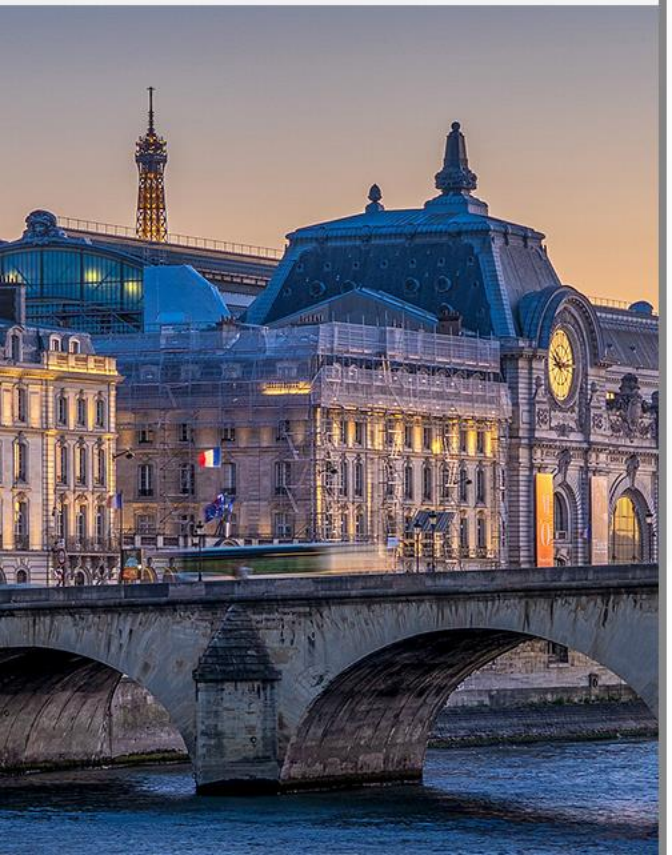
PARIS
MASH
MEETING

10th edition

September 5 & 6 2024
Institut Pasteur, Paris



# Best practices in disease monitoring of MASH

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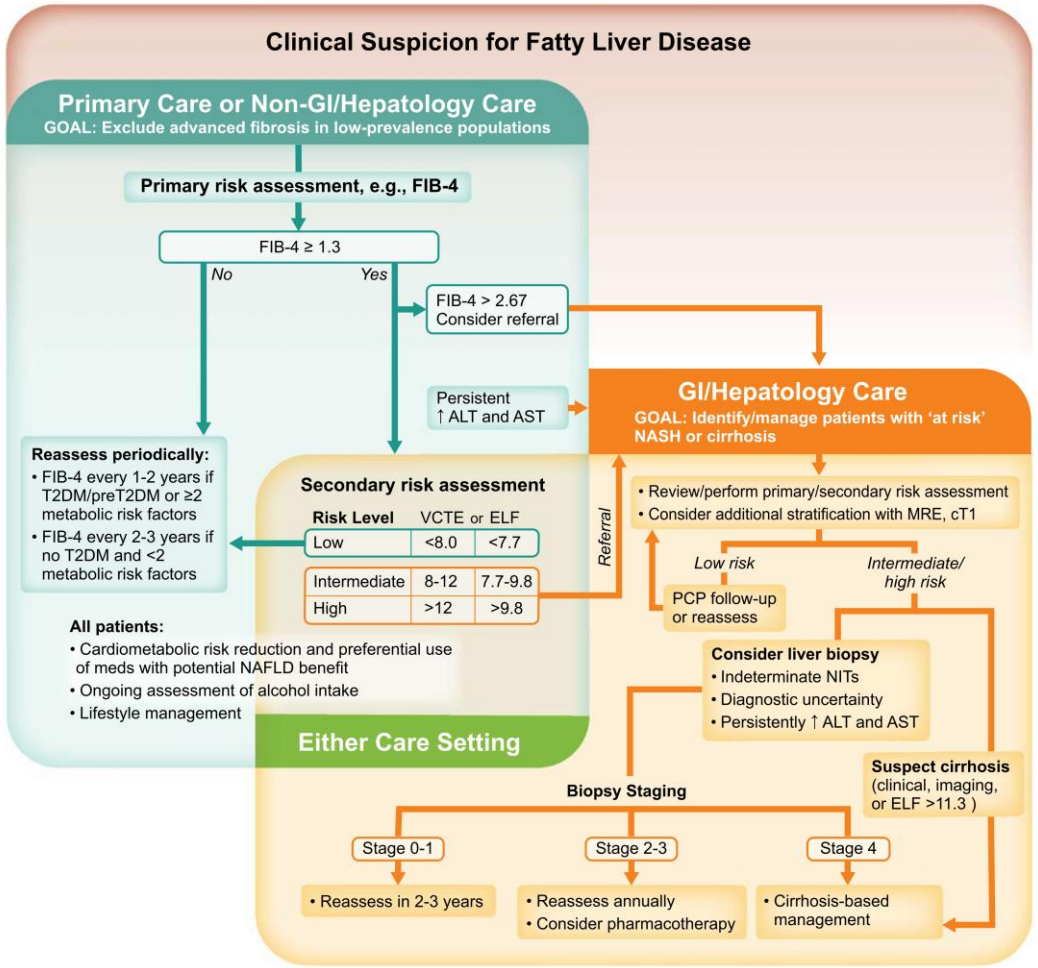
Université d'Angers et Centre Hospitalier Universitaire d'Angers

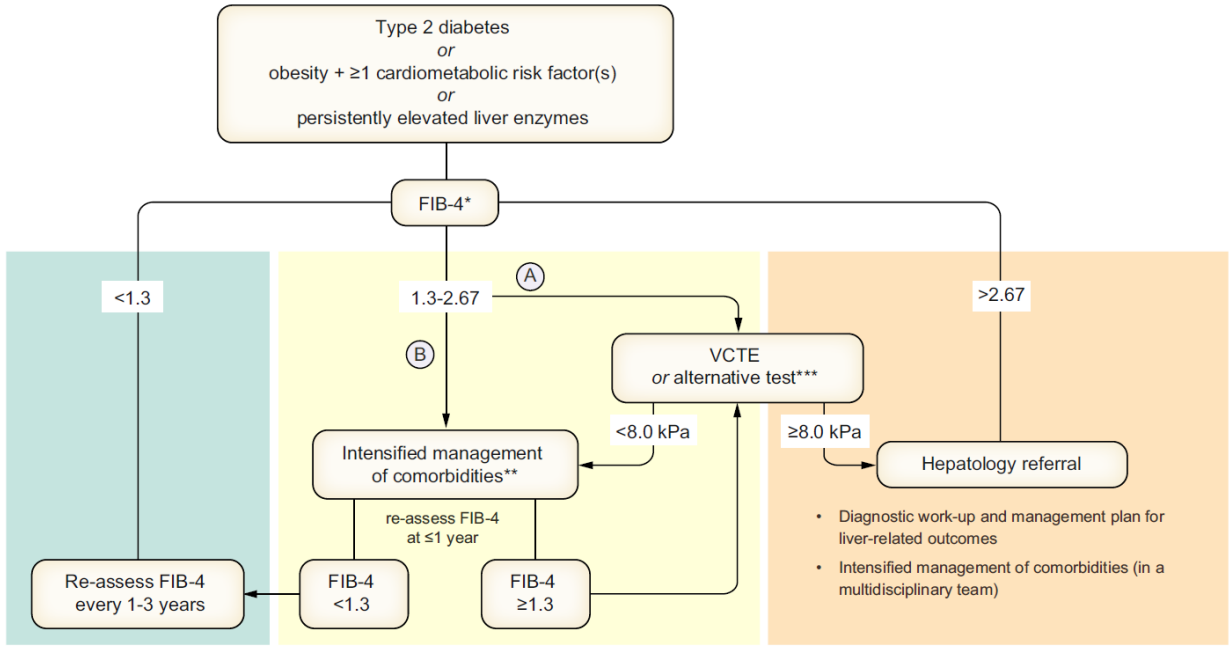
# Disclosures

- **Consultant:** Echosens, Intercept, Inventiva, Siemens
- **Board:** BMS, Intercept, Pfizer, MSD, Novo Nordisk
- **Speaker:** Abbvie, Gilead, Intercept, Siemens, Novo Nordisk
- **Funds for scientific research:** Diafir, Echosens, Gilead, Intercept, Inventiva, Ipsen, Siemens

# 1. Monitoring the disease evolution

# Recommendations for the non-invasive assessment of MASLD severity

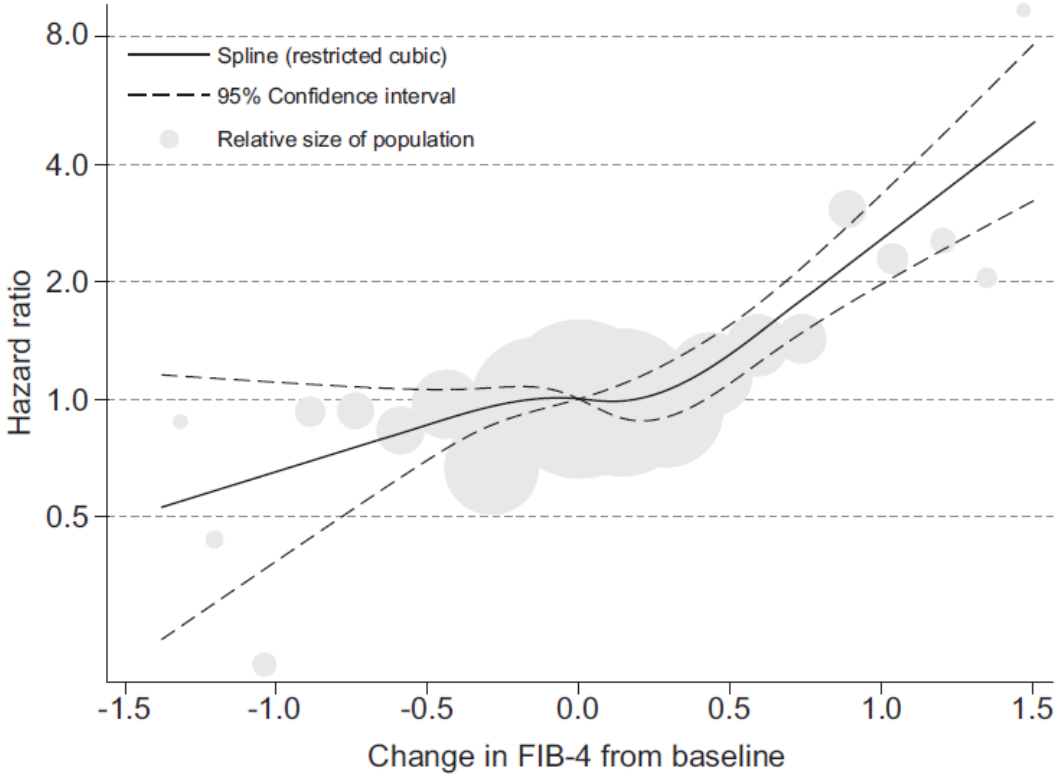


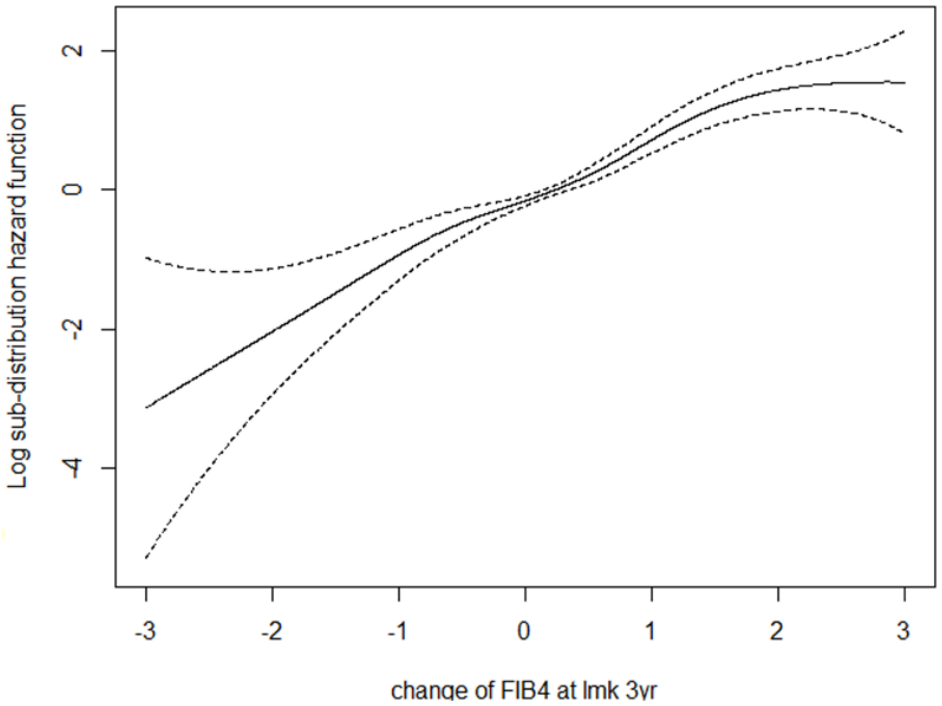

AASLD Guidelines 2023
EASL EASD EASO Guidelines 2024

# Monitoring disease progression with FIB4

**AMORIS cohort (Sweden)**
40,729 subject with repeated FIB4
Median time between FIB4 : 2.4 years [IQR: 1.3-3.9]
581 liver-related events during the median 16.2 years FU



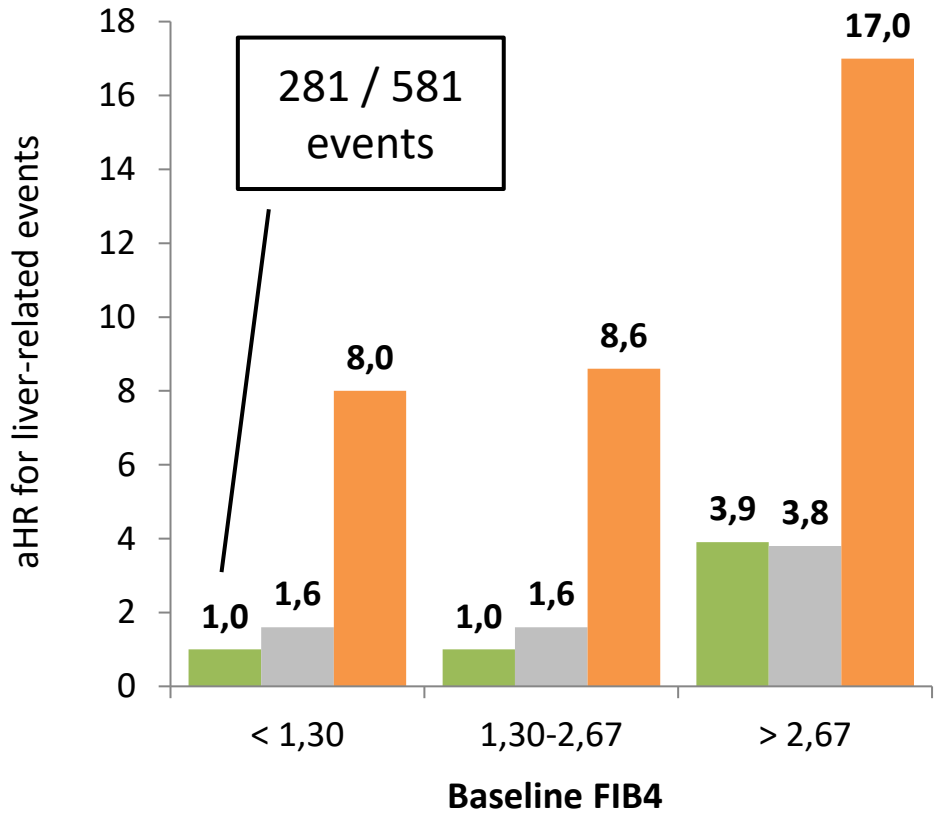

**National VA Corporate Data Warehouse (USA)**
202,319 subject with repeated FIB4 at 3-year landmark time
2,161 cirrhosis of HCC events during the mean 8.2 years FU



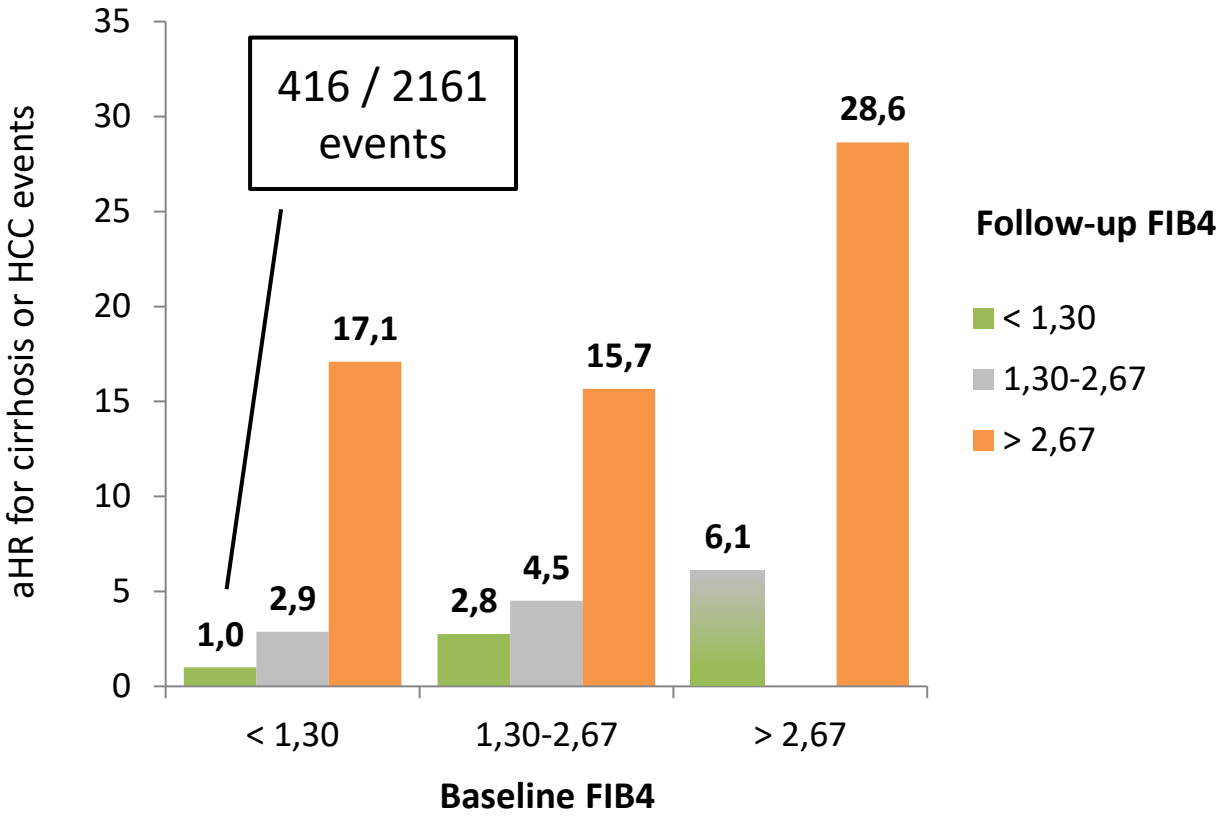

Hagstrom, J Hepatol 2020
Cholankeril, J Hepatol 2023

# Monitoring disease progression with FIB4

**AMORIS cohort (Sweden)**

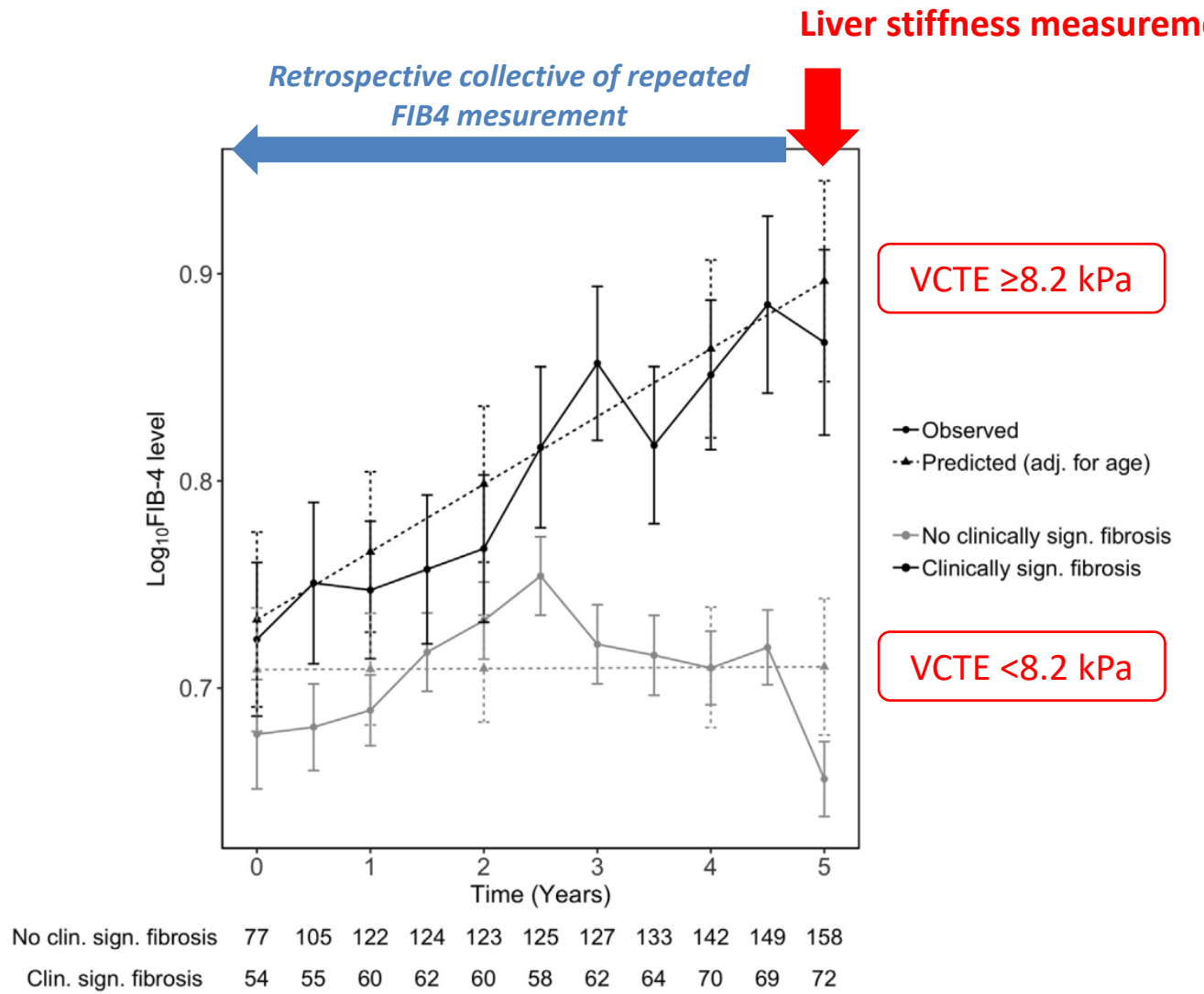



**National VA Corporate Data Warehouse (USA)**




Hagstrom, J Hepatol 2020
Cholankeril, J Hepatol 2023

# Monitoring disease progression with FIB4



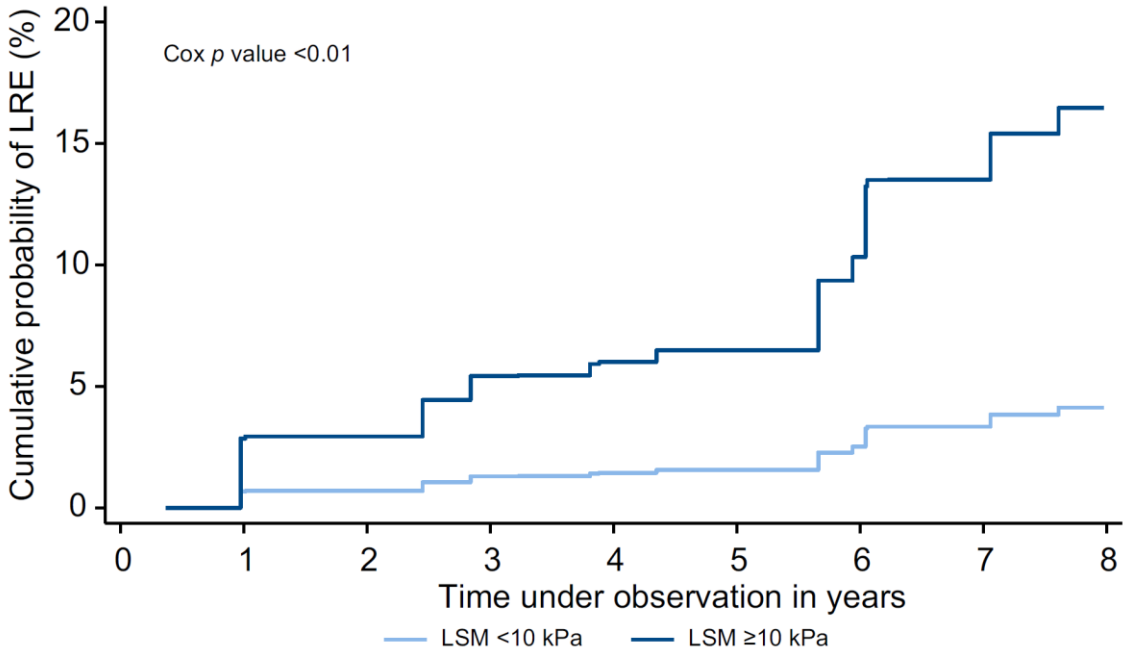

Retrospective monocentric study

252 patients with NAFLD

Patel, Clin Gastroenterol Hepatol 2020

# Monitoring disease progression with elastography

**NASH CRN cohort (USA)**
1,403 patients with biopsy-proven MASLD and repeated VCTE
89 liver-related events during the median 4.4 years FU




**Progressors**
(from <10 kPa to ≥10 kPa)
**16% LRE**

**aHR: 4.0**

**Non-progressors**
(from <10 kPa to <10 kPa)
**4% LRE**

**In patients with baseline LSM ≥ 8 kPa**

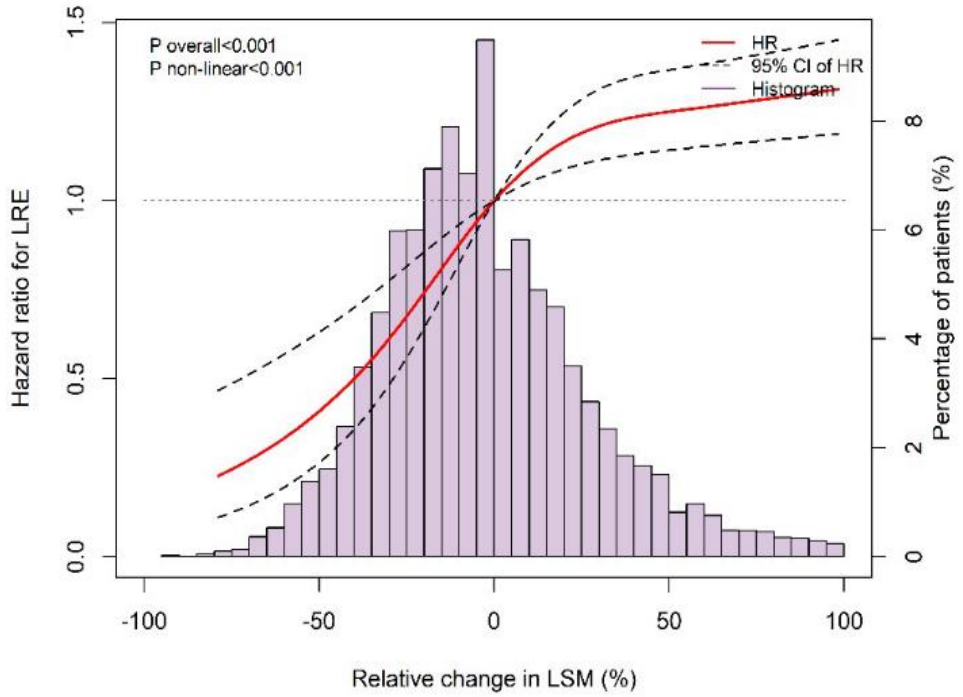
LSM ≥ 30% kPa
aHR for LRE
**1.90 (1.16-3.12)**

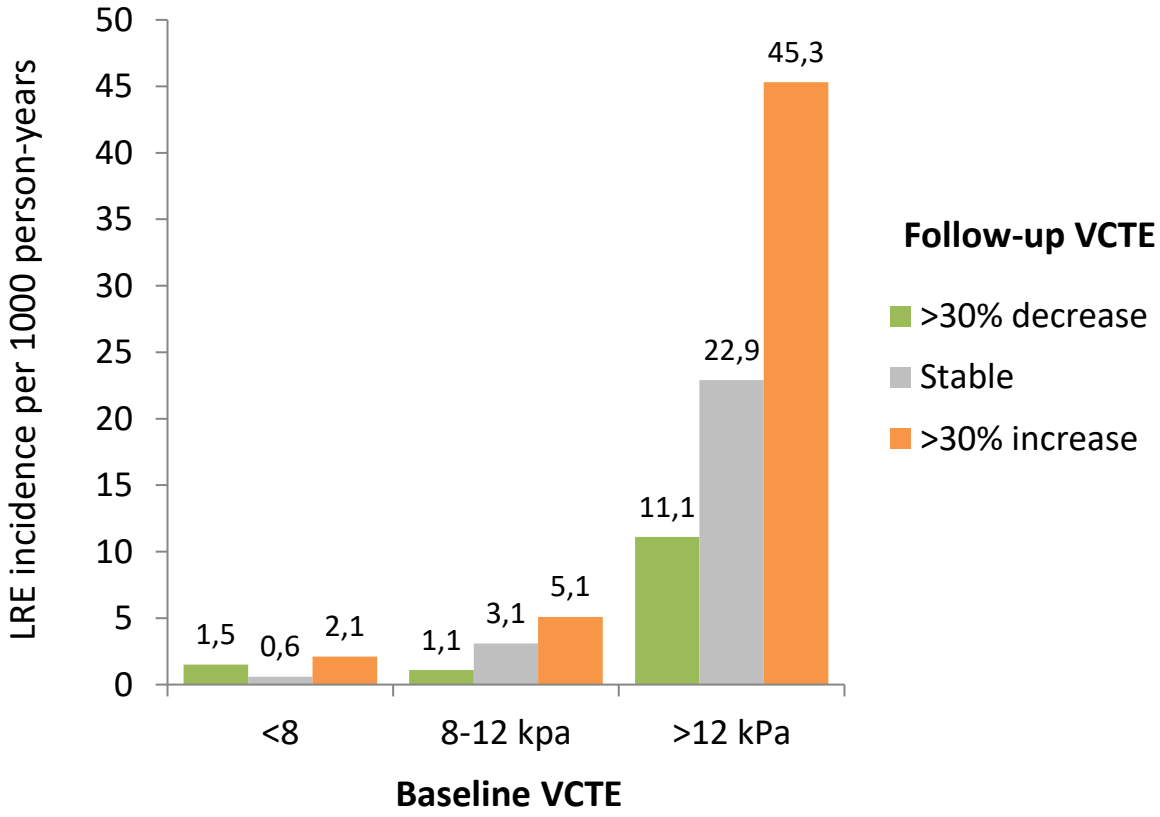
Gawrieh, J Hepatol 2024

# Monitoring disease progression with elastography

**Multicentric international cohort**

10 920 patients with MASLD and repeated VCTE (median internal: 15 months [11.3-27.7])




Lin, JAMA 2024

# Monitoring disease progression with elastography

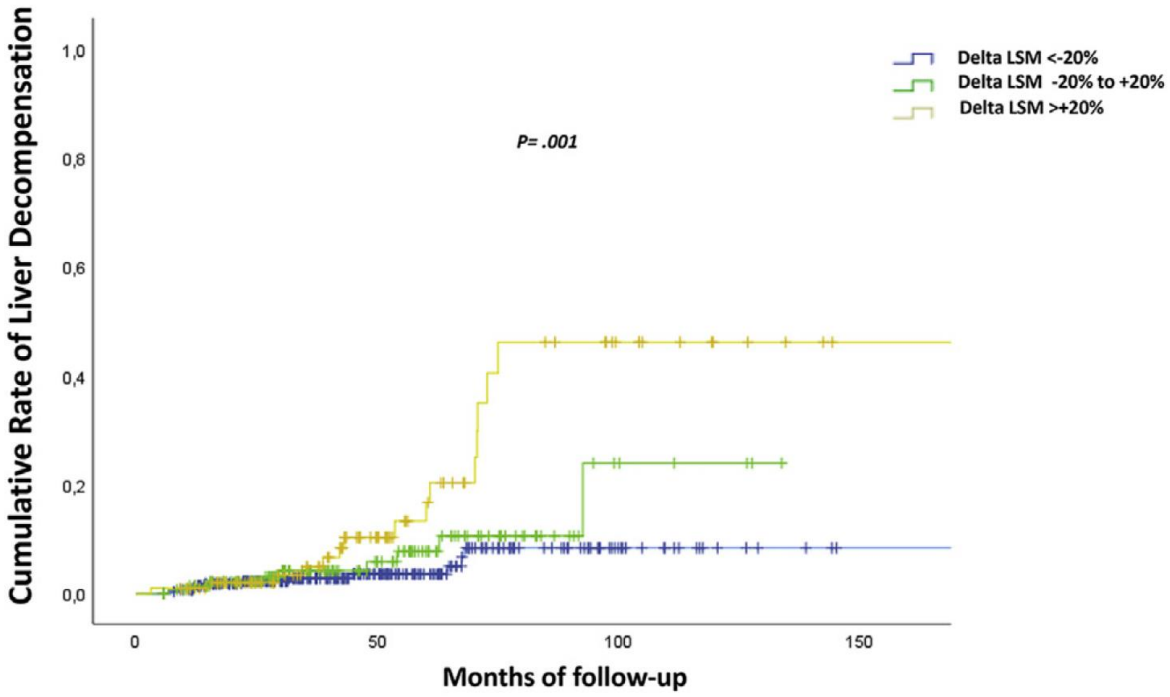
**Multicentric international cohort**

533 patients with MASLD, cALCD (VCTE >10 kPa or F3-4 at histology), and repeated VCTE within 1 year

Median follow-up : 37 months

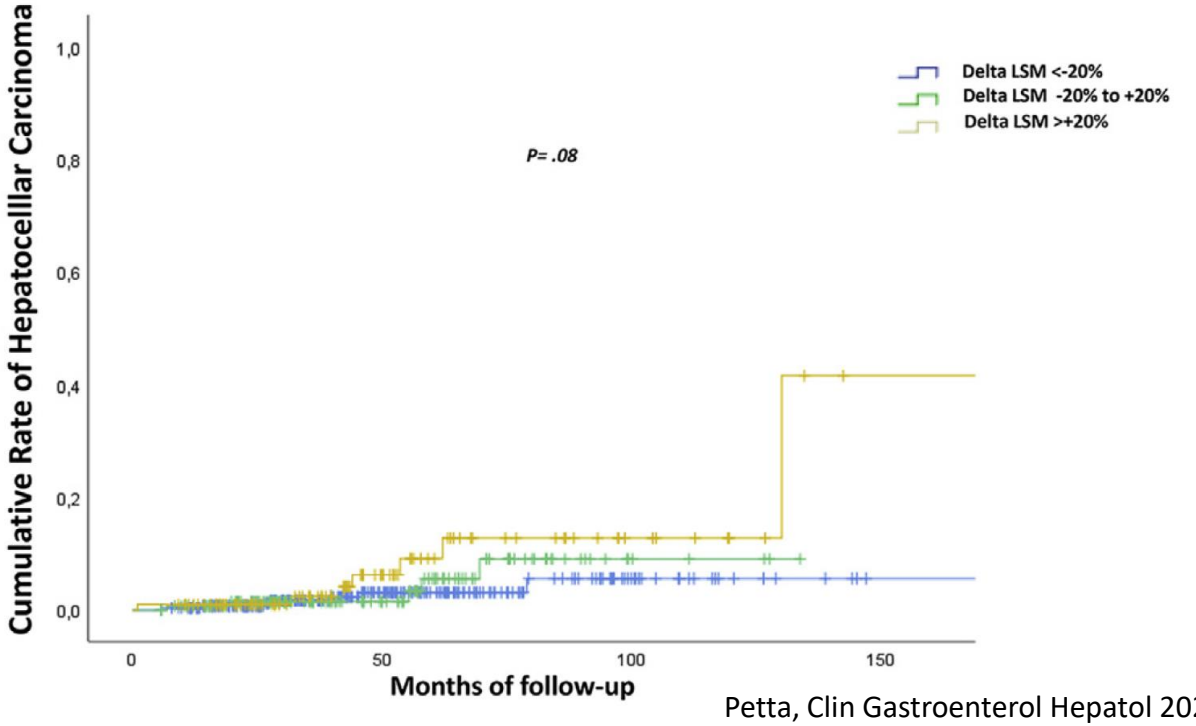
**A**

**Baseline LSM** and **delta LSM**
Predicted **liver decompensation**



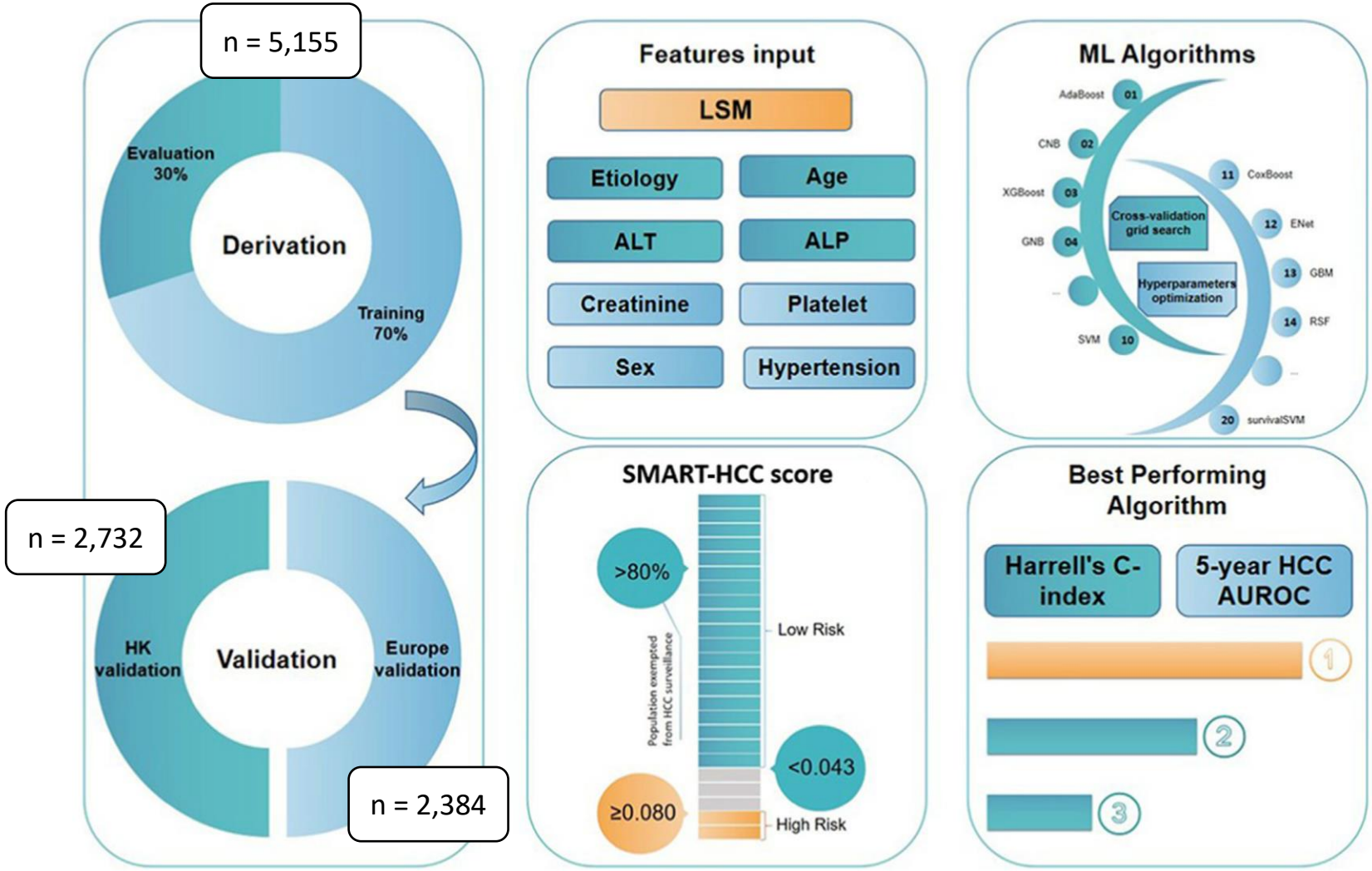

**B**

**Delta LSM**
Predicted **hepatocellular carcinoma**



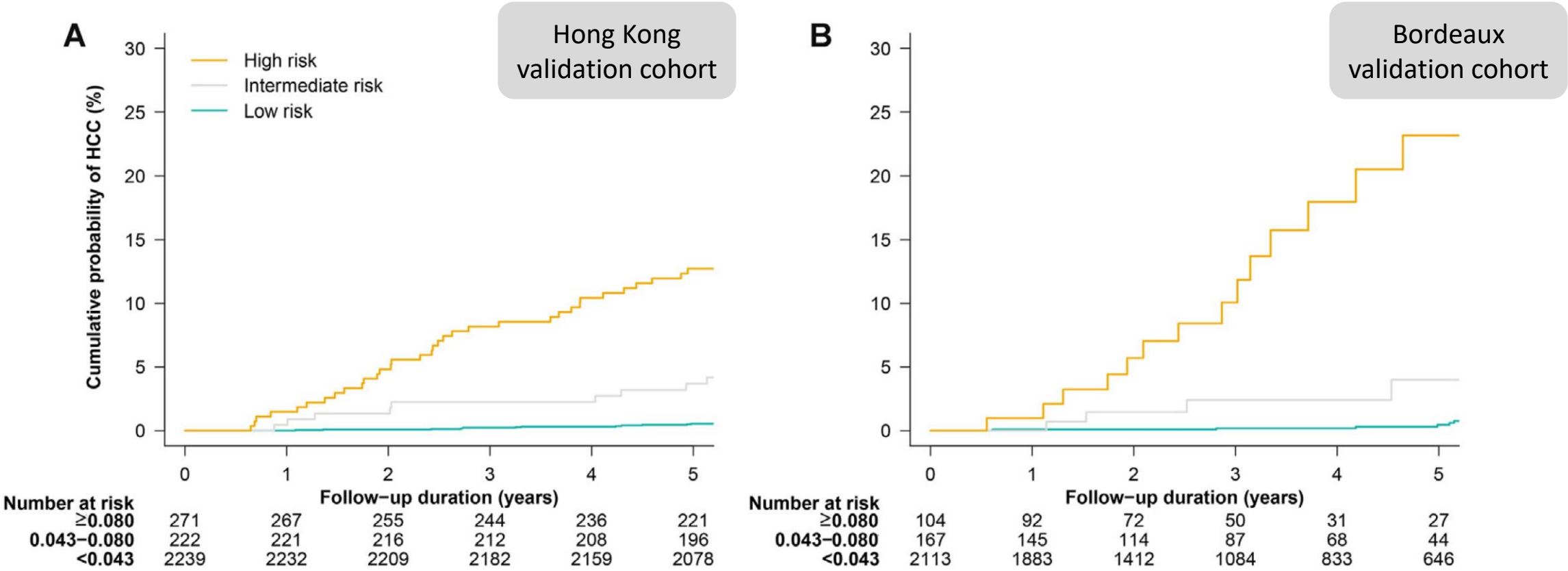

Petta, Clin Gastroenterol Hepatol 2021

# Risk equation for HCC prediction




Yin, Clin Gastroenterol Hepatol 2024

# Risk equation for HCC prediction




Significant better discrimation compared to aMAP score and Toronto HCC risk Index
No significant difference by subgroups (etiology, age, sex, T2DM, hypertension)

Yin, Clin Gastroenterol Hepatol 2024

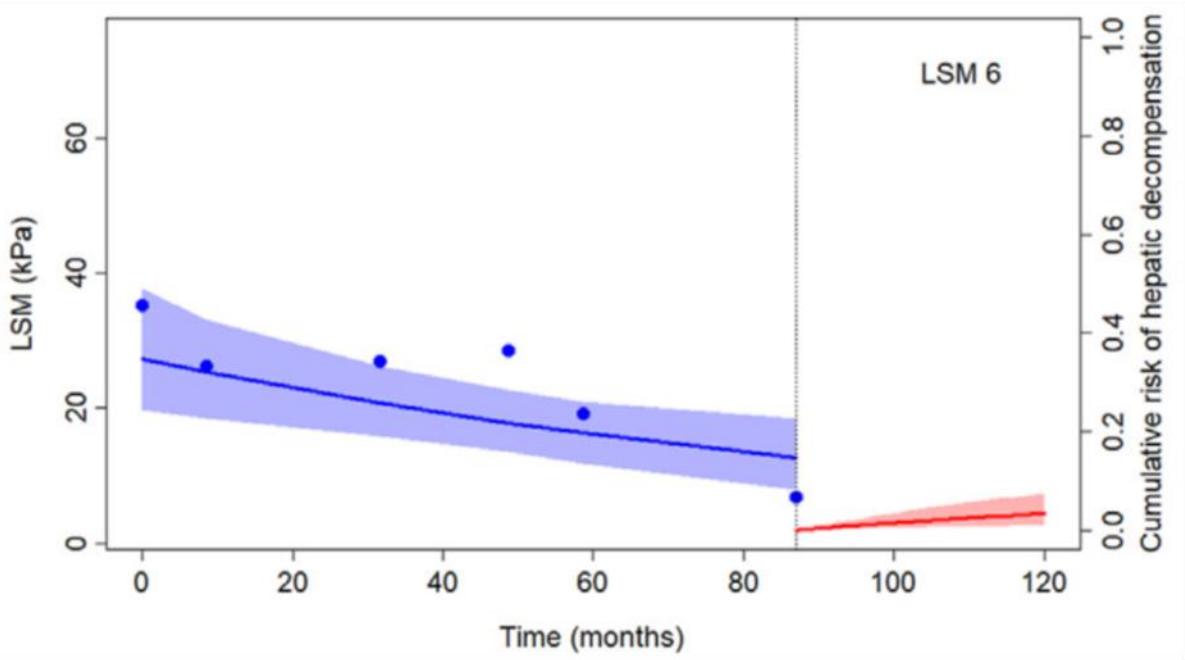
# Modelling the dynamics for a better prediction

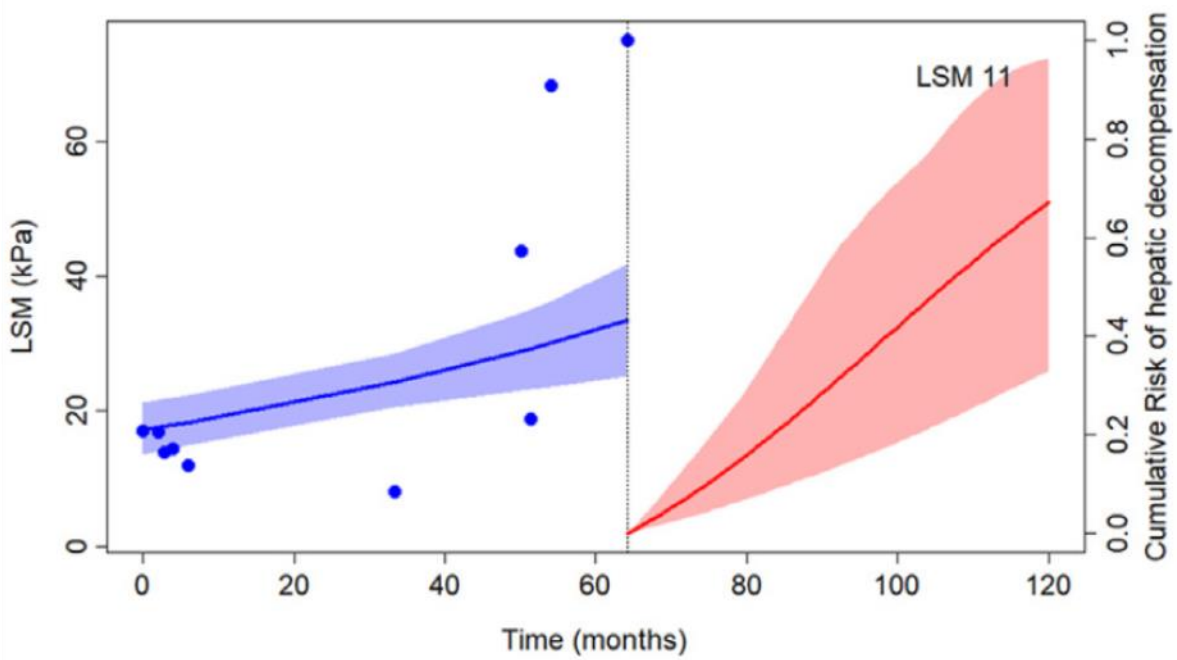
**Single center study (Vienna)**

720 patients with chronic liver disease, LSM ≥10 kPa, and ≥2 VCTE (total: 2673 VCTE)

Median follow-up : 71 months (62 events of decompensation)

Joint modeling of liver stiffness measurements dynamics




Semmler, Gastroenteroly 2023

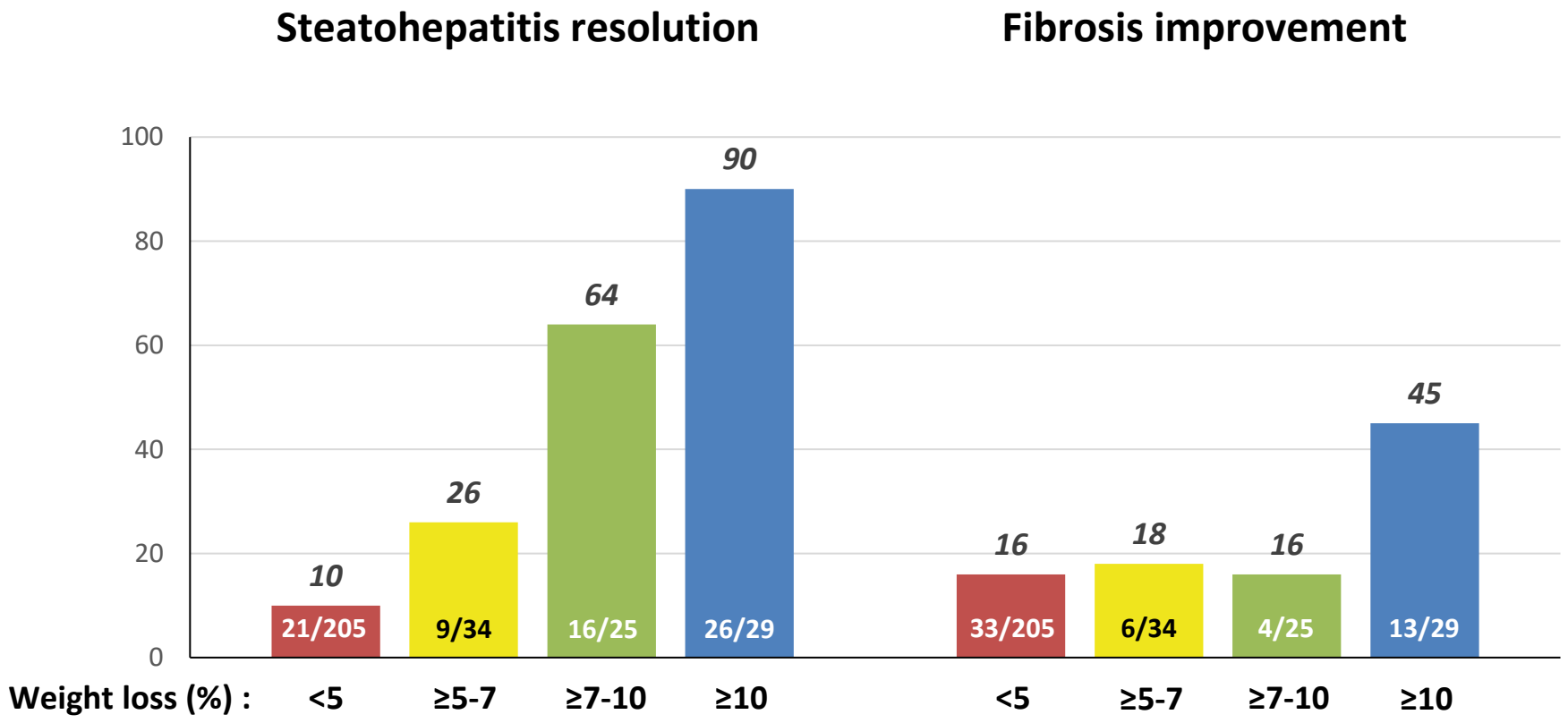
# 2. Monitoring treatment response

# Weight loss and improvement in histology

293 patients
with NASH

52 weeks
hypocaloric diet +
exercice

Paired liver biopsy

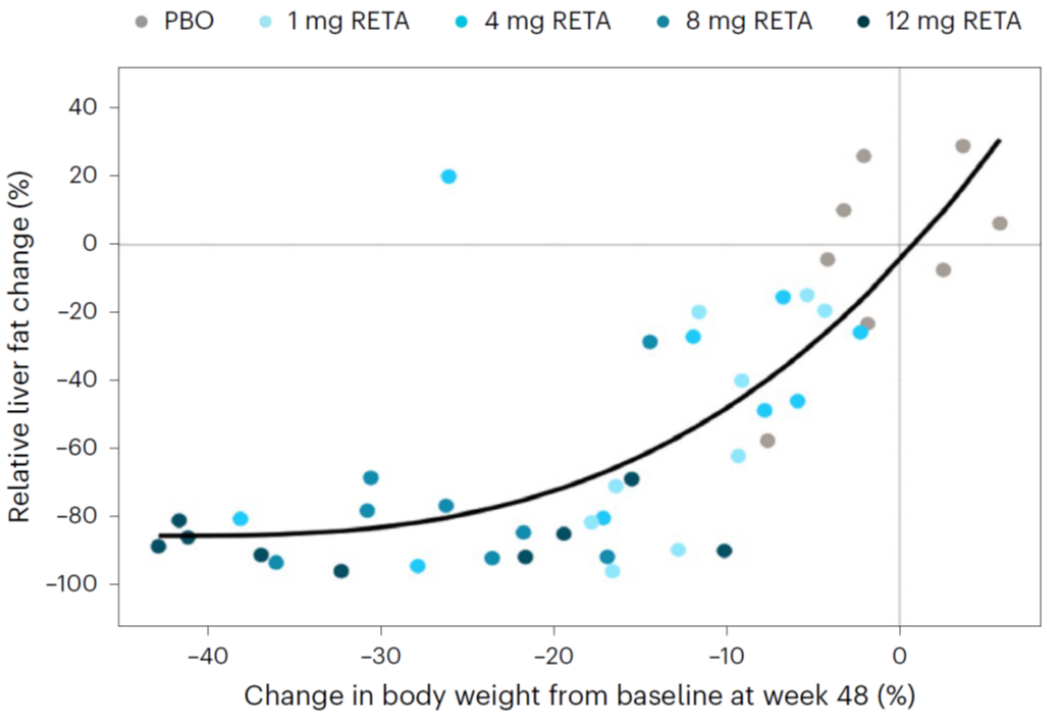



Vilar-Gomes, Gastroenterology 2015

# Weight loss and improvement in histology

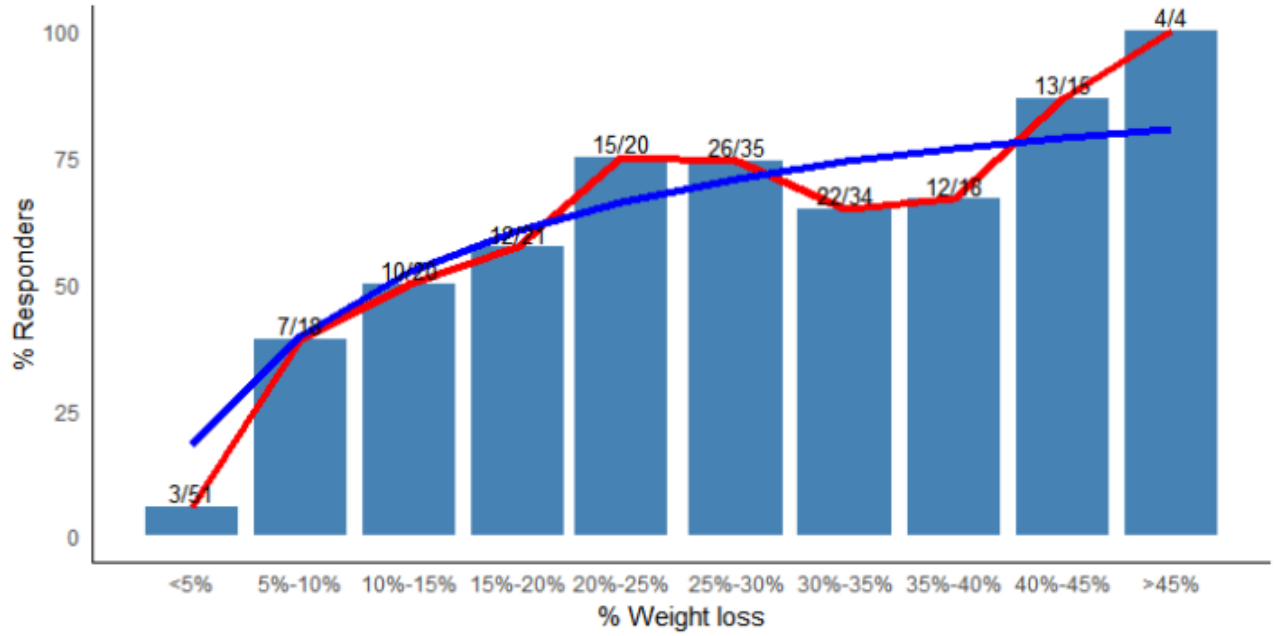
## Phase 2 Retatritude trial

Outcome : liver fat evolution (MRI PDFF)




## BRAVES study

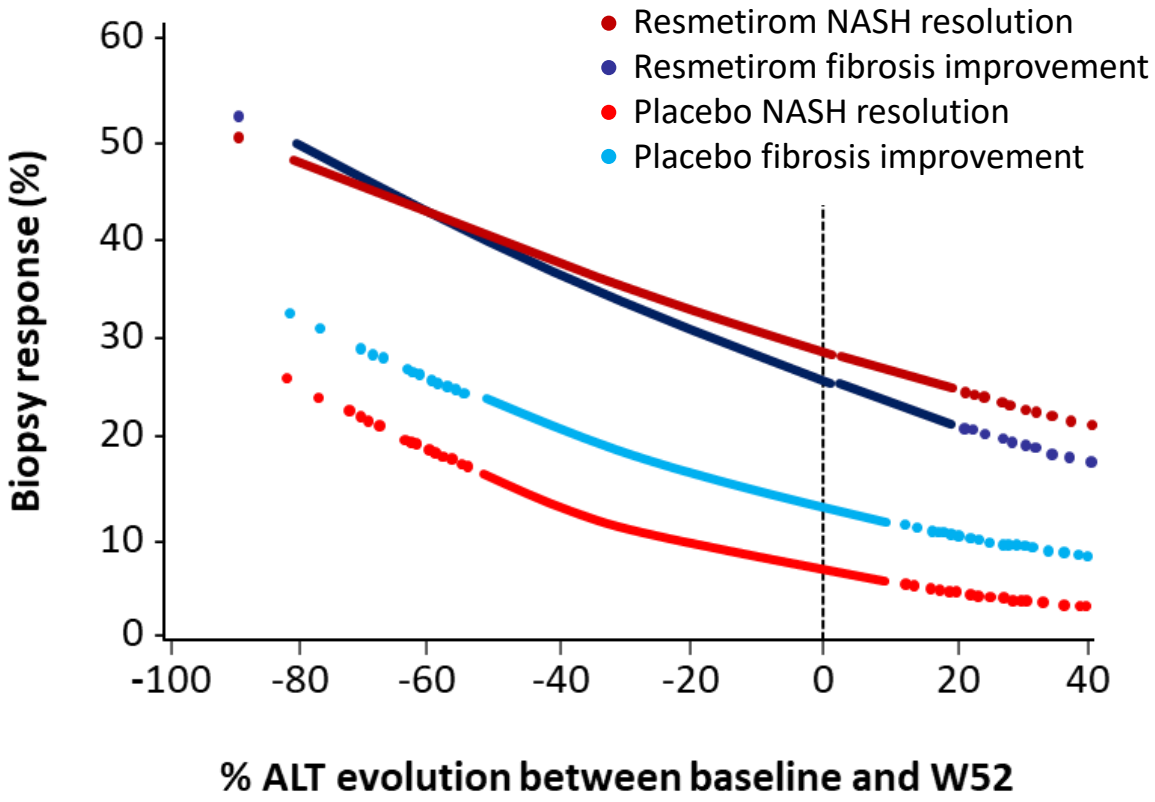
Outcome : NASH resolution without worsening of liver fibrosis



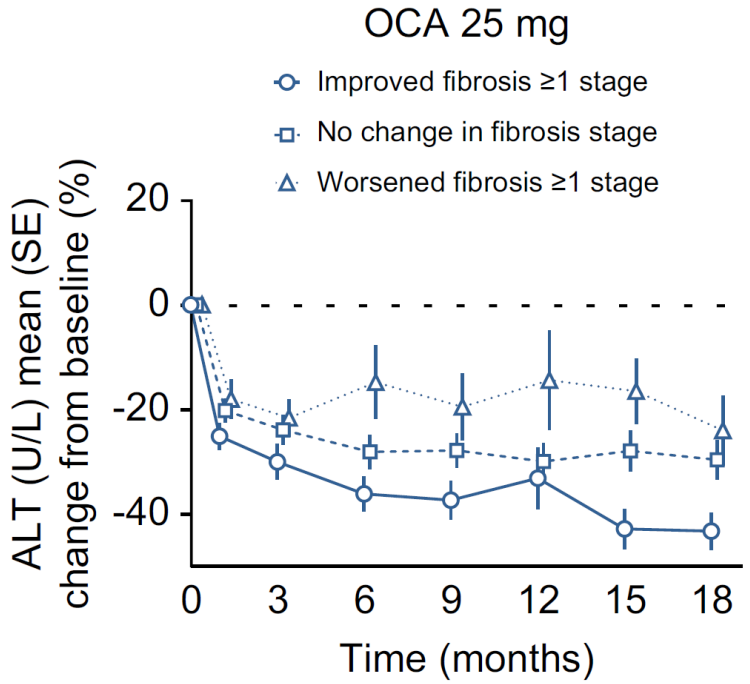

Verrastro, Lancet 2023
Sanyal, Nat Med 2024

# Monitoring treatement response with serum transaminases

## Phase 3 MAESTRO




## Phase 3 REGENERATE

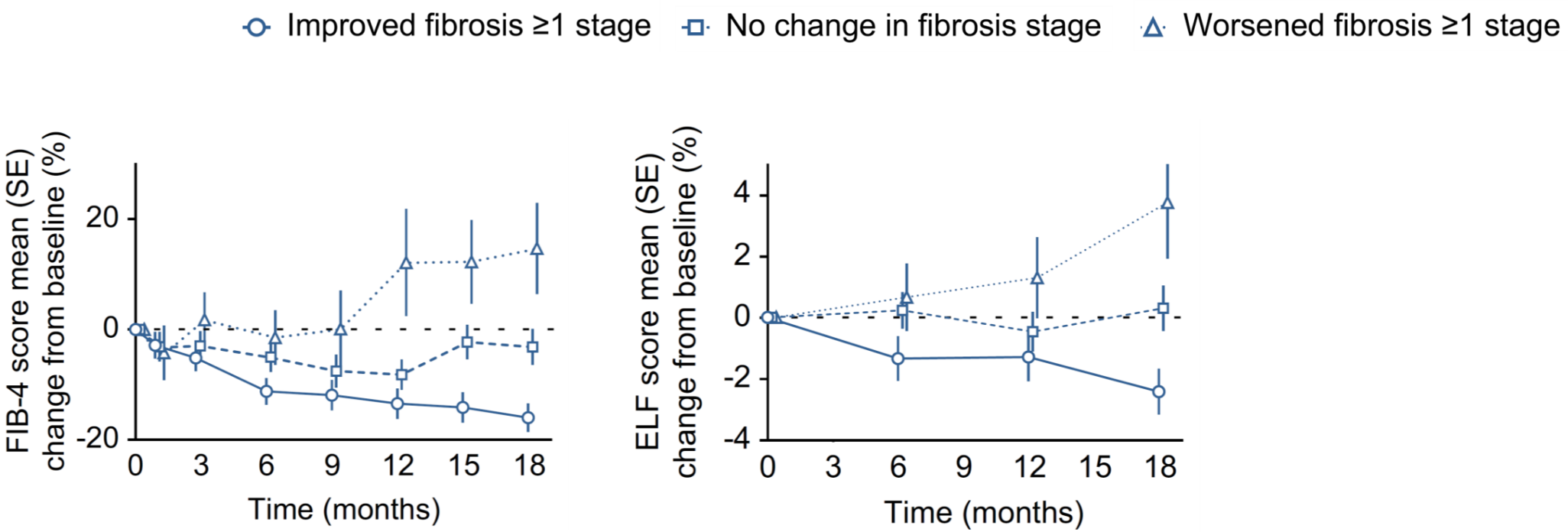



| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Improved, n = | 92 | 92 | 92 | 92 | 91 | 92 | 90 |
| No change, n = | 124 | 124 | 124 | 123 | 123 | 121 | 119 |
| Worsened, n = | 34 | 34 | 34 | 34 | 34 | 33 | 31 |

Loomba, AASLD Liver Meeting 2023
Rinella, J Hepatol 2023

# Treatment response and non-invasive tests of liver fibrosis

**Phase 3 REGENERATE – OCA 25 mg group**

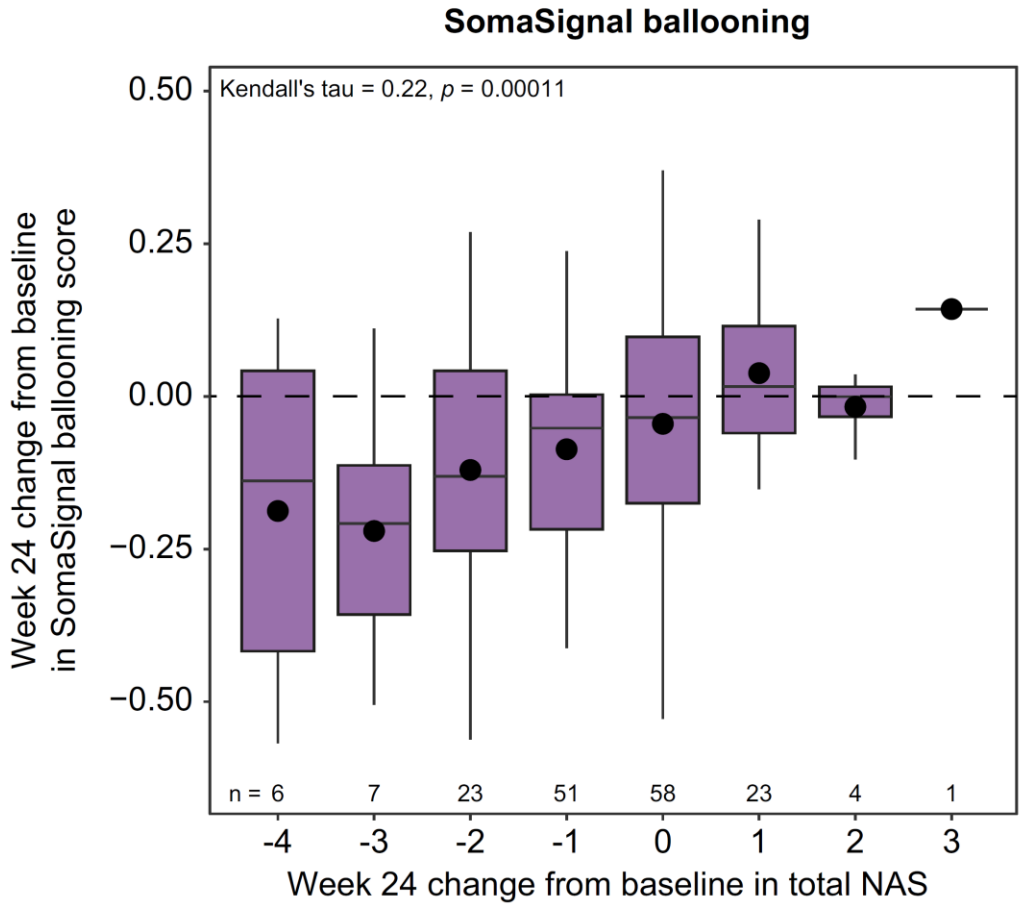



Rinella, J Hepatol 2023

# Monitoring with a test dedicated to the diagnosis of ballooning

**Phase 2b FALCON1**

**Pegbelfermin in NASH + F3**

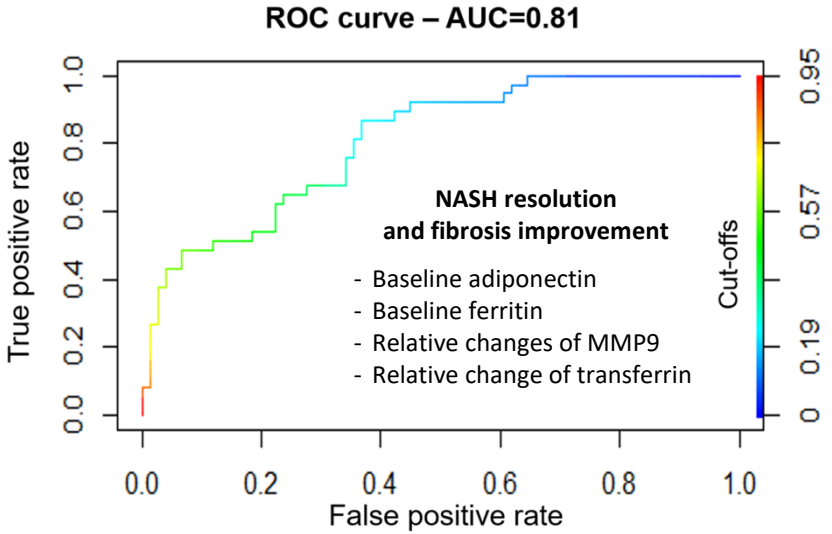


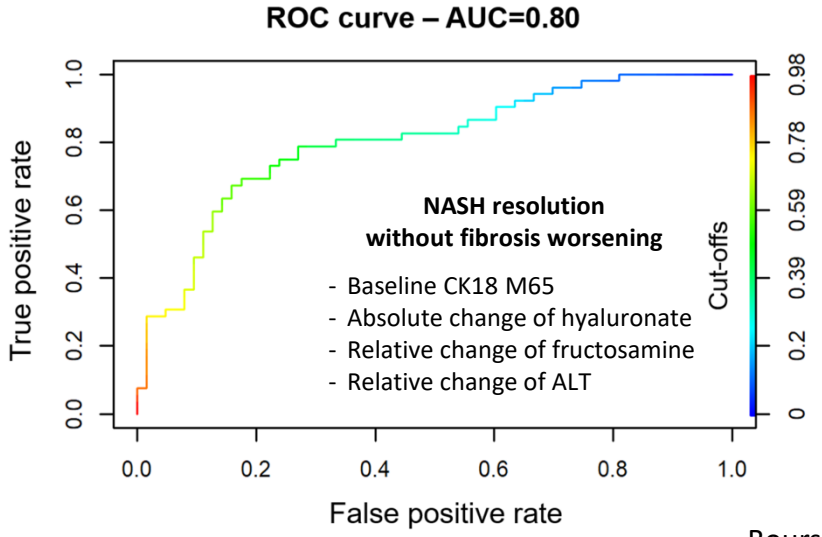

Brown, JHEP Reports 2023

# Monitoring treatment response with a dedicated test

## Phase 2 NATIVE trial - 142 patients treated 24 weeks with Lanifibranor 800 / 1200 mg

| Scores | NASH resolution and fibrosis improvement | | NASH resolution without fibrosis worsening | |
|---|---|---|---|---|
| | **Biomarkers included in the model** | **AUROC** | **Biomarkers included in the model** | **AUROC** |
| MACK-3 | Baseline raw values + absolute change at EOT | 0.76 | Baseline raw values + absolute change at EOT | 0.78 |
| FIBC3 | *None selected* | -- | Absolute change at EOT | 0.62 |
| NFS | *None selected* | -- | Absolute change at EOT | 0.62 |
| ELF | *None selected* | -- | Baseline raw values + relative changes at EOT | 0.68 |
| FIB4 | *None selected* | -- | *None selected* | -- |
| ABC3D | *None selected* | -- | *None selected* | -- |

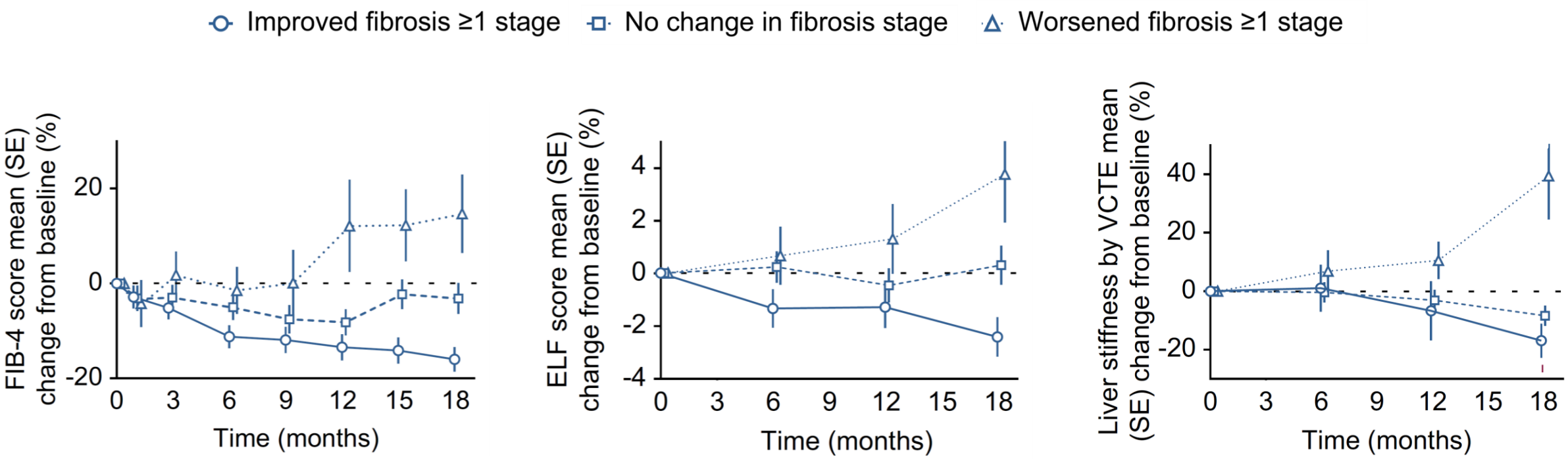



Boursier, ILC meeting 2022

# Treatment response and non-invasive tests of liver fibrosis

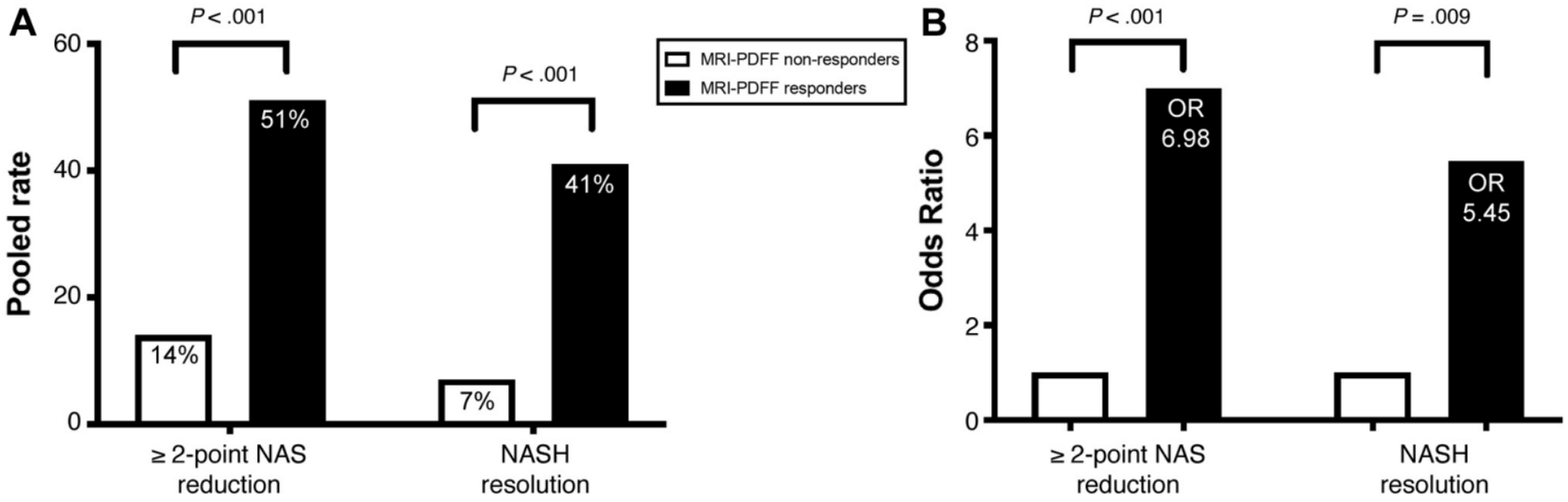
**Phase 3 REGENERATE – OCA 25 mg group**




Rinella, J Hepatol 2023

# Liver steatosis and treatment response

| Outcome | Studies (patients) | <30% reduction in MRI PDFF | ≥30% reduction in MRI PDFF | p | OR |
|---|---|---|---|---|---|
| ≥2 points improvement in NAS | 7 (346) | 51% | 14% | <0.001 | 6,98 (95% CI: 2.38-20.43) |
| NASH resolution | 6 (318) | 41% | 7% | <0,001 | 5,45 (95% CI: 1.53-19.46) |

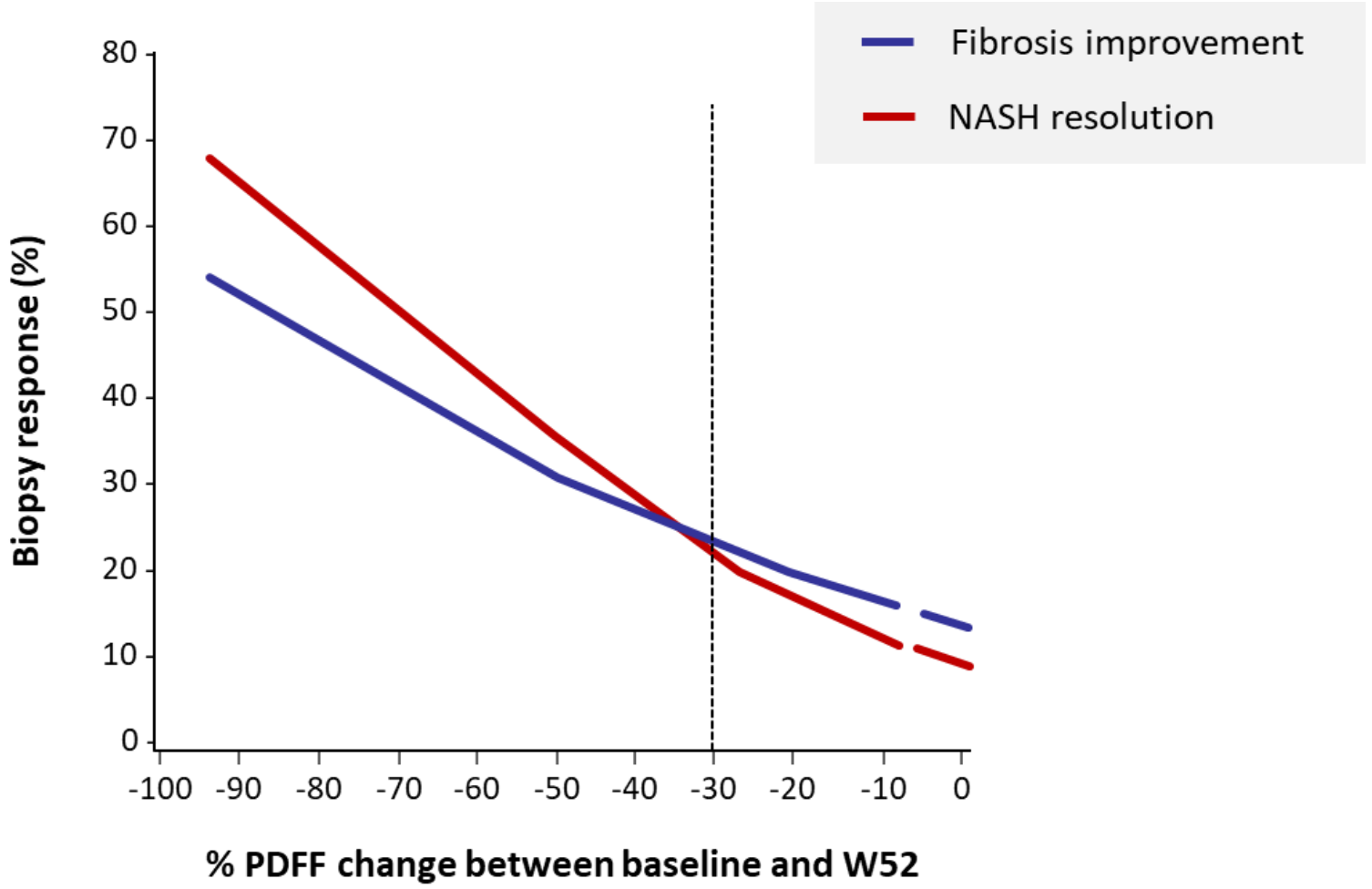



Stine, Clin Gastroenterol Hepatol 2020

# Liver steatosis and treatment response

**Phase 3 MAESTRO NASH**

**(Resmetirom)**




Loomba, AASLD Liver Meeting 2023

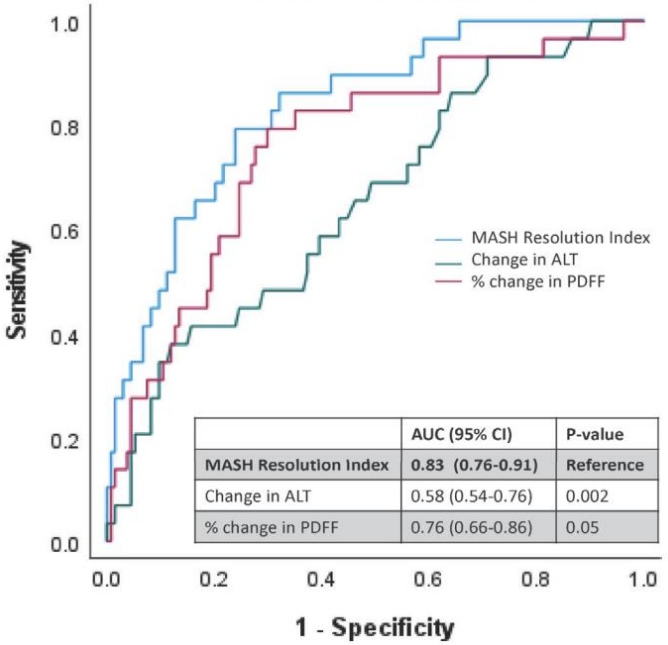
# Monitoring treatment response with a dedicated test

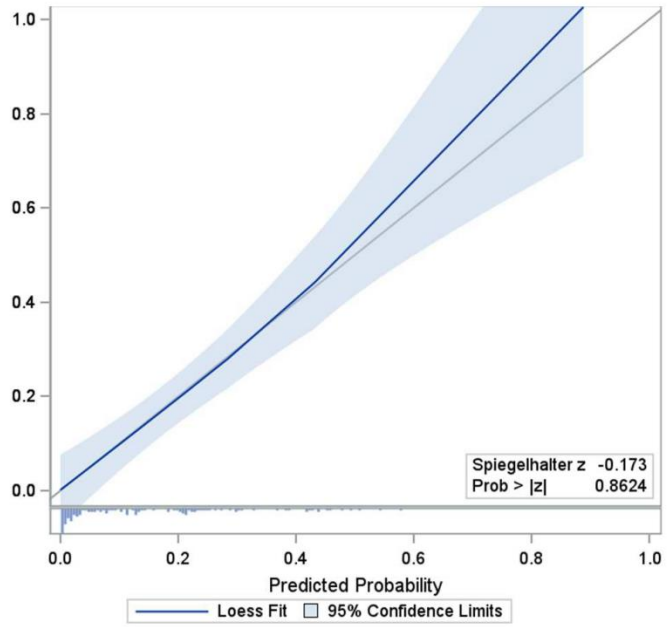
- Derivation cohort : 95 patients with MASLD from single center (San Diego)
- Validation cohort : 163 participants with MASH F2-3 from the ENLIVEN trial (FGF21 pegozafermin)

| | MASH resolution index | |
|---|---|---|
| | **Derivation cohort** | **Validation cohort** |
| AUC | 0.81, 95% CI 0.69 to 0.93 | 0.83, 95% CI 0.76 to 0.91 |
| Cut-off | MASHResInd≤−2.67 | MASHResInd≤−2.67 |
| N | 27 | 17 |
| Sensitivity | 88.9% | 100.0% |
| Specificity | 32.5% | 12.7% |
| PPV | 23.5% | 19.9% |
| NPV | 92.6% | 100.0% |
| Grey zone, N (%) | 50 (52.6%) | 57 (35.0%) |
| Cut-off | MASHResInd≥−0.67 | MASHResInd≥−0.67 |
| N | 18 | 89 |
| Sensitivity | 55.6% | 89.7% |
| Specificity | 89.6% | 53.0% |
| PPV | 55.6% | 29.2% |
| NPV | 89.6% | 95.9% |

AUC, area under the receiver operating curve; MASH, metabolic dysfunction-associated steatohepatitis; NPV, negative predictive value; PPV, positive predictive value.

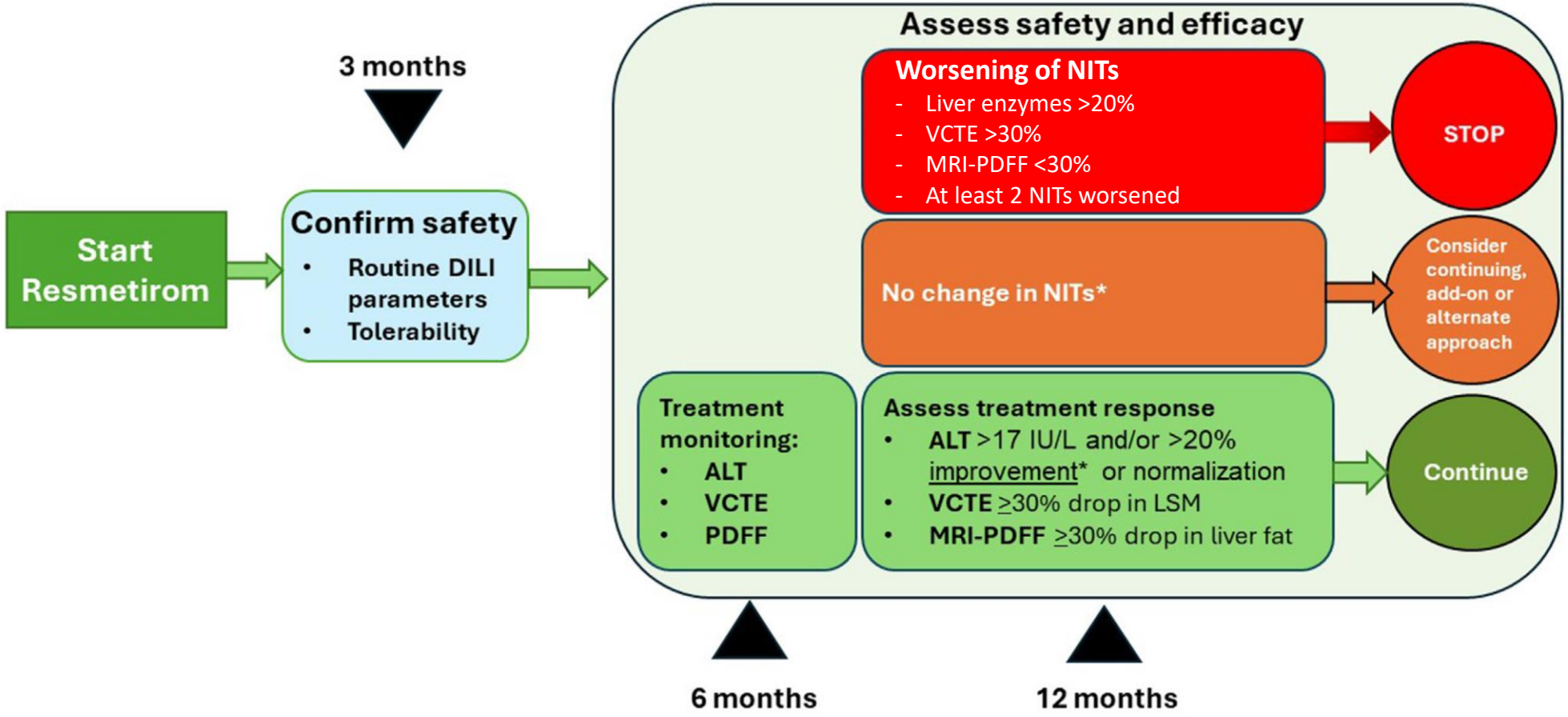
**MASH resolution index :**
baseline IRM PDFF, ALT, AST + percentage change in MRI PDFF, ALT




Loomba, Gut 2024

# Assessment of safety and treatment response on resmetirom (expert panel recommendations)




* ALT improvement should be accompagnied by improvement in imaging (≥30% reduction in MRI-PDFF)

Noureddin, Clin Gastroenterol Hepatol 2024

# Conclusion

- In untreated MASLD patients, the risk of liver-related complication can be monitored by repeating non-invasive fibrosis tests during the follow-up.

- The field of treatment response monitoring remains totally open.

  ✓ There are a lot of candidates, and ongoing phase 3 trials will help to evaluate them (histological, clinical endpoints).

  ✓ Monitoring steatosis appears a promising approach for metabolic drug,

- An ideal biomarker of treatment response should perform regardless of the drug's mechanisms, which remains an unmet Grail.