CU Medicine
HONG KONG

Noninvasive Evaluation of Hepatic Steatosis, Inflammation, and Fibrosis: Recent Advances

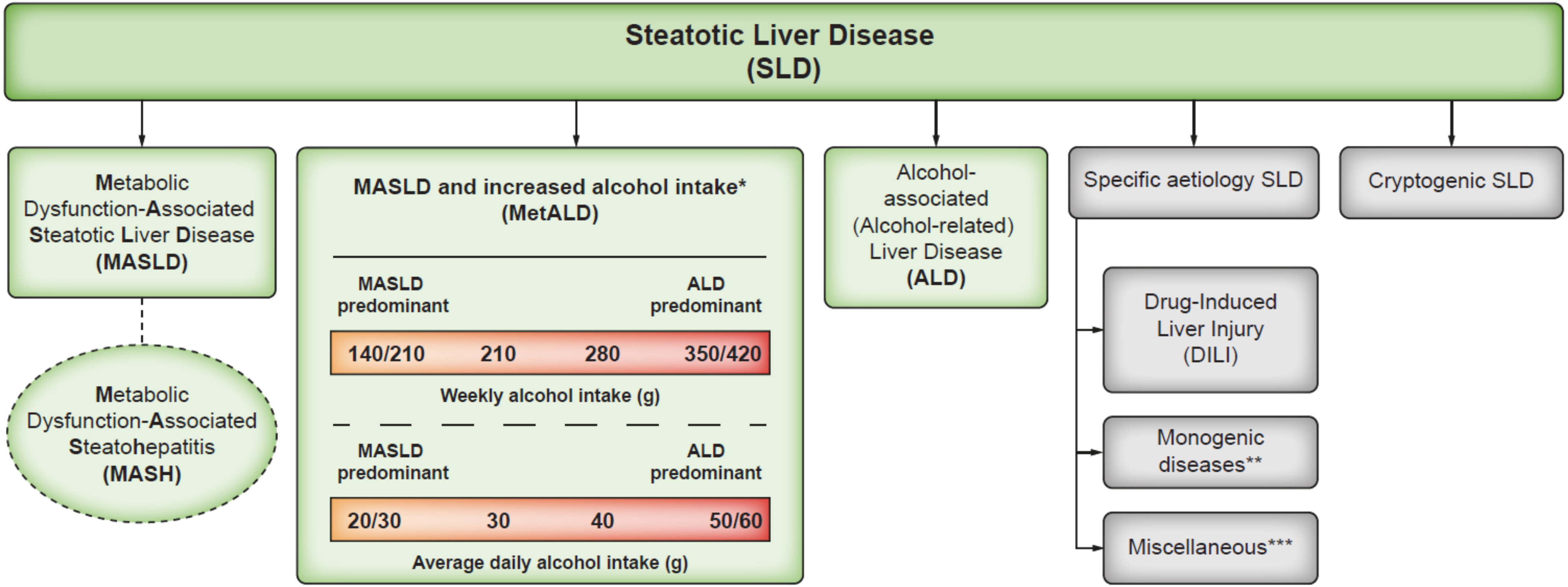
Vincent Wong
Mok Hing Yiu Professor of Medicine
Department of Medicine and Therapeutics

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Disclosures

- Consultancy: AbbVie, AstraZeneca, Boehringer Ingelheim, Echosens, Eli Lilly, Gilead Sciences, Intercept, Inventiva, Merck, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, Visirna
- Lectures: Abbott, AbbVie, Echosens, Gilead Sciences, Novo Nordisk, Unilab
- Research grants: Gilead Sciences
- Stock: Co-founder of Illuminatio Medical Technology

Subclassification of steatotic liver disease


Steatotic Liver Disease (SLD)

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Metabolic Dysfunction-Associated Steatohepatitis (MASH)

MASLD and increased alcohol intake* (MetALD)

MASLD predominant			ALD predominant
140/210	210	280	350/420

Weekly alcohol intake (g)

MASLD predominant			ALD predominant
20/30	30	40	50/60

Average daily alcohol intake (g)

Alcohol-associated (Alcohol-related) Liver Disease (ALD)

Specific aetiology SLD

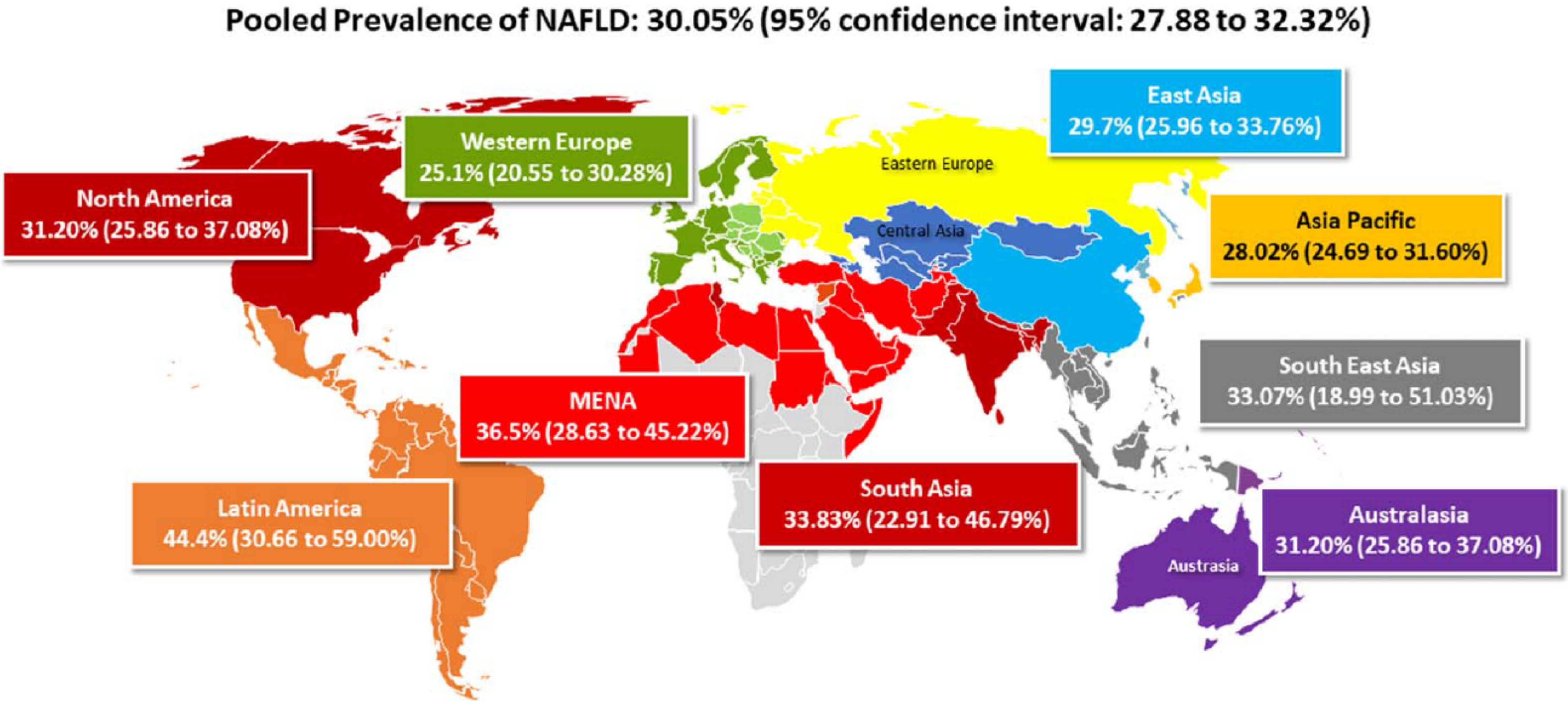
- Drug-Induced Liver Injury (DILI)
- Monogenic diseases**
- Miscellaneous***

Cryptogenic SLD

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Rinella et al. J Hepatol 2023;79:1542

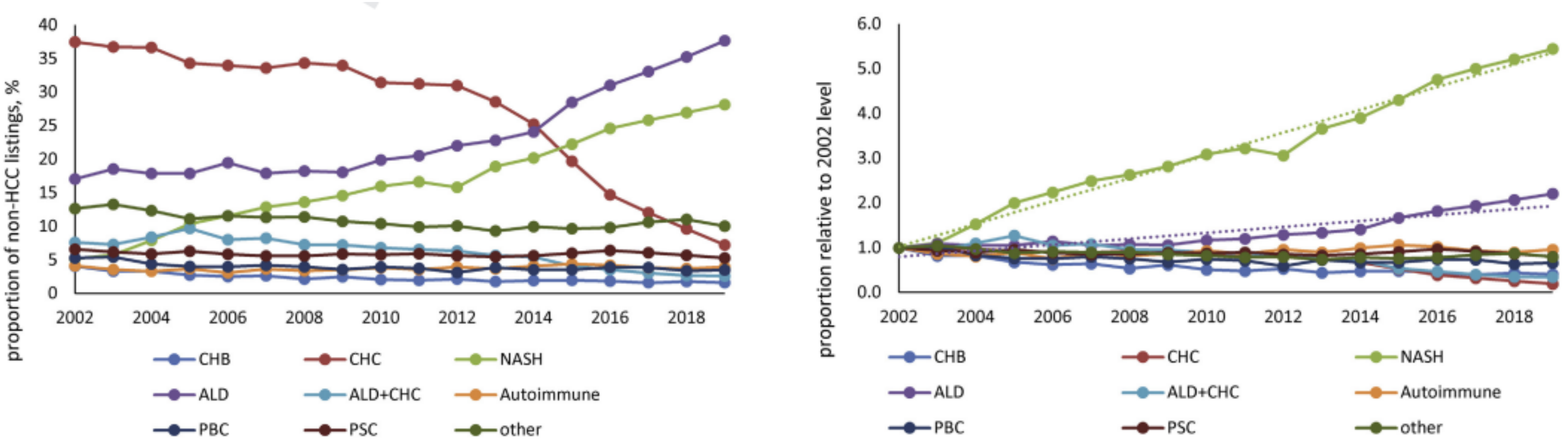
Global prevalence of MASLD in 1990-2019


Pooled Prevalence of NAFLD: 30.05% (95% confidence interval: 27.88 to 32.32%)
East Asia
29.7% (25.96 to 33.76%)
Western Europe
25.1% (20.55 to 30.28%)
North America
31.20% (25.86 to 37.08%)
Eastern Europe
Central Asia
Asia Pacific
28.02% (24.69 to 31.60%)
South East Asia
33.07% (18.99 to 51.03%)
MENA
36.5% (28.63 to 45.22%)
Latin America
44.4% (30.66 to 59.00%)
South Asia
33.83% (22.91 to 46.79%)
Australasia
31.20% (25.86 to 37.08%)
Austrasia

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Younossi et al. Hepatology 2023;77:1335

MASH is a rapidly increasing indication for liver transplantation in USA

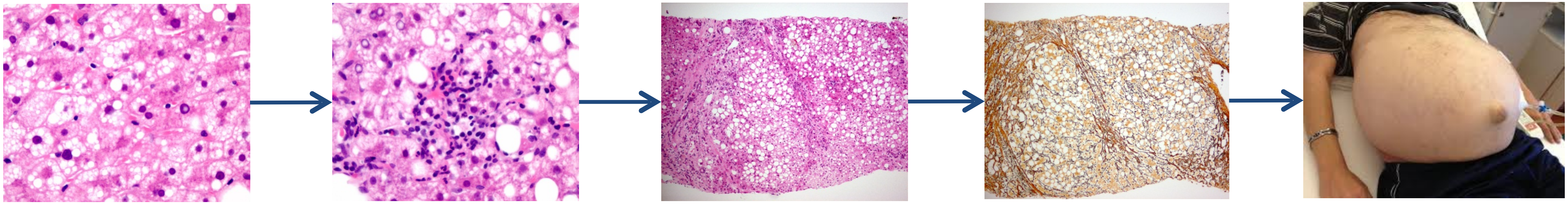


Scientific Registry of Transplant Recipients (2002-2019): N=168,441

Younossi et al. Clin Gastroenterol Hepatol 2021;19:580

香 港 中 文 大 學 醫 學 院
Faculty of Medicine
The Chinese University of Hong Kong

Natural history of MASLD



Metabolic dysfunction-associated steatotic liver (MASL)
= simple steatosis

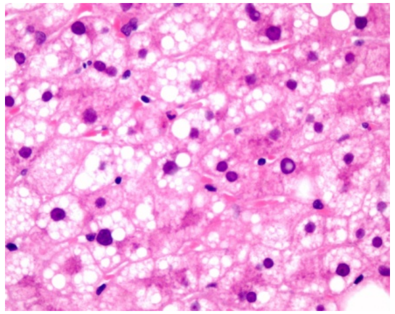
Metabolic dysfunction-associated steatohepatitis (MASH)

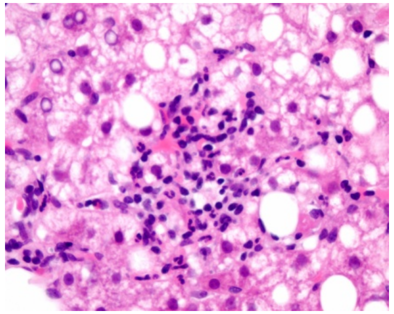
Progressive liver fibrosis

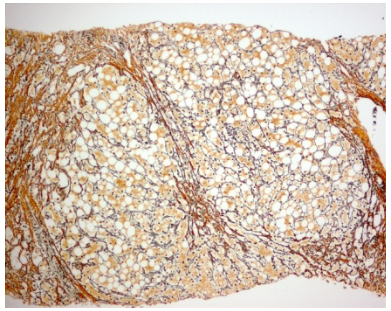
Cirrhosis

Decompensation, HCC and death

Why assess steatosis, inflammation, and fibrosis?







Steatosis

- Basis to diagnose SLD
- Reflects treatment response

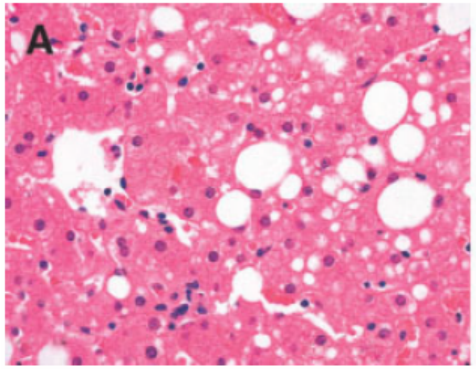
Inflammation

- More active progression
- Target population for trial enrolment
- Reflects treatment response

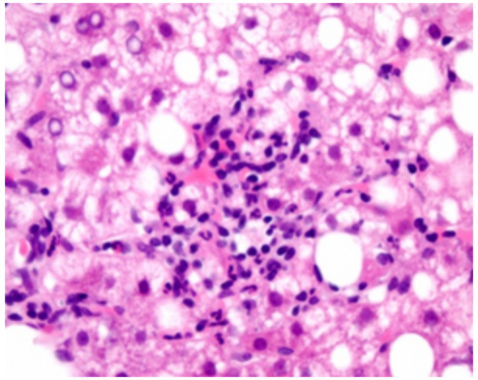
Fibrosis

- Most prognostic
- Target population for trial enrolment
- Reflects treatment response

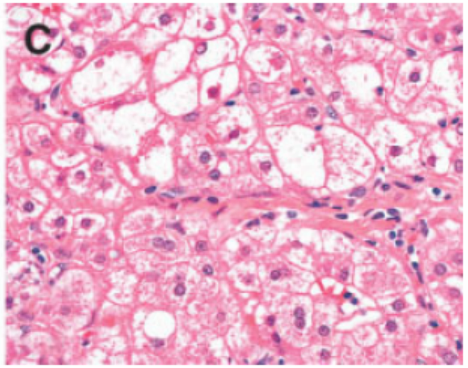
Liver biopsy for MASLD



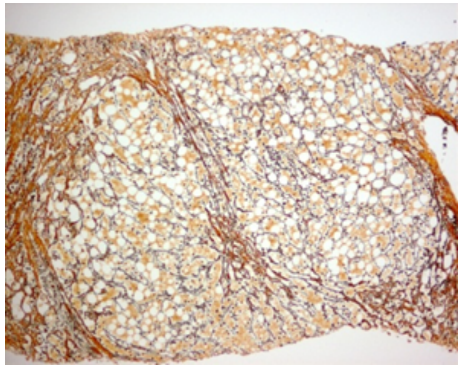
Steatosis



Lobular inflammation



Hepatocyte ballooning



Fibrosis

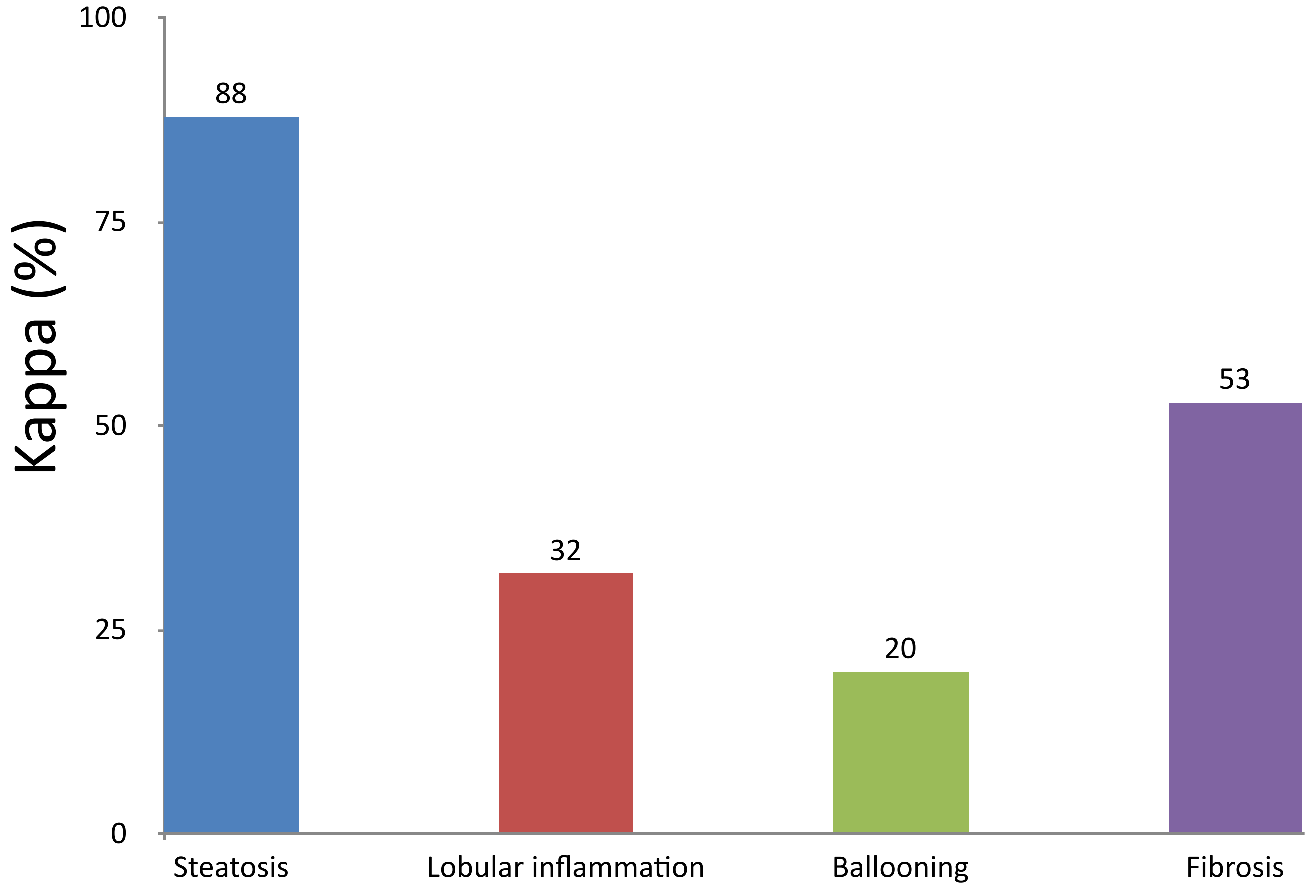
NAFLD activity score (0-8) = Steatosis (0-3) + Lobular inflammation (0-3) + Hepatocyte ballooning (0-2)

Kleiner et al. Hepatology 2005;41:1313
Courtesy of Prof Anthony Chan

Problems with liver biopsy

- Contraindications
  - Bleeding tendency
  - Ascites
- Complications
  - Pain
  - Bleeding
- Sampling error

N=41, biopsies of both lobes of liver



Merriman et al. Hepatology 2006;44:874

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Use of NITs in SLD

Biomarker	**Time**	Now	Follow-up	Future	**Targets**	Steatosis	Inflammation	Fibrosis	Cirrhosis	PHT	MALOs
Diagnostic		●				☑	☑	☑	☑	☑	

● Test

℞ Treatment

☠ Clinical outcomes

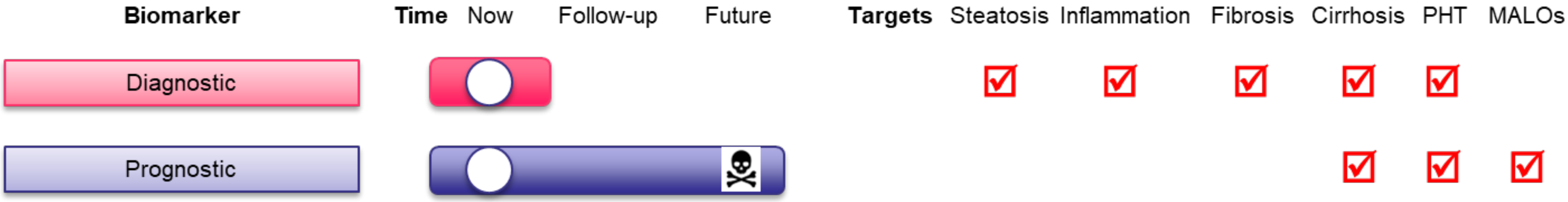
PHT, portal hypertension

MALO, major adverse liver outcomes

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, https://www.ncbi.nlm.nih.gov/books/NBK326791/, accessed on 14 Oct 2024

Use of NITs in SLD



Biomarker	**Time** Now	Follow-up	Future	**Targets** Steatosis	Inflammation	Fibrosis	Cirrhosis	PHT	MALOs
Diagnostic	○			☑	☑	☑	☑	☑	
Prognostic	○		☠				☑	☑	☑

○ Test ℞ Treatment ☠ Clinical outcomes PHT, portal hypertension MALO, major adverse liver outcomes

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, https://www.ncbi.nlm.nih.gov/books/NBK326791/, accessed on 14 Oct 2024

Use of NITs in SLD

Biomarker	**Time** Now	Follow-up	Future	**Targets** Steatosis	Inflammation	Fibrosis	Cirrhosis	PHT	MALOs
Diagnostic	○			☑	☑	☑	☑	☑	
Prognostic	○		☠				☑	☑	☑
Monitoring	○	○		☑	☑	☑	☑	☑	

○ Test

℞ Treatment

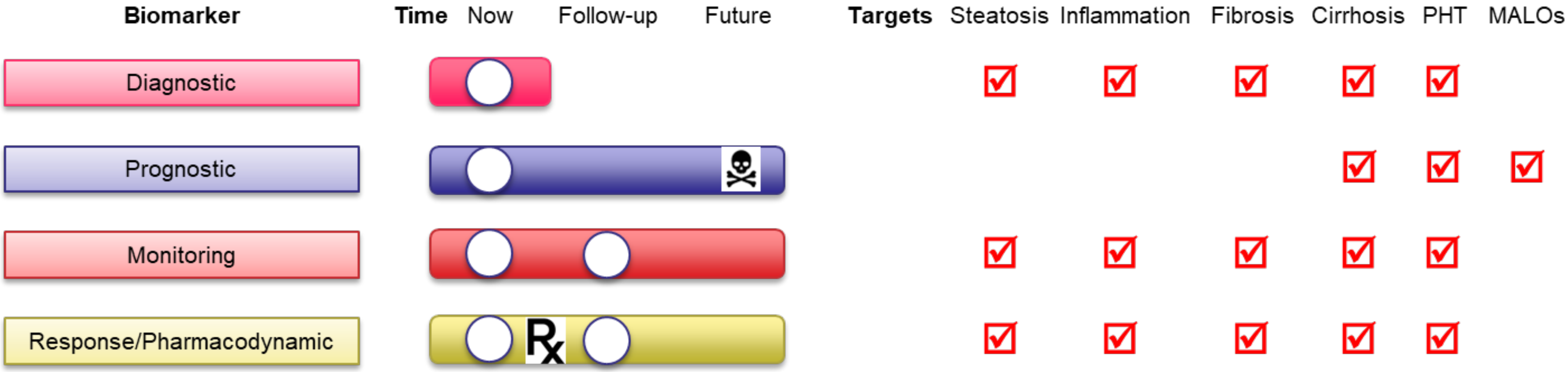
☠ Clinical outcomes

PHT, portal hypertension

MALO, major adverse liver outcomes

FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, https://www.ncbi.nlm.nih.gov/books/NBK326791/, accessed on 14 Oct 2024

Use of NITs in SLD



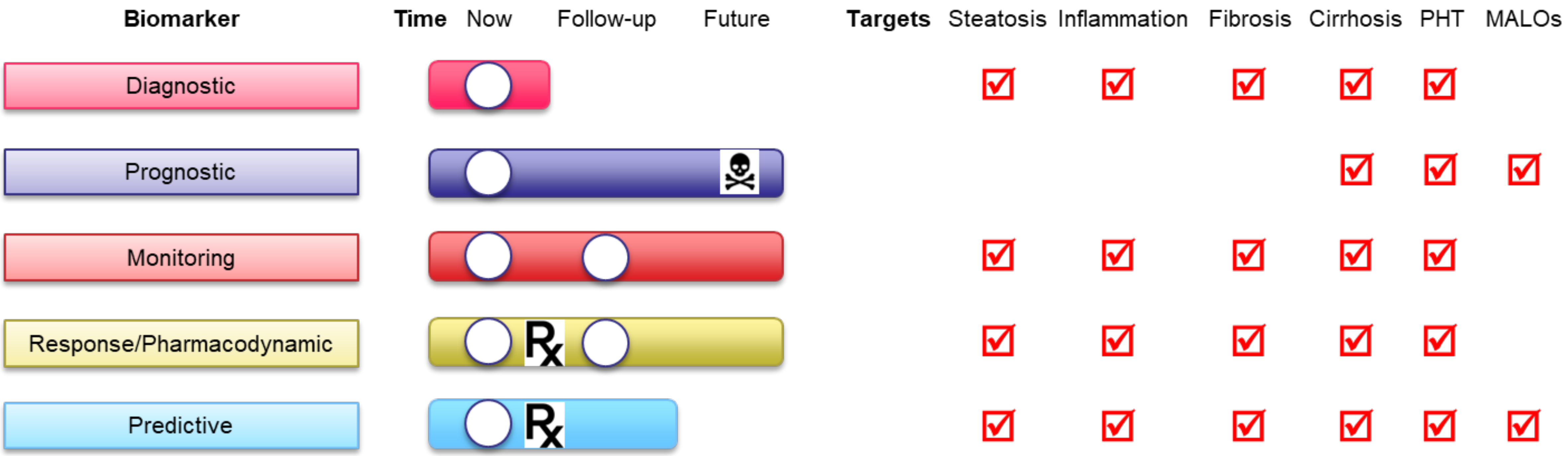
Biomarker	Time: Now	Follow-up	Future	Targets: Steatosis	Inflammation	Fibrosis	Cirrhosis	PHT	MALOs
Diagnostic	○			☑	☑	☑	☑	☑	
Prognostic	○		☠				☑	☑	☑
Monitoring	○	○		☑	☑	☑	☑	☑	
Response/Pharmacodynamic	○ ℞	○		☑	☑	☑	☑	☑	

○ Test ℞ Treatment ☠ Clinical outcomes PHT, portal hypertension MALO, major adverse liver outcomes

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, https://www.ncbi.nlm.nih.gov/books/NBK326791/, accessed on 14 Oct 2024

Use of NITs in SLD



Biomarker	**Time**			**Targets**					
	Now	Follow-up	Future	Steatosis	Inflammation	Fibrosis	Cirrhosis	PHT	MALOs
Diagnostic	○			☑	☑	☑	☑	☑	
Prognostic	○		☠				☑	☑	☑
Monitoring	○	○		☑	☑	☑	☑	☑	
Response/Pharmacodynamic	○ ℞	○		☑	☑	☑	☑	☑	
Predictive	○ ℞			☑	☑	☑	☑	☑	☑

○ Test ℞ Treatment ☠ Clinical outcomes PHT, portal hypertension MALO, major adverse liver outcomes

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, https://www.ncbi.nlm.nih.gov/books/NBK326791/, accessed on 14 Oct 2024

Use of NITs in SLD

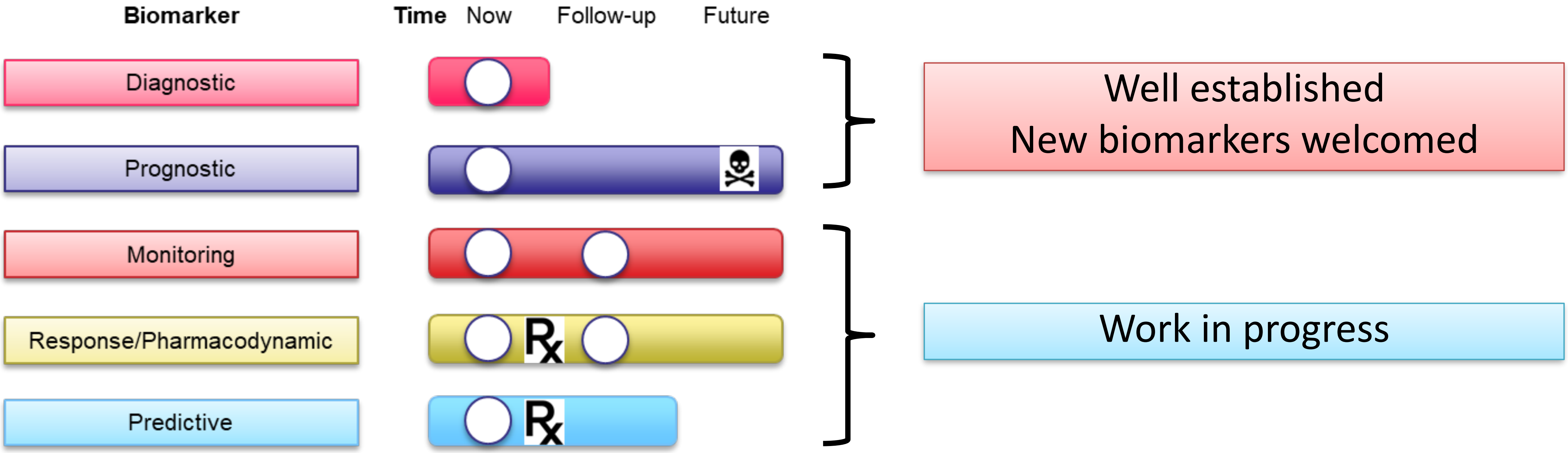
Biomarker	**Time**			**Targets**					
	Now	Follow-up	Future	Steatosis	Inflammation	Fibrosis	Cirrhosis	PHT	MALOs
Diagnostic	○			☑	☑	☑	☑	☑	
Prognostic	○		☠				☑	☑	☑
Monitoring	○	○		☑	☑	☑	☑	☑	
Response/Pharmacodynamic	○ ℞	○		☑	☑	☑	☑	☑	
Predictive	○ ℞			☑	☑	☑	☑	☑	☑

While it is desirable to have a single biomarker fulfilling all of the above (e.g., HbA_{1c} for diabetes), it is not a must.

○ Test ℞ Treatment ☠ Clinical outcomes PHT, portal hypertension MALO, major adverse liver outcomes

FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, https://www.ncbi.nlm.nih.gov/books/NBK326791/, accessed on 14 Oct 2024

Where are we in terms of NITs for SLD?



Biomarker
Time
Now
Follow-up
Future
Diagnostic
Prognostic
Monitoring
Response/Pharmacodynamic
Predictive

Well established
New biomarkers welcomed

Work in progress

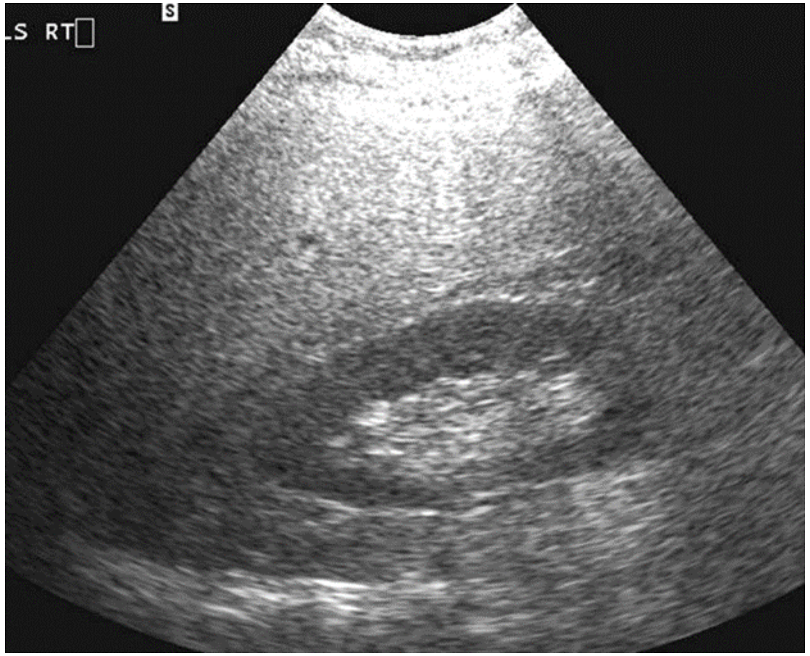
○ Test ℞ Treatment ☠ Clinical outcomes PHT, portal hypertension MALO, major adverse liver outcomes

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, https://www.ncbi.nlm.nih.gov/books/NBK326791/, accessed on 14 Oct 2024

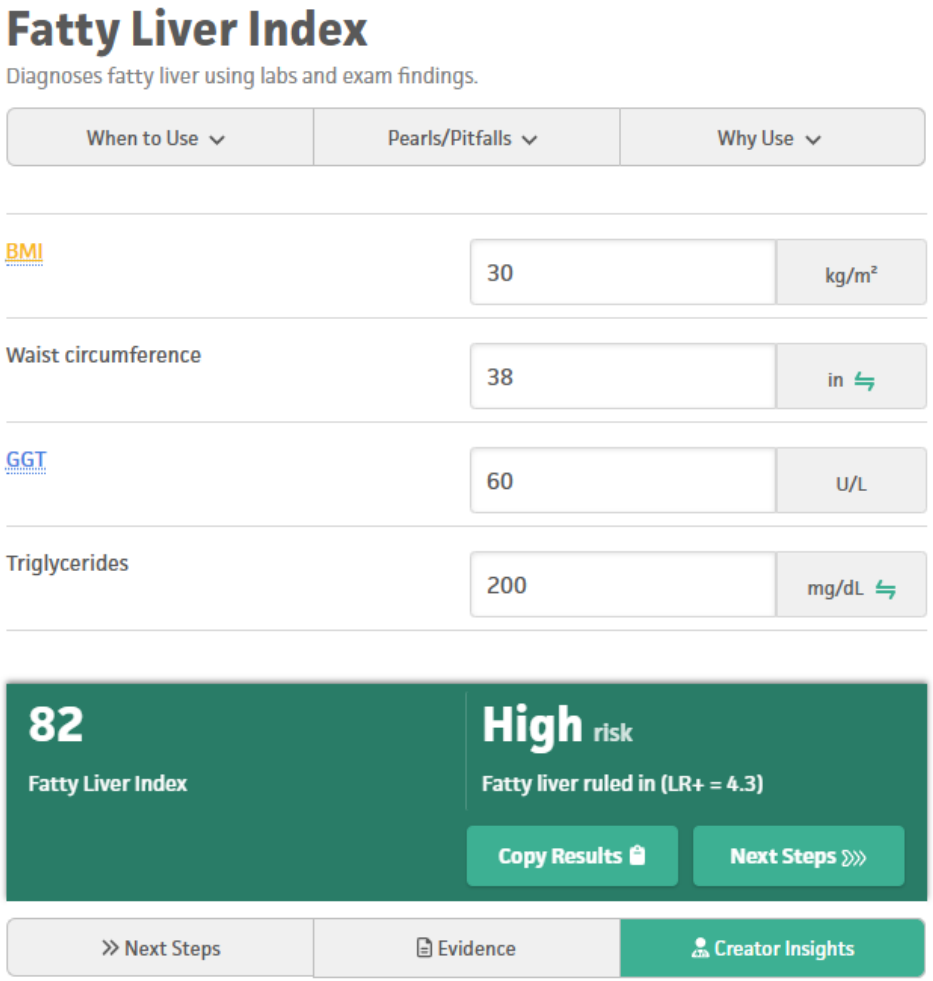
Diagnosis of MASLD

- Hepatic steatosis by imaging, blood biomarkers/scores or histology
- USG: Bright liver echotexture, deep attenuation, vascular blunting
- Presence of ≥1 of 5 cardiometabolic risk factors



Rinella et al. J Hepatol 2023;79:1542

Prediction models of hepatic steatosis


When to Use
Pearls/Pitfalls
Why Use
Copy Results
Next Steps
Next Steps
Evidence
Creator Insights

Fatty Liver Index

Diagnoses fatty liver using labs and exam findings.

BMI: 30 kg/m²

Waist circumference: 38 in

GGT: 60 U/L

Triglycerides: 200 mg/dL

82 Fatty Liver Index

High risk

Fatty liver ruled in (LR+ = 4.3)

Advantages
- Inexpensive
- Possible to study epidemiology of SLD in large retrospective registries when imaging is not available

Disadvantages
- Less helpful for individual patients
- Confounded by metabolic factors (e.g., cannot determine if adverse outcomes are due to SLD or obesity)
- Confounded by treatment

https://www.mdcalc.com/calc/10001/fatty-liver-index, accessed on 3 March 2025

Vibration-controlled transient elastography (FibroScan)

Controlled attenuation parameter (CAP)
- Measures ultrasound attenuation
- Reflects hepatic steatosis

Liver stiffness measurement (LSM)
- Measures shear wave velocity
- Reflects liver fibrosis

Diagnostic performance of CAP for hepatic steatosis

M probe

	S0 vs. S1-S3	S0-S1 vs. S2-S3	S0-S2 vs. S3
AUC	0.82	0.87	0.88
Sensitivity	69%	77%	88%
Specificity	82%	81%	78%
Optimal cutoff, dB/m	248	268	280

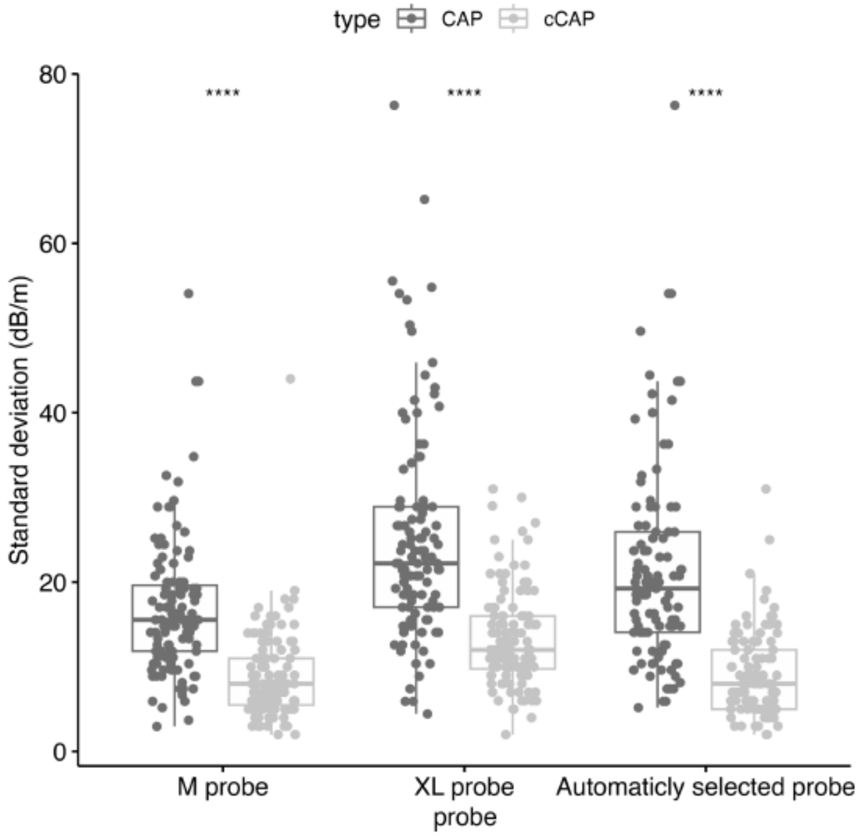
XL probe

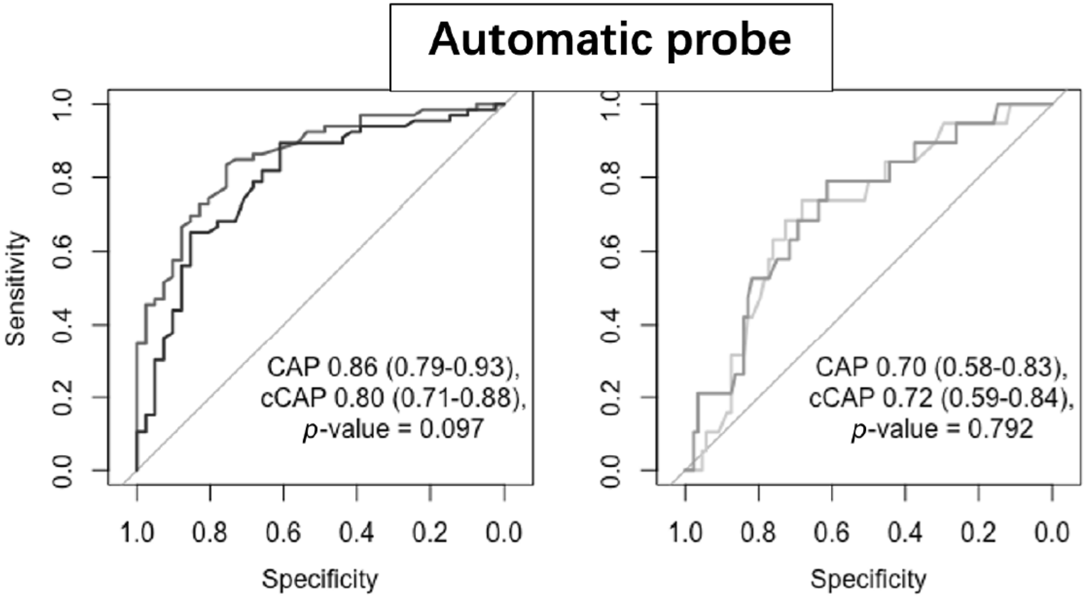
	S0 vs. S1-S3	S0-S1 vs. S2-S3	S0-S2 vs. S3
AUC	0.82	0.75	0.72
Sensitivity	80%	78%	76%
Specificity	74%	63%	60%
Optimal cutoff, dB/m	297	317	333

Karlas et al. J Hepatol 2017;66:1022, Petroff et al. Lancet Gastroenterol Hepatol 2021;6:185

Continuous CAP to reduce variability

>200 measurements are taken
with continuous CAP

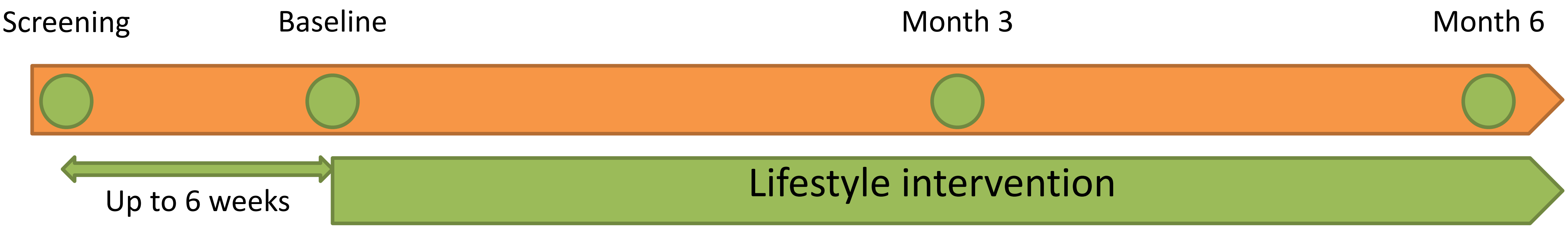




香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Song SJ et al. Liver Int 2024;44:1167

MASLD-CAP-MON Study design overview (N=150)

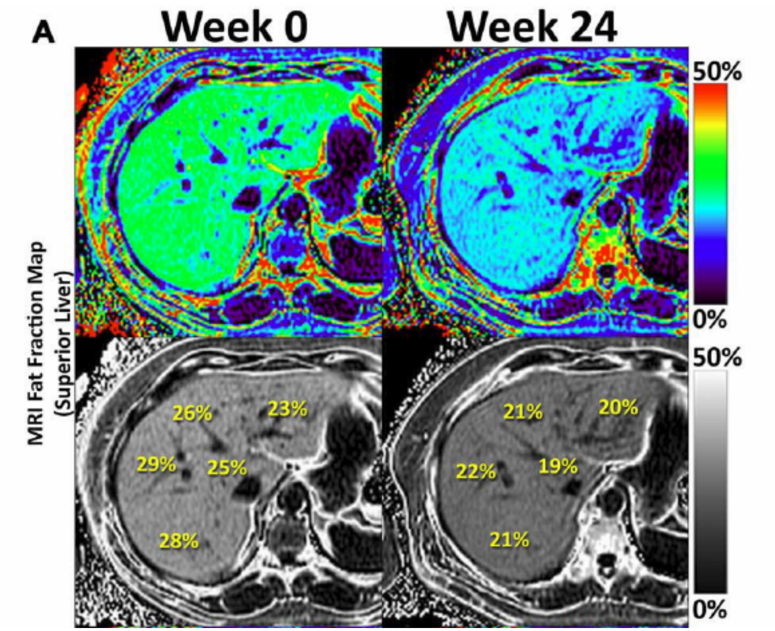

Screening
Baseline
Month 3
Month 6
Up to 6 weeks
Lifestyle intervention

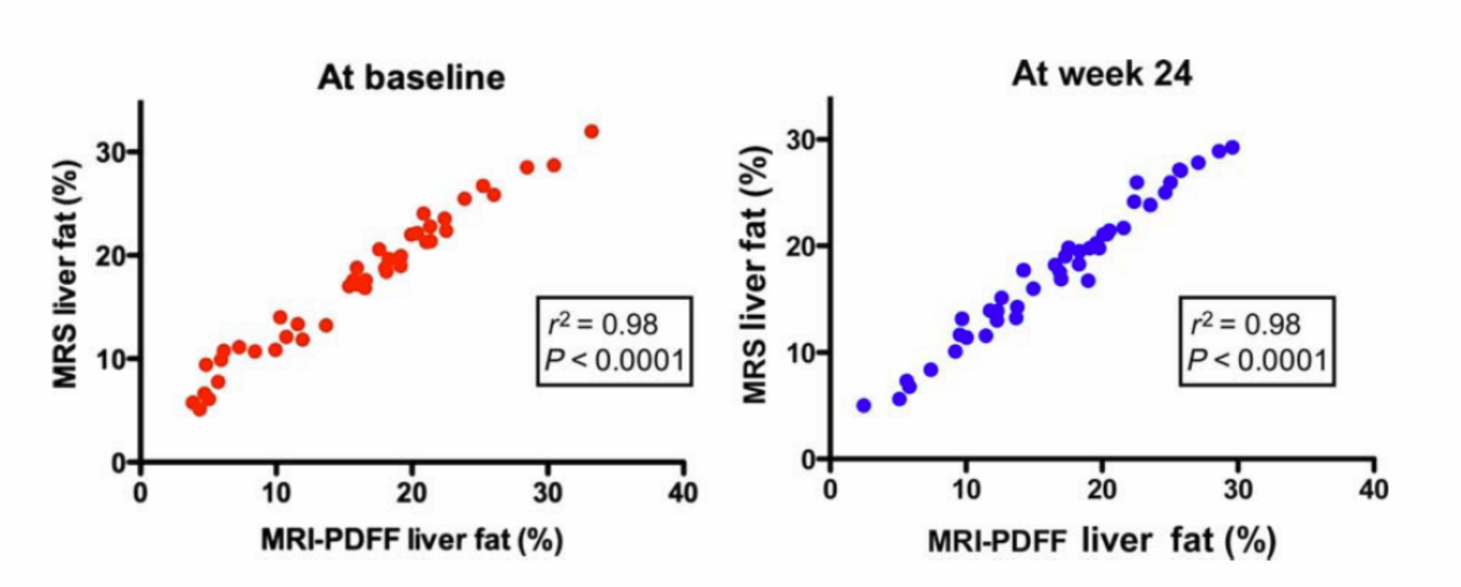
Visit	Screening	Baseline	Month 3	Month 6
Questionnaires		X	X	X
BW, BH, WC, HC, BP	X	X	X	X
Blood tests	X		X	X
HBsAg, anti-HCV	X			
VCTE	X		X	X
USG	X			X
MRI-PDFF	X			X

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

NCT06203548, GRF Project Ref 14106923

MRI assessment of hepatic steatosis


A
Week 0
Week 24
MRI Fat Fraction Map (Superior Liver)
50%
0%
50%
0%
26%
23%
29%
25%
28%
21%
20%
22%
19%
21%

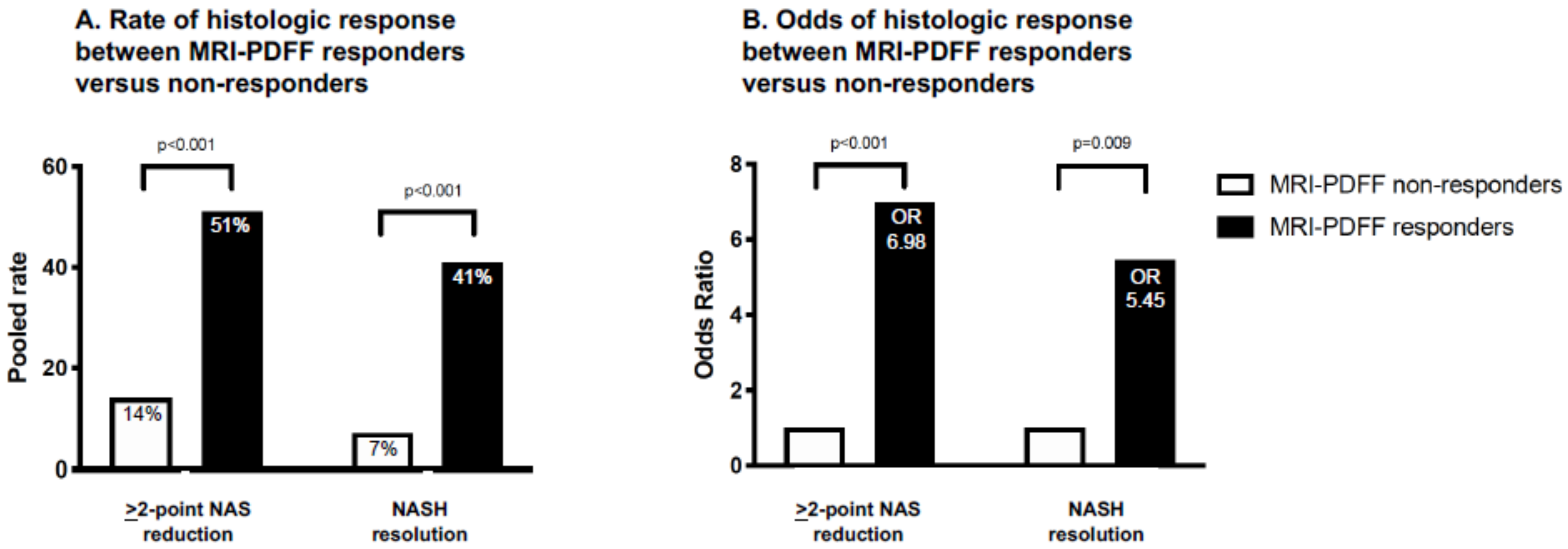


- Highly reproducible
- Not affected by obesity
- Expensive and limited availability

PDF: proton density fat fraction
MRS: magnetic resonance spectroscopy

Noureddin et al. Hepatology 2013;58:1930
Loomba et al. Hepatology 2015;61:1239

Histologic response in patients with ≥30% relative reduction in MRI-PDFF

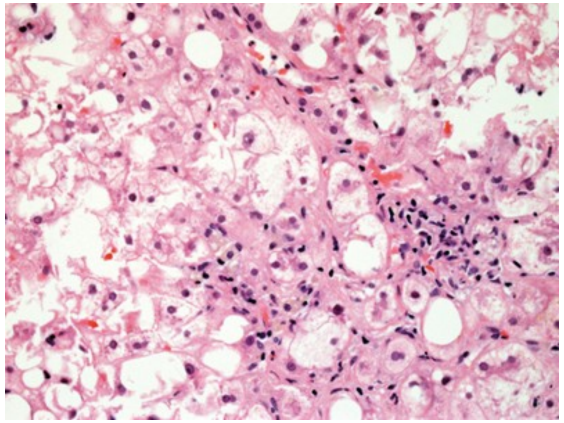


A. Rate of histologic response between MRI-PDFF responders versus non-responders

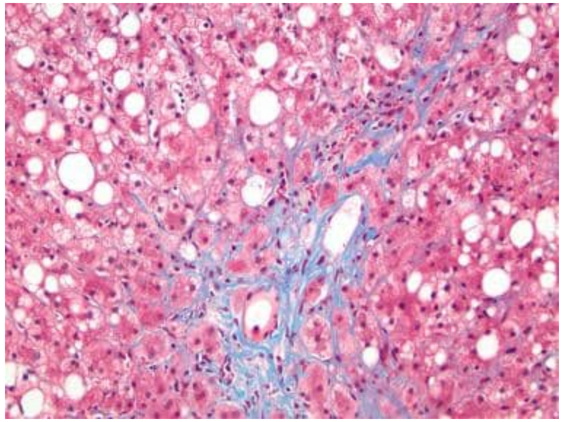
B. Odds of histologic response between MRI-PDFF responders versus non-responders

Stine et al. Clin Gastroenterol Hepatol 2021;19:2274

Key diagnostic targets for MASLD



Metabolic dysfunction-associated steatohepatitis (MASH)
Characterized by steatosis, lobular inflammation and hepatocyte ballooning



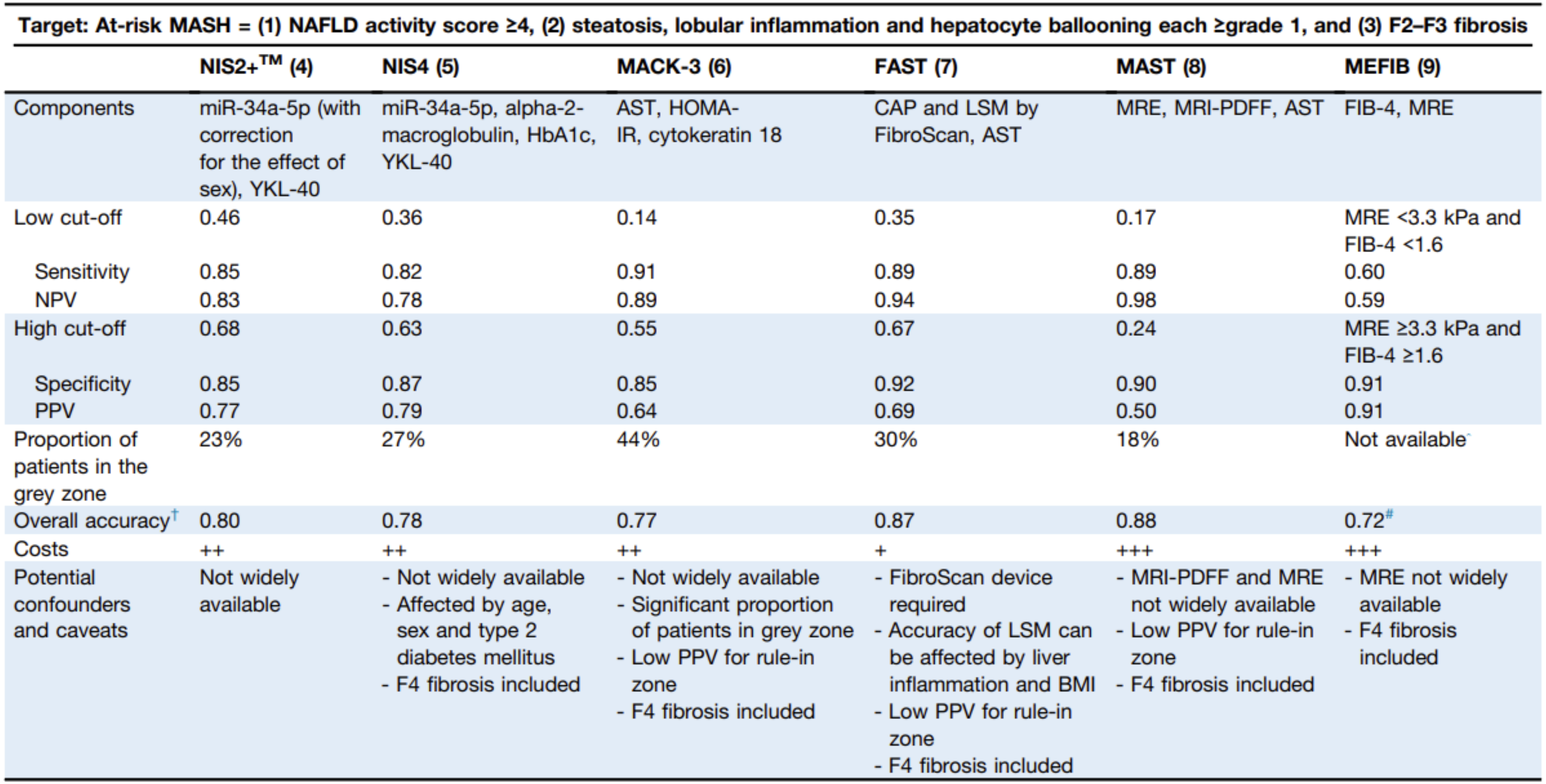
Liver fibrosis and cirrhosis
Strongly associated with liver-related outcomes

At-risk MASH

=

1. MASLD activity score ≥4
2. ≥1 point each in steatosis, lobular inflammation and ballooning
3. F2-F3 fibrosis

Performance of NITs of at-risk MASH



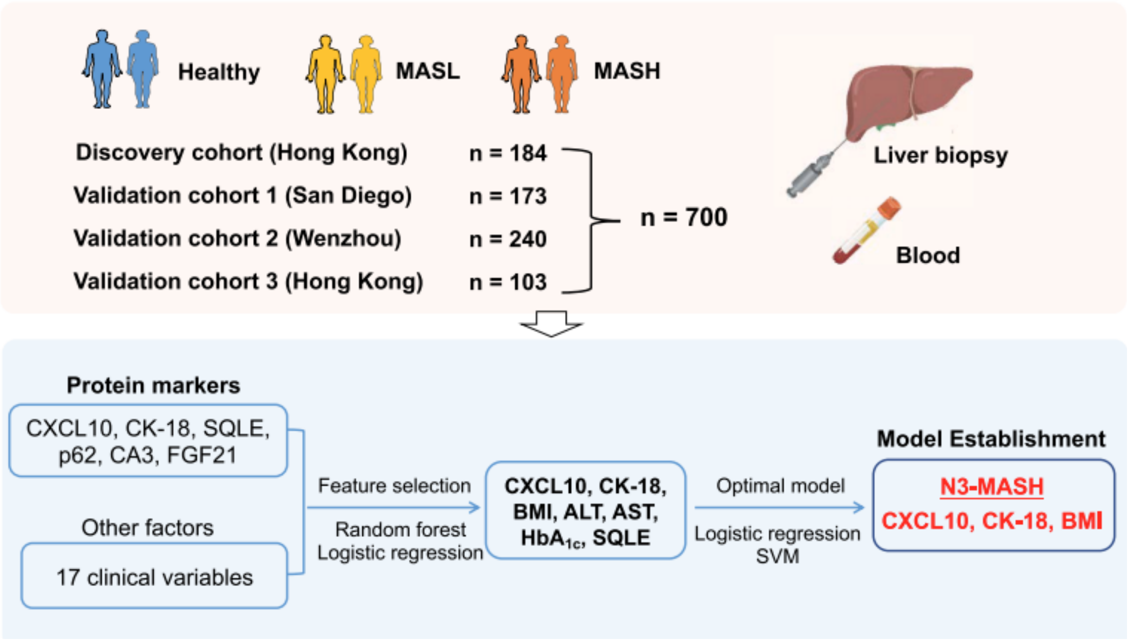
Target: At-risk MASH = (1) NAFLD activity score ≥4, (2) steatosis, lobular inflammation and hepatocyte ballooning each ≥grade 1, and (3) F2–F3 fibrosis

	NIS2+™ (4)	**NIS4 (5)**	**MACK-3 (6)**	**FAST (7)**	**MAST (8)**	**MEFIB (9)**
Components	miR-34a-5p (with correction for the effect of sex), YKL-40	miR-34a-5p, alpha-2-macroglobulin, HbA1c, YKL-40	AST, HOMA-IR, cytokeratin 18	CAP and LSM by FibroScan, AST	MRE, MRI-PDFF, AST	FIB-4, MRE
Low cut-off	0.46	0.36	0.14	0.35	0.17	MRE <3.3 kPa and FIB-4 <1.6
Sensitivity	0.85	0.82	0.91	0.89	0.89	0.60
NPV	0.83	0.78	0.89	0.94	0.98	0.59
High cut-off	0.68	0.63	0.55	0.67	0.24	MRE ≥3.3 kPa and FIB-4 ≥1.6
Specificity	0.85	0.87	0.85	0.92	0.90	0.91
PPV	0.77	0.79	0.64	0.69	0.50	0.91
Proportion of patients in the grey zone	23%	27%	44%	30%	18%	Not available[^]
Overall accuracy[†]	0.80	0.78	0.77	0.87	0.88	0.72[#]
Costs	++	++	++	+	+++	+++
Potential confounders and caveats	Not widely available	- Not widely available - Affected by age, sex and type 2 diabetes mellitus - F4 fibrosis included	- Not widely available - Significant proportion of patients in grey zone - Low PPV for rule-in zone - F4 fibrosis included	- FibroScan device required - Accuracy of LSM can be affected by liver inflammation and BMI - Low PPV for rule-in zone - F4 fibrosis included	- MRI-PDFF and MRE not widely available - Low PPV for rule-in zone - F4 fibrosis included	- MRE not widely available - F4 fibrosis included

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Lai JC and Wong VW. J Hepatol 2024;80:181

A blood-based biomarker panel for MASH



Healthy MASL MASH

Discovery cohort (Hong Kong) n = 184

Validation cohort 1 (San Diego) n = 173

Validation cohort 2 (Wenzhou) n = 240

Validation cohort 3 (Hong Kong) n = 103

n = 700

Liver biopsy

Blood

Protein markers

CXCL10, CK-18, SQLE, p62, CA3, FGF21

Other factors

17 clinical variables

Feature selection

Random forest
Logistic regression

CXCL10, CK-18, BMI, ALT, AST, HbA_{1c}, SQLE

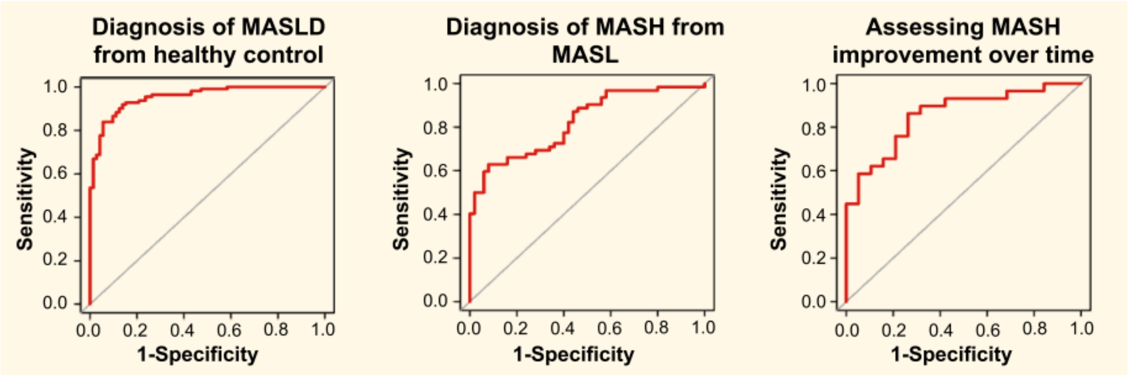
Optimal model

Logistic regression
SVM

Model Establishment

N3-MASH

CXCL10, CK-18, BMI



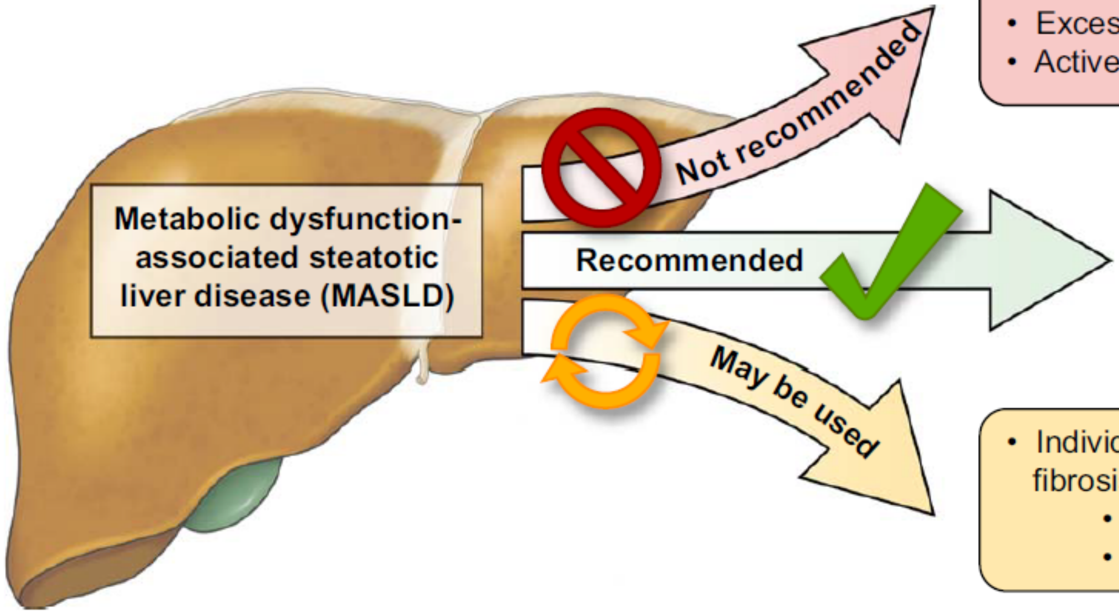
AUROC 0.95 0.82 0.86

Zhang X et al. Cell Metab 2025;37:59

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

But are MASH biomarkers required?

AASLD Guidance on Resmetirom Therapy


Metabolic dysfunction-associated steatotic liver disease (MASLD)
Not recommended
Recommended
May be used

- Cirrhosis, including LSM via VCTE >20 kPa or MRE >5 kPa
- Concomitant active liver disease
- Excess alcohol use (>20/30 g/d in women/men)
- Active thyroid disease

Imaging-based NILDA	VCTE: LSM 8 kPa - 15 kPa[a] MRE: LSM 3.1 kPa - 4.4 kPa[a]
Liver histology	MASH with F2-F3[b]

- Individualized decisions by a specialist experienced in liver fibrosis for:
  - LSM values outside the recommended ranges
  - Other NILDA data consistent with F2-F3[c]

---

[a] Modified from the AASLD NILDA guidelines.[5]

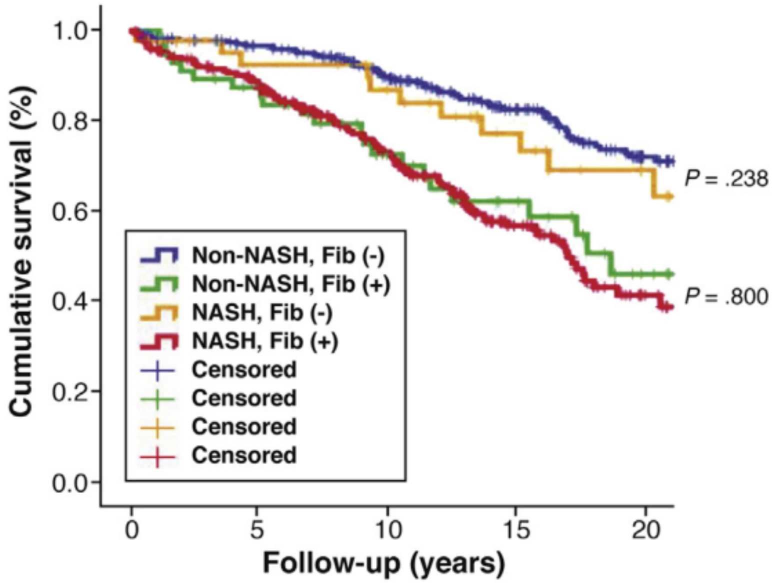
[b] Liver biopsy is not routinely recommended for staging of MASH.

[c] Imaging-based NILDA is preferred, eg, shear wave elastography (applying local standards for F2-F3) versus enhanced liver fibrosis score (9.2-10.4). The latter range is based on the interquartile range from the MAESTRO trial data; no recommendations are available from the AASLD NILDA guidelines.[6]

Chen V et al. Hepatology 2025;81:312

Potential role of MASH biomarkers

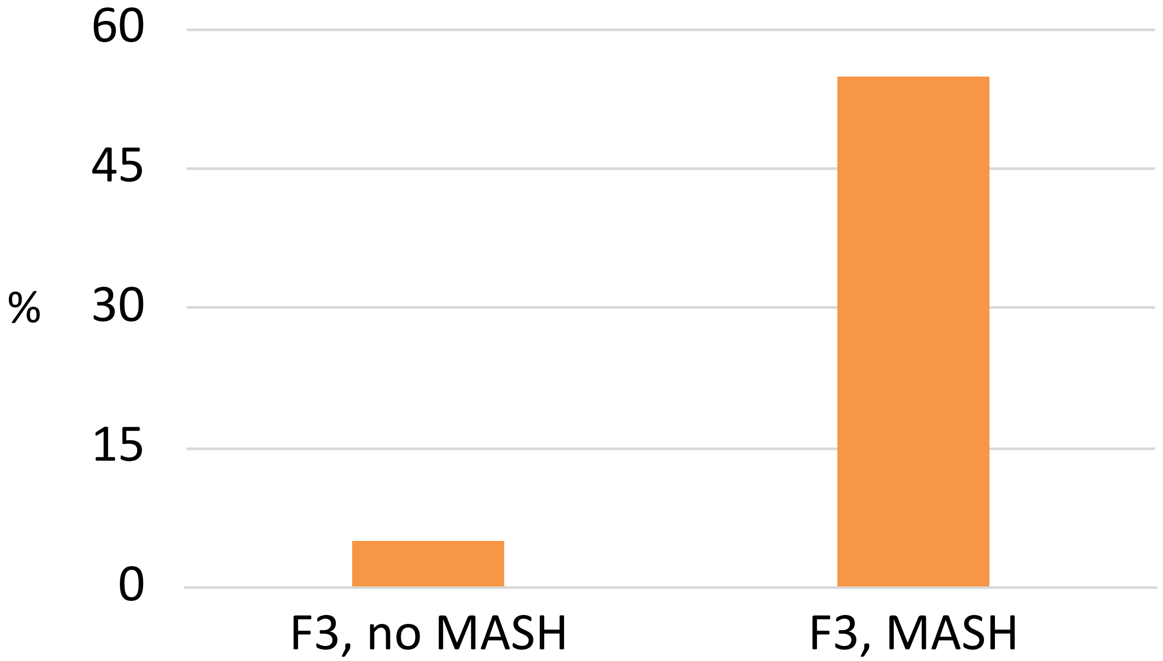
Fibrosis trumps MASH in prognostication



0	5	10	15	20	
279	241	197	137	72	Non-NASH, Fib (-)
56	46	30	19	7	Non-NASH, Fib (+)
43	35	31	20	12	NASH, Fib (-)
241	197	124	58	18	NASH, Fib (+)

Transplant-free survival

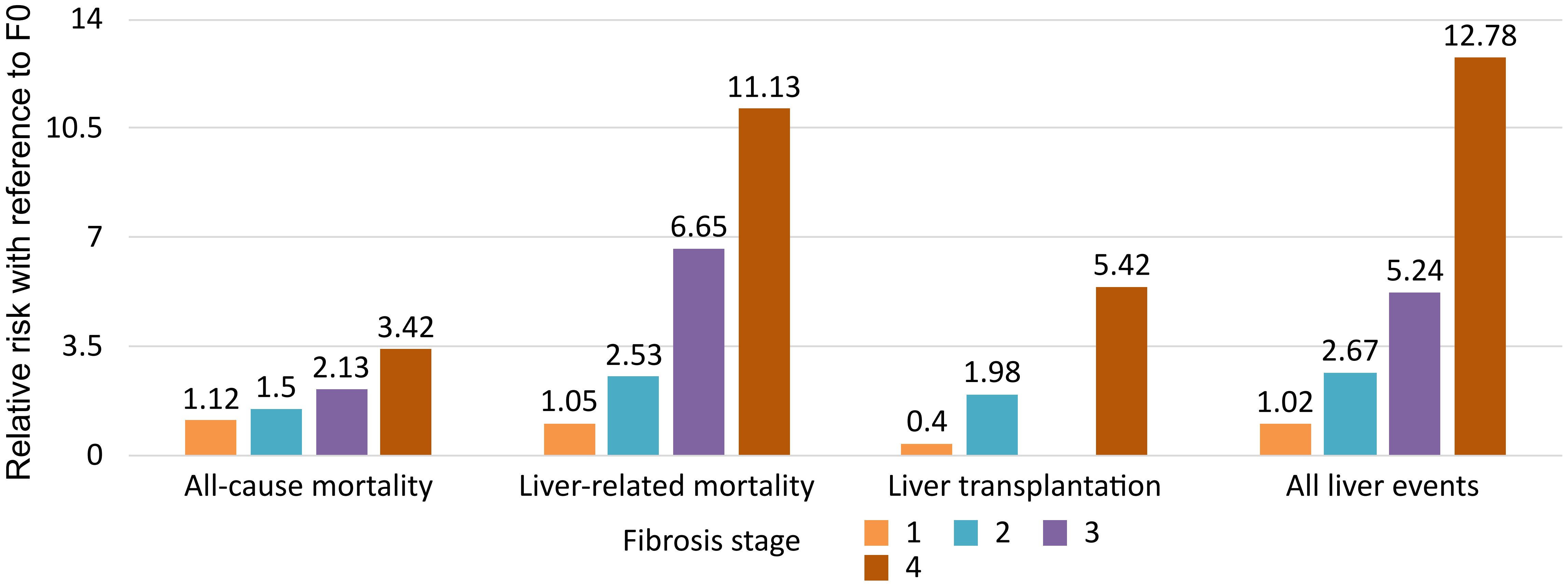
The only use of MASH biomarkers is if they can predict response to treatment



However, as most drug trials only include patients with MASH, whether a drug works differently in patients with low disease activity is currently unknown

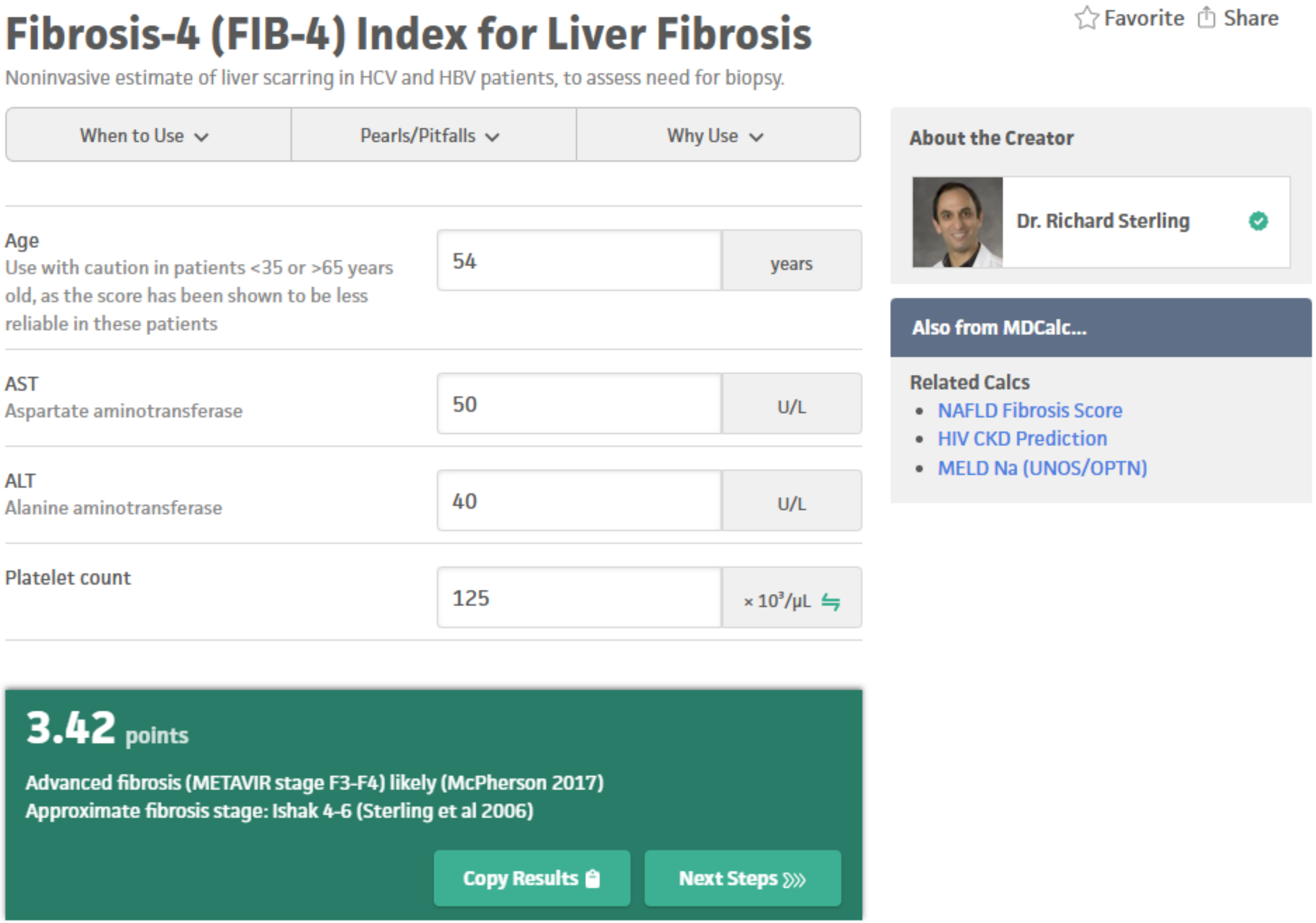
Angulo et al. Gastroenterology 2015;149:389

Fibrosis stage and clinical outcomes of MASLD



香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Taylor et al. Gastroenterology 2020;158:1611



Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

Age Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients	54	years
AST Aspartate aminotransferase	50	U/L
ALT Alanine aminotransferase	40	U/L
Platelet count	125	× 10^3/µL ⇆

3.42 points

Advanced fibrosis (METAVIR stage F3-F4) likely (McPherson 2017)
Approximate fibrosis stage: Ishak 4-6 (Sterling et al 2006)

About the Creator

Dr. Richard Sterling ✓

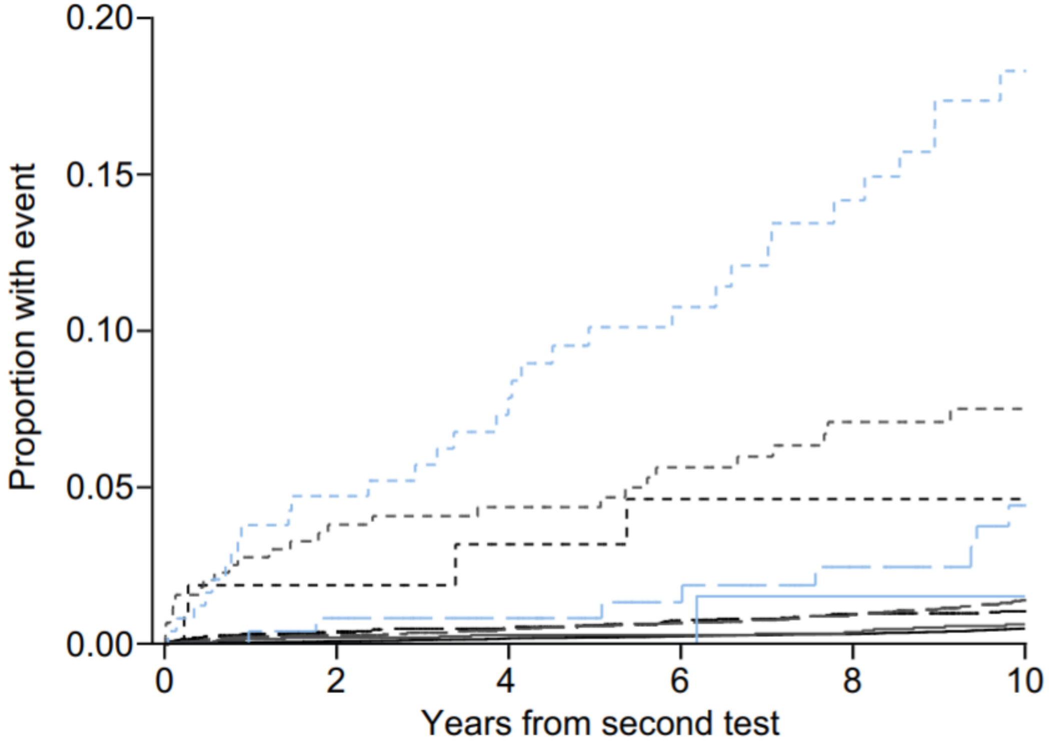
Also from MDCalc...

Related Calcs

- NAFLD Fibrosis Score
- HIV CKD Prediction
- MELD Na (UNOS/OPTN)

https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis, accessed on 3 March 2025

Serial FIB-4 predicts liver-related outcomes in the general Swedish population



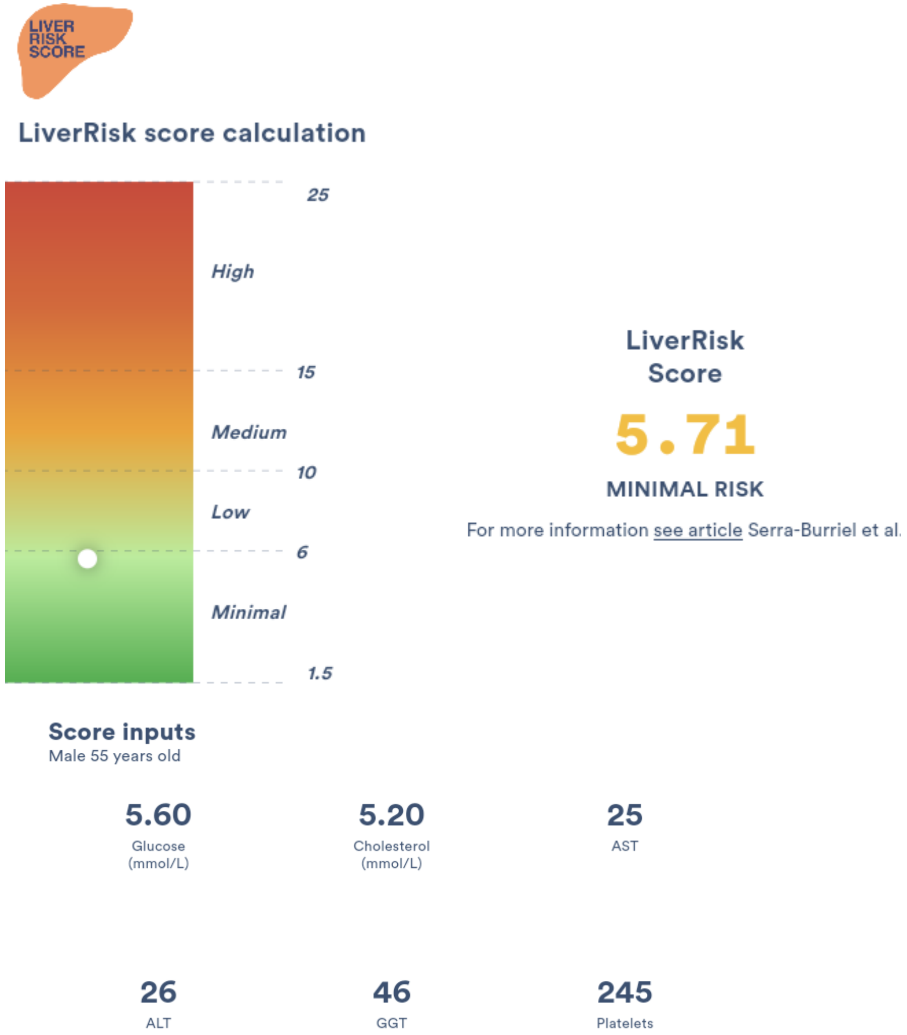
N° at risk						
Group = 11	27,466	26,588	25,870	25,158	24,359	23,575
Group = 12	4,100	3,841	3,661	3,437	3,239	3,010
Group = 13	114	81	72	64	57	55
Group = 21	2,661	2,485	2,355	2,215	2,064	1,914
Group = 22	5,332	4,946	4,599	4,269	3,882	3,466
Group = 23	451	359	326	292	242	201
Group = 31	83	70	68	66	64	59
Group = 32	272	233	213	182	163	138
Group = 33	250	198	168	138	115	81

Severe liver disease = incident cirrhosis, liver failure, HCC, liver transplantation, decompensated liver disease or liver-related death

香 港 中 文 大 學 醫 學 院
Faculty of Medicine
The Chinese University of Hong Kong

Hagström et al. J Hepatol 2020;73:1023

LiverRisk score


LIVER RISK SCORE
25
High
15
Medium
10
Low
6
Minimal
1.5

LiverRisk score calculation

LiverRisk Score

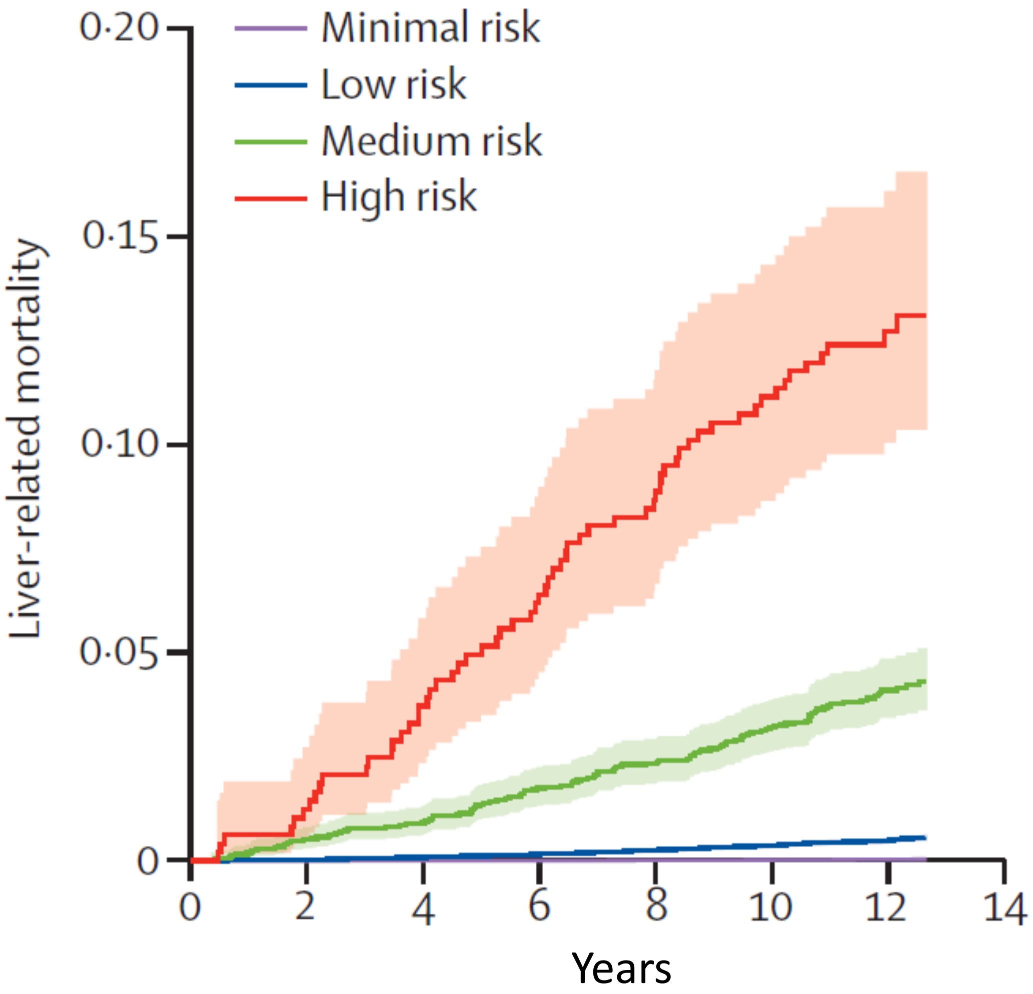
5.71

MINIMAL RISK

For more information see article Serra-Burriel et al.

Score inputs
Male 55 years old

5.60 Glucose (mmol/L)	**5.20** Cholesterol (mmol/L)	**25** AST
26 ALT	**46** GGT	**245** Platelets



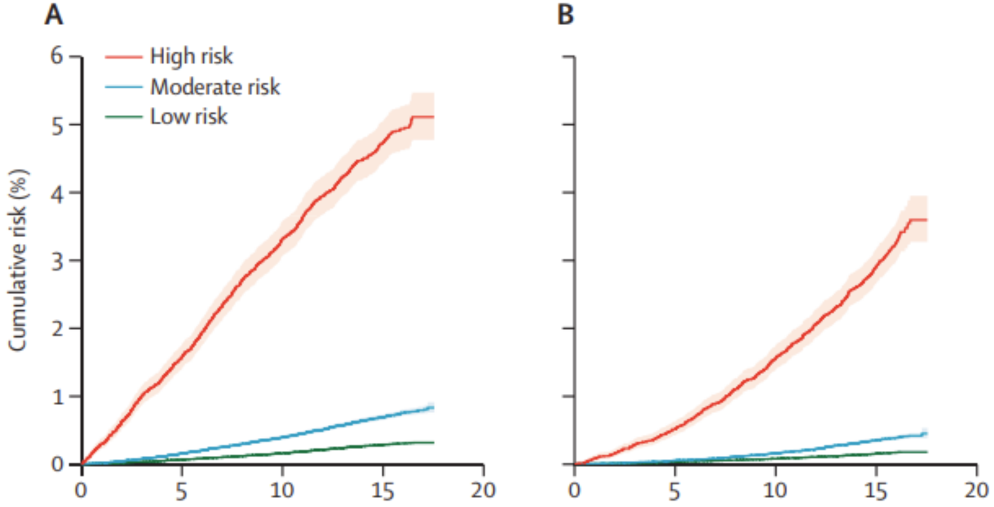
Serra-Burriel et al. Lancet 2023;402:988

LiverPRO score

- Age + 3-9 variables from the following:
    - Aspartate aminotransferase
    - Alkaline phosphatase
    - Gamma-glutamyl transpeptidase
    - INR
    - Albumin
    - Sodium
    - Bilirubin
    - Platelet count
    - Cholesterol

Liver-related events

Liver-related mortality



Number at risk (censored)	A 0	A 5	A 10	A 15	A 20	B 0	B 5	B 10	B 15	B 20
Low risk	258559	256282	251769	165105	0	258559	256371	251769	165348	0
	(2110)	(4271)	(86361)	(165075)		(256371)	(4272)	(86463)	(165318)	
Moderate risk	17797	174482	168373	109518	0	177973	174671	168784	109918	0
	(3216)	(5704)	(58375)	(109452)		(174671)	(5704)	(58561)	(109874)	
High risk	20100	18833	17238	10675	0	20100	19043	17575	10917	0
	(957)	(1274)	(6329)	(10649)		(19043)	(1274)	(6439)	(10873)	

Lindvig et al. Lancet Gastroenterol Hepatol 2025;10:55

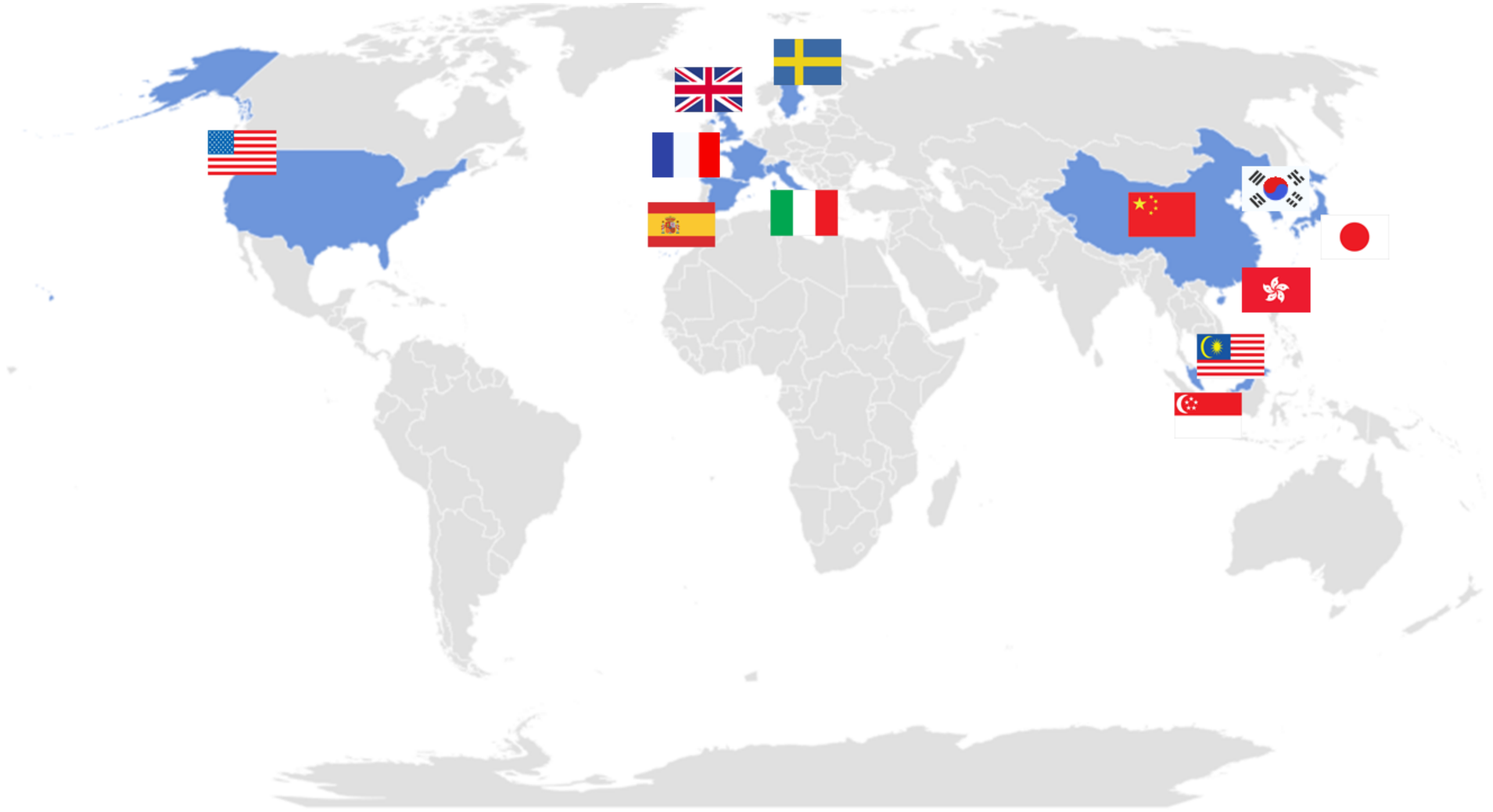
Vibration-controlled transient elastography (FibroScan)

Controlled attenuation parameter (CAP)
- Measures ultrasound attenuation
- Reflects hepatic steatosis

Liver stiffness measurement (LSM)
- Measures shear wave velocity
- Reflects liver fibrosis

VCTE-Prognosis Study Group

- 17,949 patients with MASLD who underwent VCTE from 16 centers (prospective at 14 centers)
- 14,845 Asian countries/regions
    - ➢ 9,556 Korea
    - ➢ 4,037 Hong Kong
    - ➢ 474 Japan
    - ➢ 366 China
    - ➢ 211 Singapore
    - ➢ 201 Malaysia
- 3,104 Western countries
    - ➢ 1,183 Italy
    - ➢ 724 United Kingdom
    - ➢ 382 France
    - ➢ 352 Spain
    - ➢ 302 Sweden
    - ➢ 161 United States

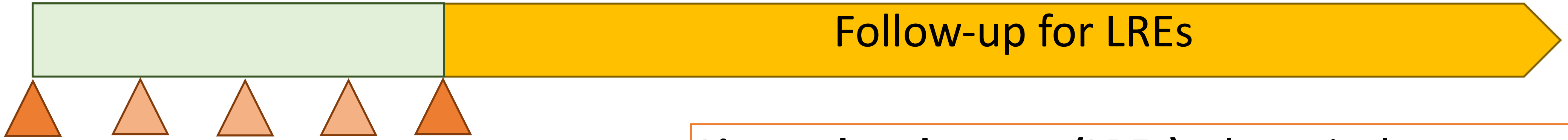


香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Lin H et al. JAMA 2024;331:1287

Study design

- We included adult patients with MASLD who underwent at least 1 additional VCTE exam within 6-60 months after the first VCTE
- We excluded patients with LREs before the first VCTE, or between the VCTE examinations in 6-60 months



First VCTE

Last VCTE within 6-60 months from the first VCTE

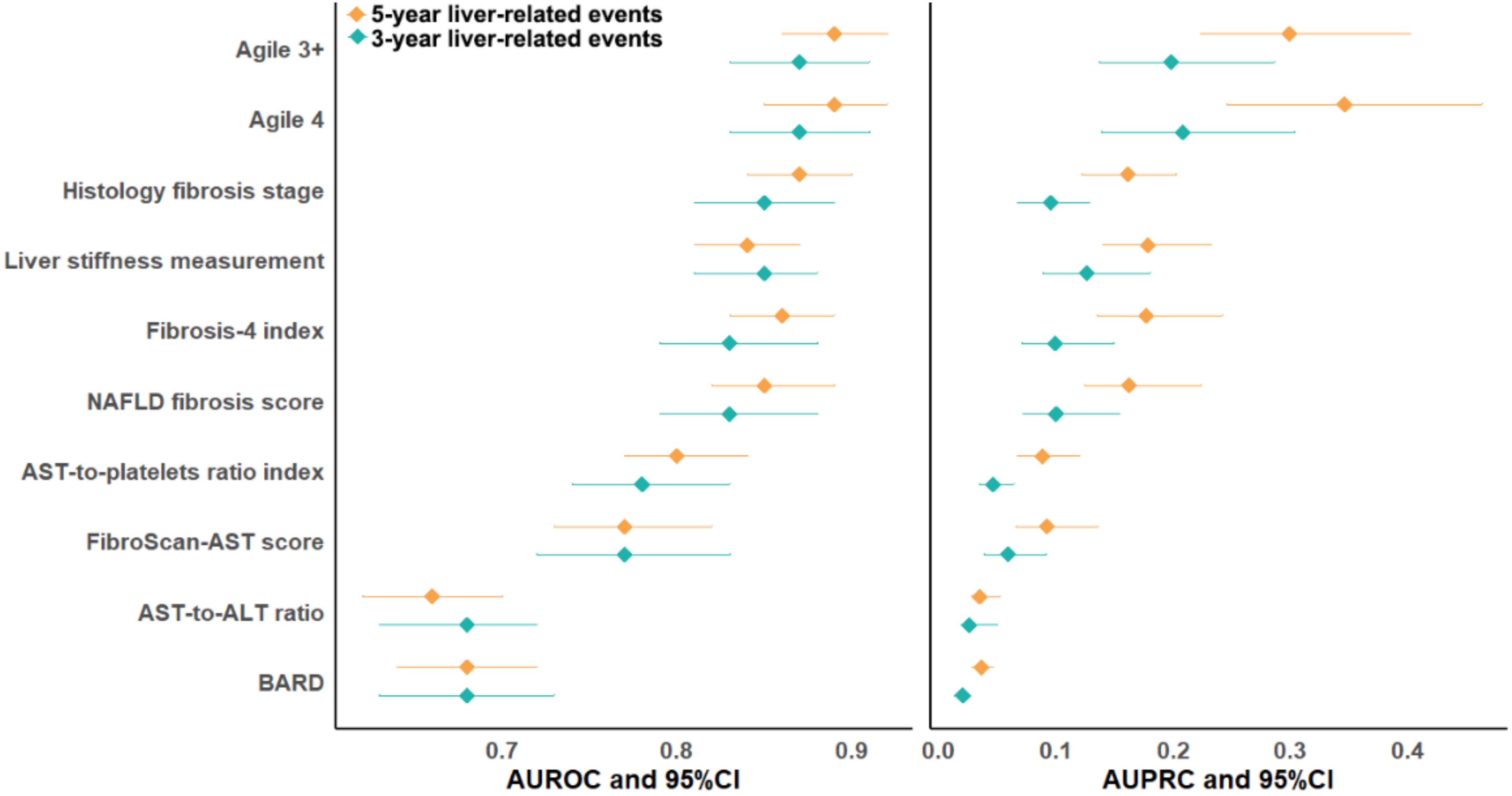
Liver-related events (LREs) = hepatic decompensation (ascites, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome-acute kidney injury), HCC, liver transplantation, or liver-related death

Lin H et al. JAMA 2024;331:1287

Agile scores are superior to histologic fibrosis stage and other fibrosis scores in prognostication

16 603 patients with MASLD from 16 centers in the US, Europe and Asia (prospective data from 14 centers)

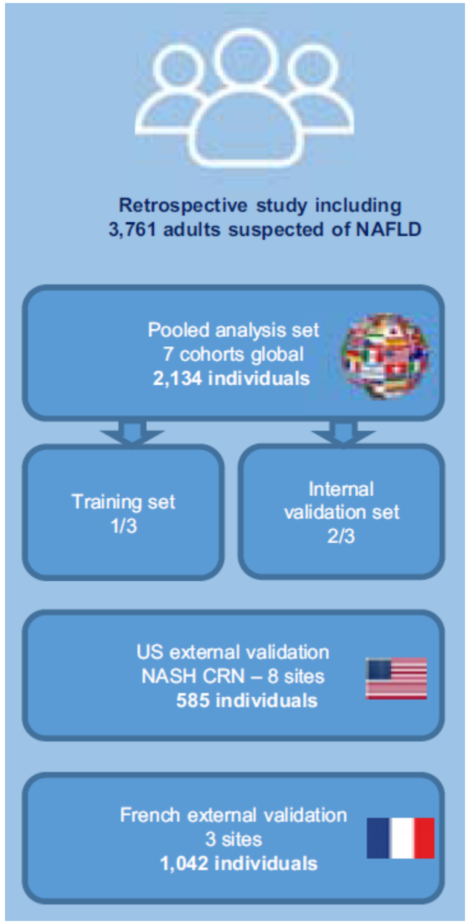
316 liver-related events (LREs; 139 HCC and 209 hepatic decompensation) at a median FU of 52 months



香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Lin H et al. JAMA 2024;331:1287

Agile scores for F3 and F4 fibrosis



Retrospective study including
3,761 adults suspected of NAFLD

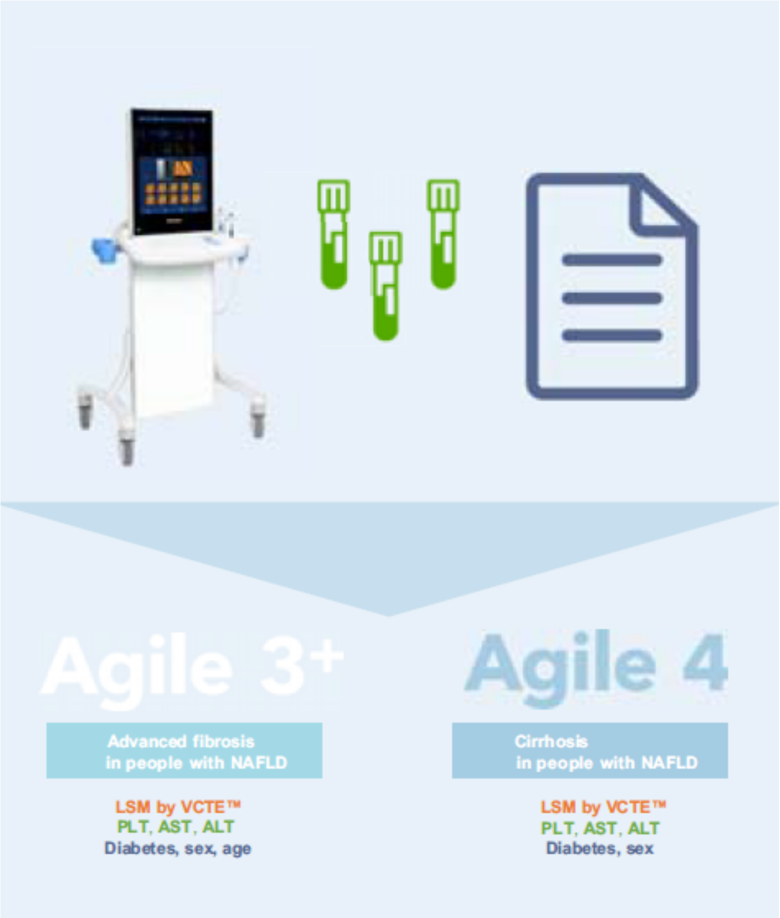
Pooled analysis set
7 cohorts global
2,134 individuals

Training set
1/3

Internal validation set
2/3

US external validation
NASH CRN – 8 sites
585 individuals

French external validation
3 sites
1,042 individuals



Agile 3+

Advanced fibrosis
in people with NAFLD

LSM by VCTE™
PLT, AST, ALT
Diabetes, sex, age

Agile 4

Cirrhosis
in people with NAFLD

LSM by VCTE™
PLT, AST, ALT
Diabetes, sex

		FIB-4	LSM	Agile 3+
F3	AUC	0.84	0.85	0.90
	Gray zone	28%	24%	17%
	Se	0.84	0.83	0.87
	NPV	0.87	0.88	0.91
	Specificity	0.57	0.57	0.69
	PPV	0.77	0.77	0.81
		FIB-4	**LSM**	**Agile 4**
F4	AUC	0.82	0.85	0.89
	Gray zone	40%	28%	16%
	Se	0.87	0.79	0.79
	NPV	0.97	0.96	0.96
	Sp	0.95	0.95	0.96
	PPV	0.48	0.52	0.64

(Internal validation set results)

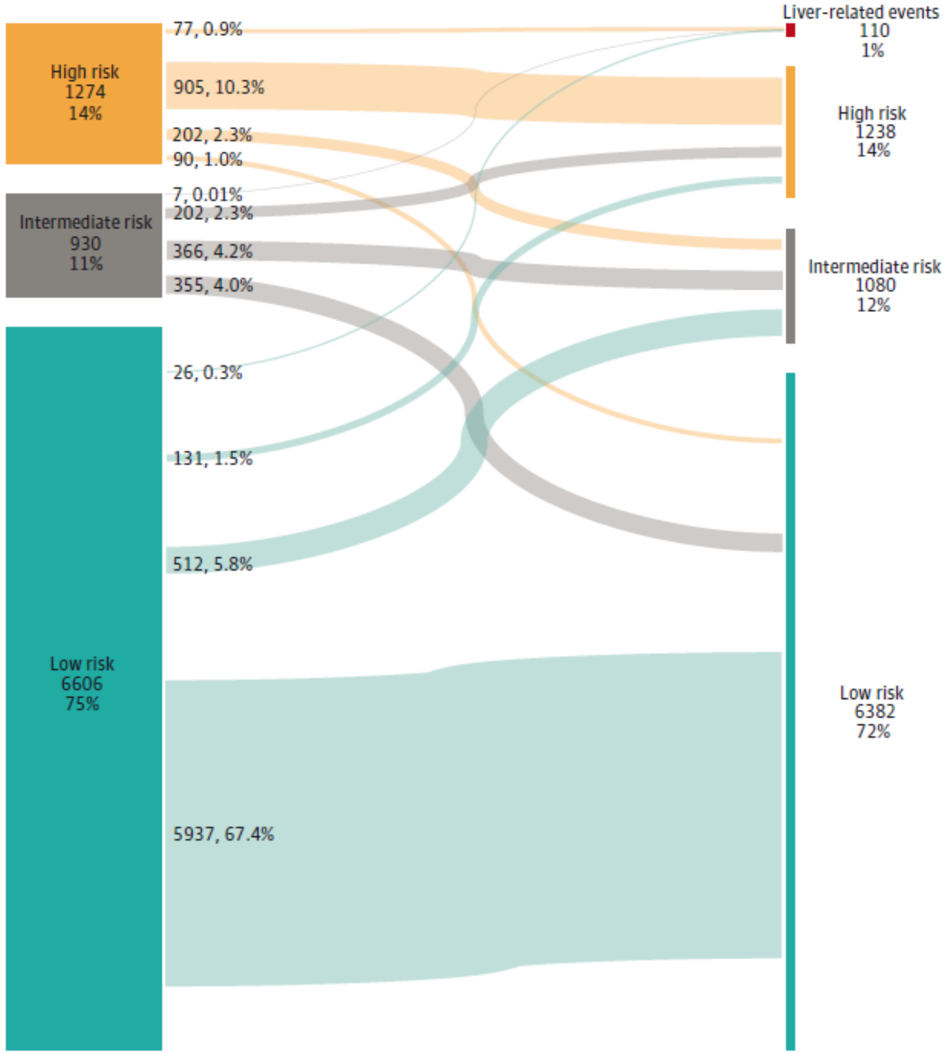
香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Sanyal et al. J Hepatol 2023;78:247

Change in the Agile scores at a median interval of 15 months

81.9% of patients had stable Agile 3+ score at 2 measurements

92.1% of patients had stable Agile 4 score at 2 measurements



Lin H et al. JAMA 2024;331:1287

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Evolution of Agile 3+ score and LREs

First test	Second test	% of patients	LRE per 1000 person-years
Low risk	Low risk	68.2	0.6
	Intermediate risk	5.8	1.9
	High risk	1.5	NA
Intermediate risk	Low risk	4.0	1.1
	Intermediate risk	4.2	2.8
	High risk	2.3	3.3
High risk	Low risk	1.0	NA
	Intermediate risk	2.3	3.3
	High risk	10.4	30.1

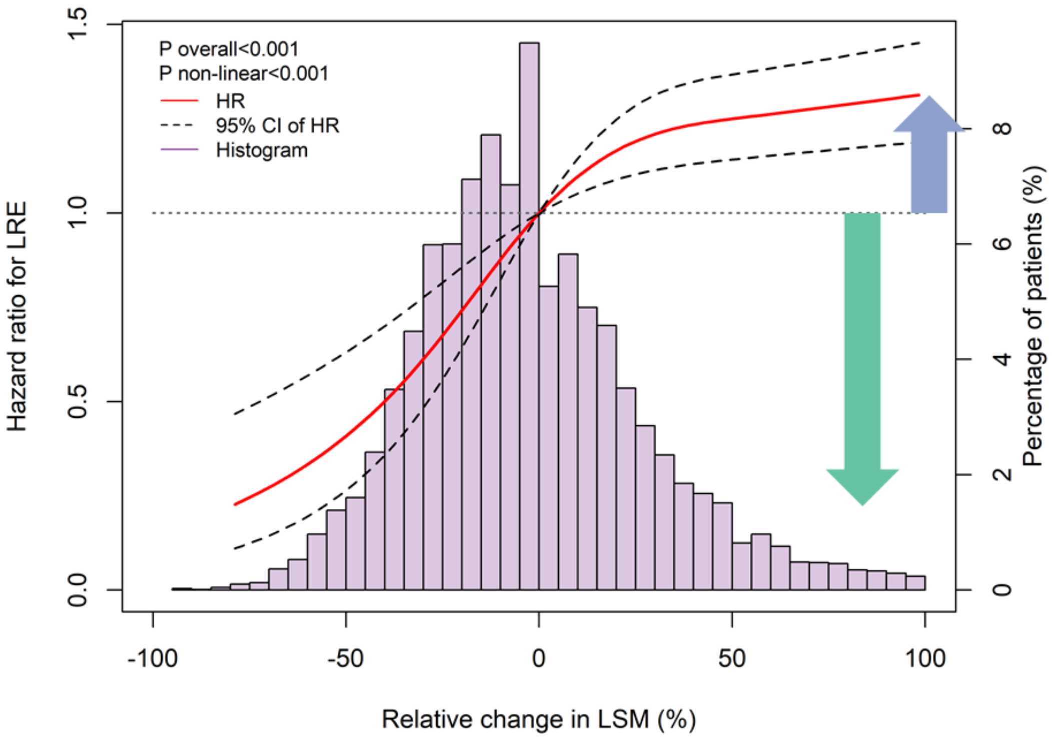
Lin H et al. JAMA 2024;331:1287

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

Lin H et al. JAMA 2024;331:1287

Relative change in LSM and the risk of LREs



*HR adjusted for baseline LSM

First VCTE	% change	% of patients	LRE per 1,000 py
Low LSM <10 kPa	>30% ↓	10%	1.4
	Stable	75%	0.7
	>30% ↑	15%	2.4
Intermediate LSM 10-15 kPa	>30% ↓	37%	0.7
	Stable	52%	7.4
	>30% ↑	11%	17.2
High LSM ≥15 kPa	>30% ↓	45%	16.1
	Stable	45%	33.3
	>30% ↑	10%	55.9

10.5x

2.3x

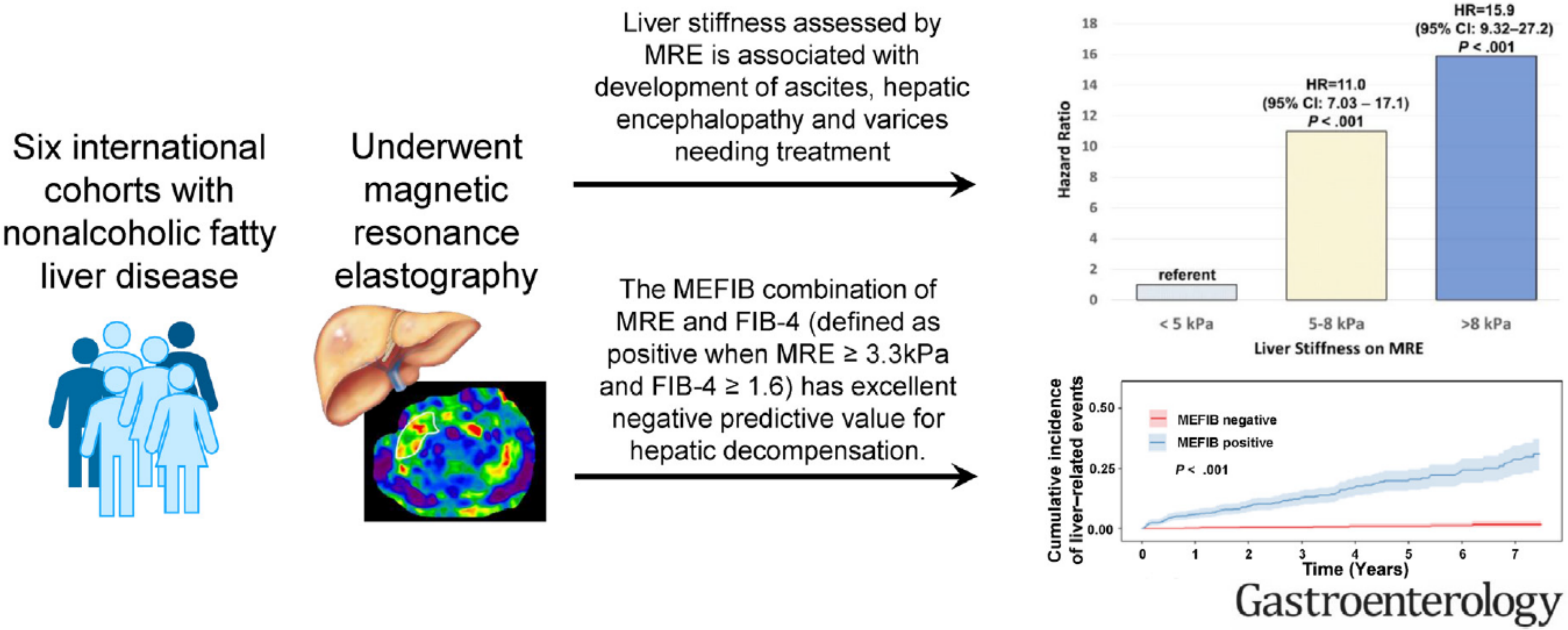
2.1x

1.7x

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Yip TC et al. EASL 2024 (GS-004)

Magnetic resonance elastography and liver-related events



Six international cohorts with nonalcoholic fatty liver disease

Underwent magnetic resonance elastography

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

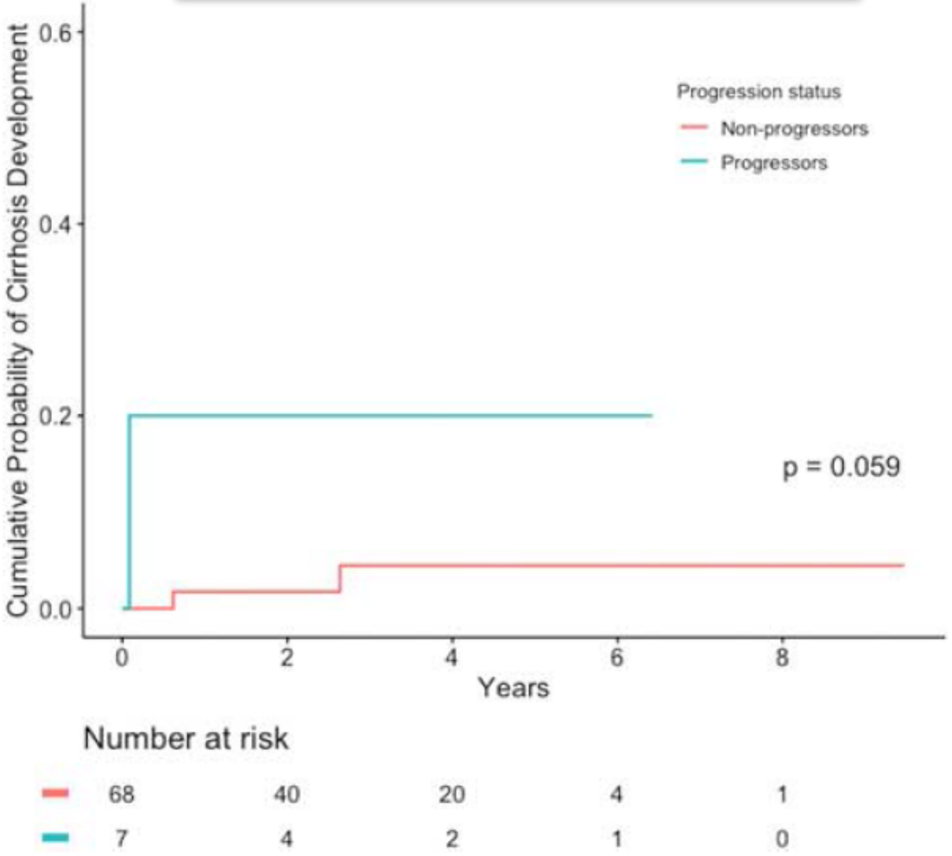
The MEFIB combination of MRE and FIB-4 (defined as positive when MRE ≥ 3.3kPa and FIB-4 ≥ 1.6) has excellent negative predictive value for hepatic decompensation.

Hazard Ratio
18
16
14
12
10
8
6
4
2
0
referent
HR=11.0
(95% CI: 7.03 – 17.1)
P < .001
HR=15.9
(95% CI: 9.32–27.2)
P < .001
< 5 kPa
5-8 kPa
>8 kPa
Liver Stiffness on MRE
Cumulative incidence of liver-related events
0.50
0.25
0.00
MEFIB negative
MEFIB positive
P < .001
0
1
2
3
4
5
6
7
Time (Years)
Gastroenterology

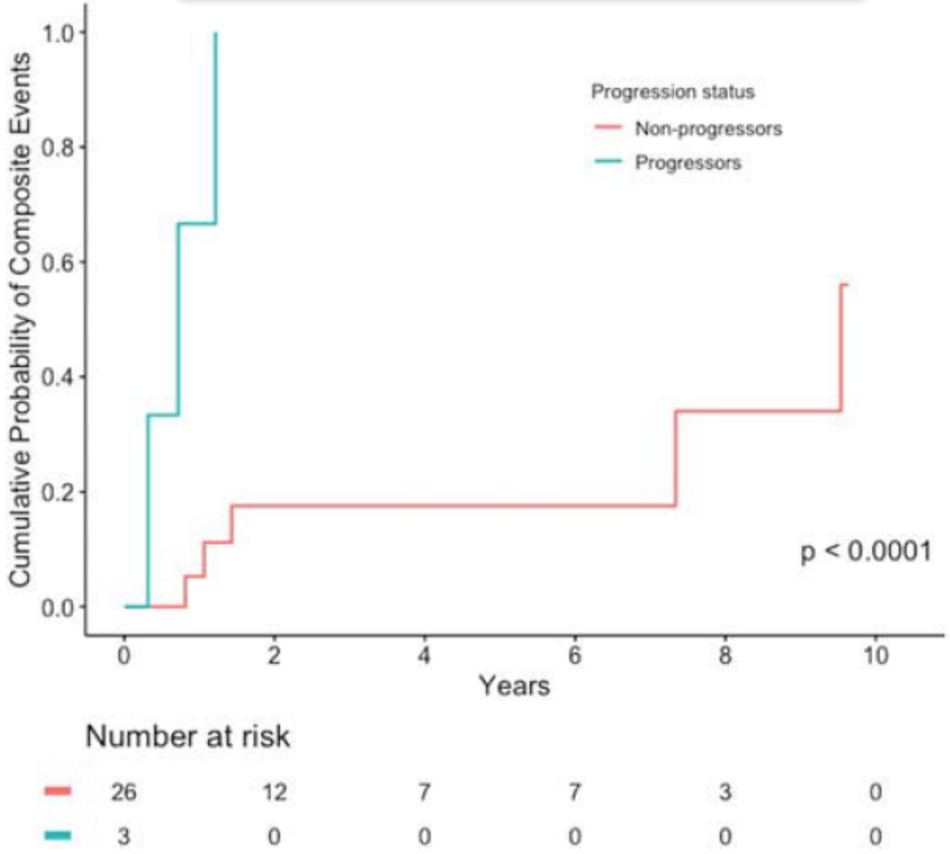
Ajmera et al. Gastroenterology 2022;163:1079

Serial MRE and liver-related events in MASLD

Incident cirrhosis

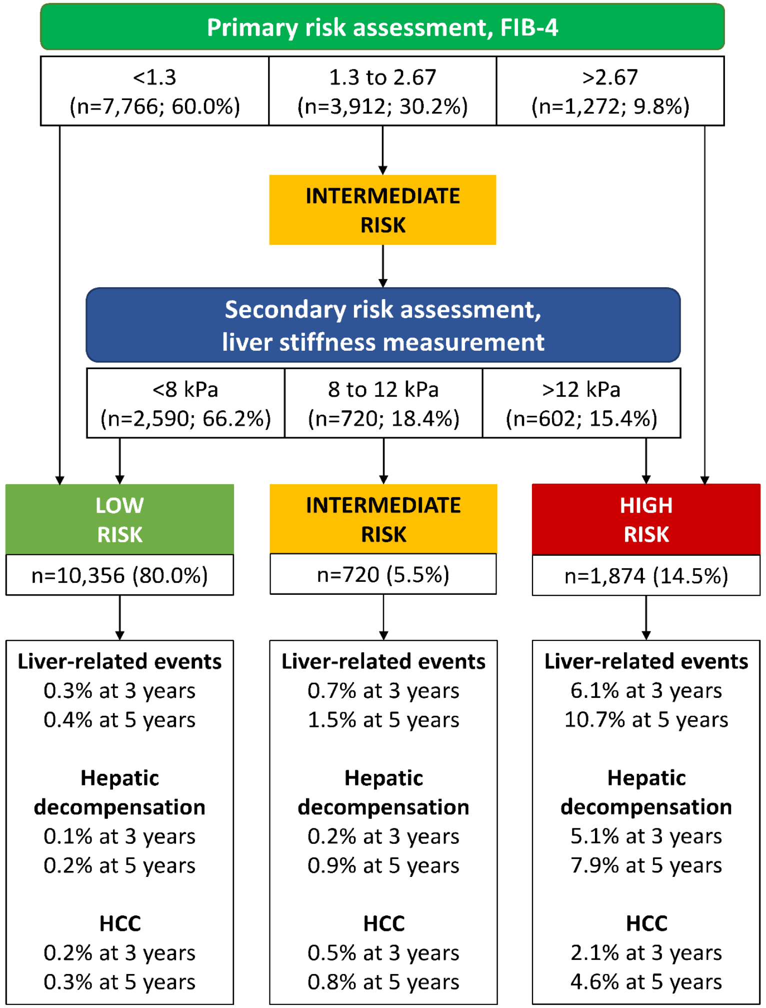


Decompensation or death



Gidener et al. Hepatology 2023;77:268

Prognostication by the 2-step approach



Primary risk assessment, FIB-4

<1.3 (n=7,766; 60.0%)	1.3 to 2.67 (n=3,912; 30.2%)	>2.67 (n=1,272; 9.8%)

INTERMEDIATE RISK

Secondary risk assessment, liver stiffness measurement

<8 kPa (n=2,590; 66.2%)	8 to 12 kPa (n=720; 18.4%)	>12 kPa (n=602; 15.4%)

LOW RISK	INTERMEDIATE RISK	HIGH RISK
n=10,356 (80.0%)	n=720 (5.5%)	n=1,874 (14.5%)
Liver-related events 0.3% at 3 years 0.4% at 5 years	**Liver-related events** 0.7% at 3 years 1.5% at 5 years	**Liver-related events** 6.1% at 3 years 10.7% at 5 years
Hepatic decompensation 0.1% at 3 years 0.2% at 5 years	**Hepatic decompensation** 0.2% at 3 years 0.9% at 5 years	**Hepatic decompensation** 5.1% at 3 years 7.9% at 5 years
HCC 0.2% at 3 years 0.3% at 5 years	**HCC** 0.5% at 3 years 0.8% at 5 years	**HCC** 2.1% at 3 years 4.6% at 5 years

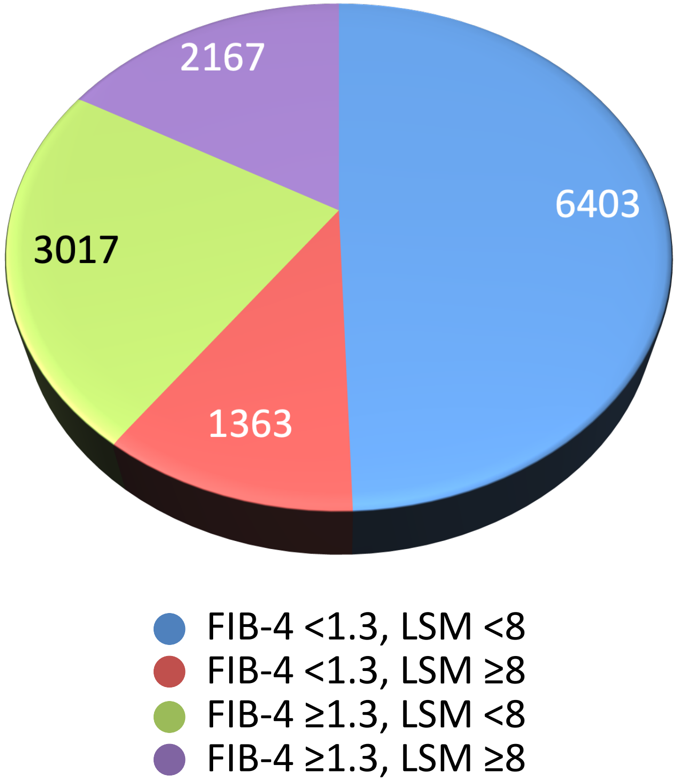
Key findings:

1. The 2-step approach is prognostic
2. With FIB-4 as the first-line test, the use of the Agile scores as the second-line test is not better than VCTE-LSM alone
3. Reserving VCTE-LSM for patients with FIB-4 1.3-2.67 is as good as VCTE-LSM for all patients

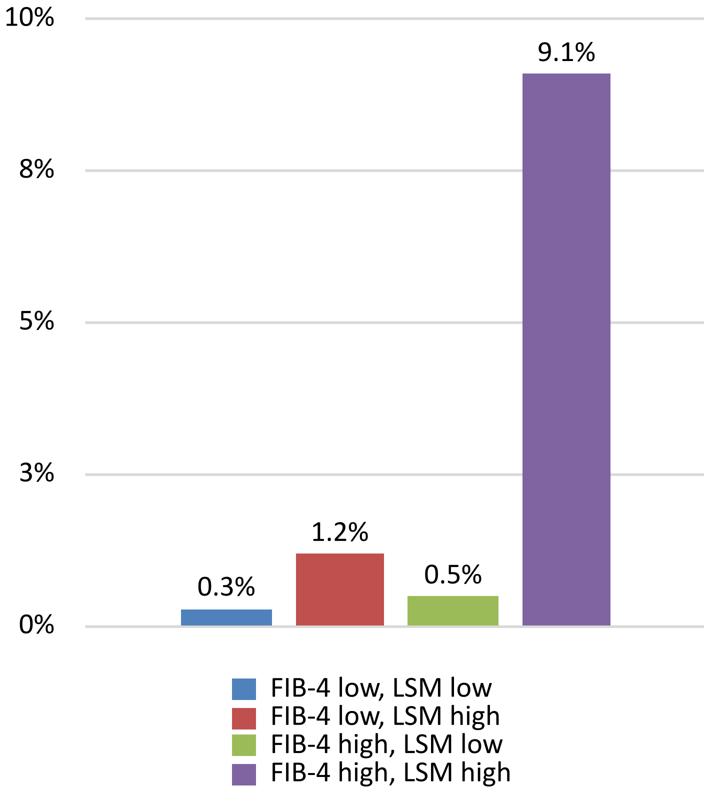
香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Yip TC et al. AASLD 2024 (oral presentation)

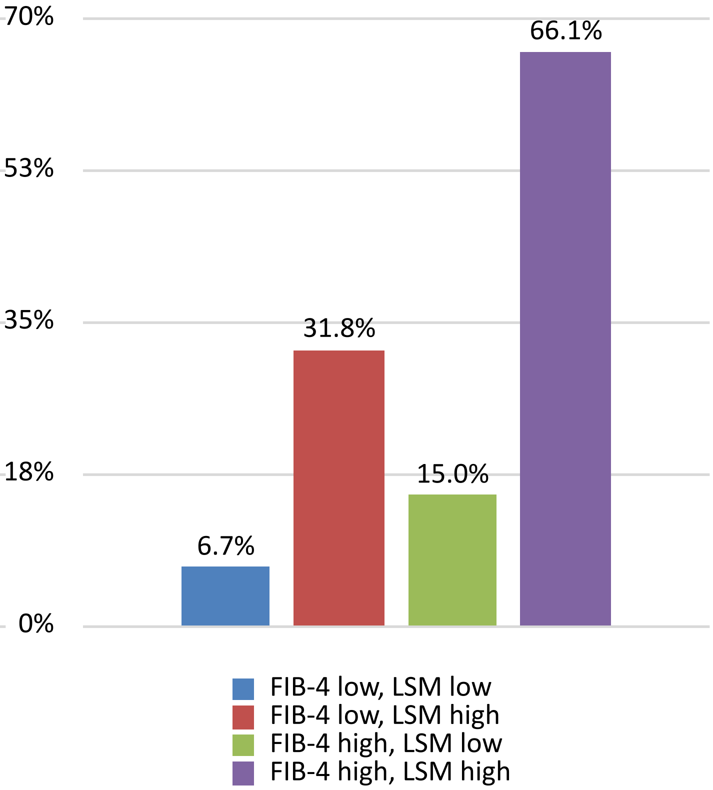
How to interpret discrepant results between FIB-4 and VCTE-LSM?



Liver-related events



Histological F3-F4 fibrosis



香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Rabbat J et al. AASLD 2024 (poster presentation)

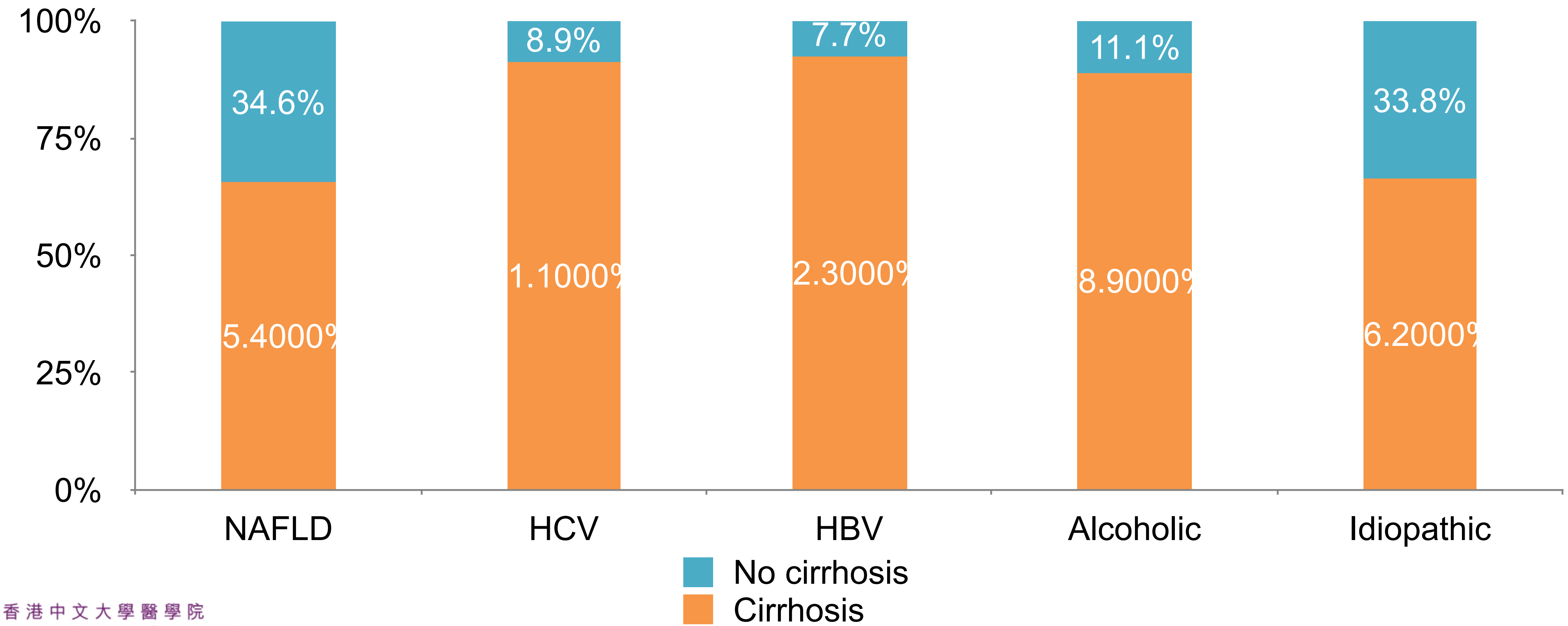
All fibrosis NITs perform better for predicting hepatic decompensation than HCC in the VCTE-Prognosis study

Tests	AUROC for decompensation at 3 years	AUROC for HCC at 3 years
Histologic fibrosis stage	0.86	0.85
Agile 3+	0.94	0.85
Agile 4	0.94	0.85
VCTE-LSM	0.92	0.77
FIB-4	0.89	0.75
NFS	0.89	0.76
APRI	0.85	0.70
FAST	0.81	0.74
AST/ALT ratio	0.71	0.63
BARD	0.73	0.61

Lin H et al. JAMA 2024;331:1287

Non-cirrhotic HCC in the VA cohort

N=1500 (8% MASLD and 3% idiopathic); cirrhosis by histology, clinical, APRI

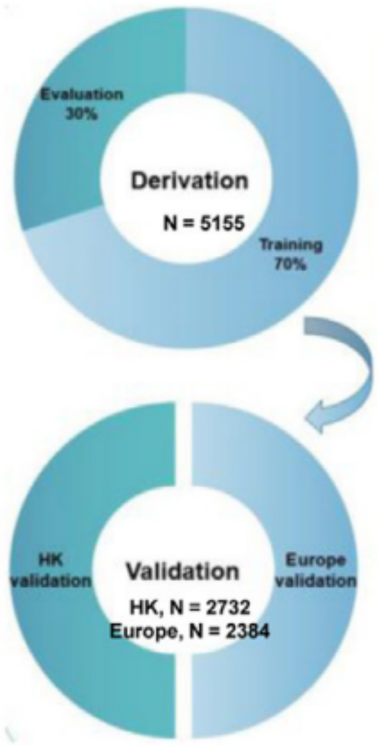


香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Mittal et al. Clin Gastroenterol Hepatol 2016;14:124

SMART-HCC score: An etiology-independent HCC risk score

Derivation/Validation


Evaluation
30%
Derivation
N = 5155
Training
70%
HK
validation
Validation
HK, N = 2732
Europe, N = 2384
Europe
validation

Features Input

LSM

Etiology

Age

ALT

ALP

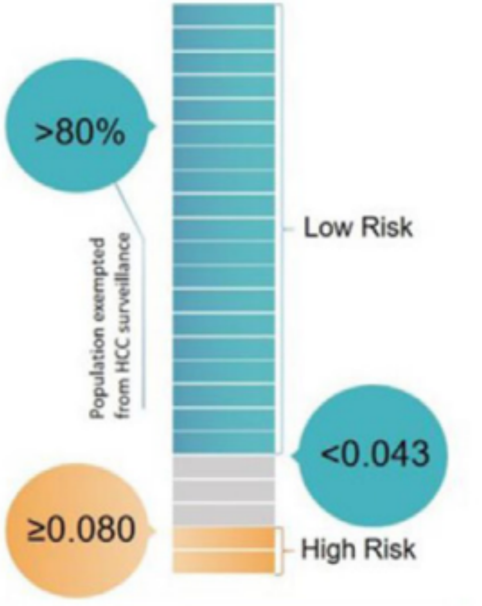
Creatinine

Platelet

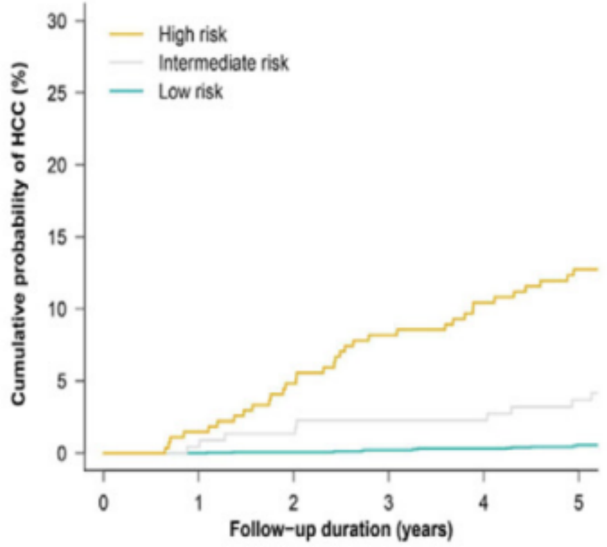
Sex

Hypertension

SMART-HCC Score


>80%
Population exempted
from HCC surveillance
Low Risk
<0.043
≥0.080
High Risk

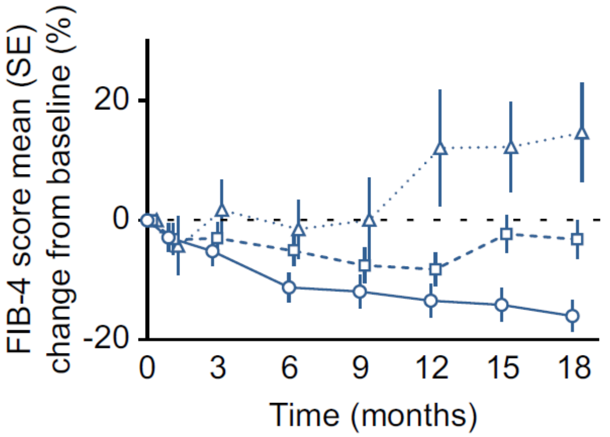
Risk Stratification



Lin H et al. Clin Gastroenterol Hepatol 2024;22:602

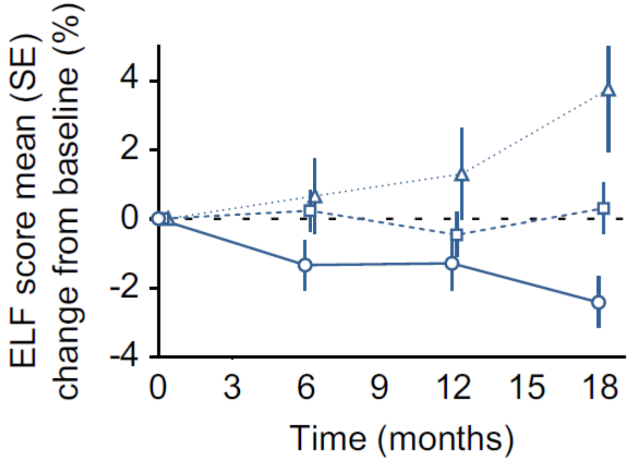
Changes in non-invasive tests in patients receiving obeticholic acid 25 mg daily in the REGENERATE study

FIB-4 index



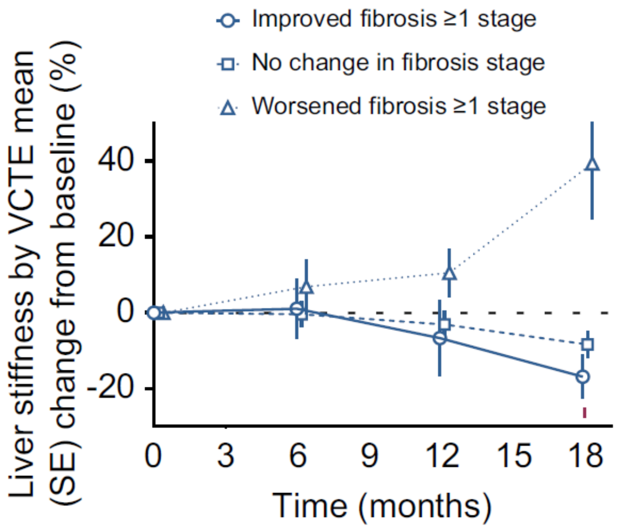
Improved, n =	93	90	91	91	91	89	90
No change, n =	124	123	123	123	121	120	119
Worsened, n =	34	34	34	34	34	33	31

ELF test



Improved, n =	89	88	88	86
No change, n =	118	117	117	114
Worsened, n =	32	33	33	31

Transient elastography



Improved, n =	66	63	59	57
No change, n =	92	90	87	82
Worsened, n =	26	25	26	25

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

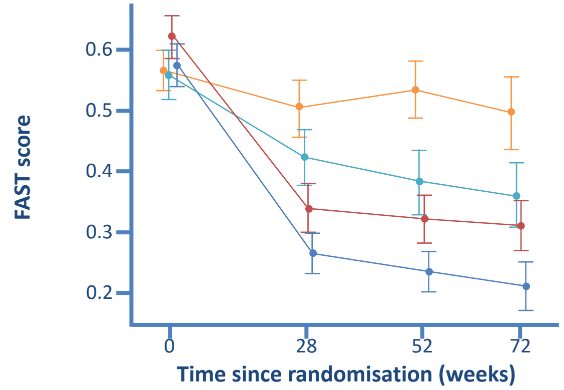
Rinella et al. J Hepatol 2022;76:536

Changes in FAST score during semaglutide treatment

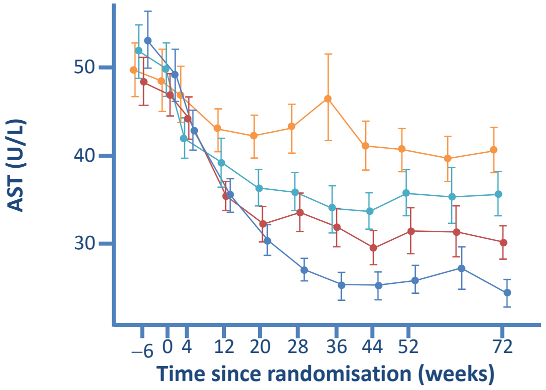
BASELINE TO WEEK 72 – SUBSET ANALYSIS (N=161)

● Semaglutide 0.1 mg OD ● Semaglutide 0.2 mg OD ● Semaglutide 0.4 mg OD

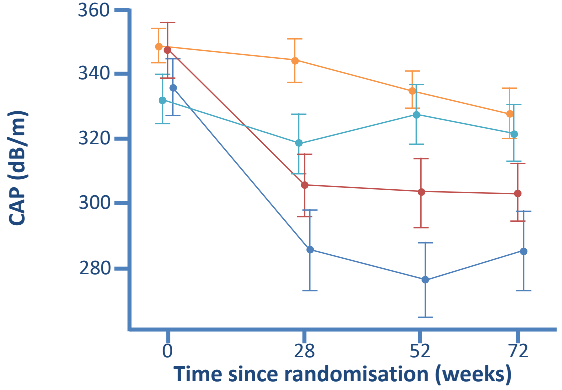
FAST Score



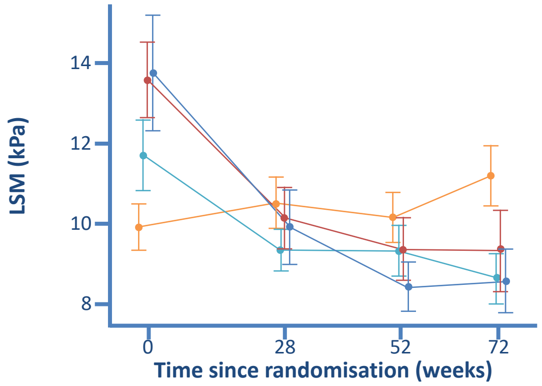
AST



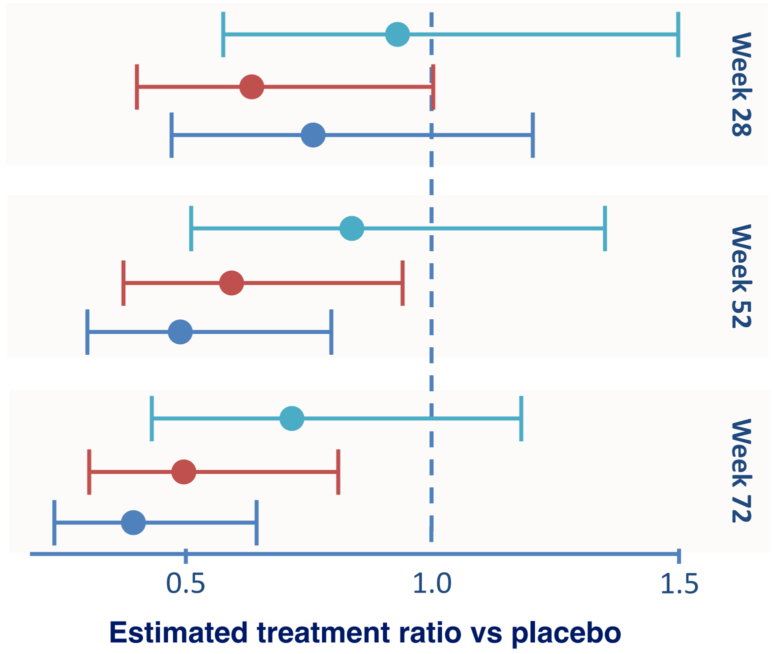
Fibroscan (CAP)



Fibroscan (LSM)



Greater reductions in FAST Score with semaglutide vs placebo



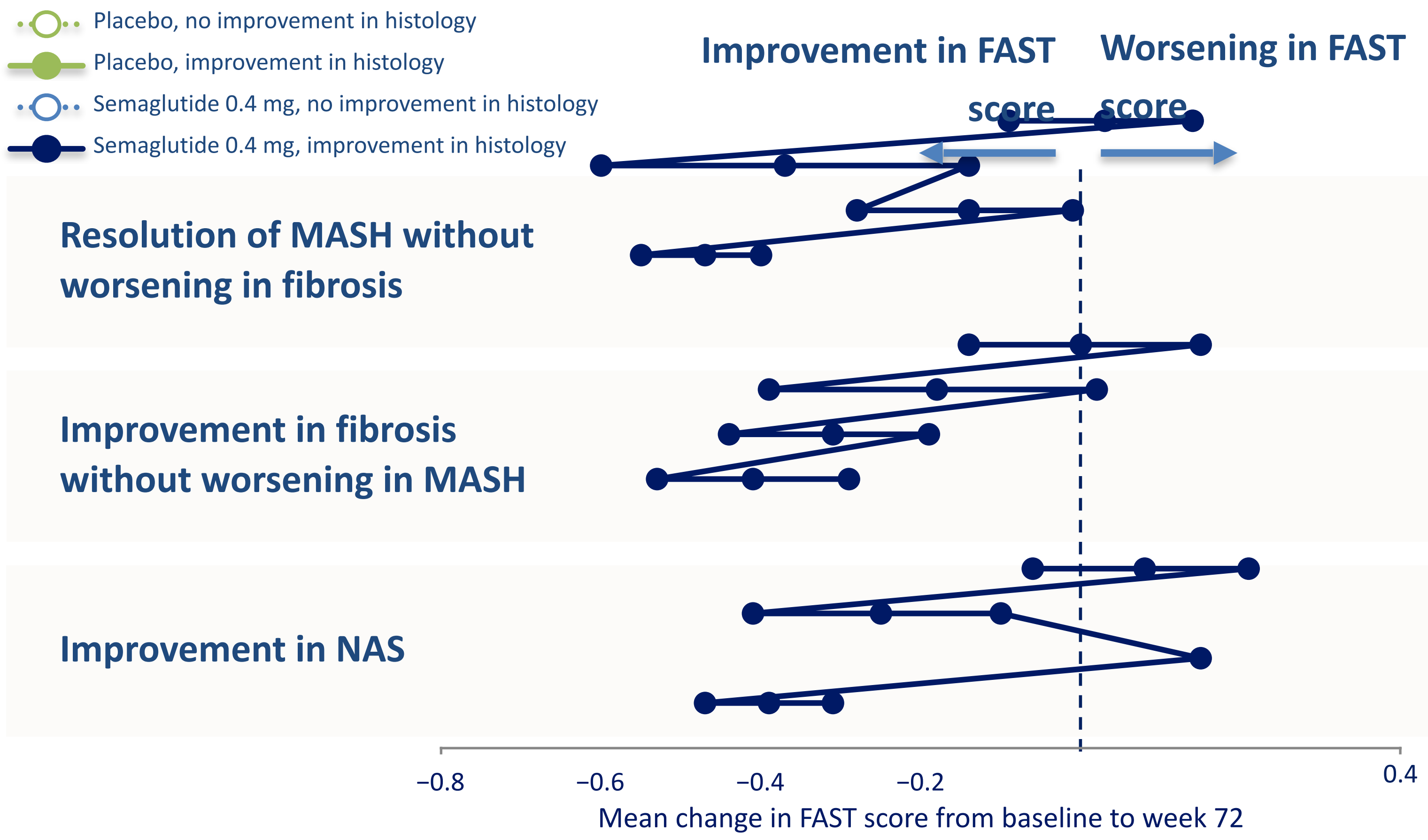
AST, FibroScan CAP and FibroScan LSM are the individual components of the FAST score. Data are for patients with FAST scores at baseline during the on-treatment period. Line plots are observed mean (±SEM). AST, aspartate aminotransferase; CAP, controlled attenuation parameter; FAST, FibroScan aspartate aminotransferase; LSM, liver stiffness measurement; OD, once-daily; SEM, standard error of the mean.

Wong VW et al. eClinicalMedicine 2023;66;102310

香 港 中 文 大 學 醫 學 院
Faculty of Medicine
The Chinese University of Hong Kong

Changes in FAST score and histologic response

BASELINE TO WEEK 72



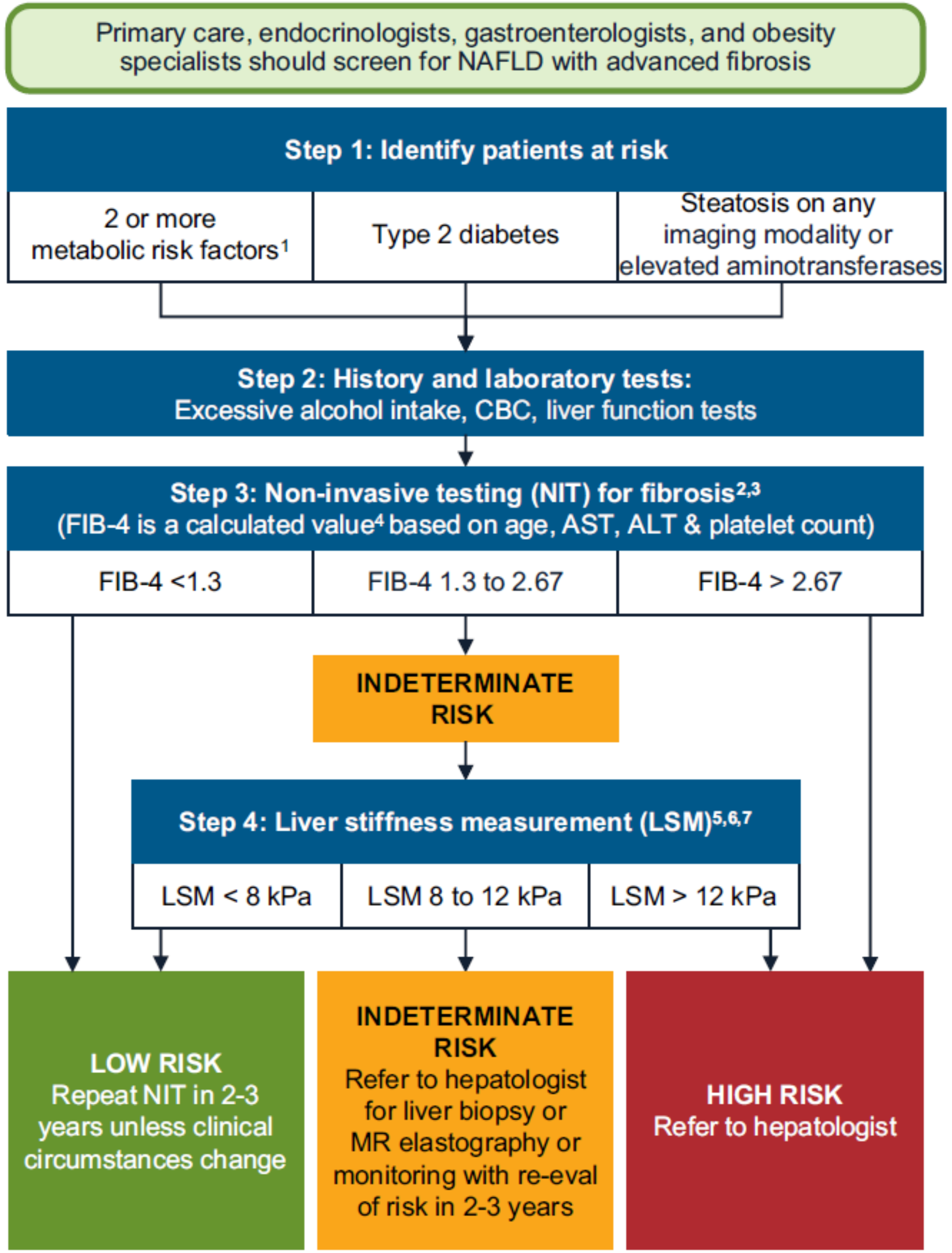
N	Mean change in FAST score (95% CI)	p-value*
19	0.03 (−0.09; 0.14)	
4	**−0.37 (−0.60; −0.14)**	**p = 0.016**
11	−0.14 (−0.28; −0.01)	
18	**−0.47 (−0.55; −0.40)**	**p = 0.008**
17	0 (−0.14; 0.15)	
6	**−0.18 (−0.39; 0.02)**	p = 0.126
16	−0.31 (−0.44; −0.19)	
13	**−0.41 (−0.53; −0.29)**	p = 0.616
14	0.08 (−0.06; 0.21)	
9	**−0.25 (−0.41; −0.10)**	**p = 0.006**
2	0.15 (NA)	
29	**−0.39 (−0.47; −0.31)**	**p = 0.005**

Data are from all randomized patients during the on-treatment period. Improvement assessed by histology. *p-value for comparisons between improvement in histology vs no improvement in histology.
CI, confidence interval; FAST, FibroScan aspartate aminotransferase; NA, not applicable; NAS, non-alcoholic fatty liver disease activity score; MASH, metabolic dysfunction-associated steatohepatitis.

Wong VW et al. eClinicalMedicine 2023;66;102310

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

AGA Clinical Care Pathway for NAFLD



Primary care, endocrinologists, gastroenterologists, and obesity specialists should screen for NAFLD with advanced fibrosis

Step 1: Identify patients at risk

2 or more metabolic risk factors[1]	Type 2 diabetes	Steatosis on any imaging modality or elevated aminotransferases

Step 2: History and laboratory tests:
Excessive alcohol intake, CBC, liver function tests

Step 3: Non-invasive testing (NIT) for fibrosis[2,3]
(FIB-4 is a calculated value[4] based on age, AST, ALT & platelet count)

FIB-4 <1.3	FIB-4 1.3 to 2.67	FIB-4 > 2.67

INDETERMINATE RISK

Step 4: Liver stiffness measurement (LSM)[5,6,7]

LSM < 8 kPa	LSM 8 to 12 kPa	LSM > 12 kPa

LOW RISK
Repeat NIT in 2-3 years unless clinical circumstances change

INDETERMINATE RISK
Refer to hepatologist for liver biopsy or MR elastography or monitoring with re-eval of risk in 2-3 years

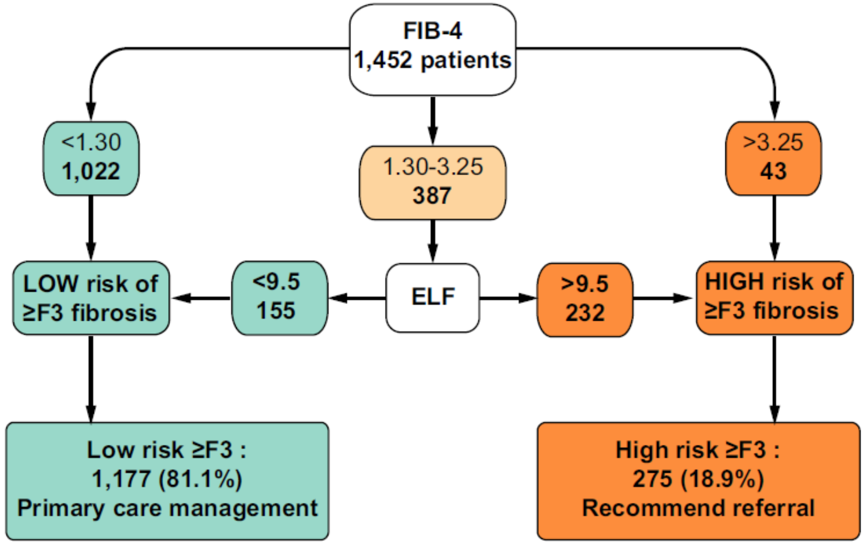
HIGH RISK
Refer to hepatologist

American
Gastroenterological
Association

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Kanwal et al. Gastroenterology 2021;161:1657

The Camden and Islington MASLD pathway for primary care settings



FIB-4
1,452 patients

<1.30
1,022

1.30-3.25
387

>3.25
43

LOW risk of ≥F3 fibrosis

<9.5
155

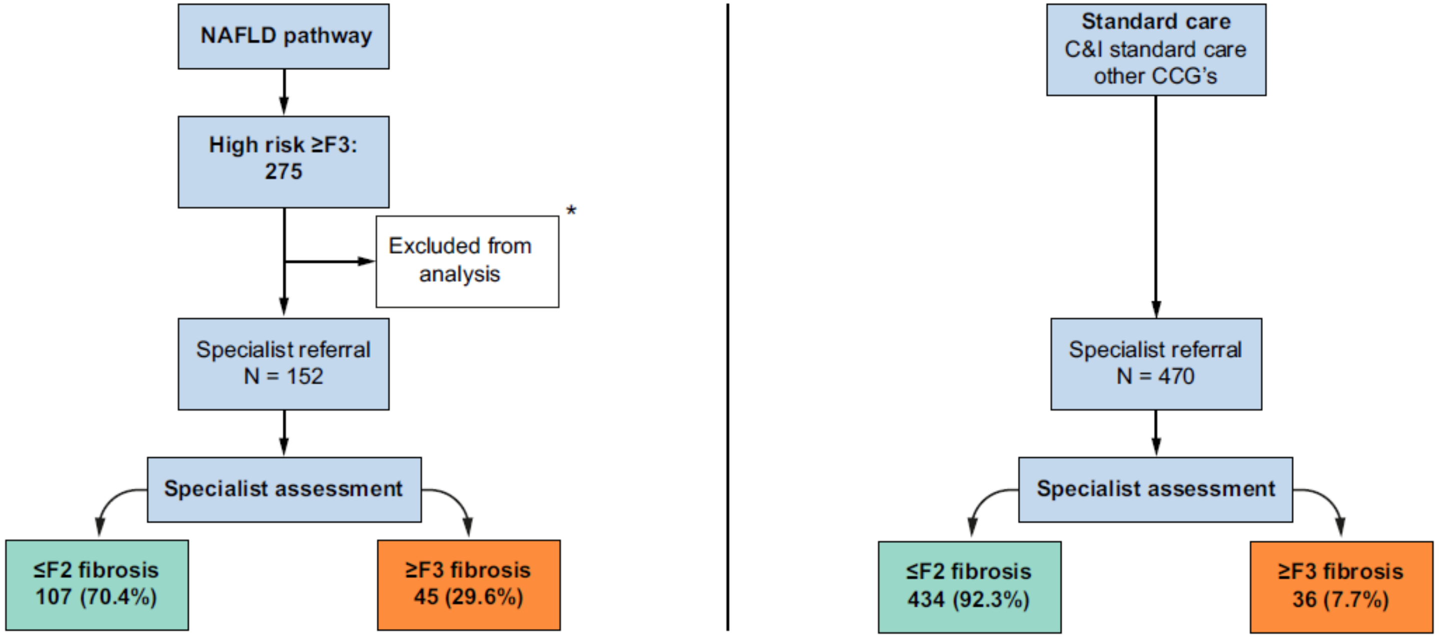
ELF

>9.5
232

HIGH risk of ≥F3 fibrosis

Low risk ≥F3 :
1,177 (81.1%)
Primary care management

High risk ≥F3 :
275 (18.9%)
Recommend referral



NAFLD pathway

High risk ≥F3:
275

Excluded from analysis *

Specialist referral
N = 152

Specialist assessment

≤F2 fibrosis
107 (70.4%)

≥F3 fibrosis
45 (29.6%)

Standard care
C&I standard care
other CCG's

Specialist referral
N = 470

Specialist assessment

≤F2 fibrosis
434 (92.3%)

≥F3 fibrosis
36 (7.7%)

- Reduce unnecessary referrals by 80%
- Increase detection of advanced fibrosis by 5-fold, cirrhosis by 3-fold

Srivastava et al. J Hepatol 2019;71:371

Clinical care pathway to detect advanced liver disease in patients with type 2 diabetes through automated fibrosis score calculation and electronic reminder messages: a randomised controlled trial

Study Population

five general medical or diabetes clinics

1061 patients with type 2 diabetes were screened between 19 May 2020 and 14 October 2021

RANDOMIZATION

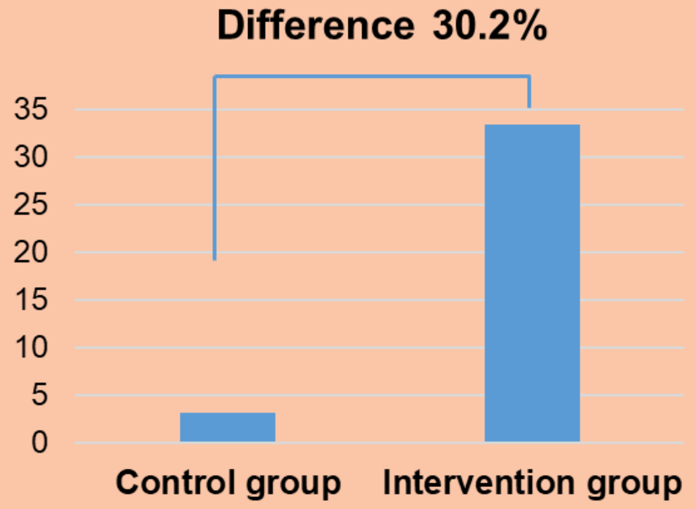
Intervention

Control (n=528):
fibrosis score calculation +
no electronic reminder messages

Intervention (n=533):
fibrosis score calculation +
electronic reminder messages if abnormal fibrosis scores

Primary outcome:
Proportion of patients with high fibrosis scores who received hepatology care or further fibrosis assessment

Outcome



Automated fibrosis score calculation and electronic reminders increase referral of patients with type 2 diabetes and abnormal fibrosis scores at non-hepatology settings

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Zhang X et al. Gut 2023;72:2364

Different roles of NITs in the management of MASLD

Susceptibility

- **Fibrogenic genetic risk**

Evidence required:

- Biological plausibility
- Relate risk marker to future development of disease

Diagnostic

- **Enrichment**
- **Full diagnostic**

Evidence required:

- Comparison to reference standard

✓

Prognostic

- **Risk stratification**

Evidence required:

- Relate baseline data to future events

✓

Disease monitoring

- **Clinical course over time**

Evidence required:

- Change in biomarker over time vs change in disease severity and outcomes

✓

Treatment response

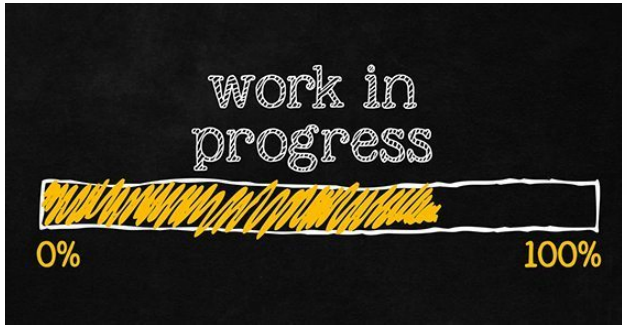
- **Responder**
- **Nonresponders**

Evidence required:

- Change in biomarker vs change in reference standard to assess benefit of treatment

Surrogate endpoint

- **Treatment response across multiple MOA**



Sanyal, Castera, Wong. Clin Gastroenterol Hepatol 2023;21:2026

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Thank you very much!

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

Vincent Wong
wongv@cuhk.edu.hk