COME E PERCHÉ CERCARE LA MASH

Luca Miele, MD PhD
UOC Medicina Interna e Trapianti di Fegato
Dip. Scienze Mediche e Chirurgiche
Fondazione Policlinico Gemelli IRCCS, UCSC-Università Cattolica S. Cuore

luca.miele@unicatt.it
@lmiele74

UNIVERSITÀ CATTOLICA del Sacro Cuore

CEMAD
Centro Malattie Apparato Digerente
Digestive Disease Center

Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

COI – Conflict of Interests

Advisor/Consultancy

Alfa-Sigma, Boehringer-Ingelheim, BMS, Echosens, Galmed, Gilead Sciences, GSK, IBSA, Intercept, Madrigal, MEDA, MyGenomics, MSD-Merck Sharp & Dohme, Mirum, Novartis, Novo-Nordisk, Pfizer, Promethera, Resalis Pharma, Rottapharm-Madaus, Siemens Healthineers, Synageva

Support for research

Investigator Driven: Gilead, Intercept, Siemens Healthineers

- Why search for MASH?
- How to detect it?

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- Why search for MASH?
- How to detect it?

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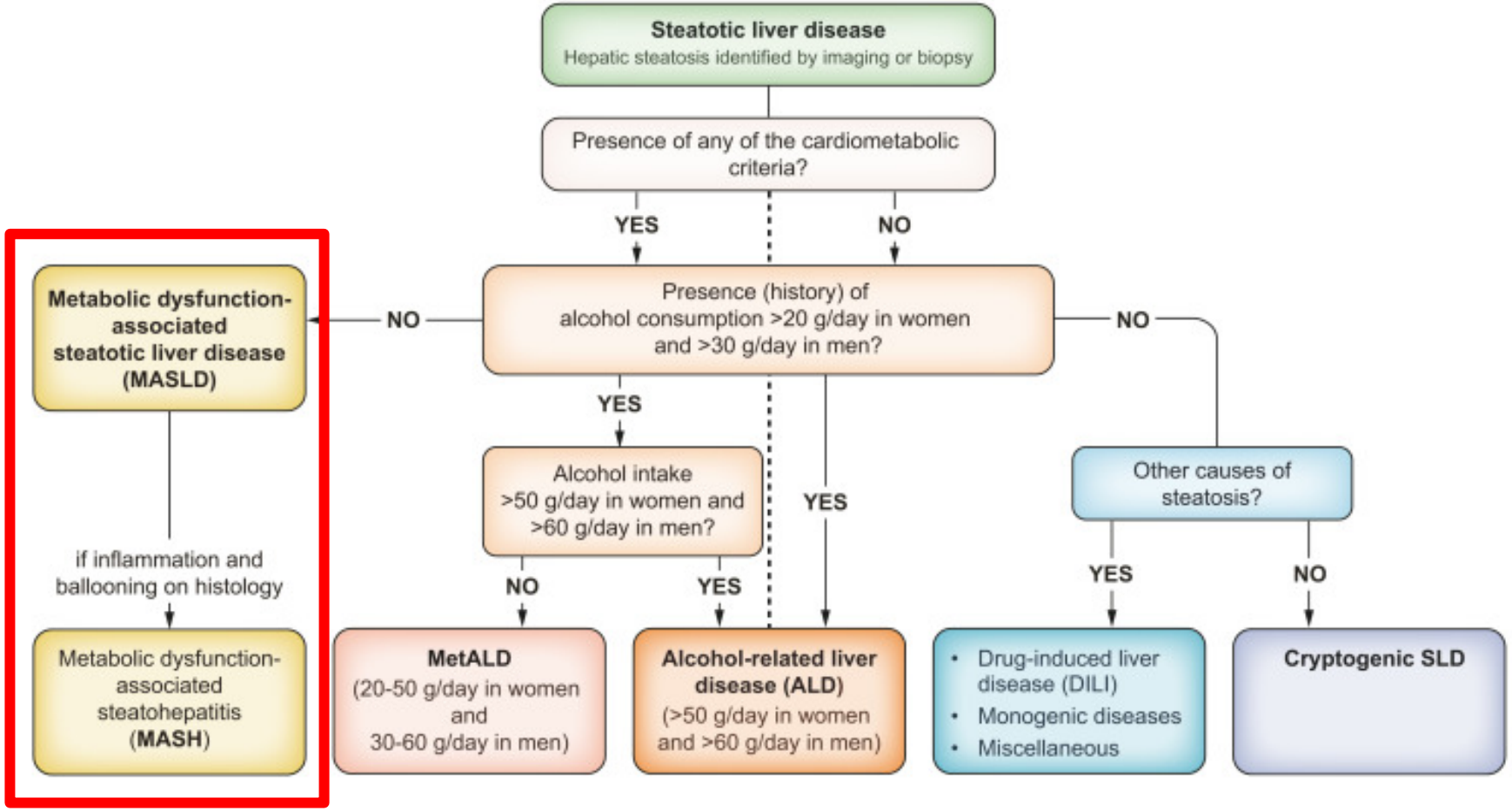
SLD – MASLD - MetALD



EASL-EASD-EASO. J HEP 2024

Liver biopsy

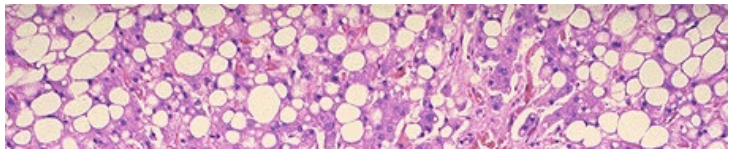



	AGA, AASLD, ACG [21]	CLDA [19]	IASL [20]	EASL [17]	APWP [18]	ESPGHAN [22]
Liver biopsy	+ (restricted to selected patients)	+ (restricted to selected patients)	+ (restricted to selected patients)	+ (restricted to selected patients)	+ (restricted to selected patients)	+ (restricted to selected patients)

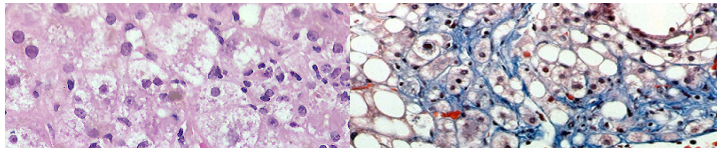
+, recommended; -, not recommended; /, not mentioned.

Liver Biopsy: The Imperfect Gold Standard

Isolated Steatosis



Steatohepatitis/NASH



Benefits

- Establishes diagnosis of NASH
- Assesses early fibrosis
- Determines prognosis
- Rules out other processes: alpha-1 antitrypsin, iron overload, autoimmune component

Limitations

- Risk of bleeding, pain
- Sampling variability (especially with IR biopsies if they are small)
- Long interval between serial biopsies to monitor disease progression
- Cost

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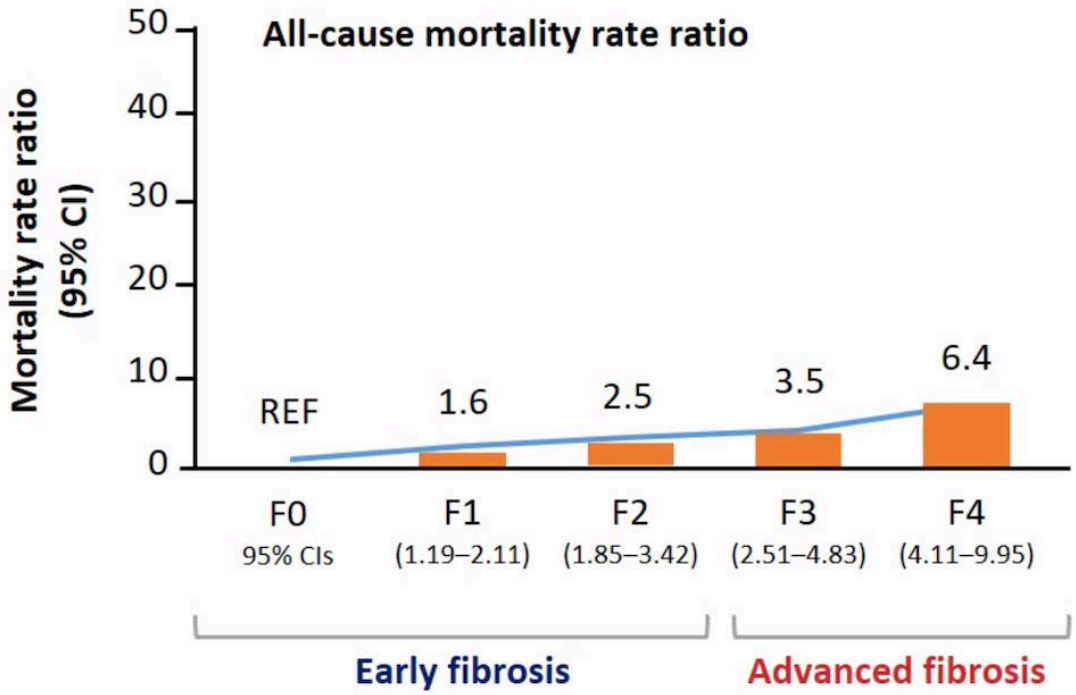
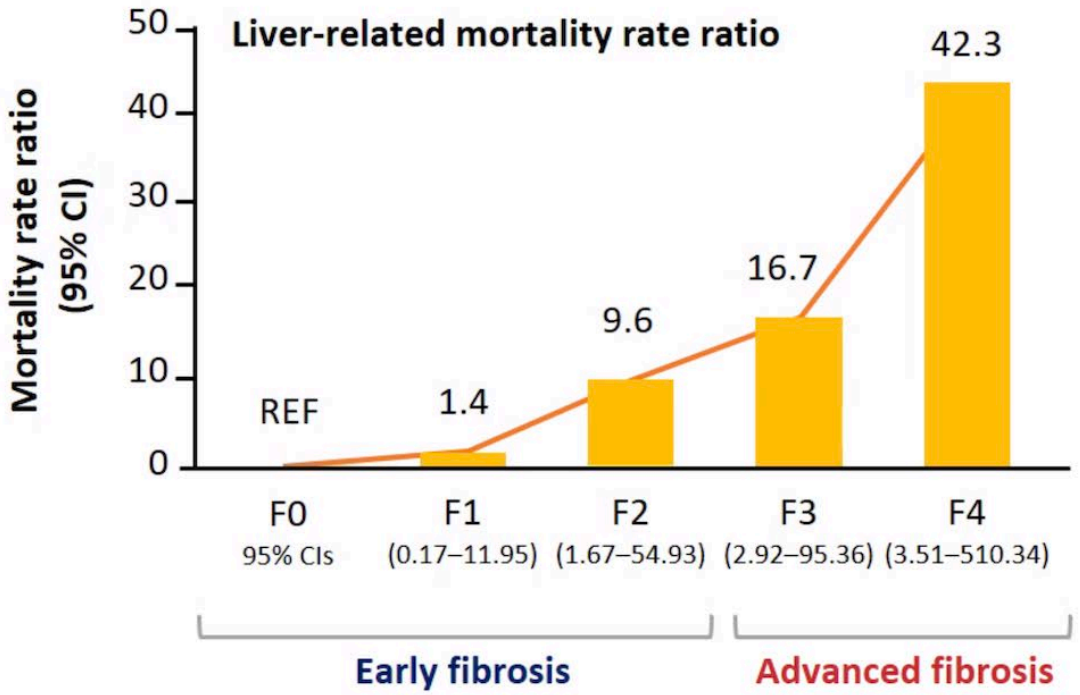
Rockey. Hepatology. 2009;49:1017. Kleiner. Hepatology 2005;41:1313. Bedossa. Hepatology. 2012;56:1751.

Natural history of MASLD





CI, confidence interval; PYF, patient–years of follow-up
Dulai PS et al. Hepatology 2017;65:1557–65

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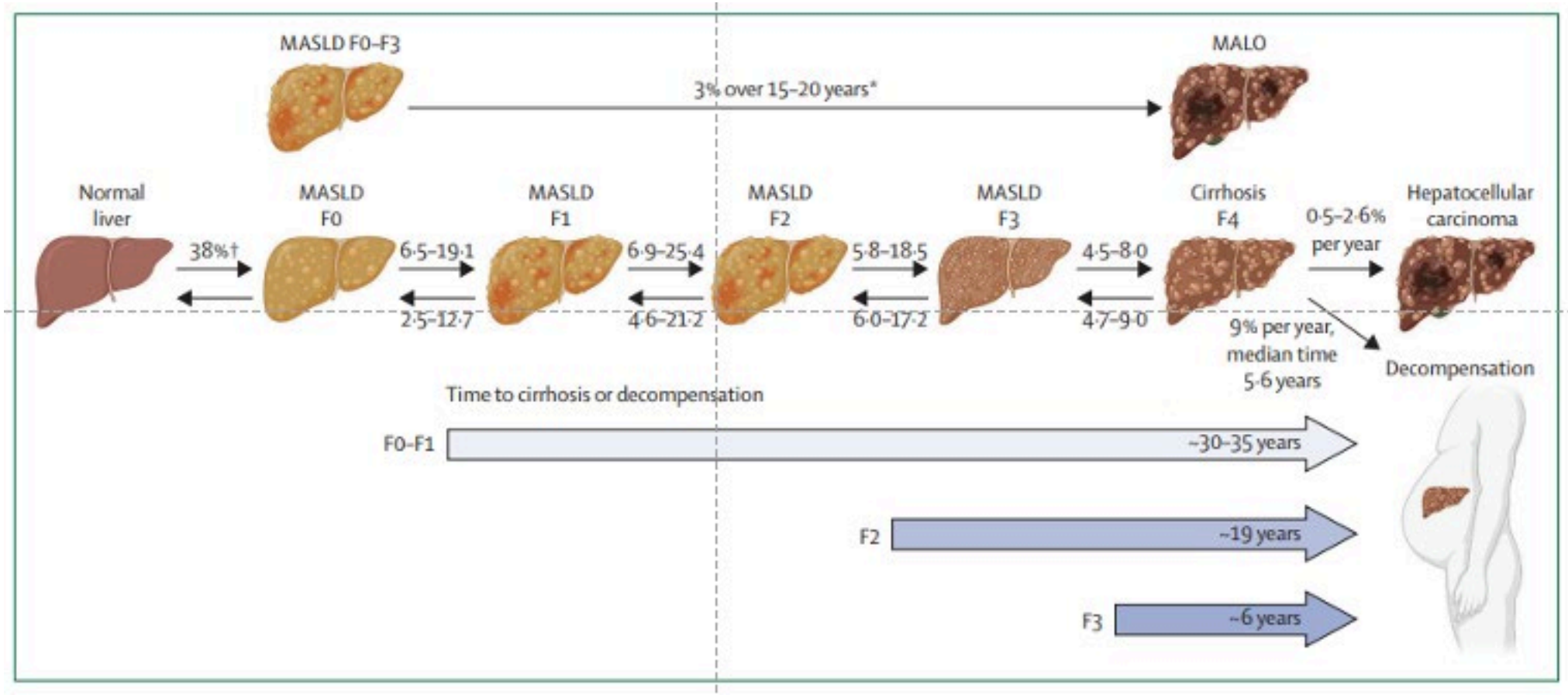
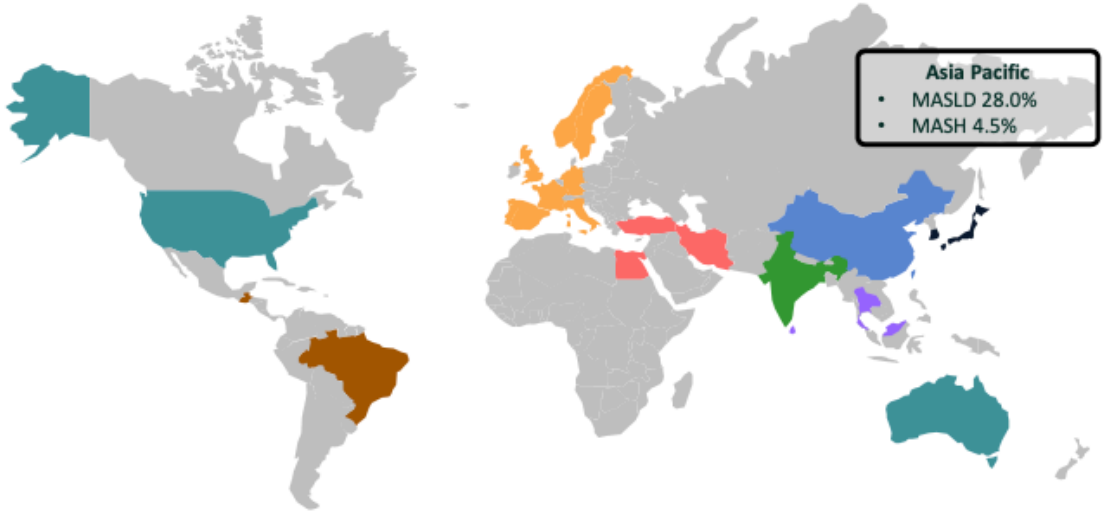
Natural history of MASLD



Hangstrom et al. Lancet Gastro Hep 2025

Global burden

Global prevalence* of MASLD is 30.1% and MASH is 5.3%[1]



Regional prevalence shows some variation

- MASLD ranges from 25.1% (Western Europe) to 44.4% (Latin America)
- MASH ranges from 4.0% (Western Europe) to 7.1% (Latin America)

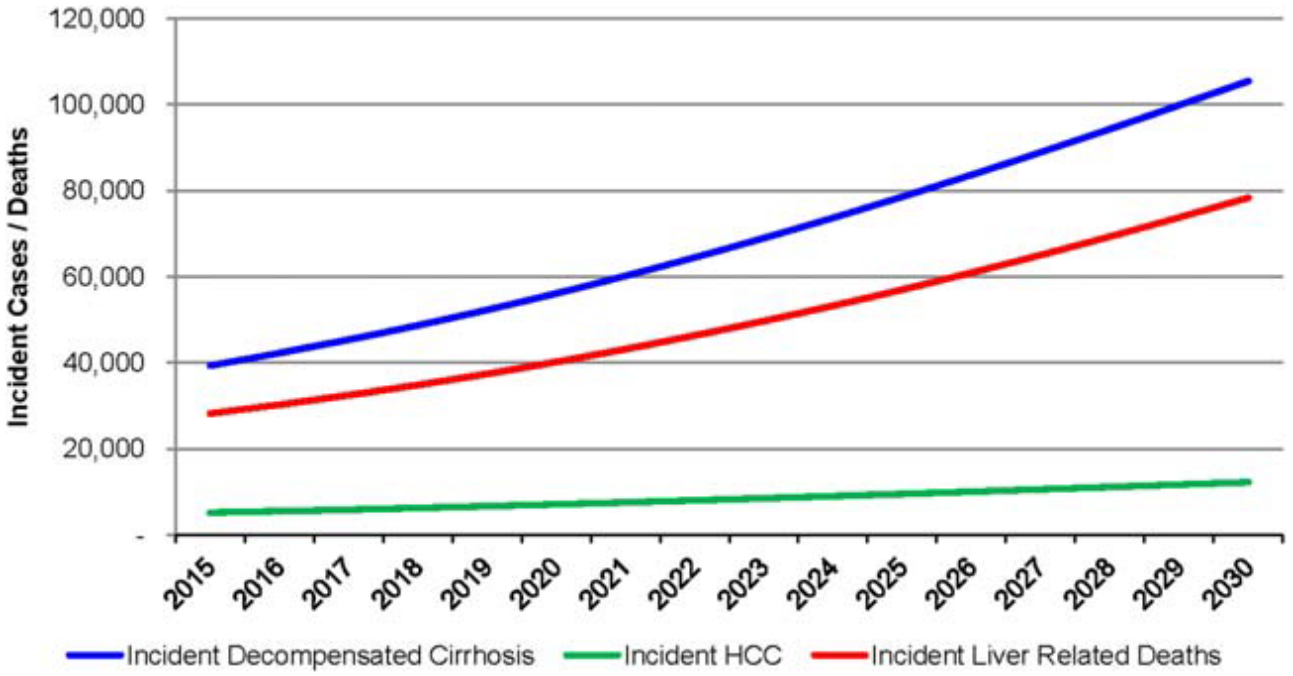
Global prevalence of MASLD and MASH in people living with overweight/obesity[2]

- Systematic review and meta-analysis
- N=101 028

	Overweight	Obesity
Prevalence of MASLD (%)	70.0	75.3
Prevalence of MASH (%)	33.5	33.7

[1]Younossi et al. Hepatology 2023
[2]Quek et al. Lancet Gastroenterol Hepatol 2023

Global trends of fatty liver (from 2018)



Decompensated cirrhosis will increase by 168% to 105.430 cases

HCC will increase by 137% to 12,240 cases

Liver deaths will increase by 178% to 78.300 deaths

Estes et al. J Hep 2018

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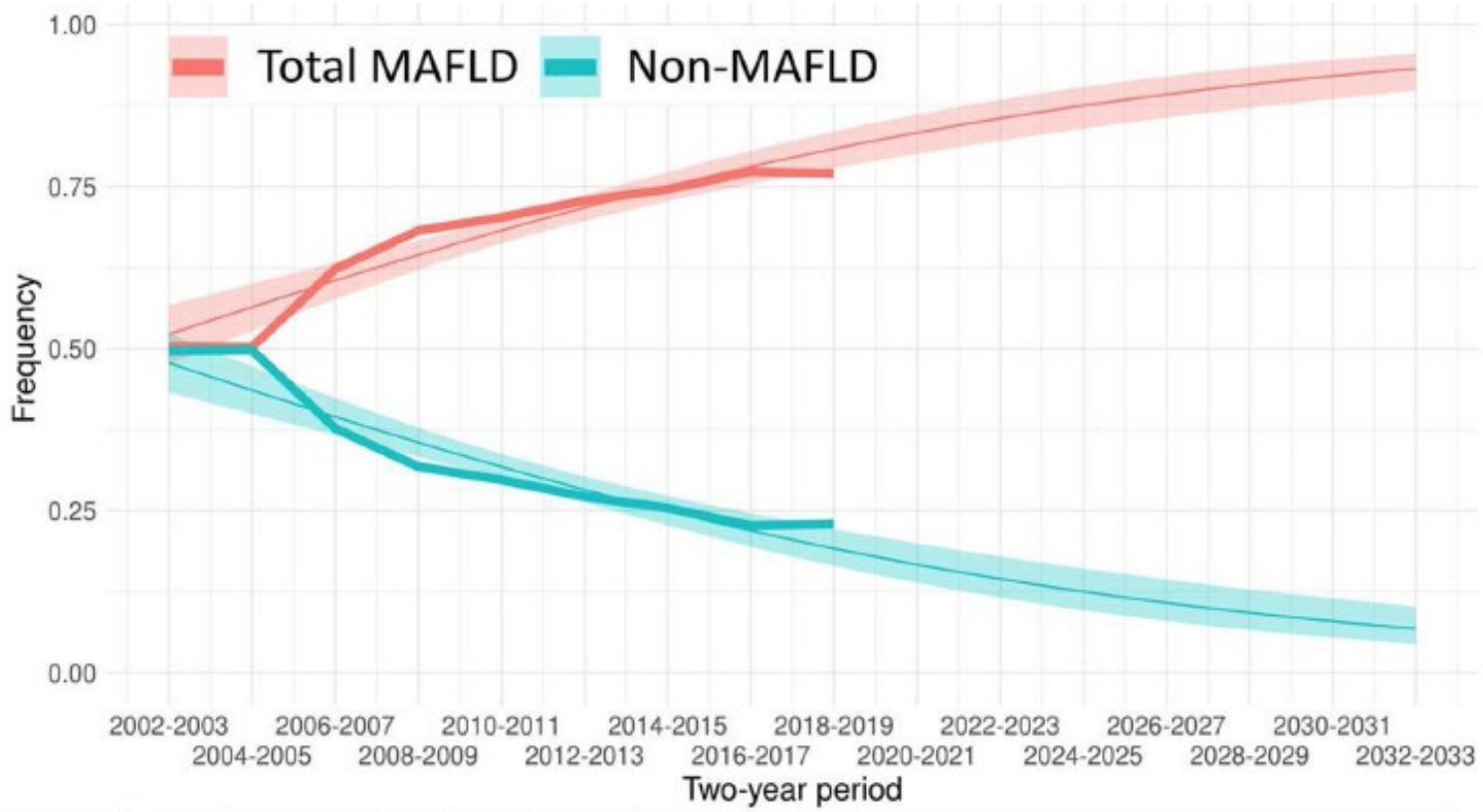
Evolving aetiology of HCC (database 2018)



Total MAFLD	302	207	289	455	630	770	858	742	452	---
Non-MAFLD	390	205	175	212	268	287	293	214	133	---

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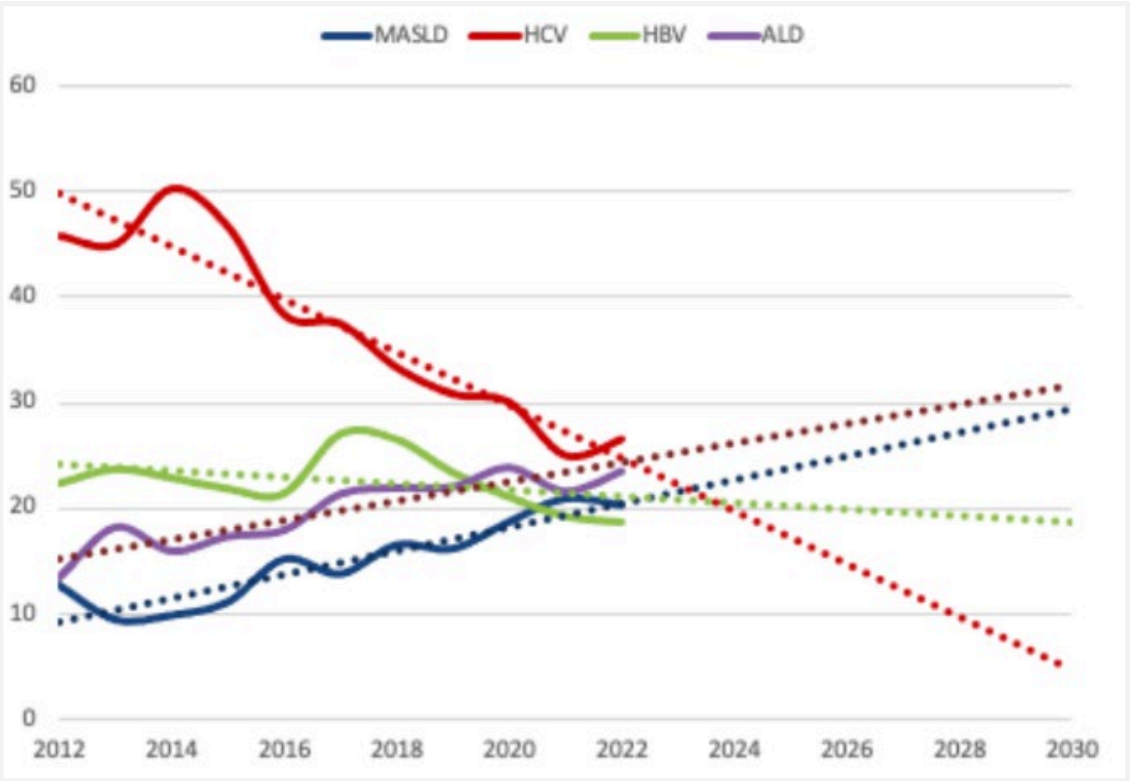
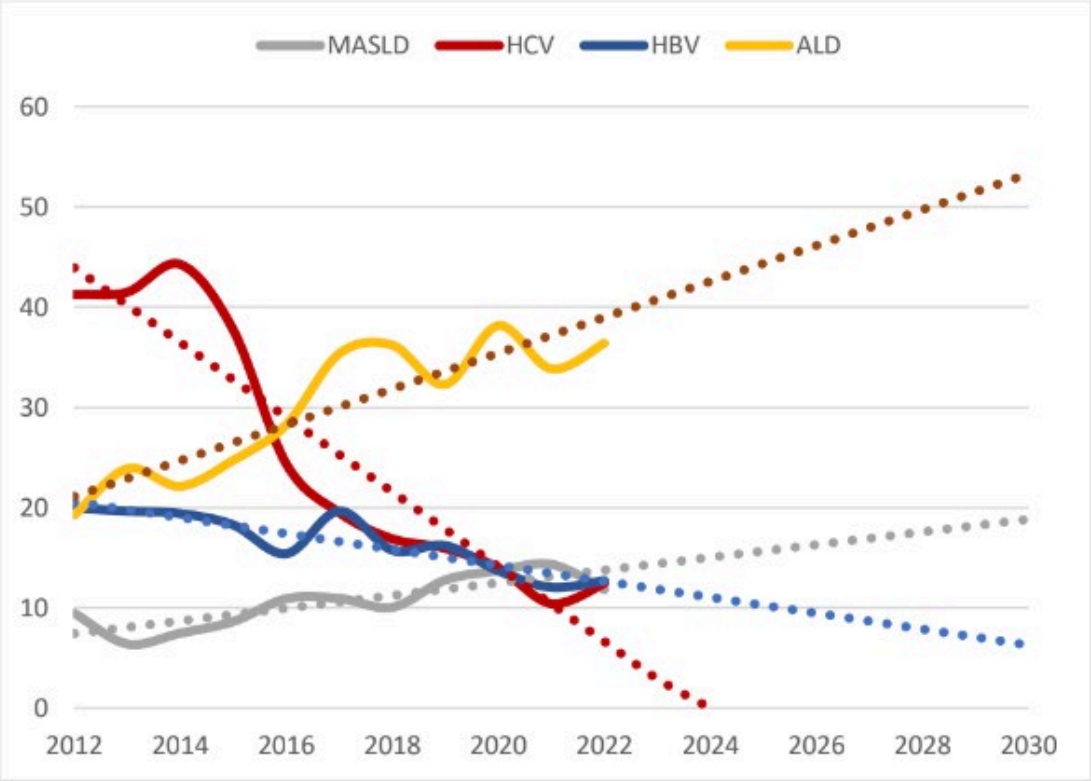
Vitale, Miele et al. Gut 2023

Italian data on Liver Transplant





Vitale et al. J HEP Rep 2024

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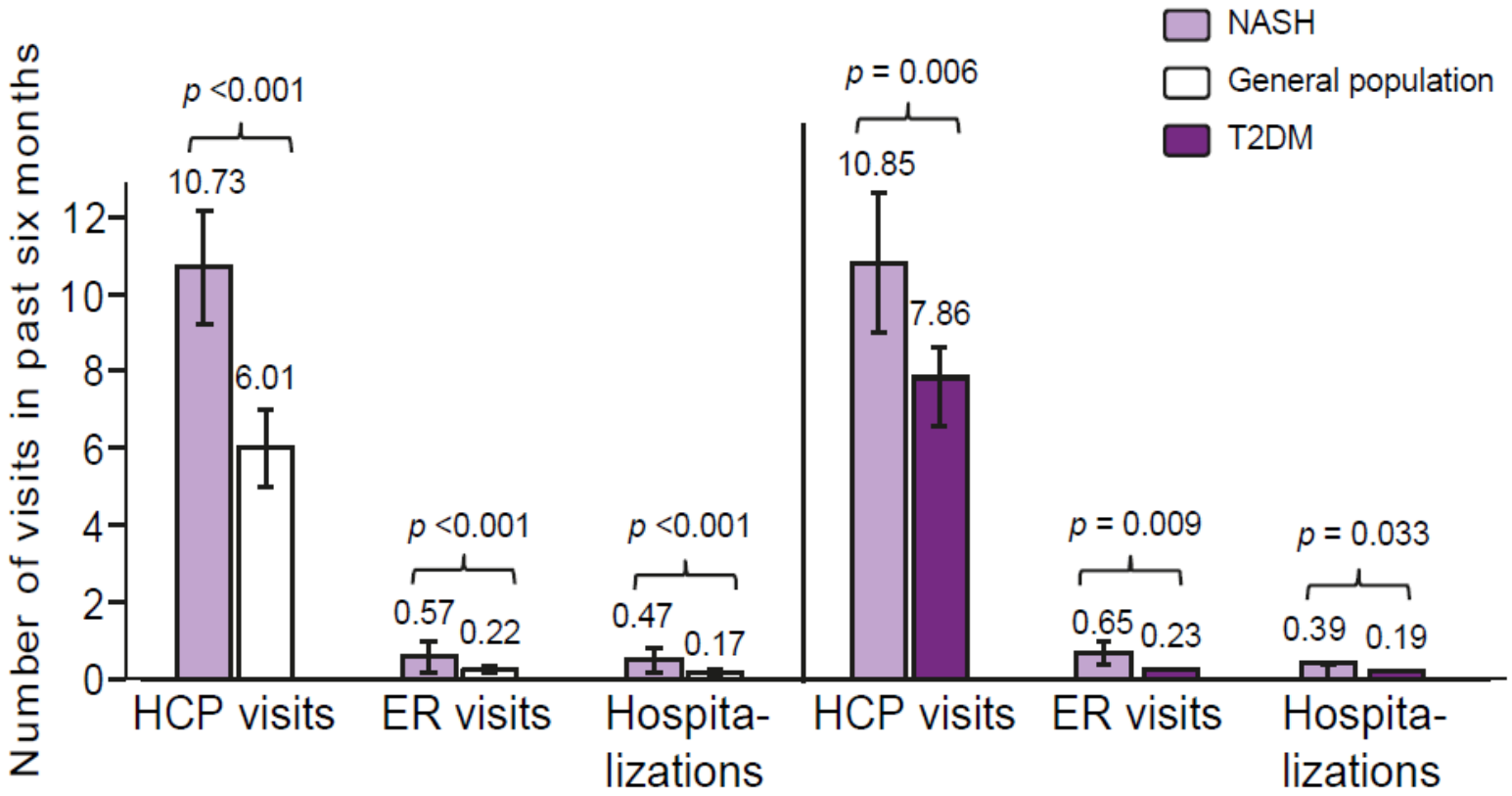
Burden of NASH: real world data from Europe

Data from 5 European countries: Germany, France, Spain, Italy, UK
184 NASH patients



The NASH cohort, relative to the matched general population or T2DM population reported significantly higher Healthcare professional (HCP) visits, Emergency room (ER) visits Hospitalizations

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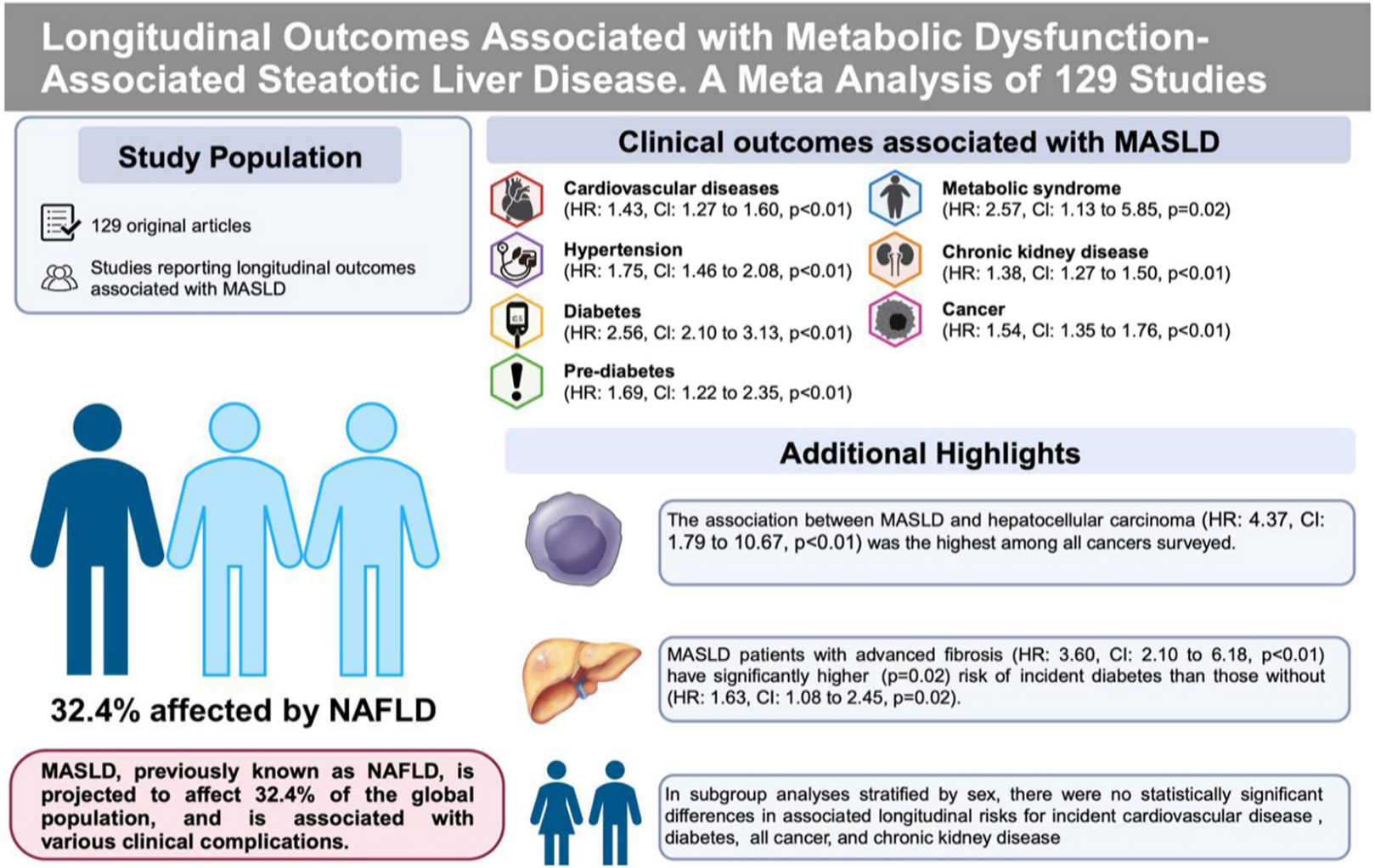
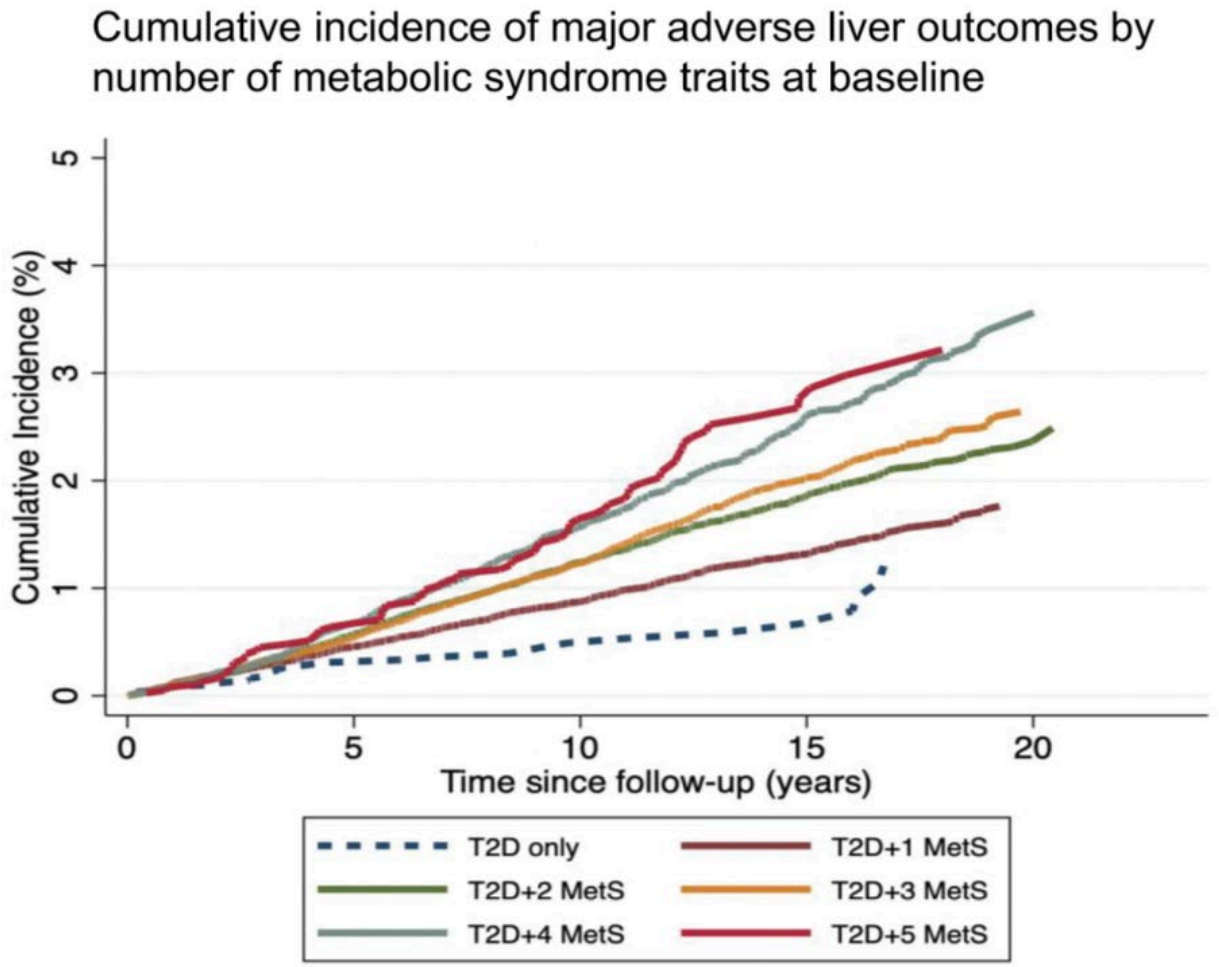
Balp et al. J Hep Rep 2019

Natural history of MASLD



Chan et al. CGH 2024

Natural history of MASLD in dysmetabolic disorders



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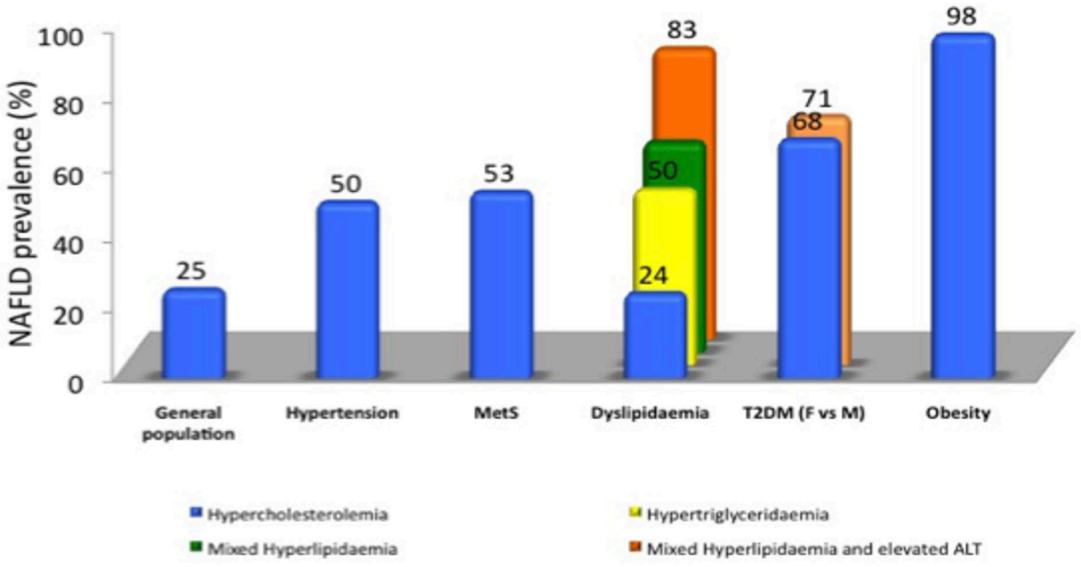
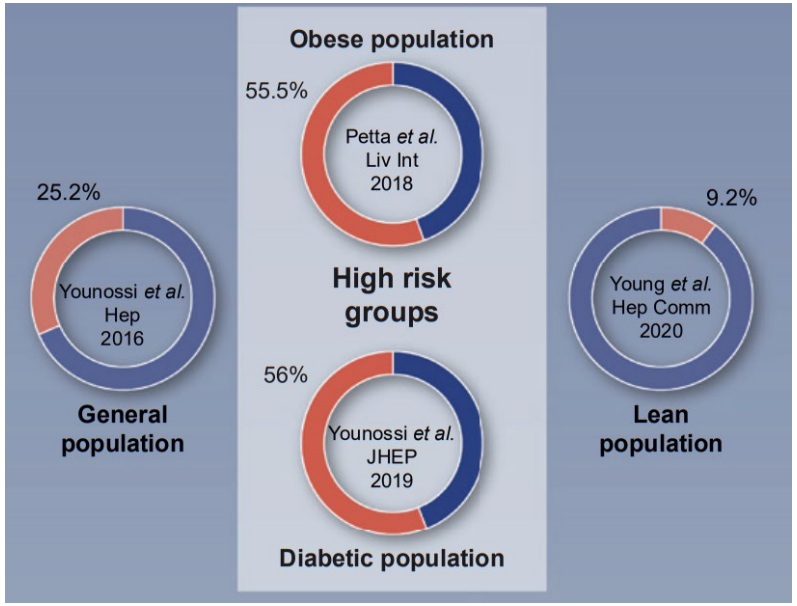
Fatty liver in high risk populations



Lonardo, Miele et al. DLD 2015



Bugianesi E. J Hepatol. 2022

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- Why search for MASH?

- How to detect it?

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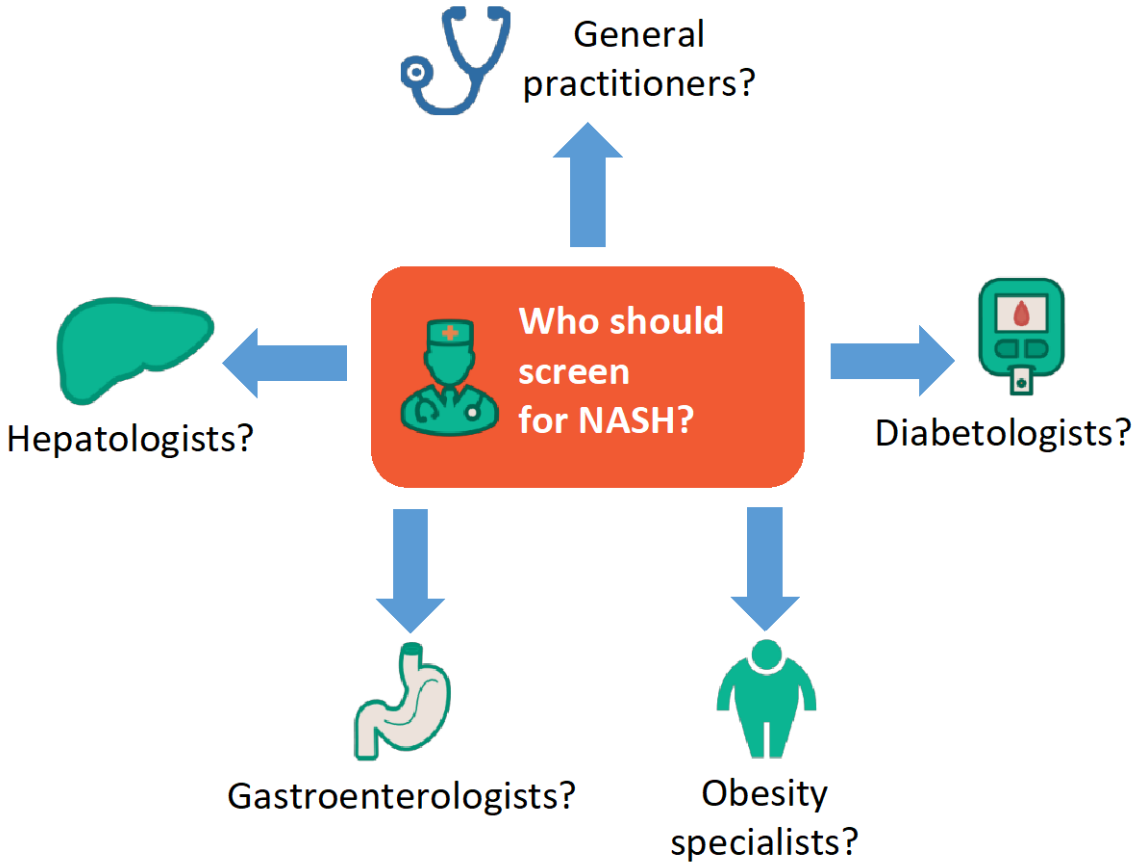
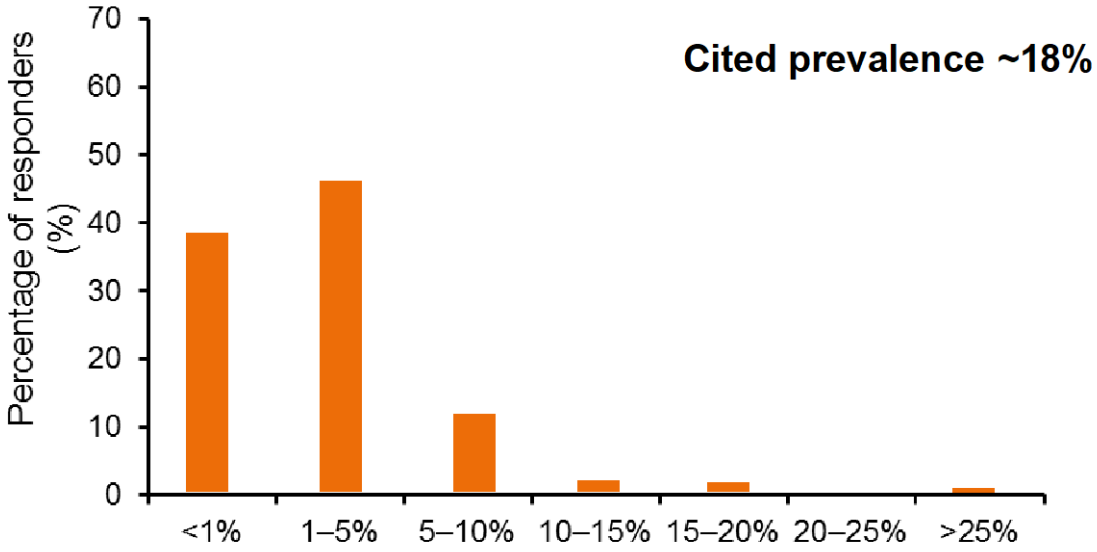
To screen or not to screen?



Patients are not identified

What proportion of all the patients that you see in clinic with diabetes do you think have advanced liver fibrosis or cirrhosis?[2]



The prevalence of advanced fibrosis was underestimated by respondents

NASH, non-alcoholic steatohepatitis.

1. Marjot T, et al. Diabet Med 2018;35:89–98; 2. Online survey of 133 diabetes specialists in the UK.

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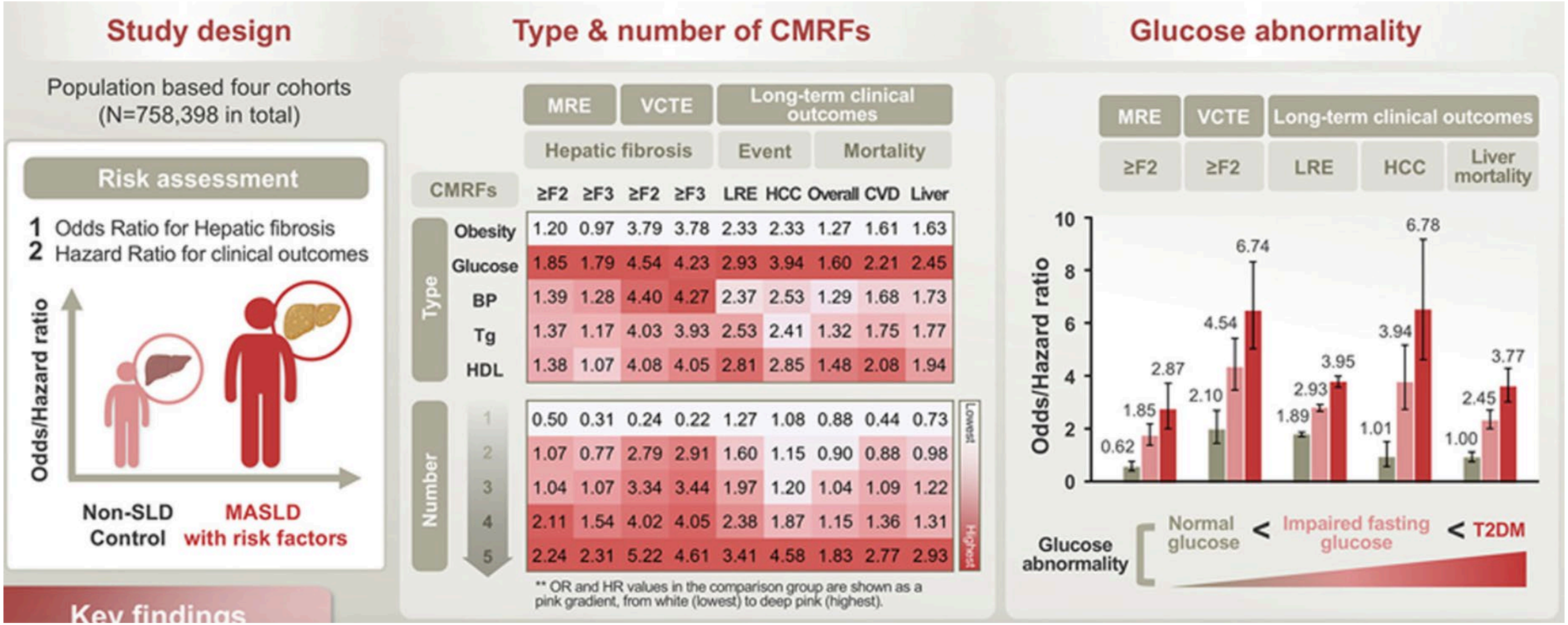
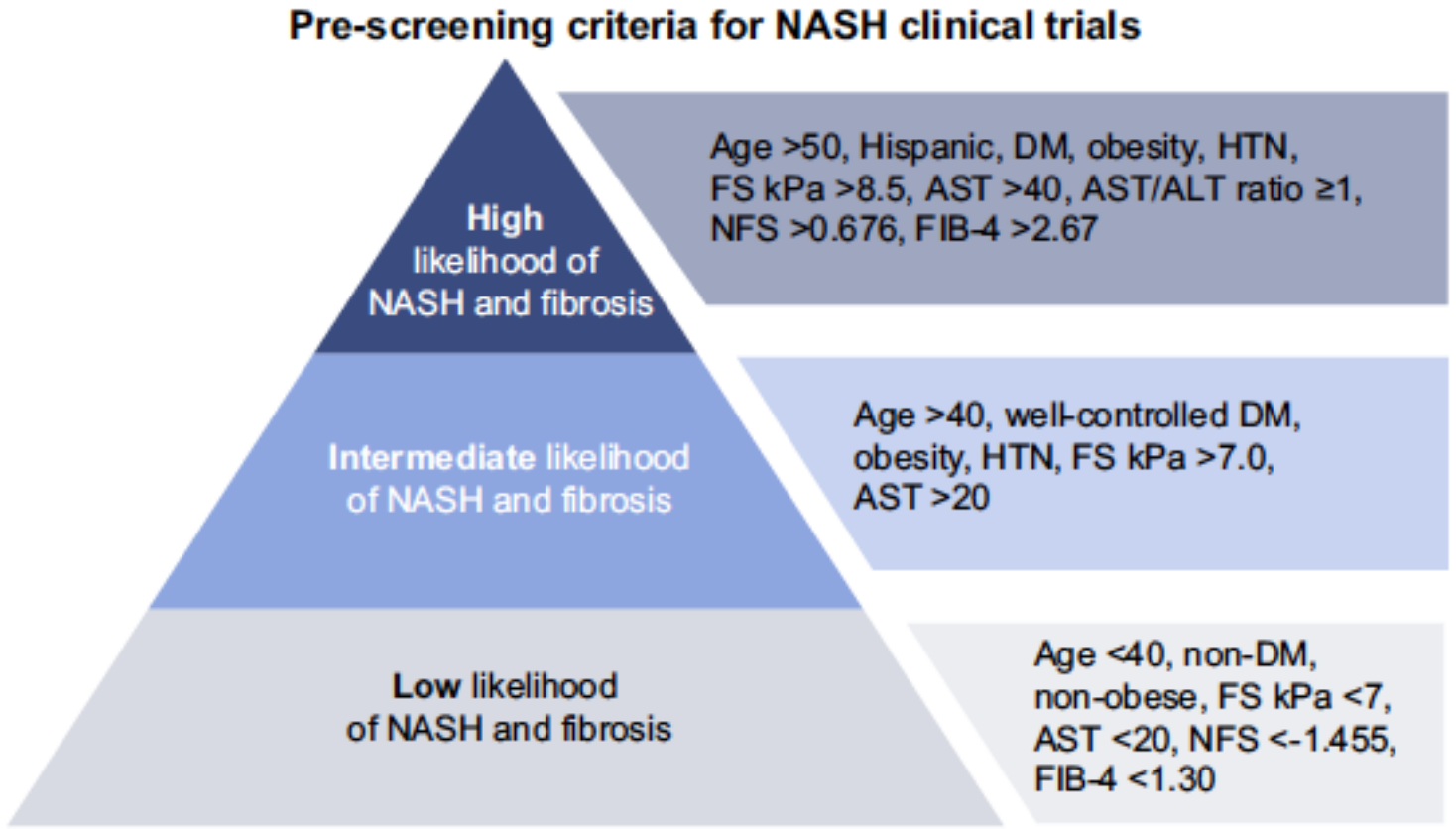
Natural history of MASLD and T2D



Park et al. J Hep Rep 2025

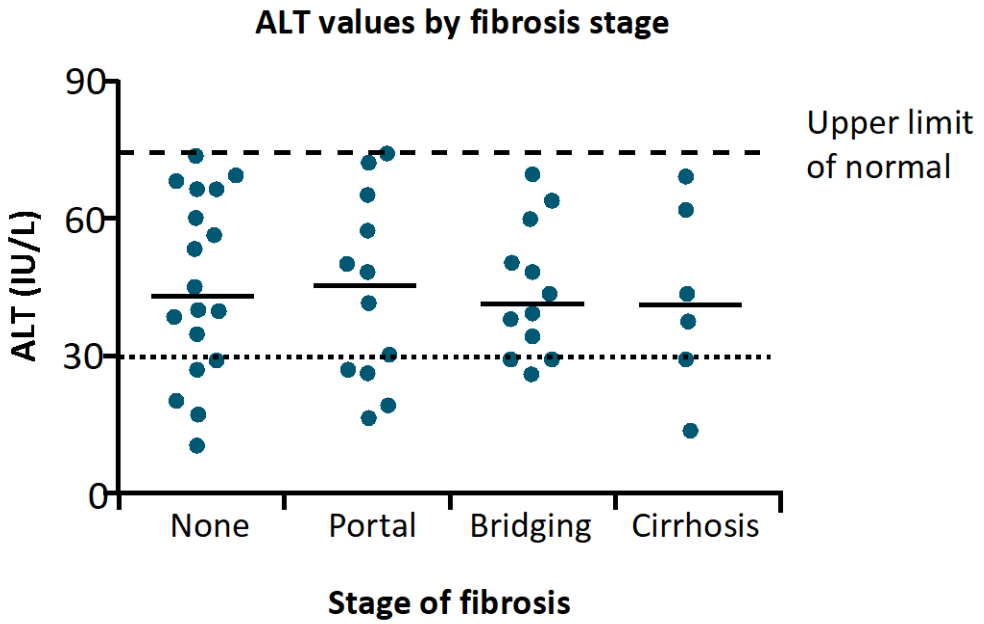
At risk of MASH



Konerman, J Hepatol 2018

Liver function tests and fibrosis

Pattern	Normal ALT (n = 51)	Abnormal ALT (n = 50)	p-value
Fat alone, n	8	10	NS
Fat + scattered inflammation, n	8	10	NS
Fat + ballooning ± inflammation, n	13	11	NS
Fat + ballooning ± Mallory hyaline ± pericellular fibrosis, n	22	19	NS



ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease; NS, non significant.
Mofrad et al. Hepatology. 2003 Jun;37(6):1286-92.

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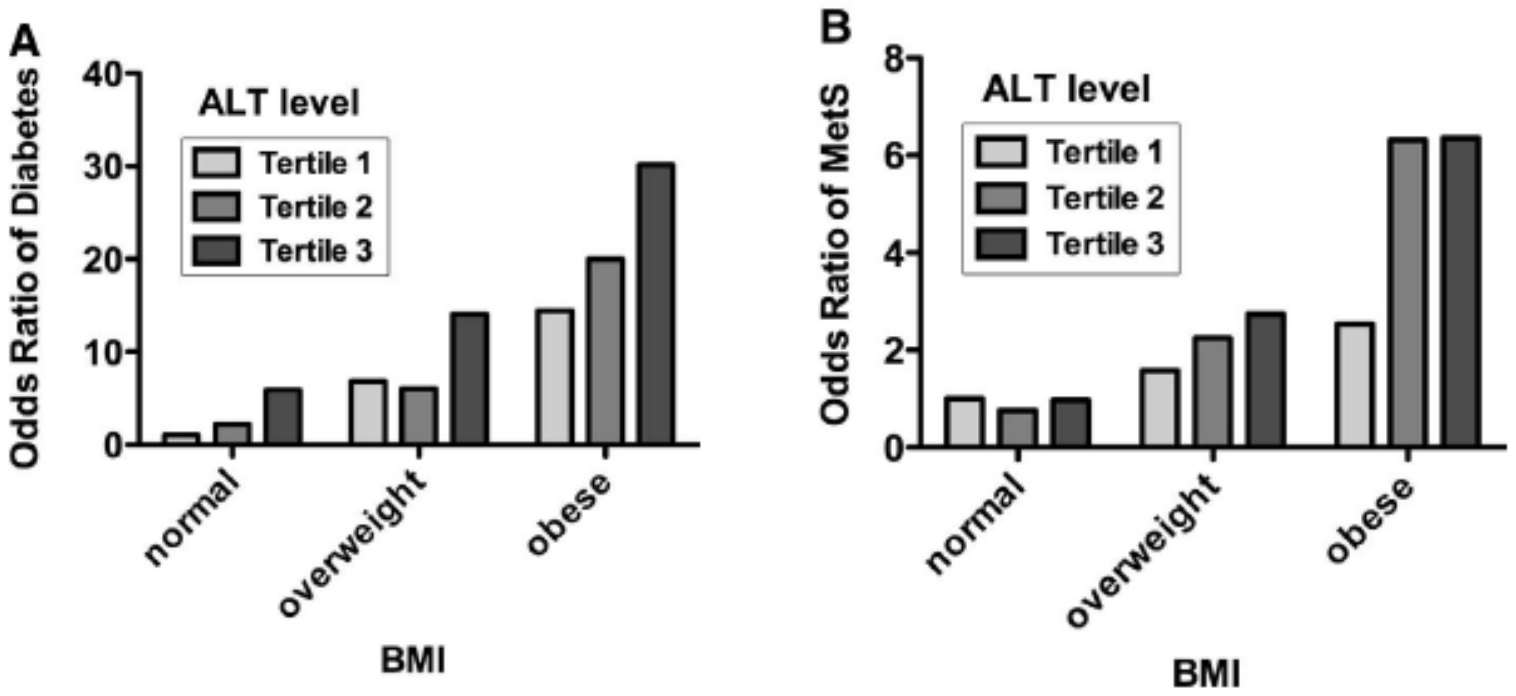
Liver function tests and risk of T2D

Aminotransferase Levels predicts the 20-Year Risk of Metabolic Syndrome and Type 2 Diabetes

Framingham Offspring Heart study n = 2812, mean age 44 yrs.



Over 20 yrs of f.u. per 1 standard deviation increase in log ALT level from baseline, increased odds of the development of:

1. Metabolic Syndrome (OR: 1.21,*P* < .001)
2. Diabetes (OR: 1.48; *P* < .0001).

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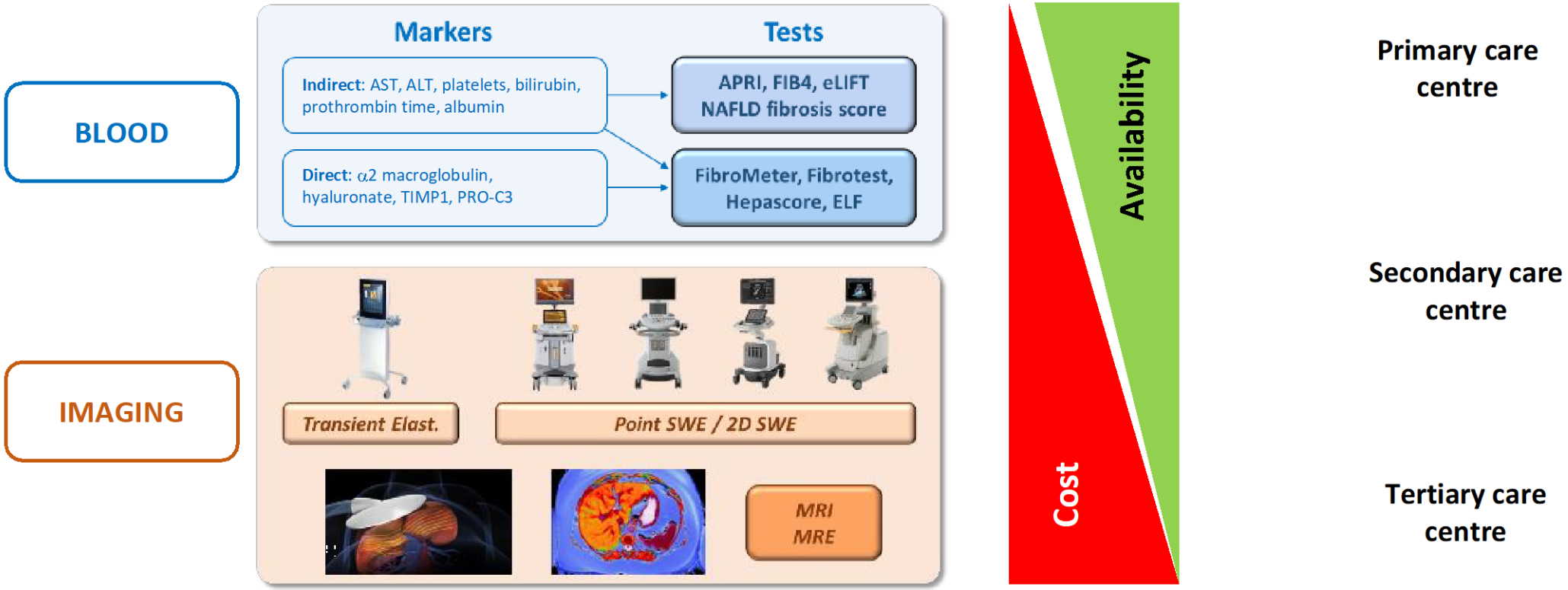
Goessling, Gastro 2008

Ideal biomarker for MASH



ALT, aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NASH, non-alcoholic steatohepatitis; PRO-C3, N-terminal type 3 collagen propeptide; SWE, shear wave elastography; TIMP, tissue inhibitor metalloproteinase; 2D SWE, two dimensional SWE.
Crossan C, et al. Health Technol Assess 2015;19:1–409 (Appendix 9).

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Role of biomarker for MASH

- Simple, noninvasive to identify:
  - ✓ *Advance fibrosis > further assesment and closer follow-up*
  - ✓ *Low risk patient > reassure and etabilish a periodic follow-up*
- Estimate the severity of liver fibrosis as prognostic factor for progression and outcome (liver and ‘non-liver’ related events)
- Recommended by scientific and professional societies (AASL, AGA, AGA, EASL-EASD-EASO)

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Question
Which are the variables included in FIB4?

A. Age, AST, HbA1c, Platelets

B. Age, AST, ALT, Platelets

C. HDL, AST, HbA1c

D. BMI, AST, Albumin, Platelets

Question
Which are the variables included in FIB4?

A. Age, AST, HbA1c, Platelets

B. Age, AST, ALT, Platelets

C. HDL, AST, HbA1c

D. BMI, AST, Albumin, Platelets

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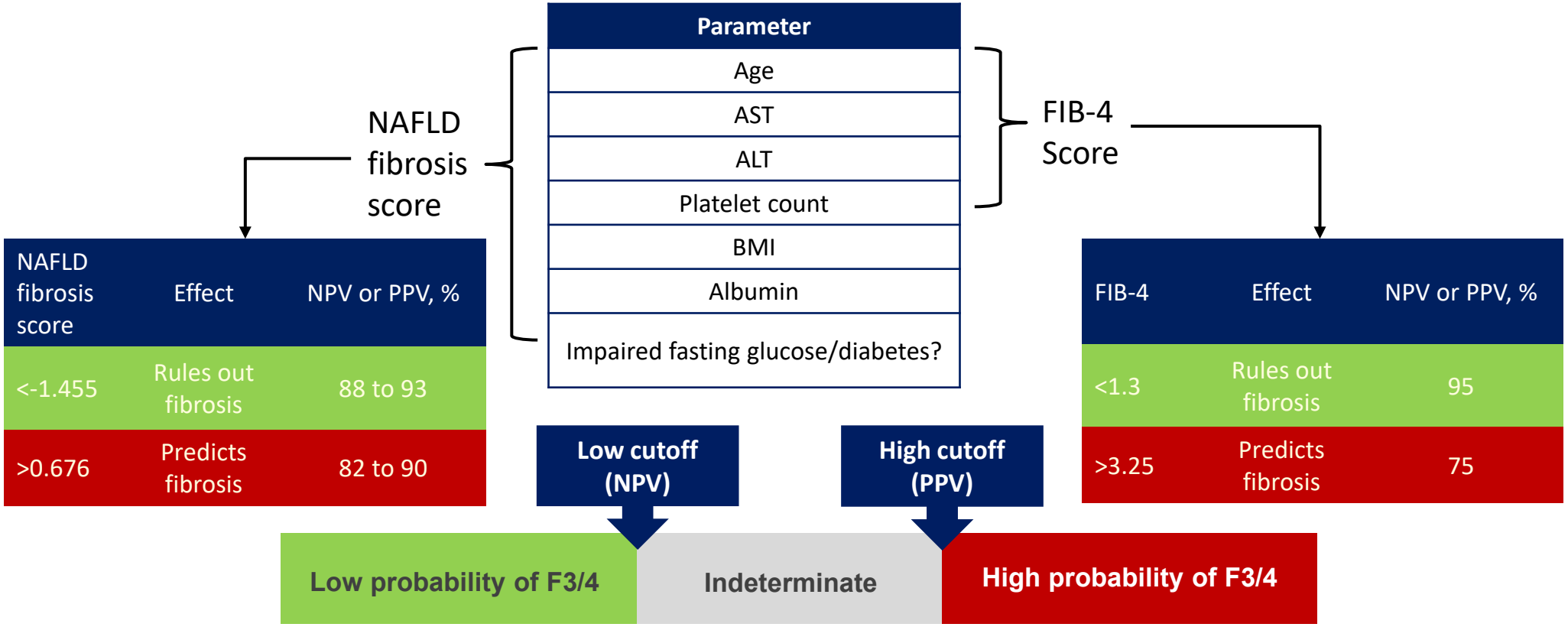

Angulo P, et al. Hepatology 2007; Sterling RK, et al. Hepatology 2006; McPherson S, et al. Gut 2010

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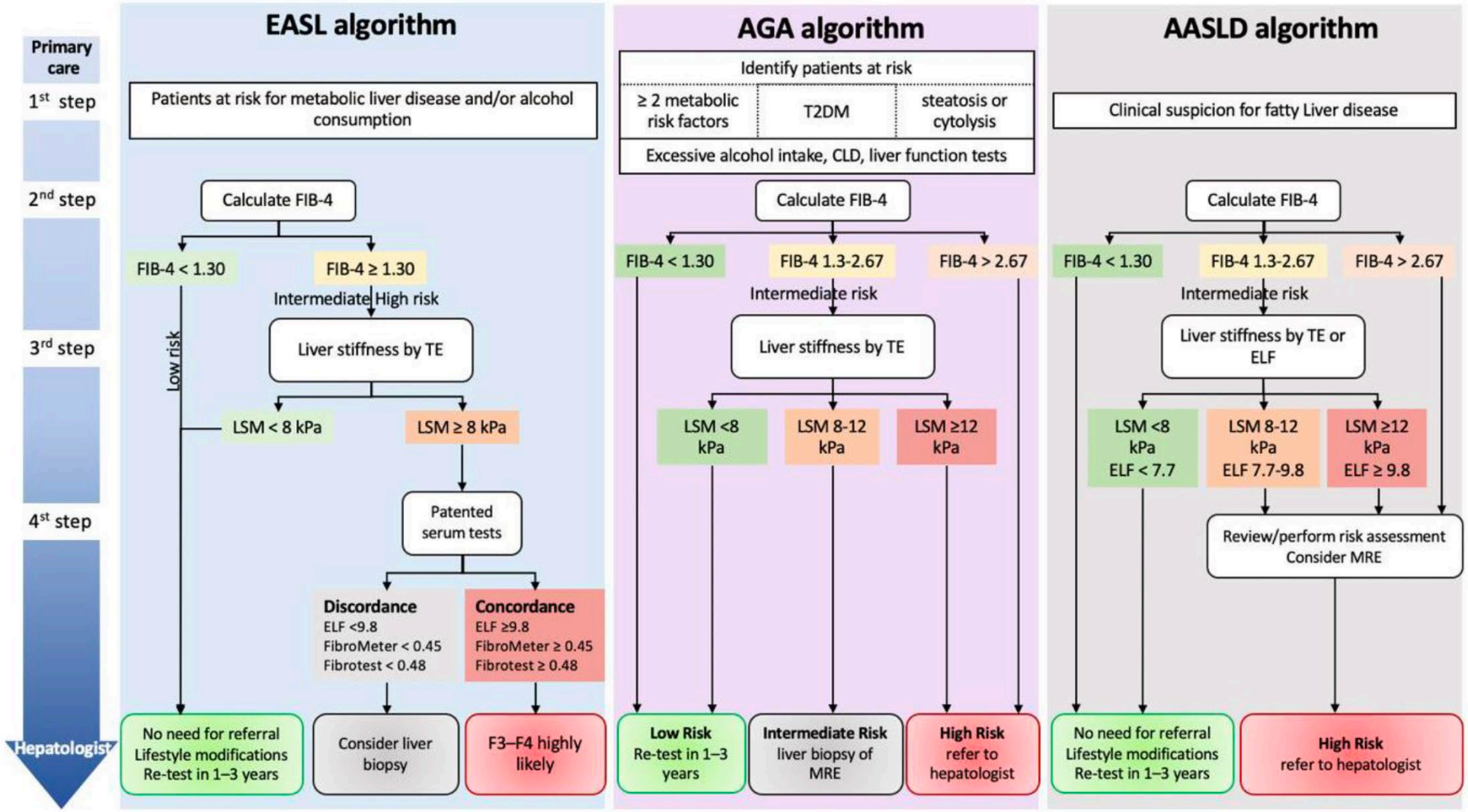

Canivet, Diagnostics 2022

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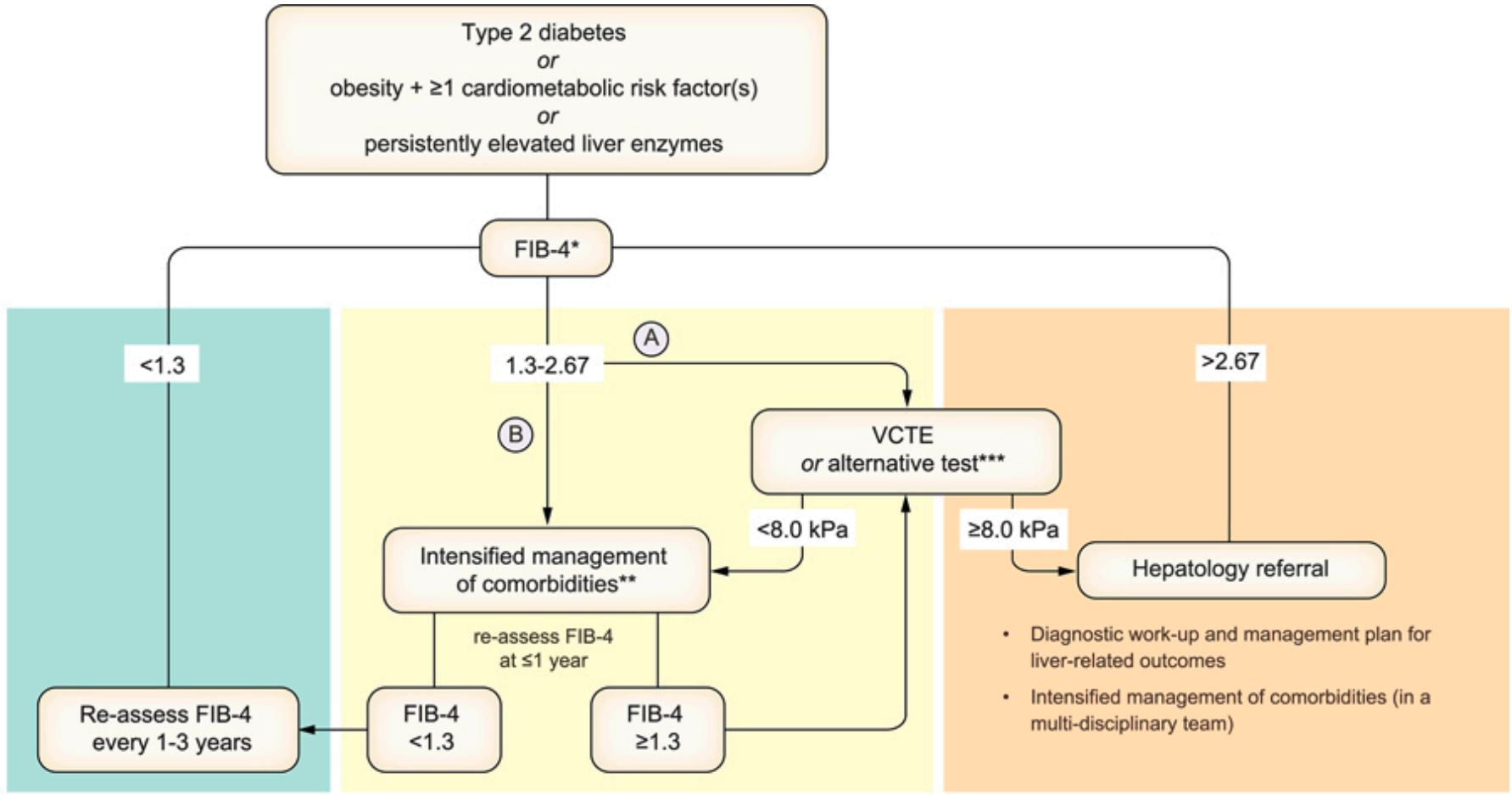
EASL-EASD-EASO Guidelines



* FIB-4 thresholds valid for age ≤65 years (for age >65 years: lower FIB-4 cut-off is 2.0)
** *e.g.* lifestyle intervention, treatment of comorbidities (*e.g.* GLP1RA), bariatric procedures
*** *e.g.* MRE, SWE, ELF, with adapted thresholds
Ⓐ and Ⓑ are options, depending on medical history, clinical context and local resources

J Hep 2024

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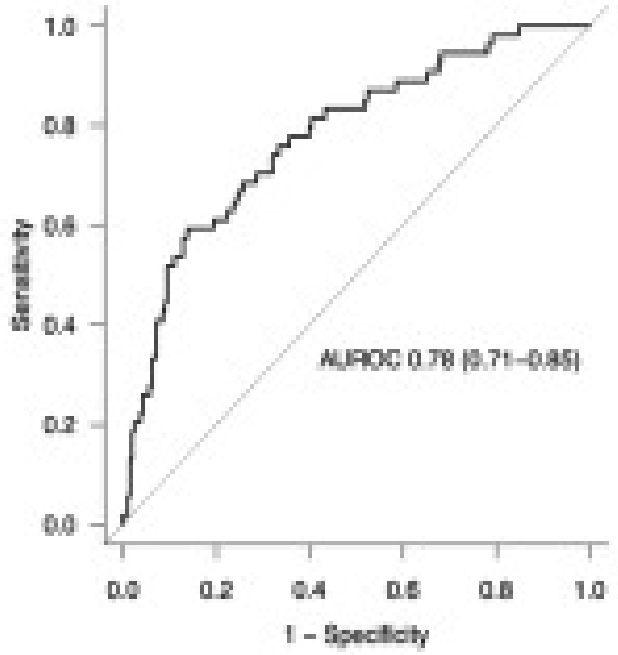
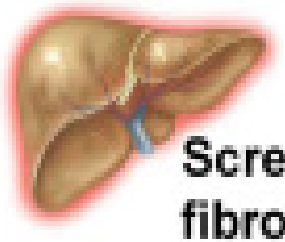
Fibrotic NASH Index

Fibrotic NASH Index (FNI)
(AST, HDL, HbA1c)



Primary care, diabetology and endocrinology clinics

High-risk individuals
(overweight/obesity, type 2 diabetes, metabolic syndrome)



Screening for fibrotic NASH
(NASH + NAS≥4 +F≥2)

FNI

Liver clinic

Transient elastography, follow-up, clinical trials

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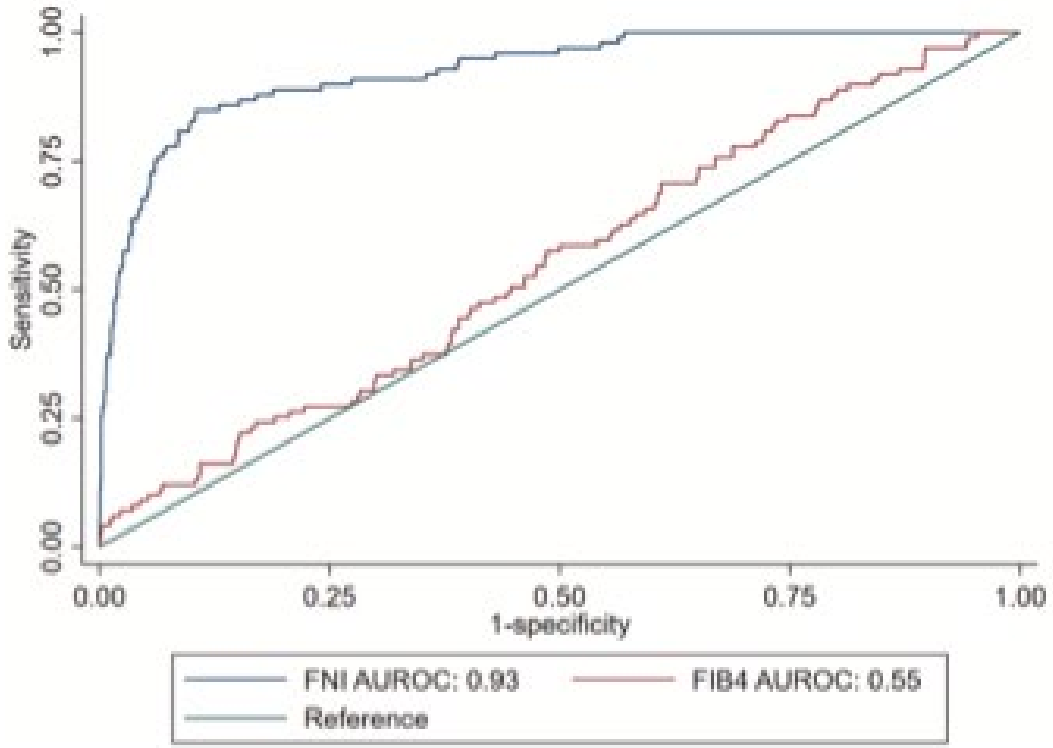
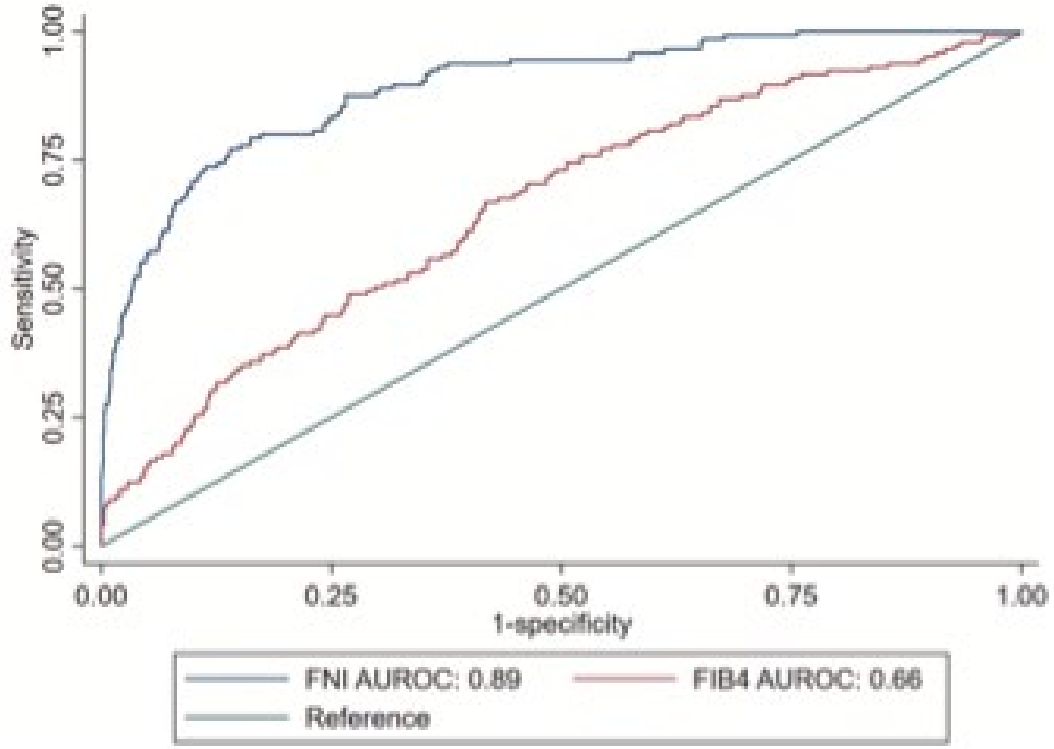
Tavaglione et al. CGH 2022

Fibrotic NASH Index



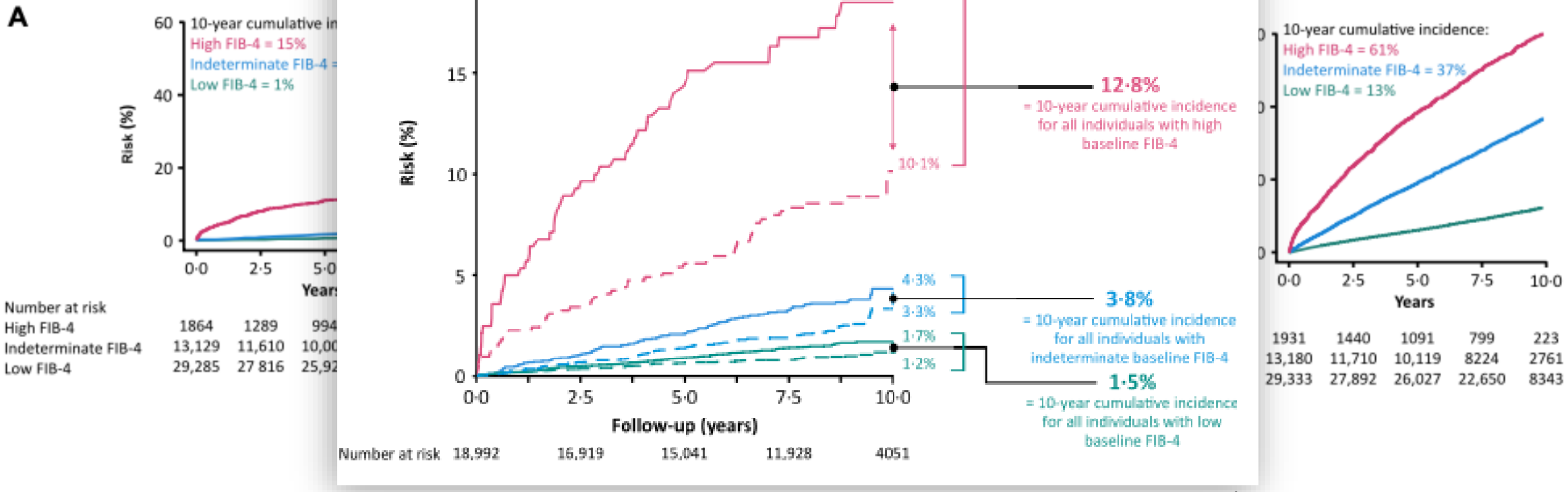


Ciardullo et al. Diabetes Res Clin Pract 2023

FIB-4 predicts key clinical outcomes in obese populations and/or type 2 diabetes

Total study population (

Liver Events



Anstee et al. Lancet Regional Health-Europe 2024

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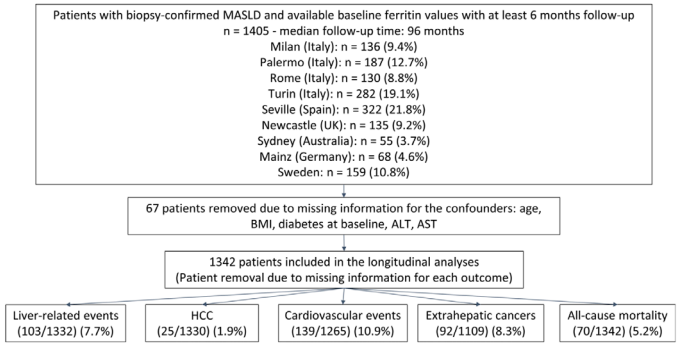
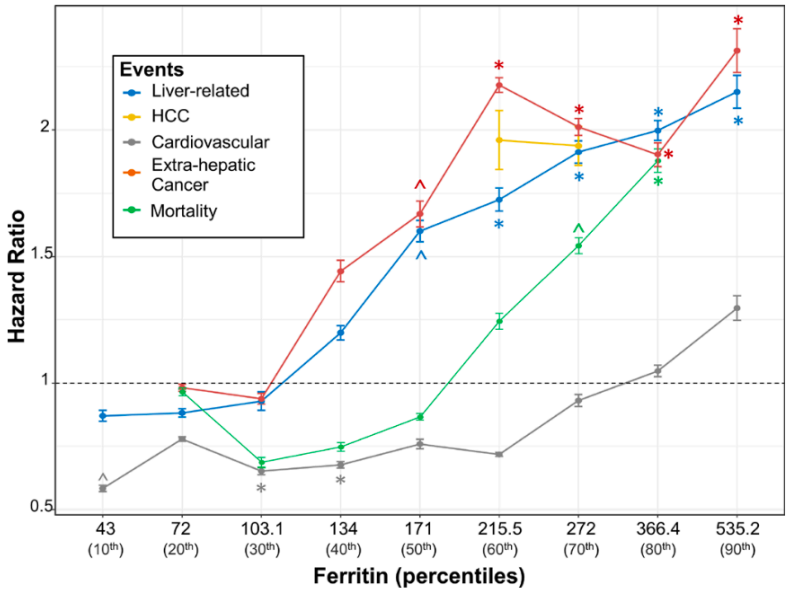
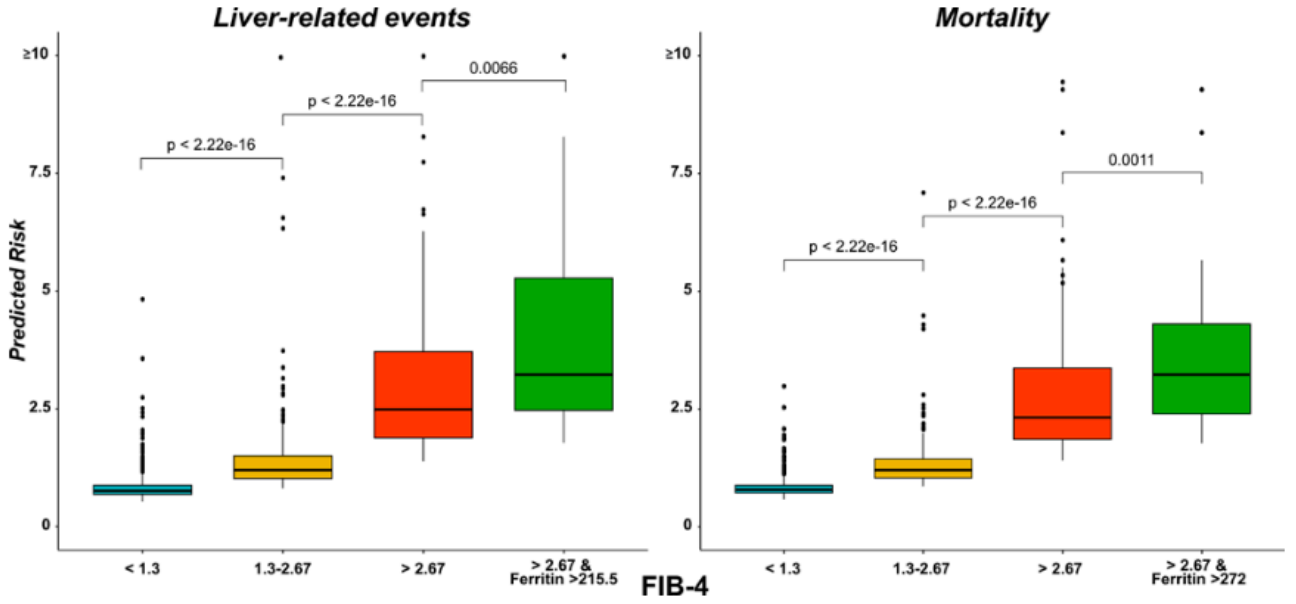
Ferritin and MASLD

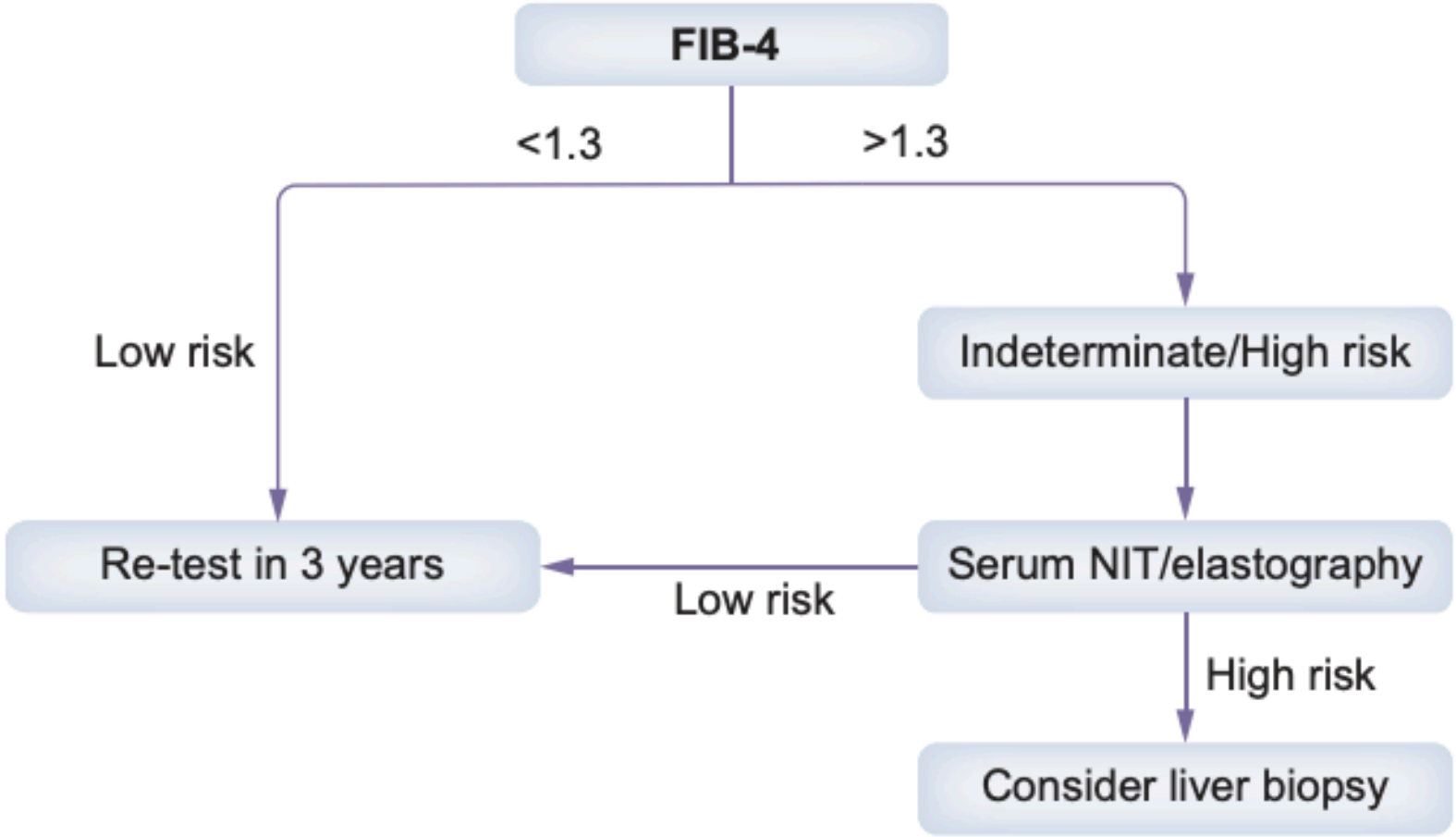






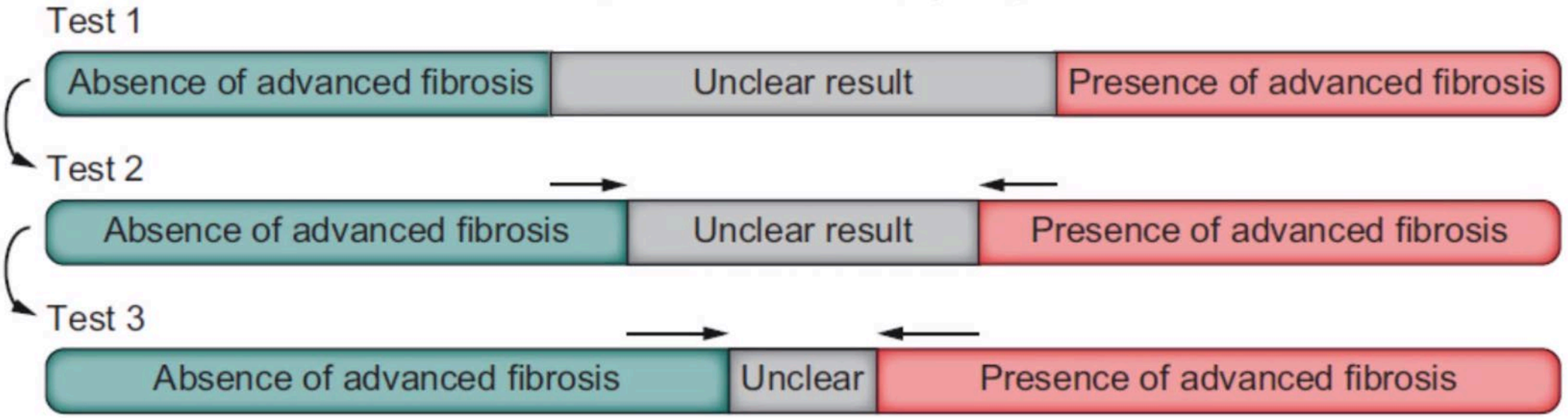
Armandi et al. Gut 2024

Common non-invasive path for MASH



Boursier & Tzochachis. J Hep Rep 2021

Non-Invasive Tests (NITs)



Combination of tests in a sequential fashion mantains sensitivity and specificity and reduces the indeterminate zone

Non-alcoholic fatty liver disease: A patient guideline J HEP Reports 2021

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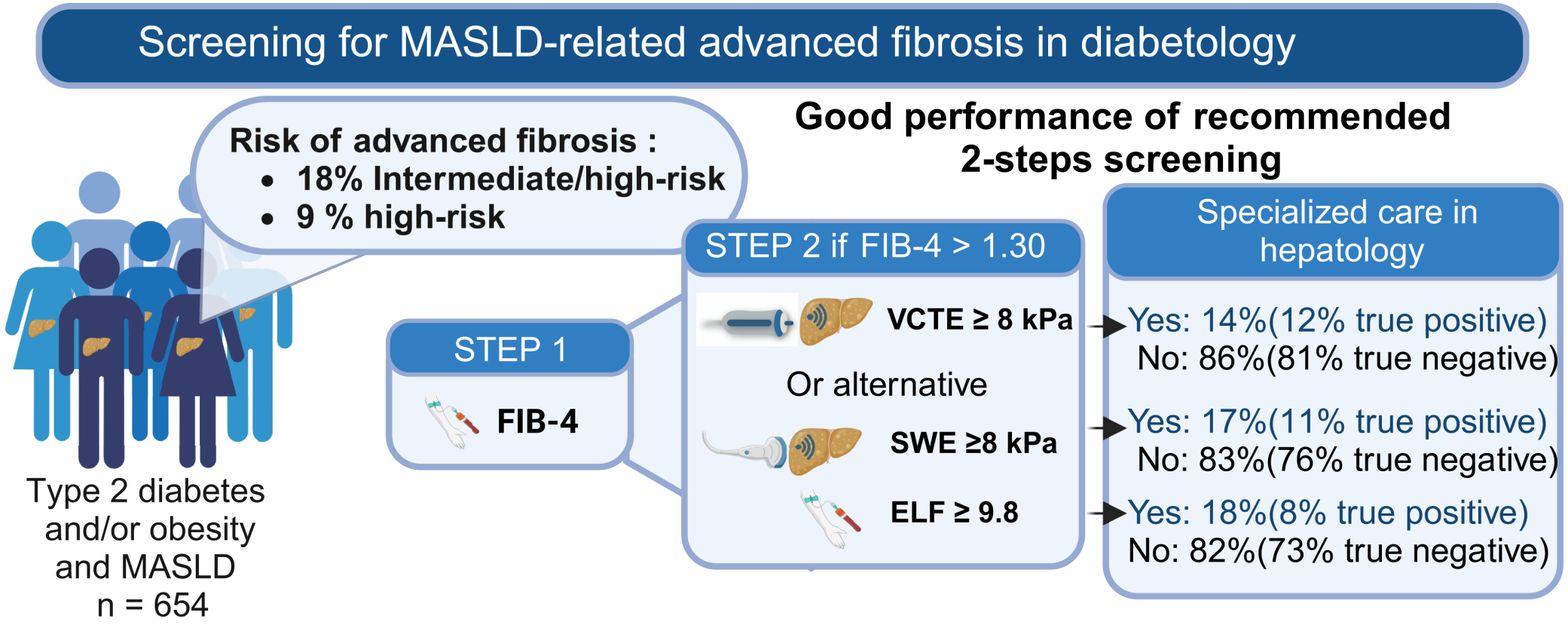
Screening for MASLD–Related Advanced Fibrosis in Diabetology: A Prospective Multicenter Study

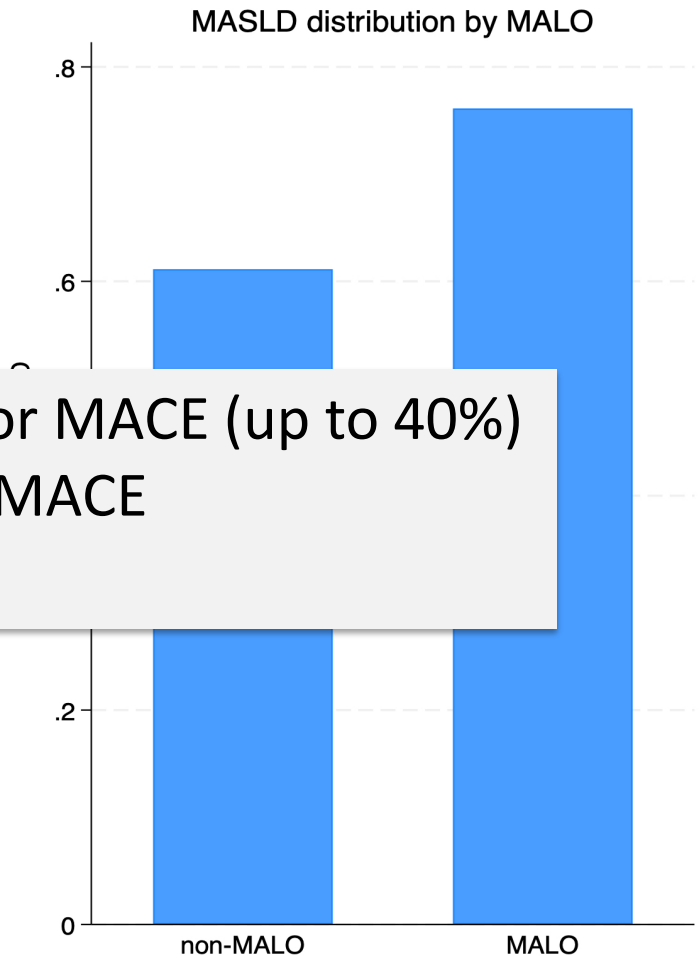


Diabetes Care 2025

Screening for MASLD–Related MALO in Diabetology

Characteristics	Cohort (n=1711)	MALO (n=67)	non-MALO (n=1644)	P-value
Age (years), Mdn (IQR)	67.0 (58.0-74.0)	66.0 (58.5-75.5)	67.0 (58.0-74.0)	0.760
Sex (female), n (%)	647 (37.81%)	30 (44.78%)	617 (37.53%)	0.231
BMI (Kg/m2), Mdn (IQR)	28.0 (25.90-30.38)	28.0 (25.54-31.02)	28.0 (25.95-30.26)	0.902
FU (months), Mdn (IQR)	37.0 (25.0-42.0)	39.0 (33.0-43.0)	37.0 (25.0-42.0)	0.080
Cirrhosis, n (%)	216 (12.62%)	37 (55.22%)	179 (10.89%)	**<0.001**
MASLD, n (%)				
AST (UI/L), Md				
ALT (UI/L), Md				
PLT (x10^9/L),				
HbA1c (mmol/mol), Mdn (IQR)	56.3 (49.0-67.0)	64.0 (50.96-76.48)	56.3 (49.0-66.12)	**0.006**
Tryglicerides (mg/dL), Mdn (IQR)	140.0 (108.0-189.0)	141.0 (102.0-219.5)	140.0 (108.0-188.0)	0.595
HDL, Mdn (IQR)	40.0 (34.0-48.0)	37.0 (25.0-44.5)	40.0 (34.0-48.0)	0.002
FIB4, Mdn (IQR)	1.67 (1.44 -1.96)	3.39 (1.66 -5.80)	1.67 (1.44-1.90)	**<0.001**
FIB4 > 2.67, n (%)	248 (14.49%)	38 (56.72%)	210 (12.77%)	**<0.001**

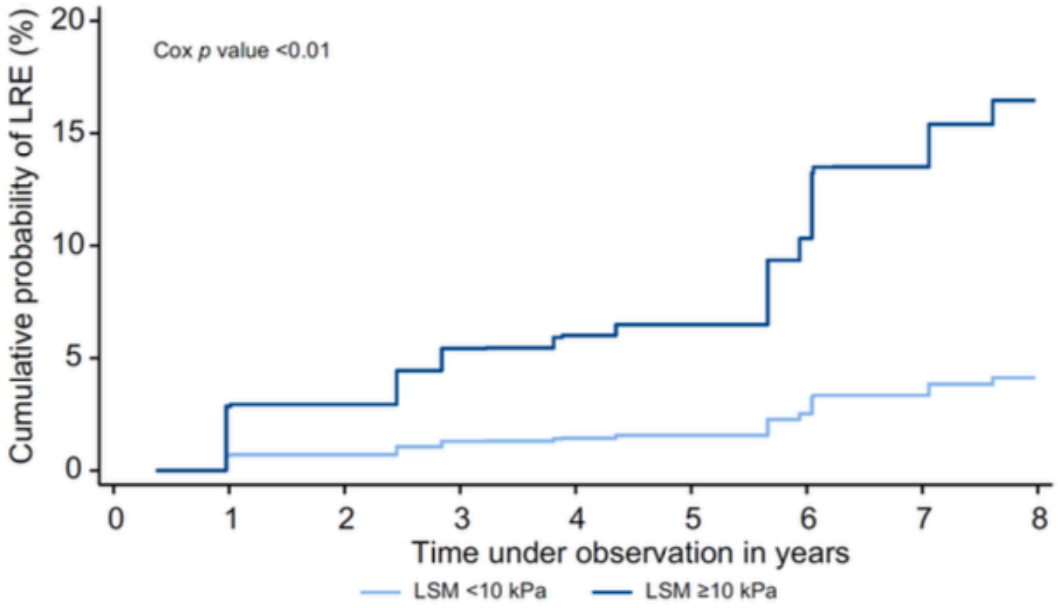
- MASLD: 2x risk for MALO and increased risk for MACE (up to 40%)
- FIB4 > 2.67 = 3x risk for MALO and 2x risk for MACE
- HbA1c Independent predictor of MALO



FPG DIANA Study, preliminary data

Annual control of VCTE

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

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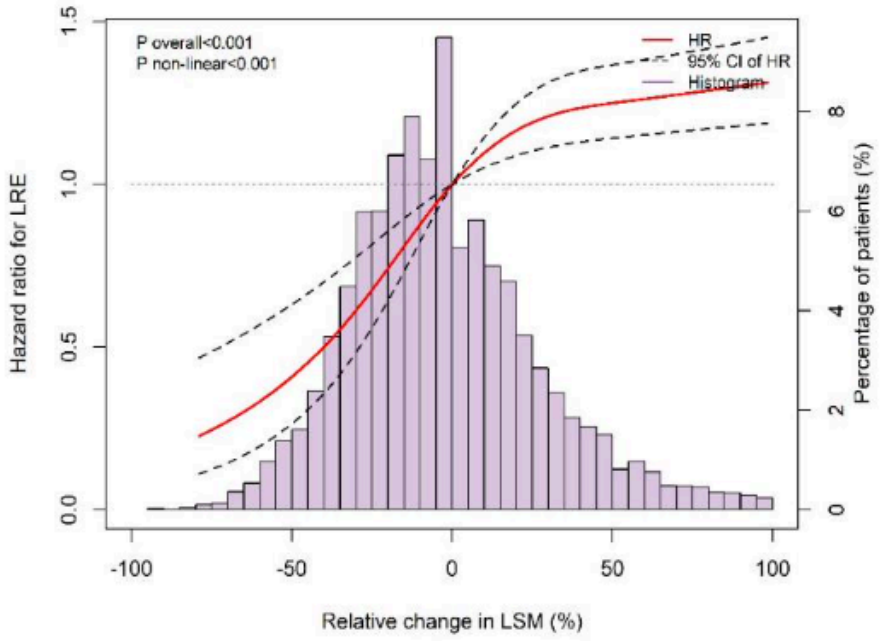
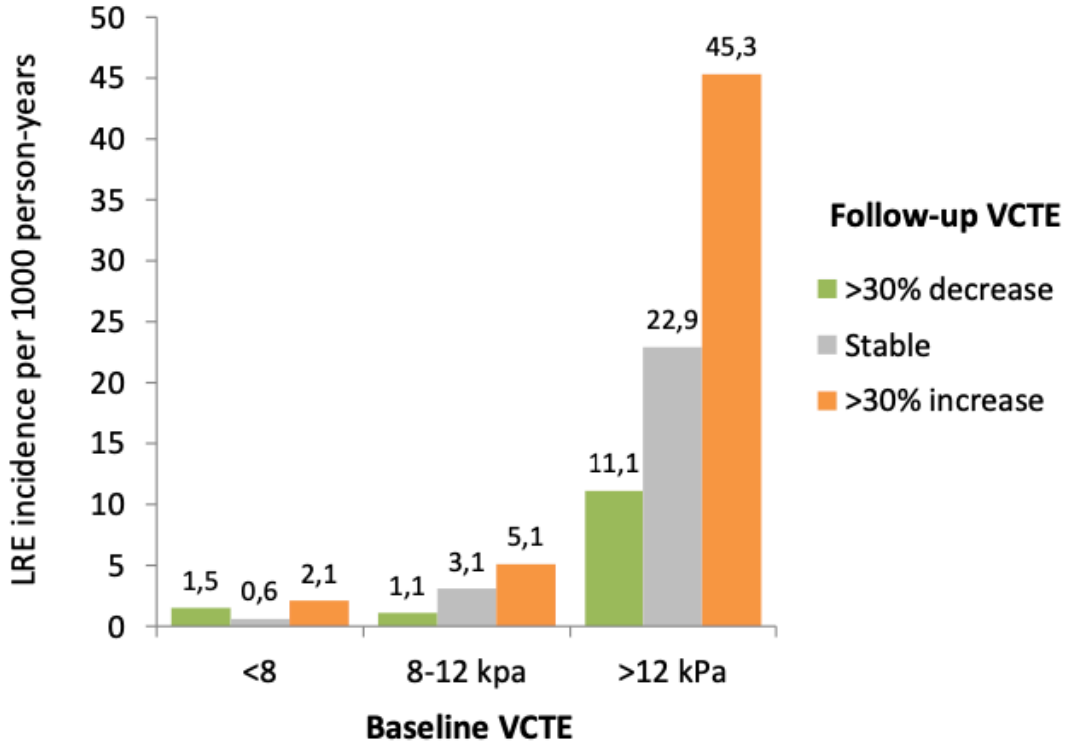
Annual control of VCTE

Multicentric international cohort

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





Lin, JAMA 2024

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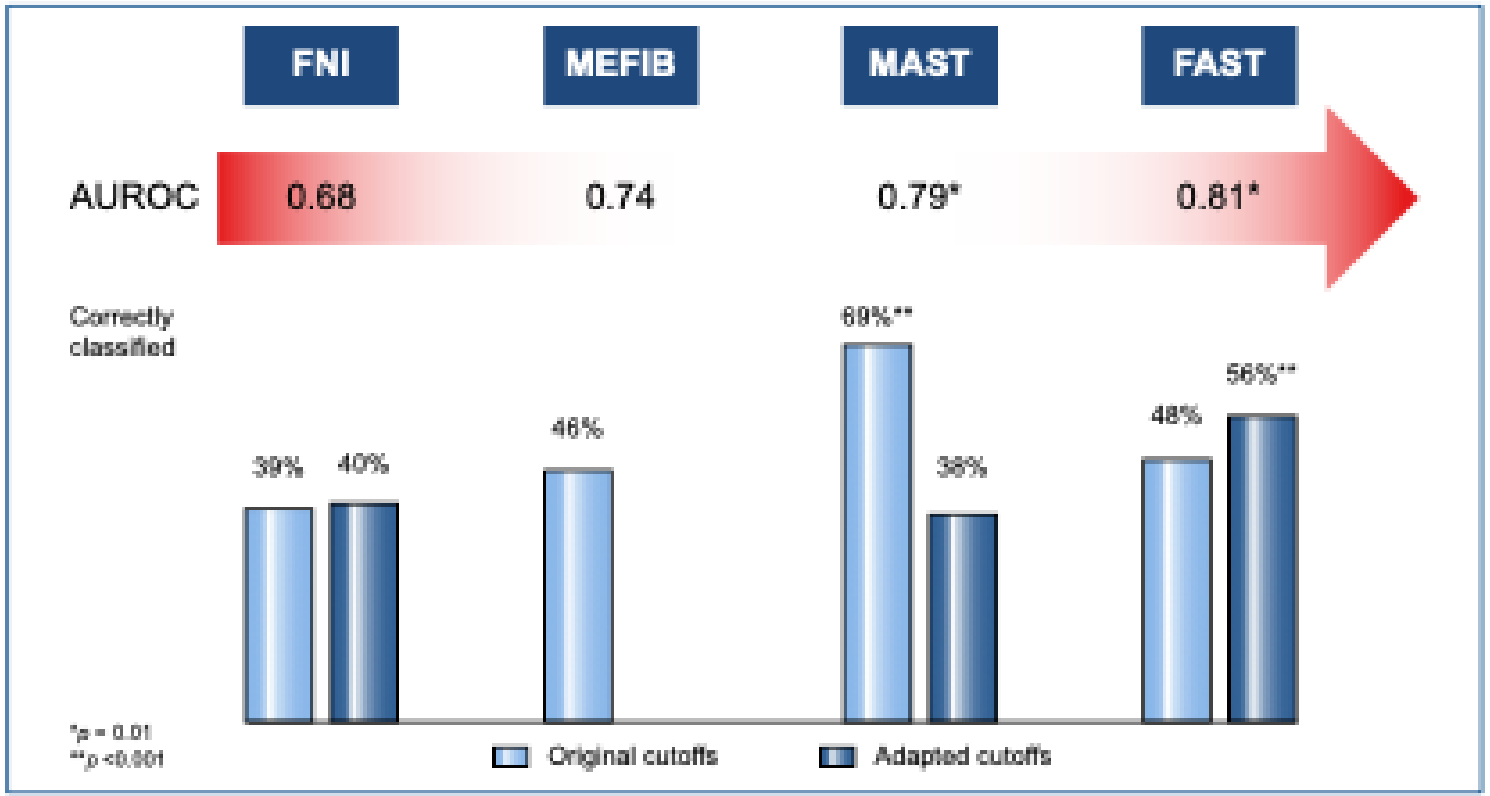
Prospective cohort and risk of fibrotic MAH



Conclusion: FAST, MAST, MEFIB, and FNI are accurate non-invasive tools to identify patients with type 2 diabetes and fibrotic MASH in secondary/tertiary diabetes clinics. Cut-offs adapted to type 2 diabetic population should be used.

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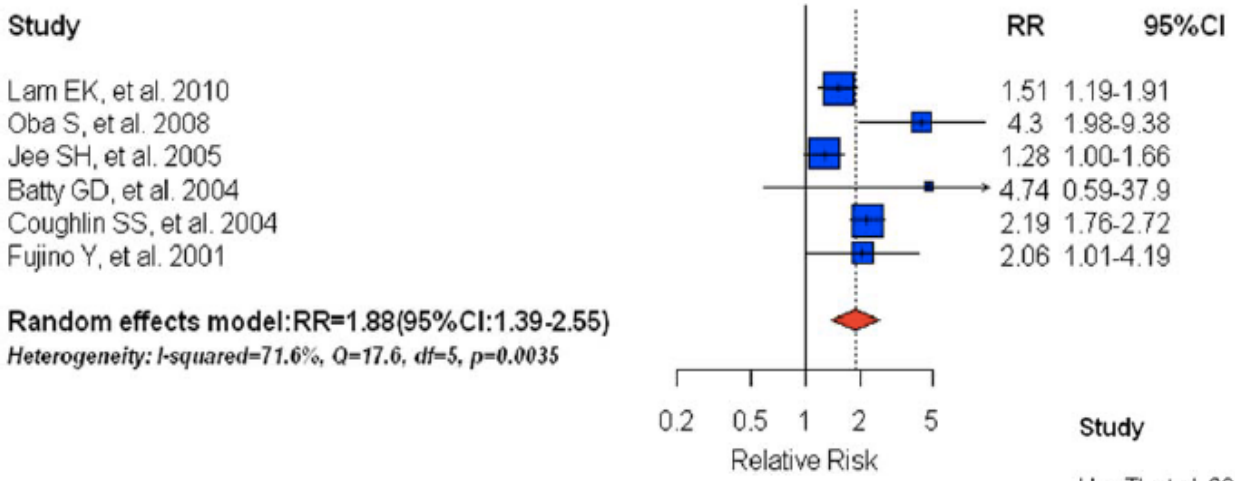
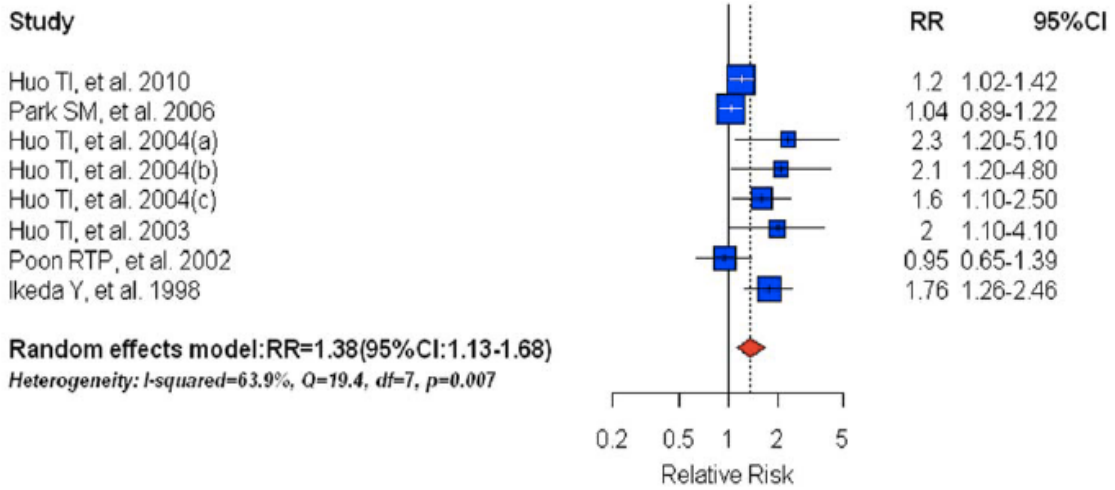
Castera et al. J Hep 2024

Diabetes and HCC



Relative Risk RR of HCC specific mortality is 88% higher in patients with diabetes, and all cause mortality is 38% higher



Yang et al. Plos ONE 2011

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Diabetes and HCC - surveillance

Condition	AASLD[29]	AGA[81]	EASL[11]	APASL[122]
Cirrhosis	Surveillance recommended in Child–Pugh stages A or B; individuals in Child–Pugh stage C should only undergo surveillance if they are eligible for liver transplantation	None	Surveillance is recommended in Child–Pugh stages A and B; individuals in Child–Pugh stage C should only undergo surveillance if they are awaiting liver transplantation	Surveillance is recommended for individuals with cirrhosis
Chronic hepatitis B without cirrhosis	Surveillance is recommended for men from endemic countries aged >40 years; women from endemic countries aged >50 years; people from Africa; people with a family history of HCC; people with a PAGE-B score ≥10	None	Individuals at intermediate or high risk of HCC (PAGE-B score ≥10)	Surveillance is recommended for Asian men aged >40 years, Asian women aged >50 years, Black people aged >20 years and people with a family history of HCC
Chronic hepatitis C without cirrhosis	Routine surveillance is not recommended	None	Individuals with stage 3 fibrosis may be considered for surveillance	Surveillance is recommended for patients with HCV cure treated with DAAs, regardless of fibrosis stage
NAFLD without cirrhosis	Routine surveillance is not recommended	Consider surveillance in advanced (stage 3–4) fibrosis	Individuals with stage 3 fibrosis may be considered for surveillance	None

AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterology Association; APASL, Asia-Pacific Association for the Study of the Liver; DAA, directly acting antiviral; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease.

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Singal A et al Hepatology 2023; Loomba R et al Gastroenterology 2020;
EASL HCC CGP J Hepatol 2018; Kanda T et al Hepatol Int 2019

Prediction of liver events and HCC

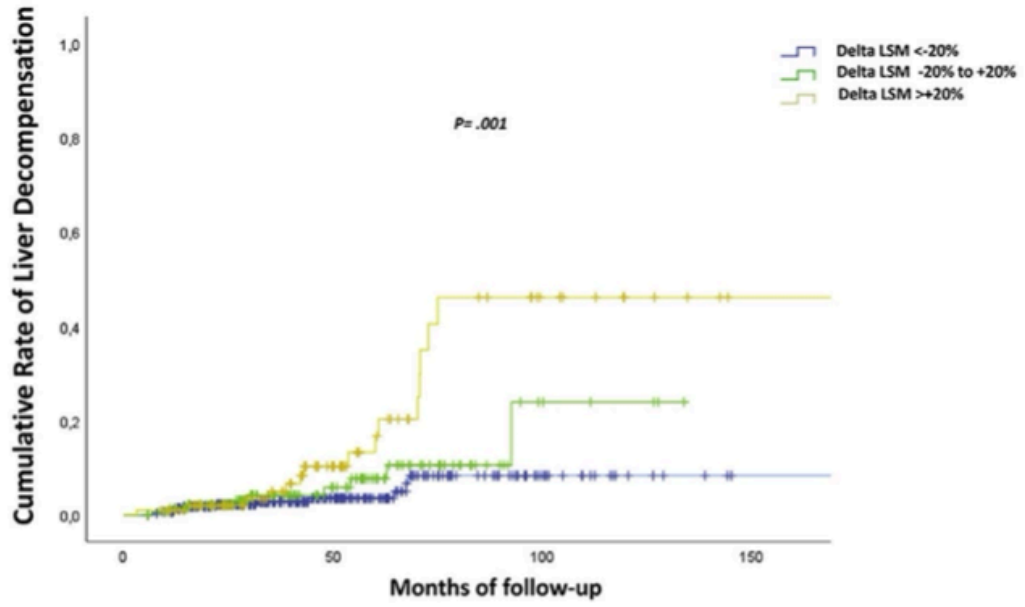
Multicentric international cohort

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

Median follow-up : 37 months

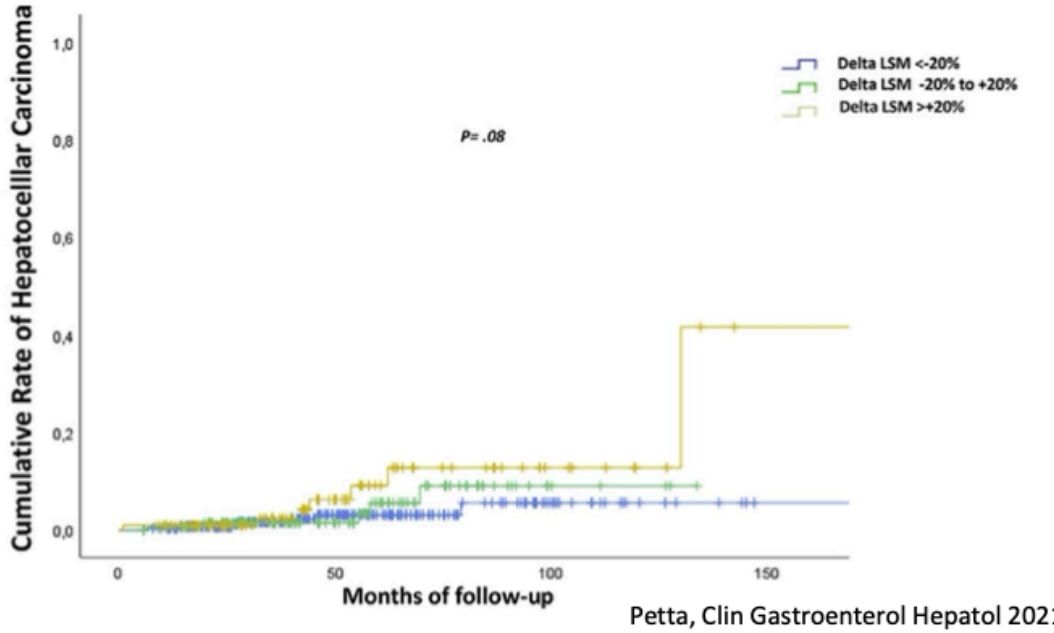
A

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



B

Delta LSM
Predicted **hepatocellular carcinoma**



Petta, Clin Gastroenterol Hepatol 2021

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Screen with VCTE in high risk population and primary care

GRIPonMASH

Home Partners News & Events Contact

GRIPonMASH screens first patient and reports strong first-year results

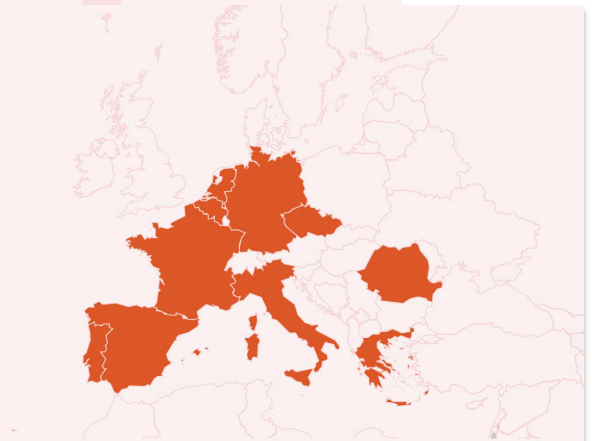
Breaking milestones reached in project aiming to improve prevention and care of Metabolic dysfunction-Associated SteatoHepatitis (MASH).

Press release

10 Enrolling Countries & PIs

Each of the 10 enrolling countries will contribute with 1000 subjects, ensuring a robust and diverse dataset. Logistics and coordination are meticulously managed by the Centre of Excellence (CoE), with recruitment efforts seamlessly conducted at Primary Care Practices (PCP) and clinics.

- The Netherlands
- Belgium
- Germany
- France
- Portugal
- Spain
- Italy
- Czech Republic
- Romania
- Greece



ambulatoriosteatosi@policlinicogemelli.it

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Take home – Why and how to screen MASH in T2D

- High Prevalence: Up to 70% of Type 2 Diabetes (T2D) patients have MASLD, and 15-20% develop MASH.
- Increased Risk of Progression: Diabetic patients have a 2-3x higher risk of fibrosis progression and cirrhosis.
- Silent Disease: MASH remains asymptomatic until advanced stages, making early screening essential.
- Increased Mortality Risk: Diabetes increases the risk of liver-related mortality, independent of other liver diseases.
- Early screening in diabetes clinics is crucial to prevent liver-related complications.
- Simple, stepwise approaches (FIB-4 → Imaging) can be easily integrated into routine diabetes care.
- MASH is treatable – but only if detected early!