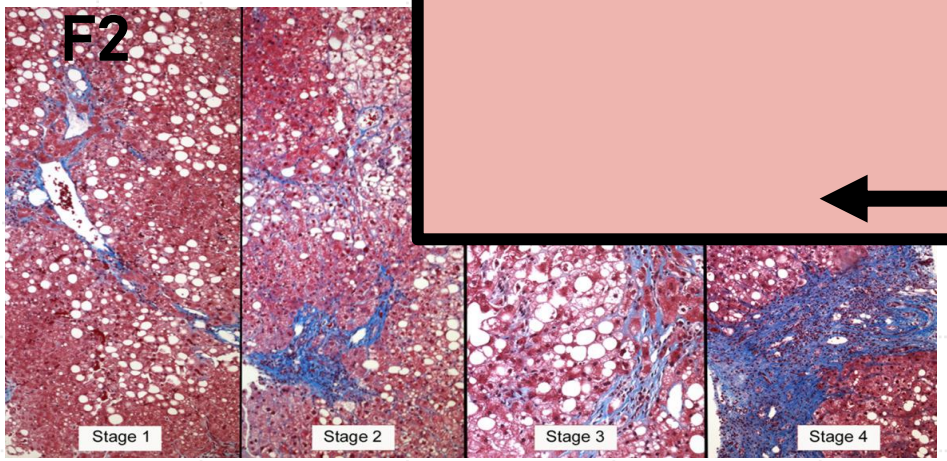
NITs Reasonably Likely Predict Outcomes

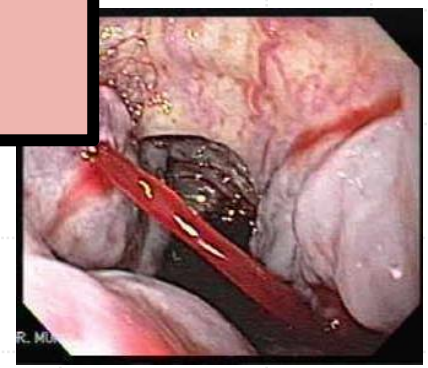
Fibrosis





MASH with F2





Let's Backpaddle

AASLD: Noninvasive parameters for 'at risk' MASH

Identification of 'at risk' NASH				
Combined	FAST	≥0.67	<0.35	• ≤0.35 (sensitivity 90%) • ≥ 0.67 (specificity 90%) • In validation cohorts, the PPV of FAST ranged between 0.33 and 0.81.(1-2)
Combined	MEFIB	FIB-4 ≥ 1.6 plus MRE ≥ 3.3 kPa	FIB-4 < 1.6 plus MRE < 3.3 kPa	• Sequential approach identifies patients with at least stage 2 fibrosis with > 90% PPV.(3)
	MAST	≥0.242	≤0.165	0.242 (specificity 90%), 0.165 (sensitivity 90%)(4)
	cT1	≥ 875 msec	< 825 msec	• Requires further validation as data is derived from one study(4)

Newsome et al. Lancet Gastro Hep 2020 [1]; Woreta et al PLoSONE 2022 [2]; Jung et al. Gut 2021 [3]; Noureddin M et al. J Hepatol 2022 [4] Andersson et al. CGH 2022 [5]

Composite scores for Identifying at-risk MASH
(NAS ≥4 + F2 ≥2)

- **FAST** = CAP + AST + LSM (VCTE)

$$\frac{e^{-1.65 + 1.07 \times \mathrm{Ln(LS)} + 2.66\times10^{-8} \times \mathrm{CAP}^3 - 63.3 \times \mathrm{AST}^{-1}}}{1+e^{-1.65 + 1.07 \times \mathrm{Ln(LS)} + 2.66\times10^{-8} \times \mathrm{CAP}^3 - 63.3 \times \mathrm{AST}^{-1}}}$$

- Rule-in: **≥ 0.67**
- Rule-out: **≤ 0.35**
- Grey-zone: 0.35~0.67

Newsome P et al. Lancet GH 2020; 5: 362-73

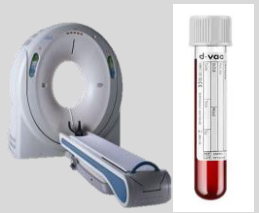
- **MAST** = PDFF + AST + LSM (MRE)

$$\frac{e^{-12.17 + 7.07 \log \mathrm{MRE} + 0.037\ \mathrm{PDFF} + 3.55 \log \mathrm{AST}}}{1+e^{-12.17 + 7.07 \log \mathrm{MRE} + 0.037\ \mathrm{PDFF} + 3.55 \log \mathrm{AST}}}$$

- Rule-in: **> 0.242**
- Rule-out: **<0.165**
- Grey zone: 0.165~0.242

Noureddin M et al. J Hepatol. 2022; 76: 781-87

- **MEFIB** = LSM (MRE) + FIB-4
  - Rule-in: **MRE ≥ 3.3 kPa + FIB-4 ≥ 1.6**
  - Rule-out: **MRE < 3.3 kPa + FIB-4 < 1.6**
  - Grey-zone: neither rule-in nor rule-out

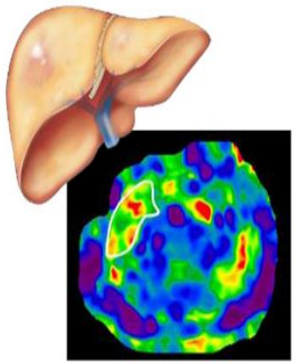


Jung et al. Gut 2021; 70: 1946–53

MRE is Predicts Liver Outcomes

1 KaP ~
OR of 3ish

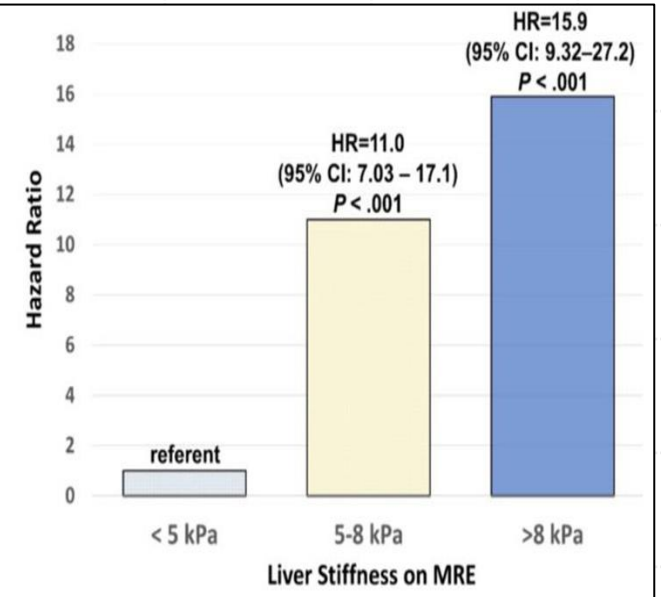
Underwent magnetic resonance elastography

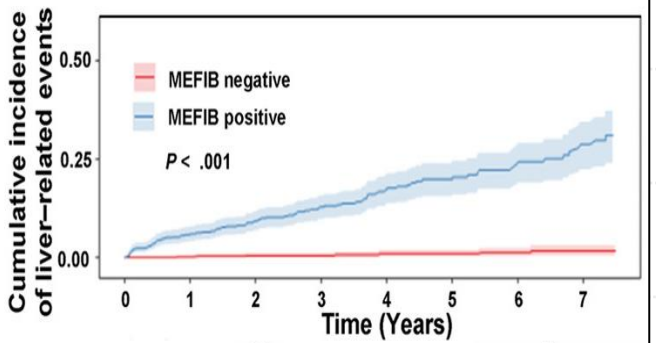


Liver stiffness assessed by MRE is associated with development of ascites, hepatic encephalopathy and varices needing treatment

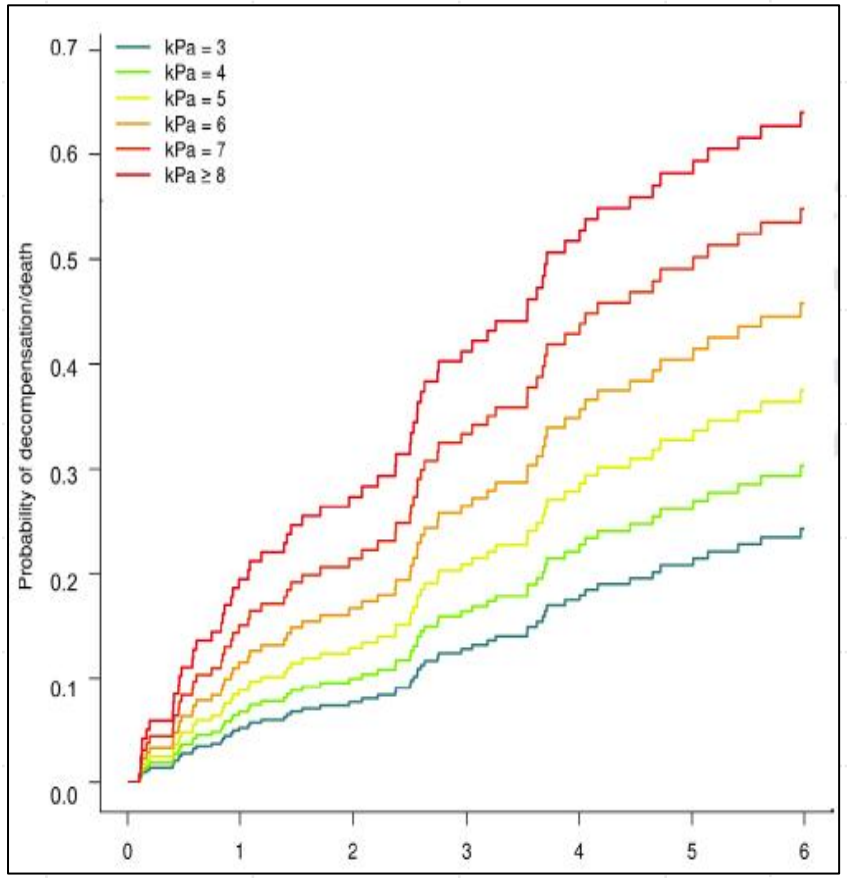
The MEFIB combination of MRE and FIB-4 (defined as positive when MRE ≥ 3.3kPa and FIB-4 ≥ 1.6) has excellent negative predictive value for hepatic decompensation.

Ajmera et al; Gastro 2022



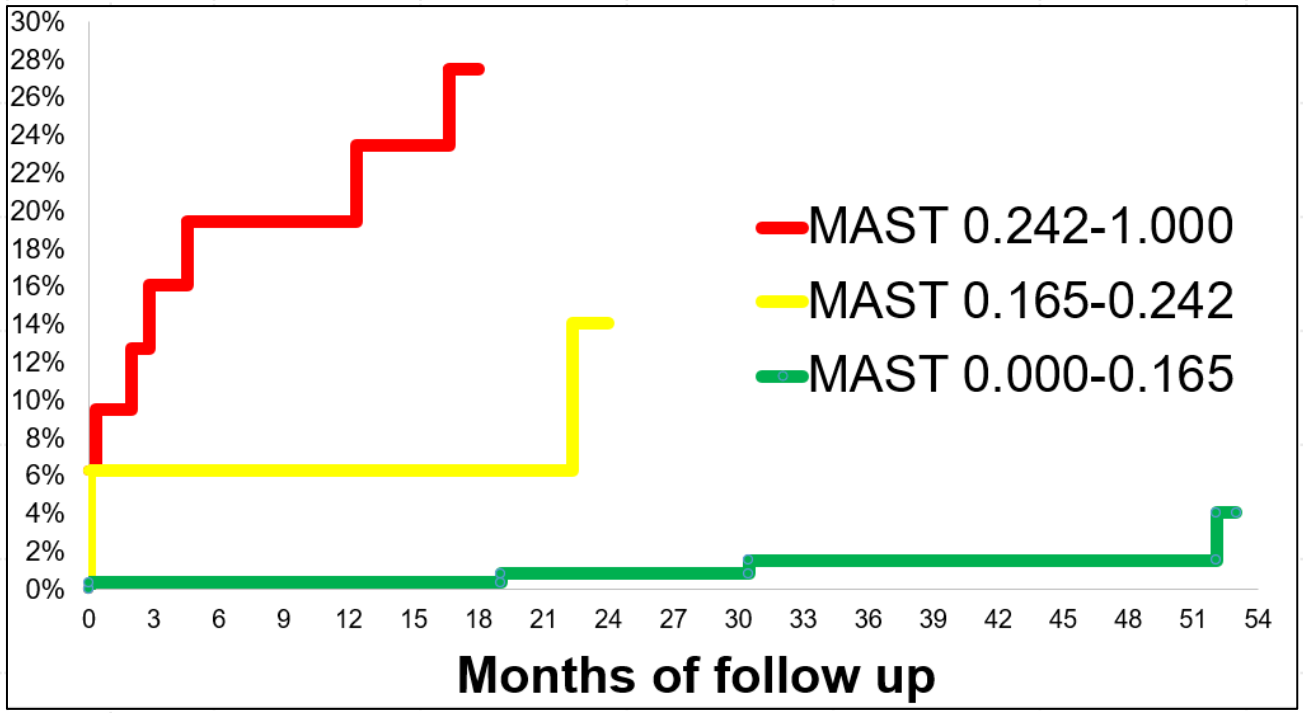


Gastroenterology



Gindener T…Allen A; CGH 2021

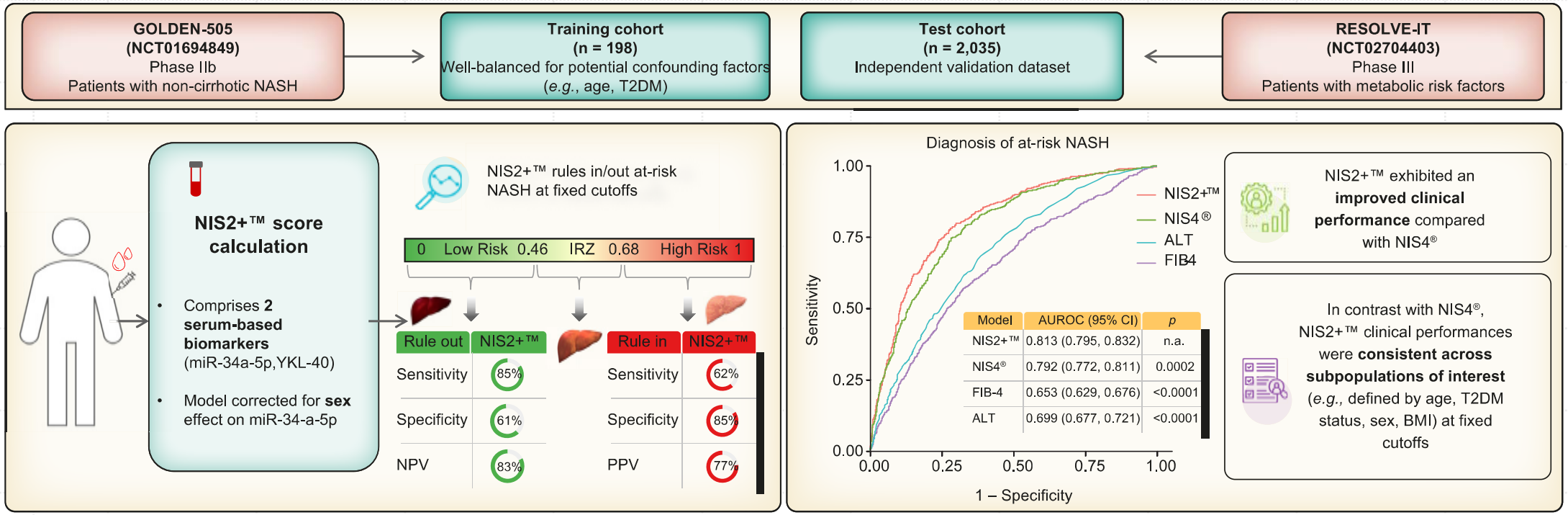
The MAST Score is Accurate in Predicting Major Adverse Liver Outcome (MALO), Hepatocellular Carcinoma, Liver Transplant, and Liver-Related Death



- MAST score accurately:
  - Identifies NASH patients at highest risk for disease progression
  - Predicts up to 22-fold increased risk of adverse outcomes (MALO, liver transplant, HCC, and liver-related death)
  - **C statistic of prediction: 0.92**

Troung E; ..Noureddin M; CGH 2023

NIS-2 score



NIS2+™ detects at-risk NASH non-invasively in patients with metabolic risk factors and could optimize screening for clinical trials and routine practice

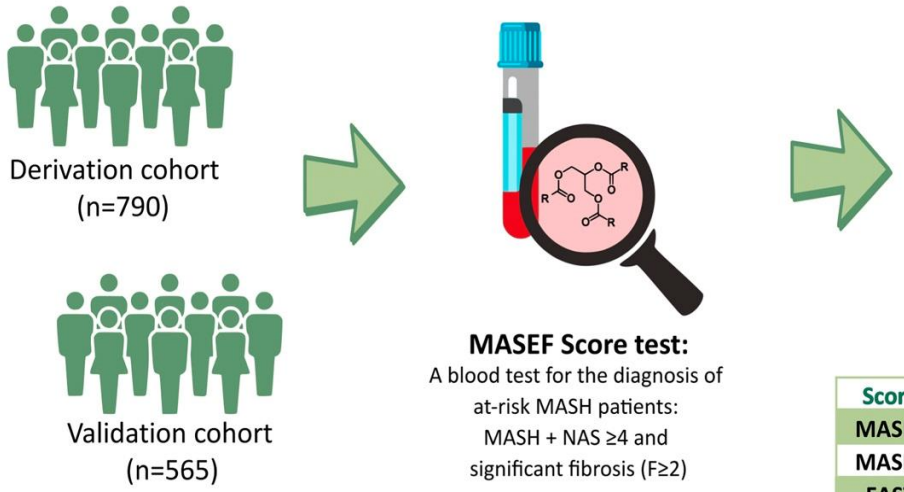
Harrison et al; J Hep 2023

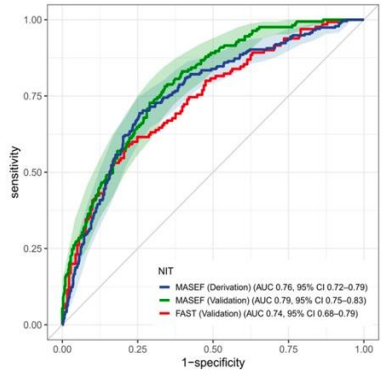
The serum identification of At-Risk MASH: The Metabolomics-Advanced steatohepatitis fibrosis score (MASEF)

- Metabolomics serum-based test: 12 lipids, BMI, AST and ALT
- Derivation: 790 Validation:565

Need More Data

Serum Identification of At-Risk MASH: The Metabolomics-Advanced Steatohepatitis Fibrosis Score (MASEF)





Score	N	Sample	ROC area	Sensitivity	Specificity	PPV	NPV
MASEF	790	Derivation	0.756	0.694	0.744	0.534	0.852
MASEF	565	Validation	0.789	0.782	0.652	0.481	0.879
FAST	311	Validation	0.736	0.585	0.790	0.667	0.726

The MASEF score is blood-based test that non-invasively indentifies patients with at-risk MASH

MASEF score could be used alternatively to LSM by VCTE in the algorithm that is currently recommended by several guidance publications

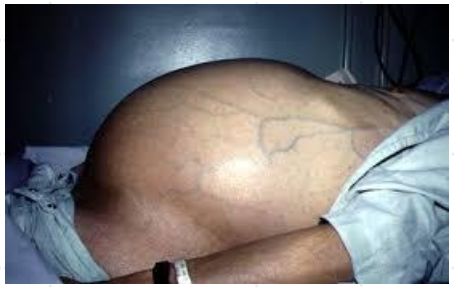
Noureddin, Truong, Mayo, et al. *Hepatology.*

HEPATOLOGY

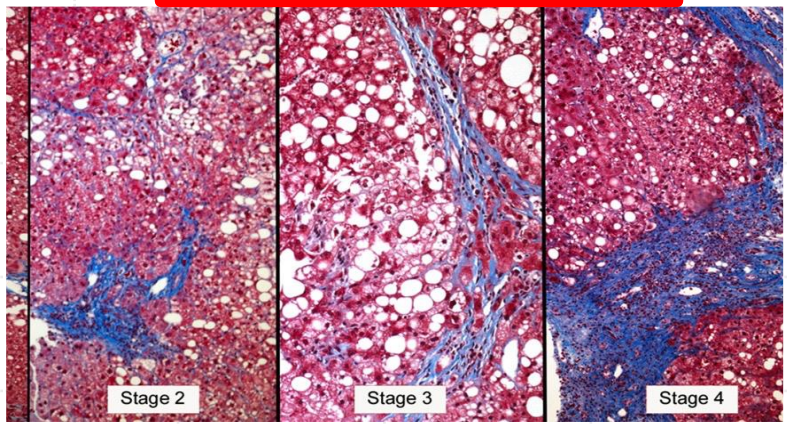
"Potential Proposals for the Hopefully Near Future"

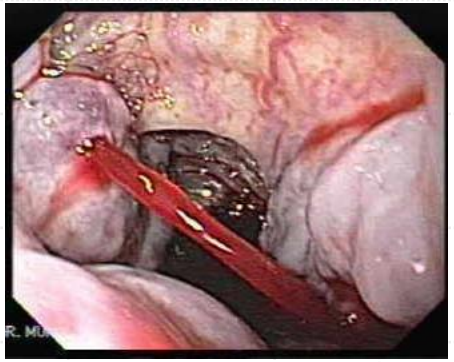
Noninvasive Biomarkers as Surrogates to MALO: Where Are We Today

Closing the Gaps

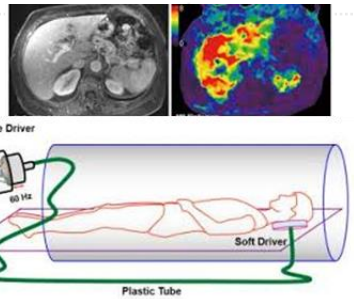


??? NASH Resolution
Fibrosis Improvement





Surrogate

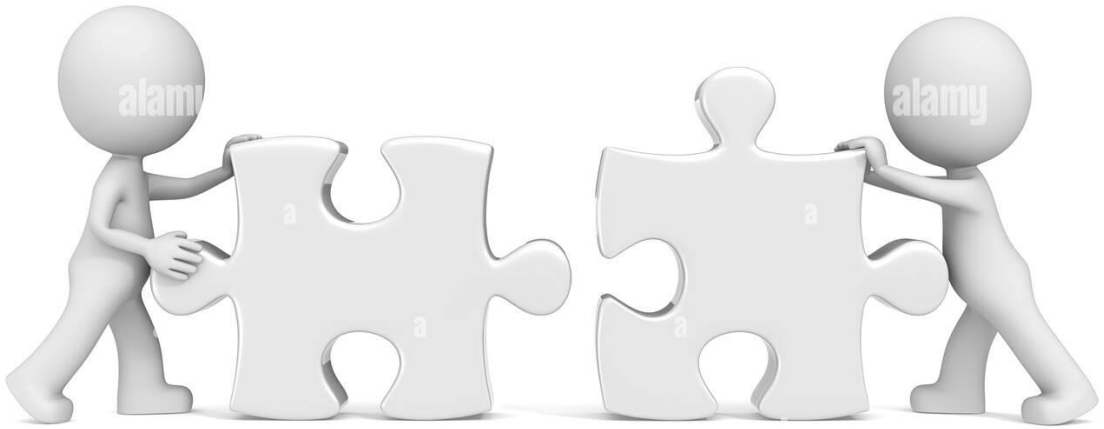


Non-invasive Biomarkers

Outcome

Prognostic Data

1- FIB-4
2- ELF (FDA approval)
3- Emerging: Pro-C3
4- MELD labs
5- Clinical (e.g. progression of varices, spleen, Platelets)



Serum + Imaging

1) VCTE & MALO
   Bousier J et al J Hep 2022

2) VCTE changes
   Petta et al; CGH 2021
   Mozes et al. Lancet GH 2023
   Serra-Burriel M; Lancet 2023
   Lin et al; JAMA 2024

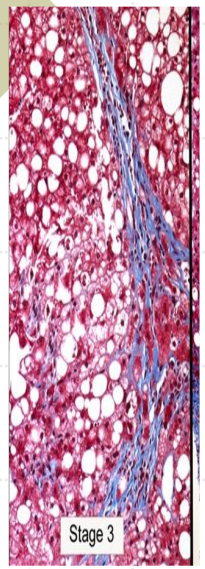
3) VCTE ><10 kPa or decrease by 5
   Baveno VII

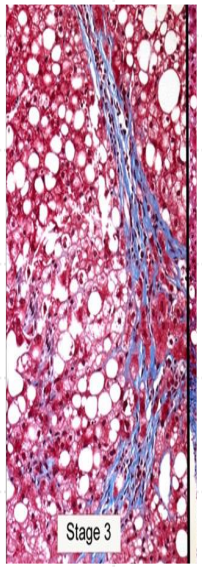
4) MRE & MALO
   - Han et al; Liv Int 2021
   - Gindener et al; CGH 2021
   - Ajmera el al; Gastro 2022

5) MAST
   - Troung et al; CGH 2023

6) MEFIB
   - Ajmera el al; Gastro 2022

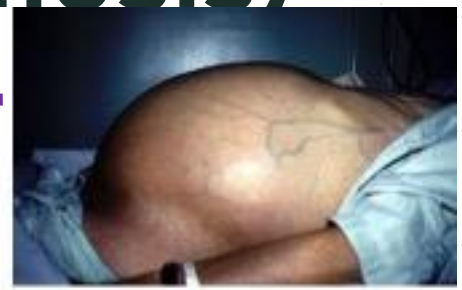
The Status Quo
Phase 3 At-risk MASH (Pre-Cirrhosis)

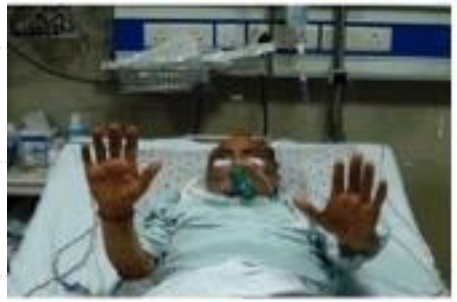




Primary End Point:
NASH Resolution
Fibrosis Improvement

Subpart H





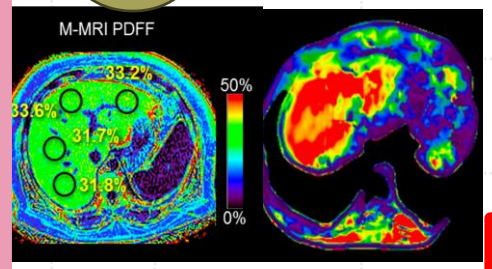
Progression to cirrhosis on histopathology

Outcome

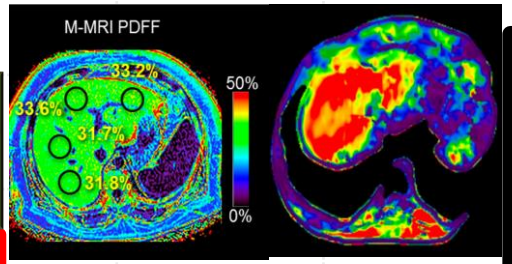
MOA: Metabolic Drug (E.g.: GLP1 or DNL drug)
Phase 3 At-Risk MASH Pre-Cirrhosis

Proposal

Inclusion



6 months interim Analysis
12 months Trial



Primary End Points

- >30% in MRI-PDFF + one of
- >30% VCTE
- ELF to <9.8 or by 0.5

Caution w GLP-1

Secondary:

- MAST /MEFIB
- ALT
- Pro-C3

Experimental (Blood):

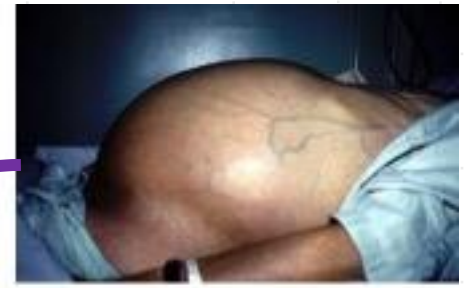
- MASEF
- NIS2

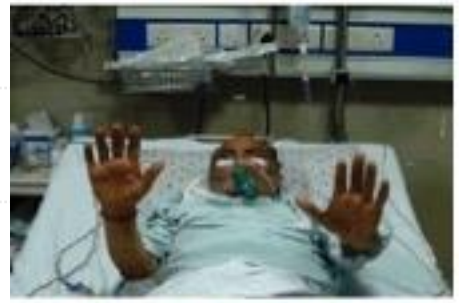
Labs

Labs

Support H

Outcome





Progression to cirrhosis

Presenter (Noureddin) suggestions
Needs Further consensus

Conclusions

- Biopsy issues
- Serum NITs have made a significant progress since the last assessment for NASH/MASH RCT endpoints
- Imaging NITs have made greater progress
- The combination of both can give us confidence
- **NITs are Reasonably likely to Predict Outcomes**
- **Cirrhosis trials can be the first to by 100% NITs dependent**
- **Subpart H can continue to be a safety valve**
- **We have data, we need more but it is time to re-organize our thoughts**

Thank you

- The Best Way to Predict the Future is to Create It……

  Abraham Lincoln

•@noureddinmd