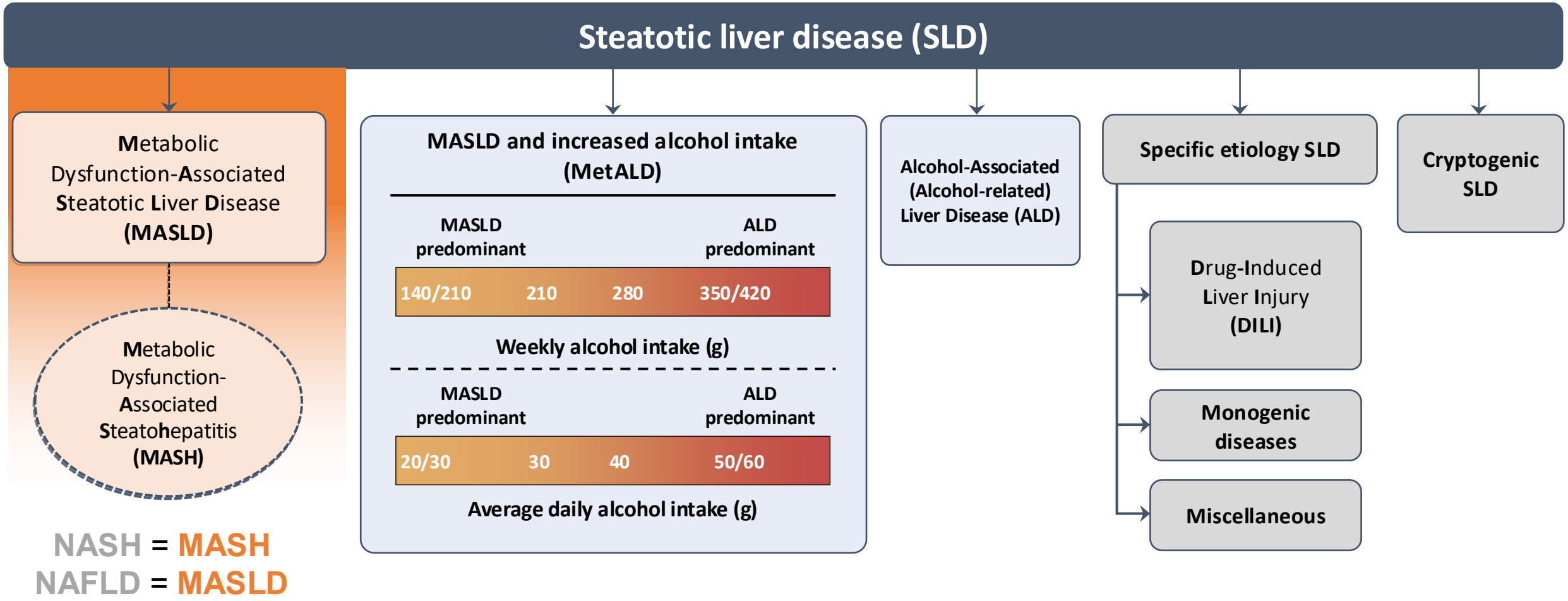
When is Fatty Liver Disease Worrisome?

Krishna Venkata, MD
Texas Liver Institute
San Antonio, TX

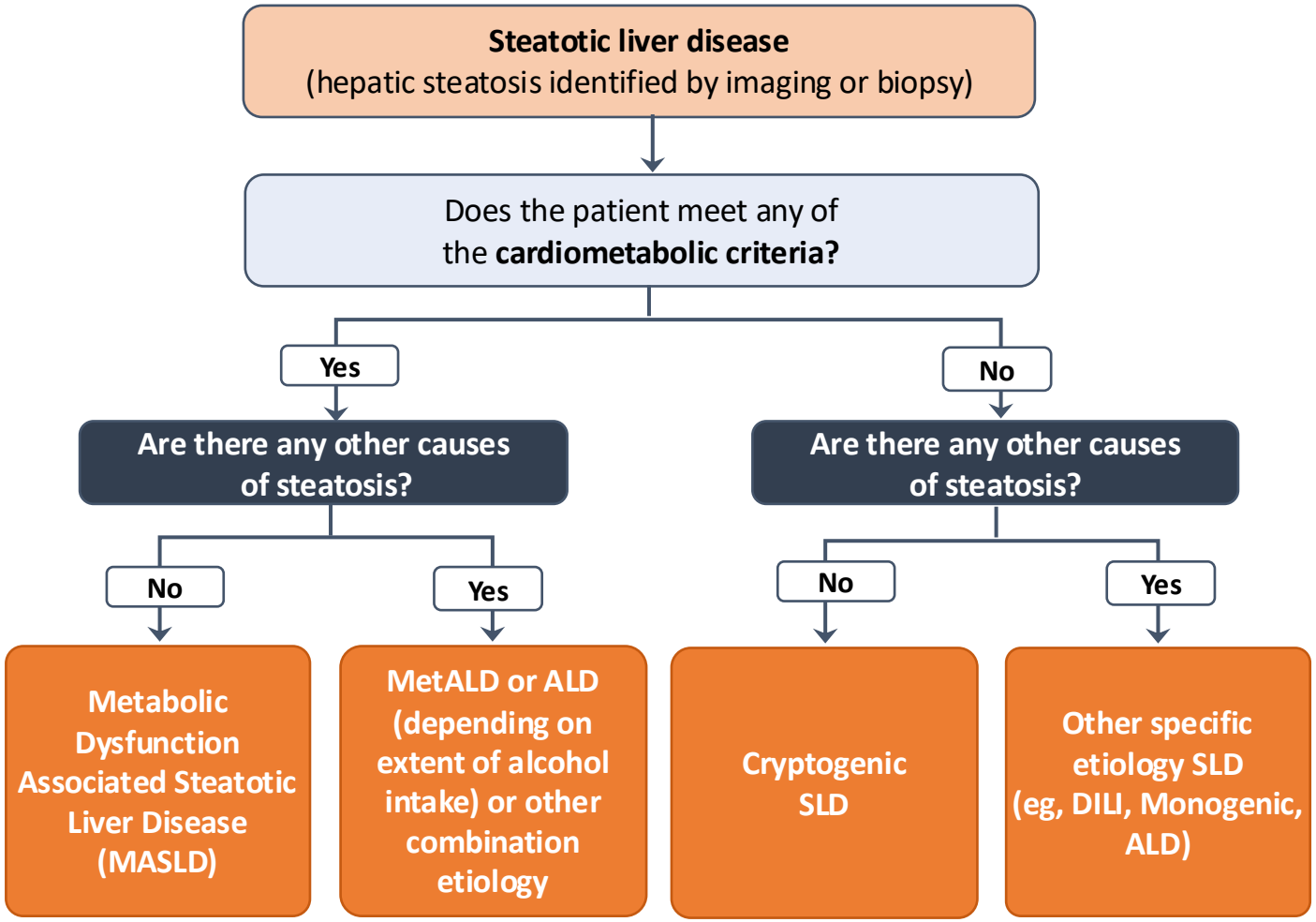
Nomenclature and Natural History

Nomenclature: Steatotic Liver Disease and Beyond



Rinella ME et al. *Hepatology.* 2023;78:1966-1986.

Categorizing Steatotic Liver Disease



Adult cardiometabolic criteria

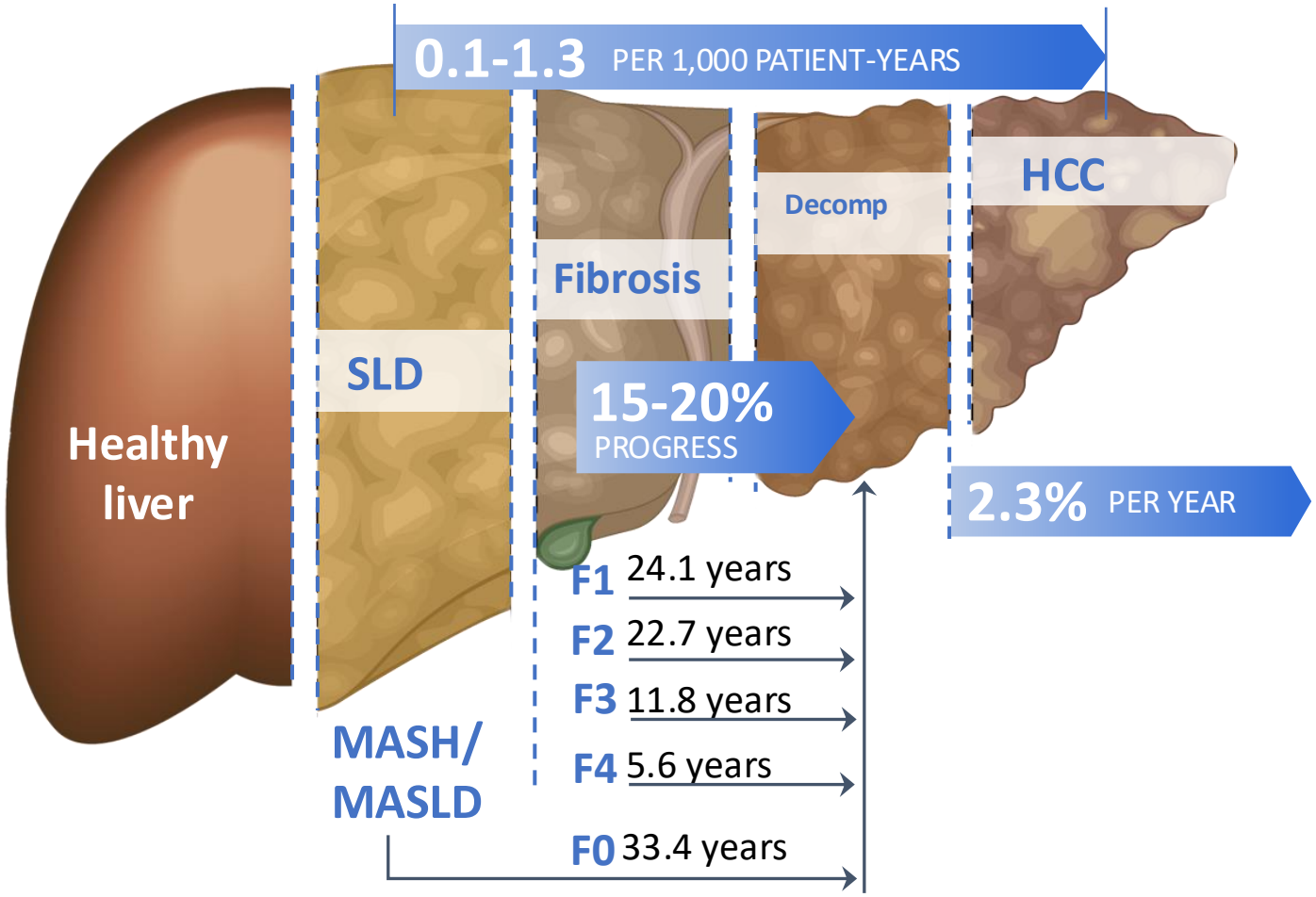
At least 1 out of 5:

- ❑ BMI ≥25 kg/m^2 [23 Asia] **WC>94 cm (M) / >80 cm (F) OR** ethnicity-adjusted equivalent
- ❑ Fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL) **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L (≥140 mg/dL) **OR** HbA1c ≥5.7% (39 mmol/L) **OR** type 2 diabetes **OR** treatment for T2DM
- ❑ Blood pressure ≥130/85 mmHg **OR** specific antihypertensive drug treatment
- ❑ Plasma triglycerides ≥1.70 mmol/L (150 mg/dL) **OR** lipid lowering treatment
- ❑ Plasma HDL-cholesterol ≤1.0 mmol/L (40 mg/dL) (M) and ≤1.3 mmol/L (50 mg/dL) (F) **OR** lipid lowering treatment

ALD, alcohol-related liver disease; BMI, body mass index; DILI, drug-induced liver injury; SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; WC, waist circumference.

Rinella ME et al. *Hepatology*. 2023;78:1966-1986.

Natural History of MASLD and MASH



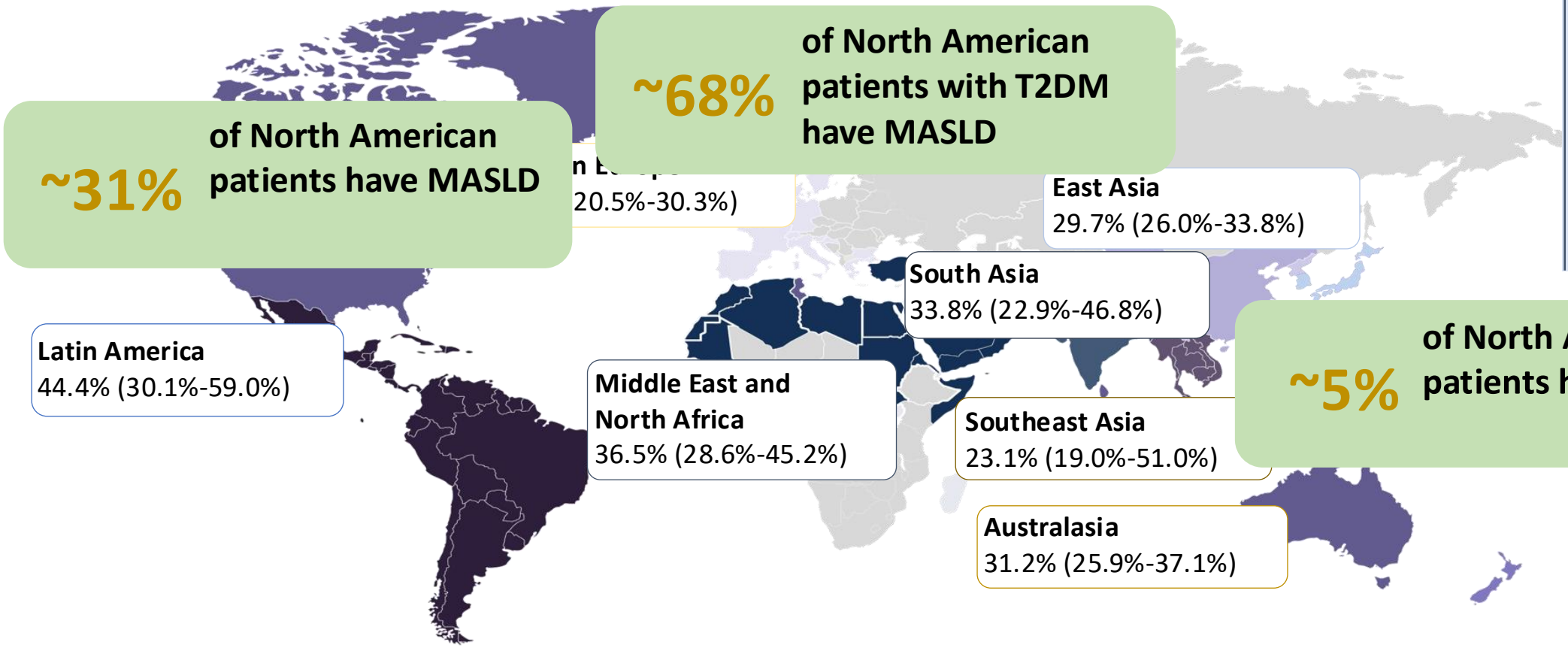
SLD, steatotic liver disease; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma.

1. Younossi Z et al. *EMJ Hepatol*. 2022; 2. Sayiner M et al. *Clin Liver Dis*. 2016;20(2):205-214; 3. Younossi ZM et al. *Hepatology*. 2016; 64(5):1577-1586; 4. Lequoy M et al. *Horm Mol Biol Clin Investig*. 2020;29;41(1); 5. Younossi Z et al. *Hepatology*. 2018; 6. Younossi Z J. *Hepatology*. 2019.

Defining the MASLD & MASH Problem

MASLD/MASH Is a Current and Growing Crisis in the US and Worldwide

Prevalence (95% CI) of MASLD by global regions data, 1990-2019



Younossi Z et al. *Hepatology*. 2023;77:1335-1347.

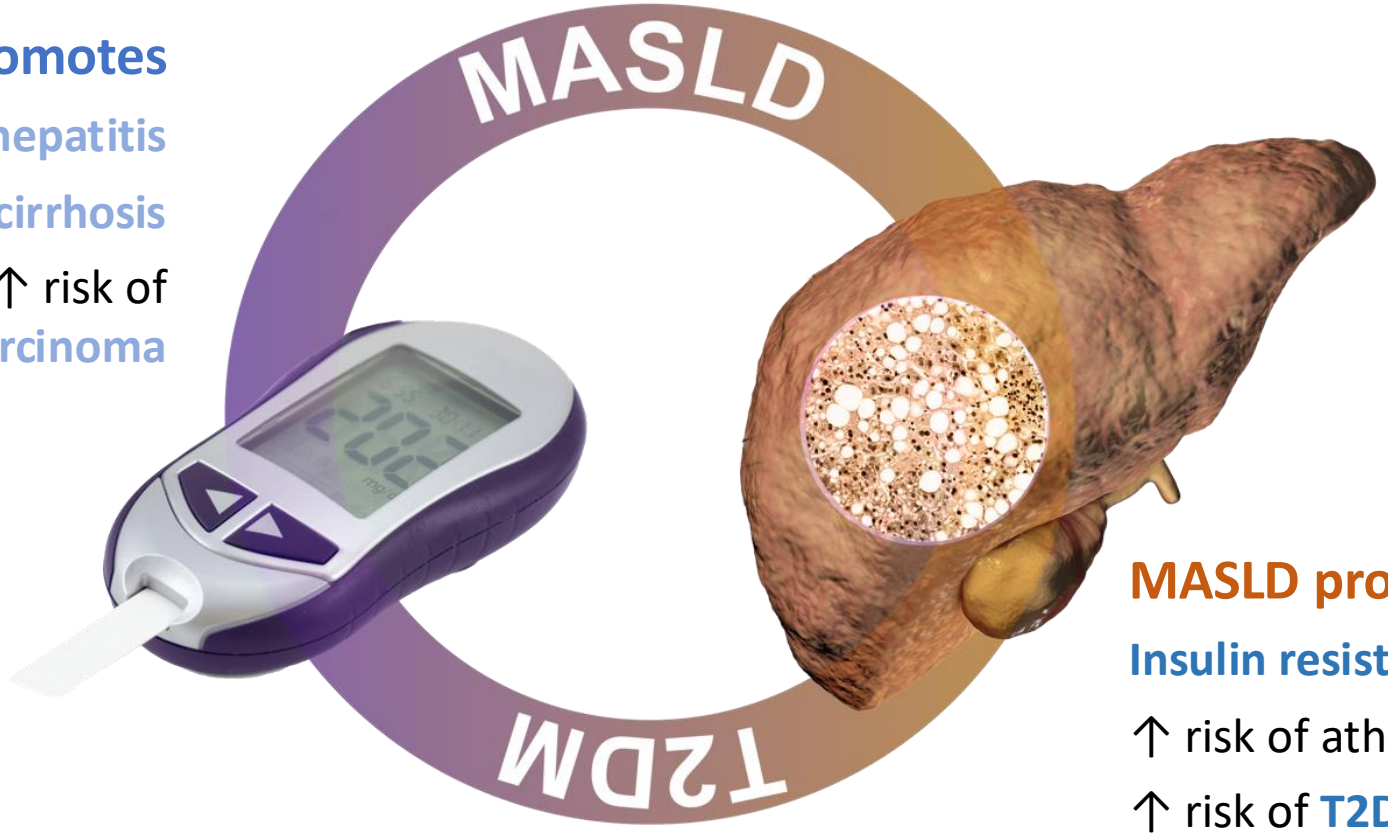
The Connectivity Between T2DM and MASLD

Diabetes promotes

↑ risk of **steatohepatitis**

↑ risk of **cirrhosis**

↑ risk of **hepatocellular carcinoma**



MASLD promotes

Insulin resistance

↑ risk of atherogenic **dyslipidemia**

↑ risk of **T2DM** and difficulty in management

↑ risk of **CVD**

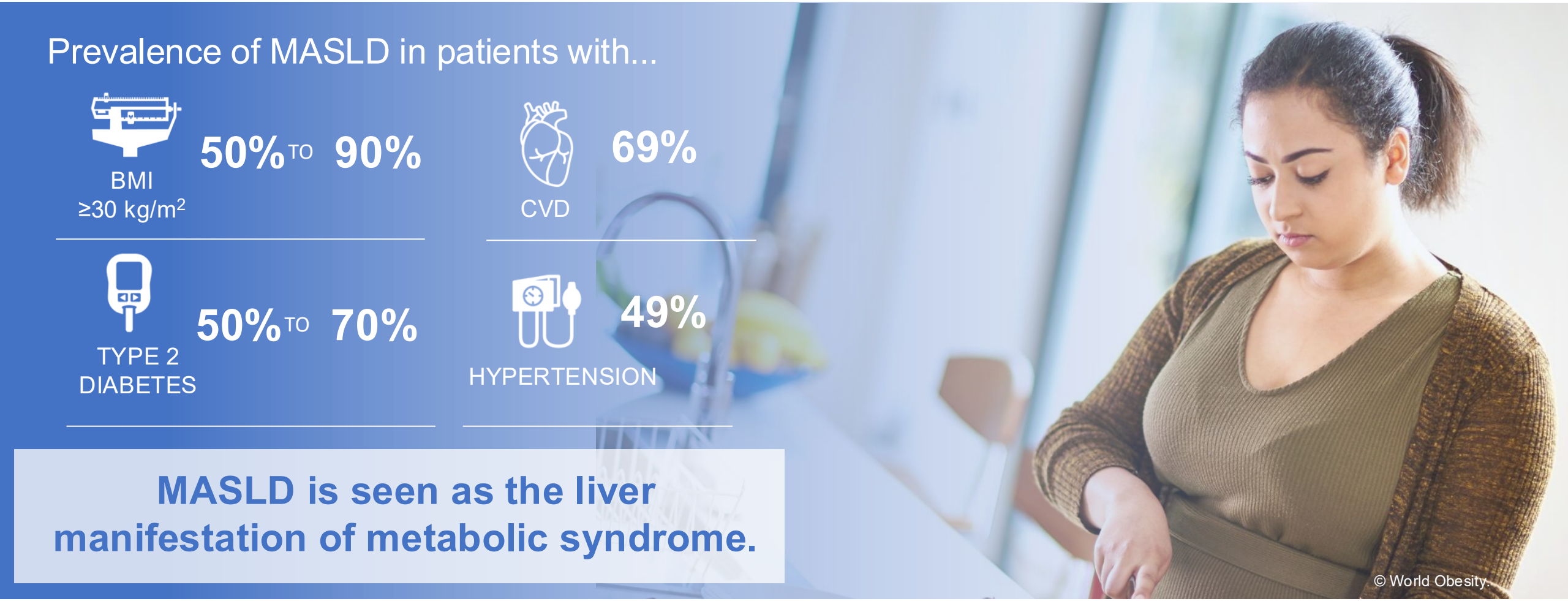
CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.
Budd J, Cusi K. *Am J Med*. 2020;133:536-543.

Individuals With Metabolic Diseases Are at High Risk of Developing or Having MASLD

Prevalence of MASLD in patients with...

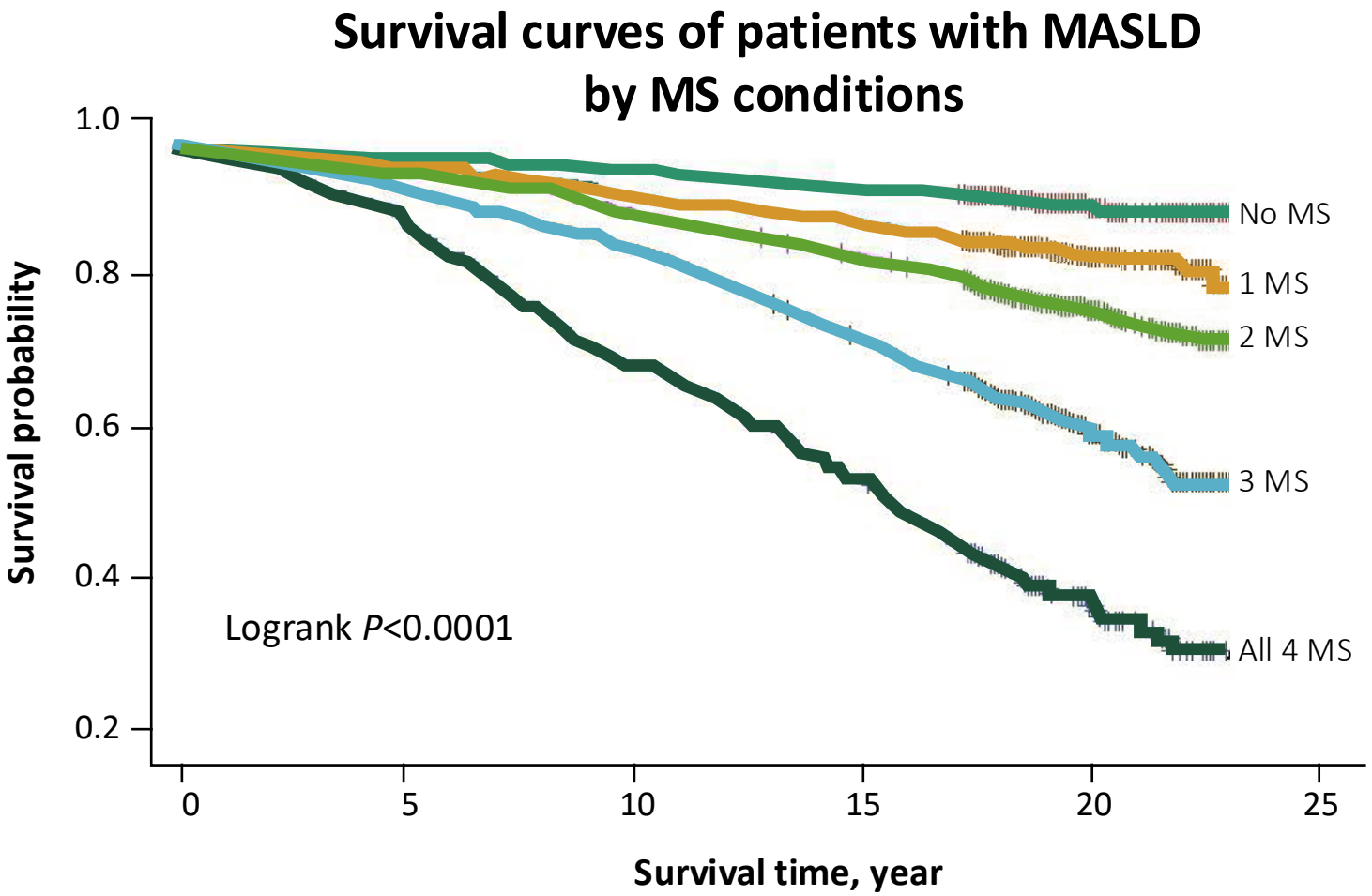
- BMI ≥30 kg/m^2: **50% TO 90%**
- CVD: **69%**
- TYPE 2 DIABETES: **50% TO 70%**
- HYPERTENSION: **49%**

MASLD is seen as the liver manifestation of metabolic syndrome.



1. Divella R et al. *Int J Biol Sci*. 2019;15(3):610-16; 2. Zhao YC et al. *Hypertension*. 2020;75:275-284; 3. Bedogni G et al. *Hepatol*. 2007;46(5):1387-1391; 4. Kasper P et al. *Clin Res Cardiol*. 2020. https://doi.org/10.1007/s00392-020-01709-7; 5. Estes C et al. *Hepatology*. 2018;67:123-33.

Clinical Predictors of Outcomes in MASLD: Impact of Cardiometabolic Risks

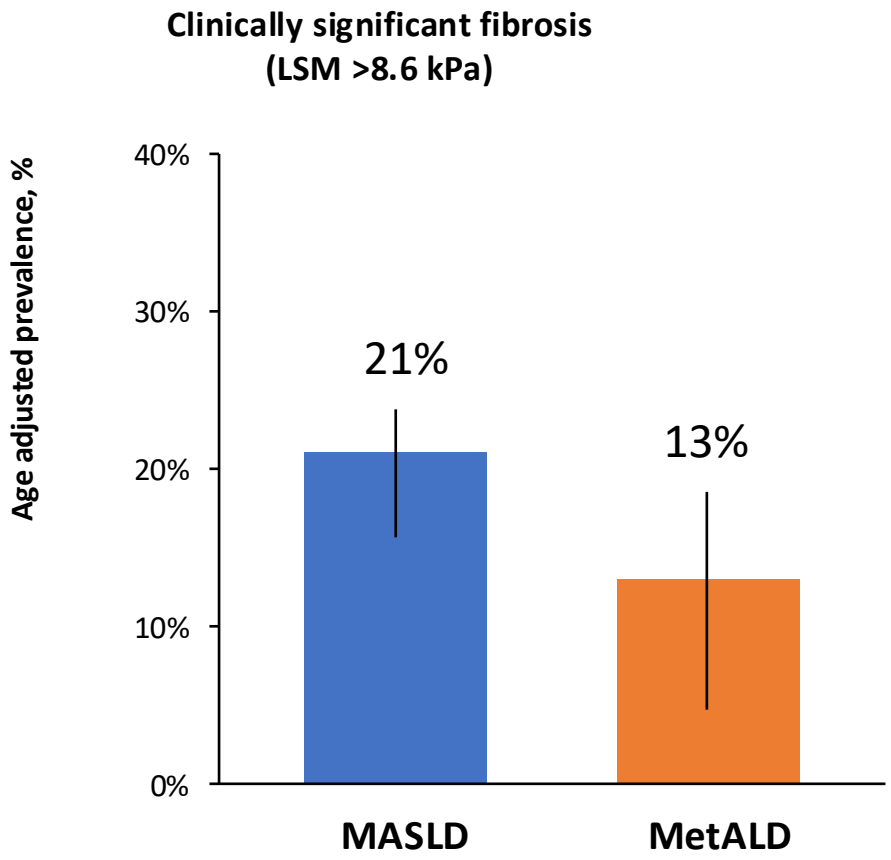


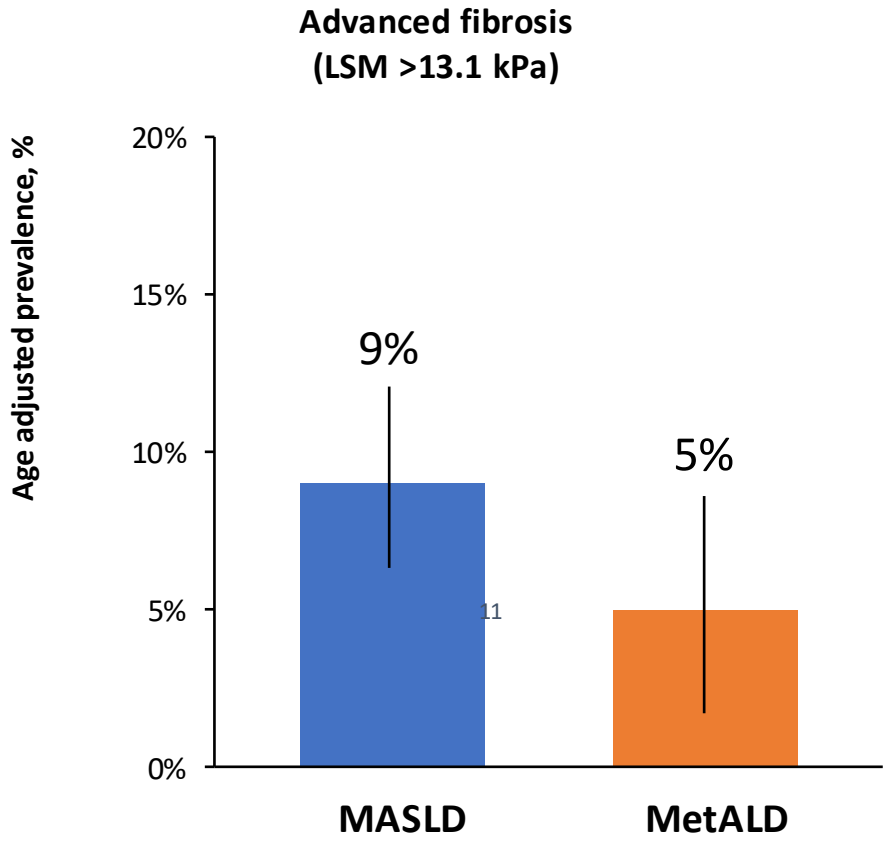
Increasing number of metabolic risks are associated with mortality

MS, metabolic syndrome.

Golabi P et al. *Medicine.* 2018;97(13):e0214.

Estimated Prevalence of Fibrosis in US Patients with MASLD vs MetALD (NHANES)

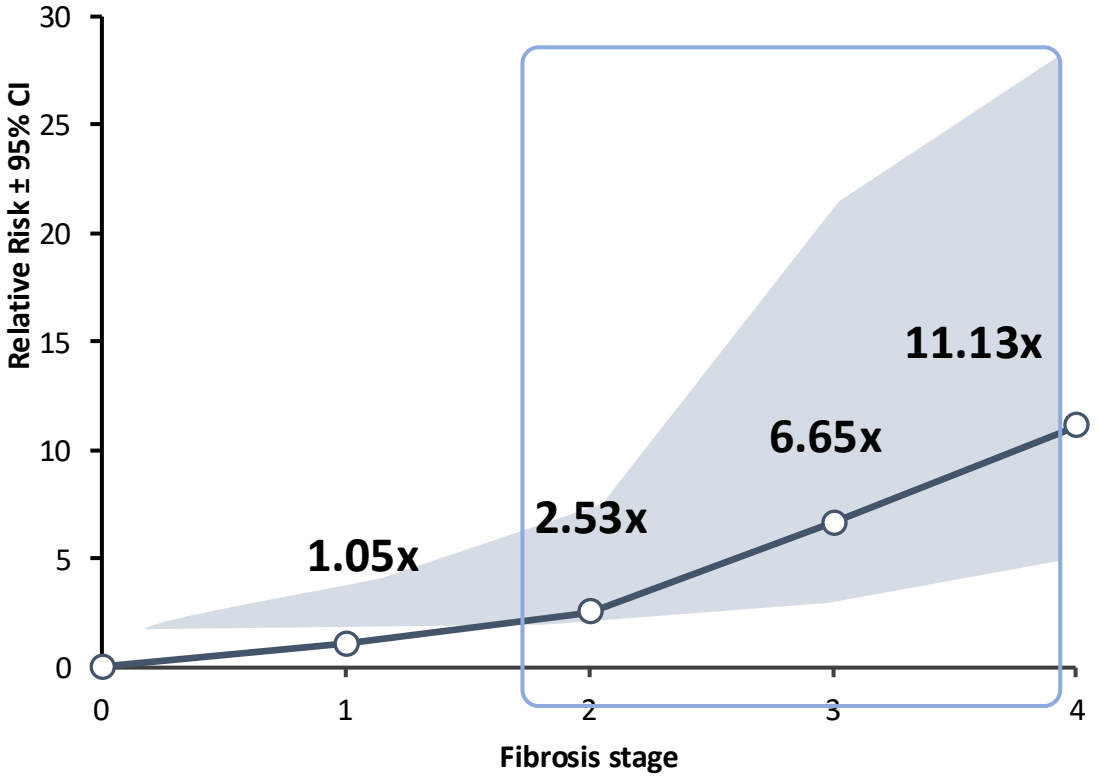




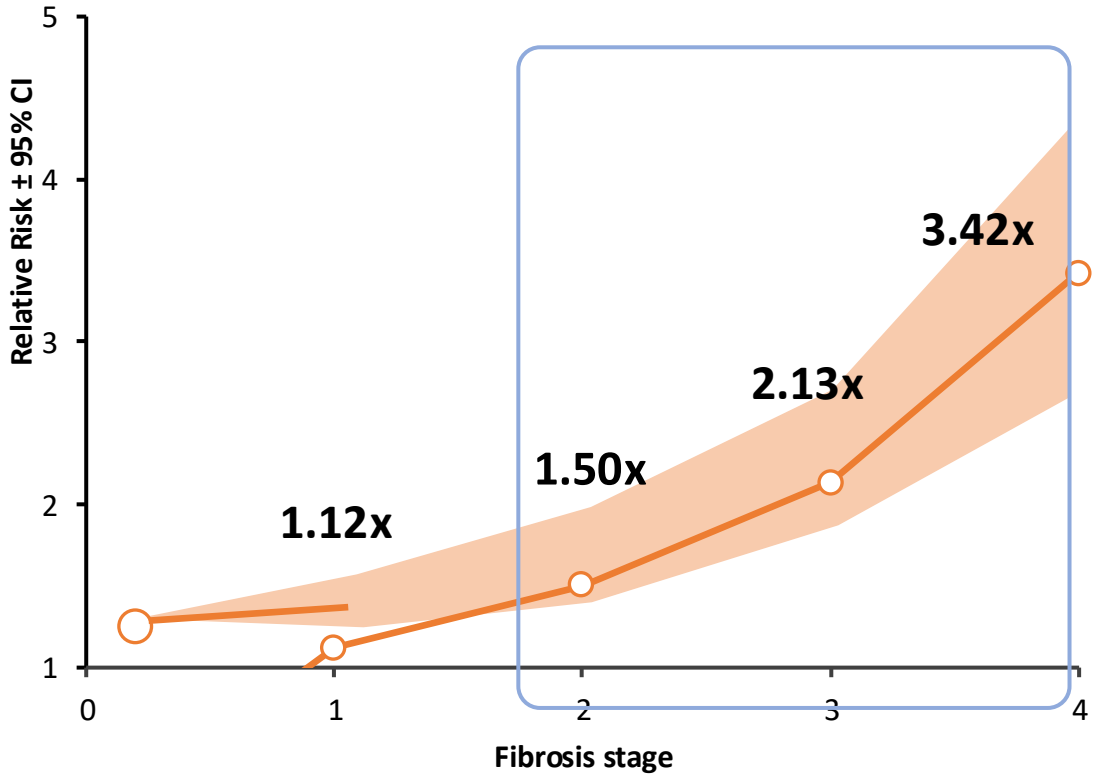
Modified from Kalligeros M et al. *Clin Gastroenterol Hepatol.* 2024;22(6):1330-1332.e4.

Fibrosis Stage Predicts Major Adverse Liver Outcomes and Mortality in Patients with MASLD

Liver-related mortality
(meta-analysis of 7 studies)



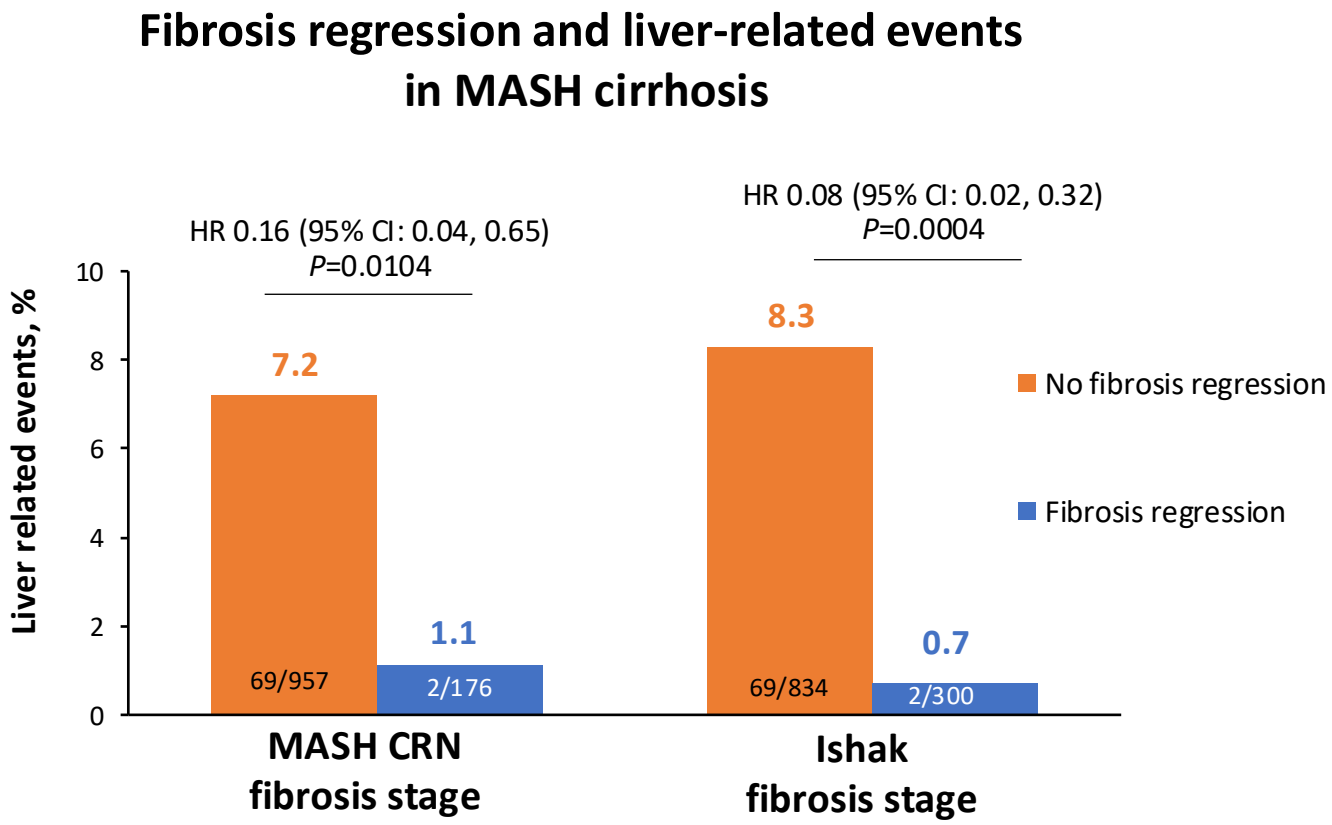
All-cause mortality
(meta-analysis of 8 studies)



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

Regression of Fibrosis Leads to Improved Clinical Outcomes

- MASH cirrhosis (STELLAR-4 and simtuzumab clinical trials)
  - Regression: Any reduction in fibrosis (MASH CRN or Ishak)
  - Liver-related events: ascites, portal hypertension, hemorrhage, HE, MELD >15, LT and death
- In MASH-cirrhosis, regression was observed in 16% over 48 weeks



Sanyal AJ et al. *Hepatology*. 2022;75(5):1235-1246.

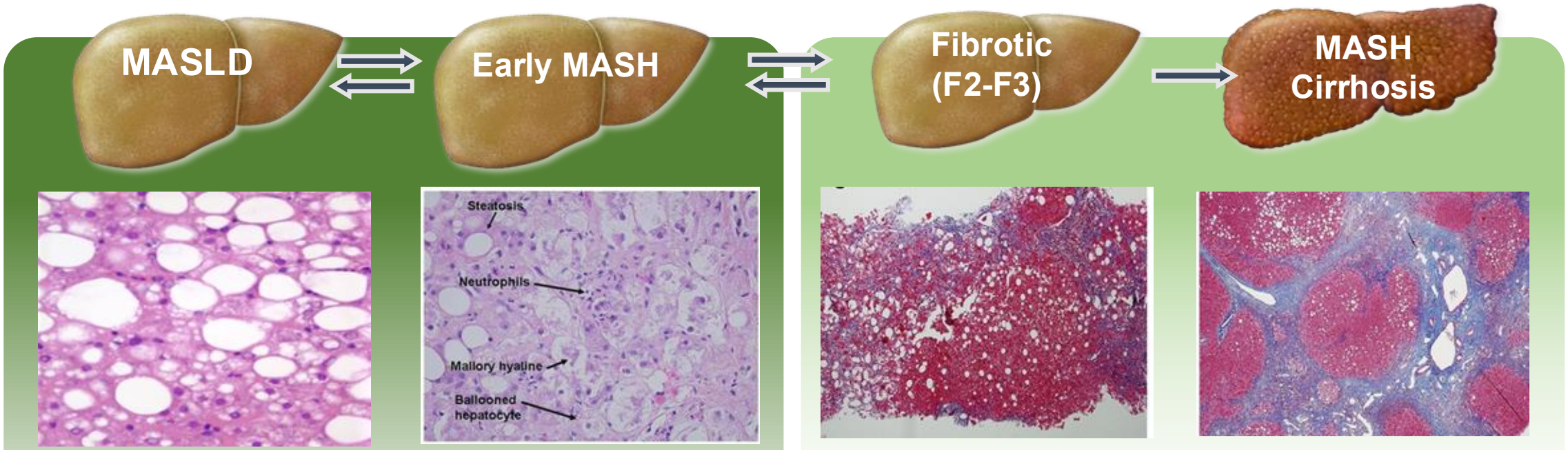
Who Should be Screened for Advanced Fibrosis?

- General population-based screening for MASLD is not advised.
- Screen for advanced fibrosis in high-risk group
  - Pre-DM or DM
  - Obesity
  - 2 cardiometabolic risk factors
  - Steatosis on imaging
  - Elevated ALT/AST

Staging and Monitoring Fibrosis

Disease Staging

Historically, MASH has been diagnosed by liver biopsy. **Currently, non-invasive tests (NITs) can distinguish between lower risk patients and patients with "at-risk MASH" with reasonable reliability.**



Patients with steatosis alone or early MASH can focus on weight management and optimizing metabolic syndrome with primary care.

Patients with "at-risk MASH" should be identified for liver-focused treatment.

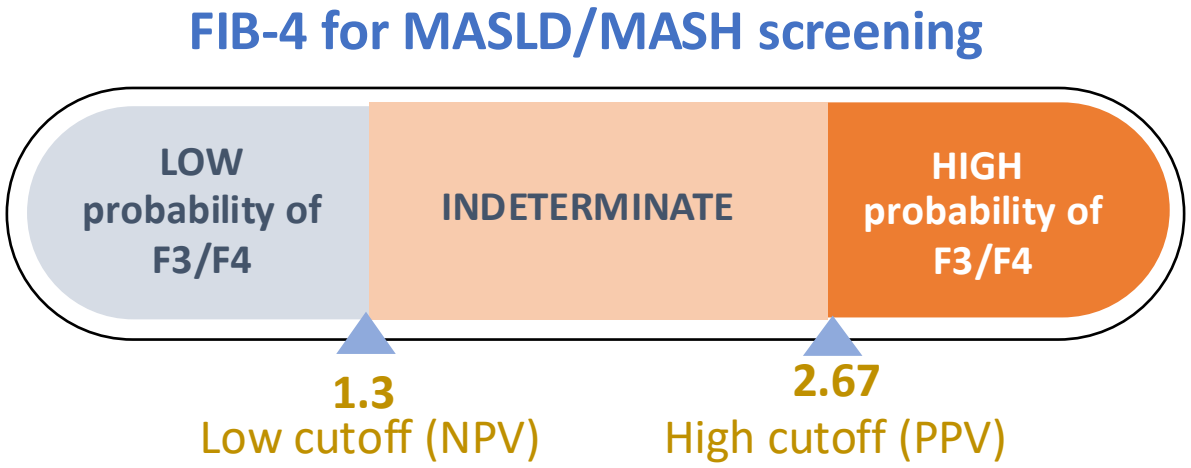
Noninvasive Tests

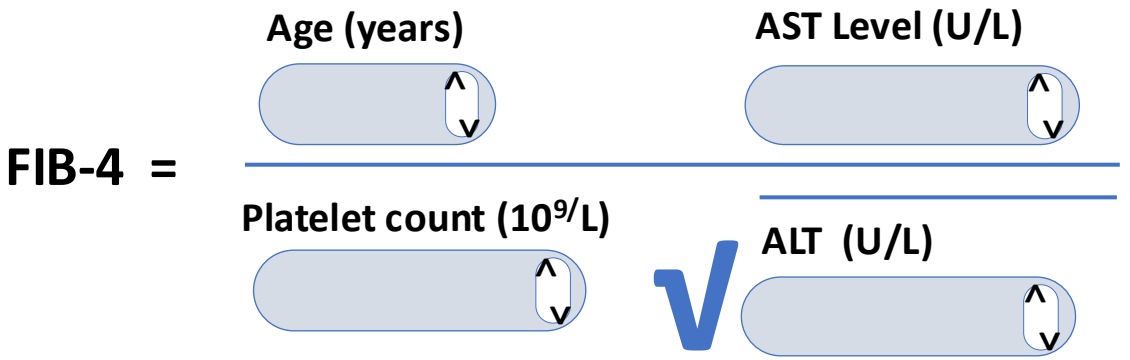
Simple Scores
FIB-4 Index ★
NAFLD Fibrosis Score
AST/ALT Ratio
APRI

Proprietary Predictive Scores
ELF ★
FibroSURE
LiverFASt

Imaging
VCTE ★
MR Elastography ★
LiverMultiScan

FIB-4: Staging

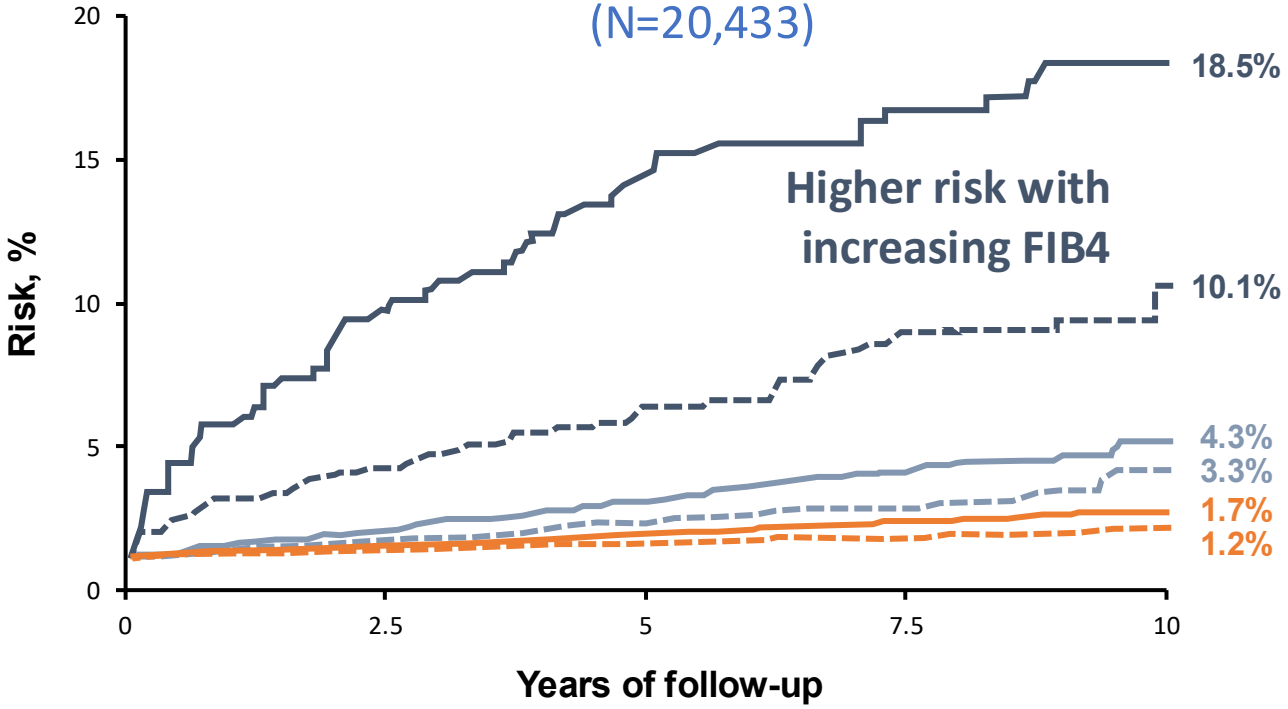




1. Sterling et al. *Hepatology*. 2006. 2. Eddowes et al. *Gastroenterology*. 2019. 3. Vali Y et al. *J Hepatology*. 2020;73(2):252-262.
4. Day J et al. *J Appl Lab Med*. 2019;3(5):815-826. 5. Newsome et al; *Lancet Gastro Hep*. 2020.

FIB-4: Predicting Outcomes

Cumulative incidence of liver events according to 12-month change in FIB-4 score[1]
(N=20,433)



Baseline FIB-4 risk category
- High (>2.67)
- Indeterminate (1.30–2.67)
- Low (<1.30)

12-month FIB-4 change
- Increase
- Decrease

Cumulative incidence of liver events

12.8% All with high baseline FIB-4

10.1% FIB-4 decrease

18.5% FIB-4 increase

Longitudinal cohort study of 20,433 patients to evaluate the association of 12-month changes in FIB-4 with risk of developing severe MASH-related clinical events. UK Clinical Practice Research Datalink linked with Hospital Episodes Statistics and Office for National Statistics data (2001–2020).

1. Anstee Q et al. *Lancet Reg Health Eur*. 2023;36:100780. **2.** Vilar-Gomez E et al. *Hepatology*. 2023;77(4):1241-1252. **3.** Younossi ZM et al. *Gastroenterology*. 2021;160:1608-19. **4.** Han MAT. *Liver Int*. 202040(9):2242-51.

Transient Elastography (eg, FibroScan®): Staging

- CAP measures rate of decay of the ultrasound wave as it travels through tissue
  - Correlates to fat content in the liver
- Propagation speed of the shear wave is measured with pulse echo ultrasound and this correlates with stiffness and fibrosis
  - Reported in kPa

Measures liver stiffness over an area estimated to be 100x greater than that of liver biopsy

Failure to obtain readings is more likely in patients with a high BMI (>30 kg/m^2); however, use of XL probe may help overcome this limitation

Overestimation of fibrosis can occur in cases of hepatitis, cholestasis, liver congestion, and if mass lesions are present in the liver

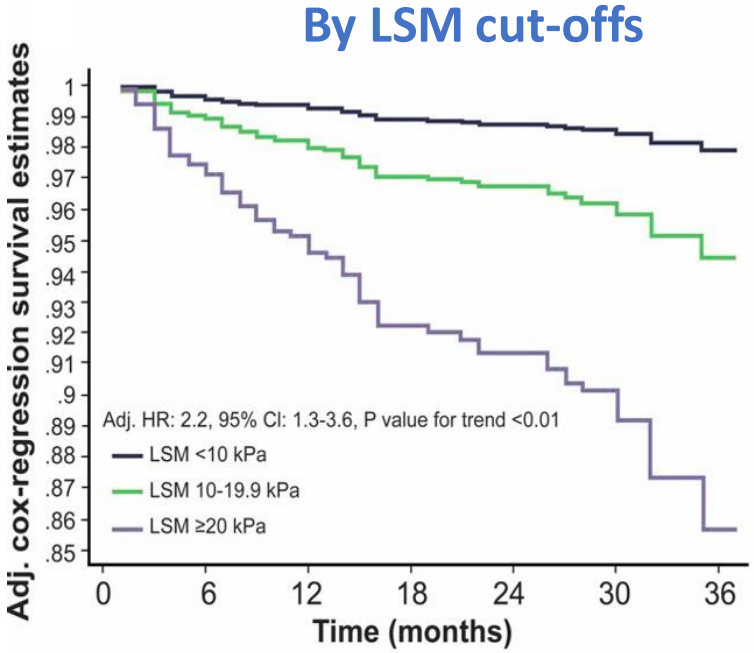
CAP, controlled attenuation parameter.

Transient Elastography: Predicting Outcomes

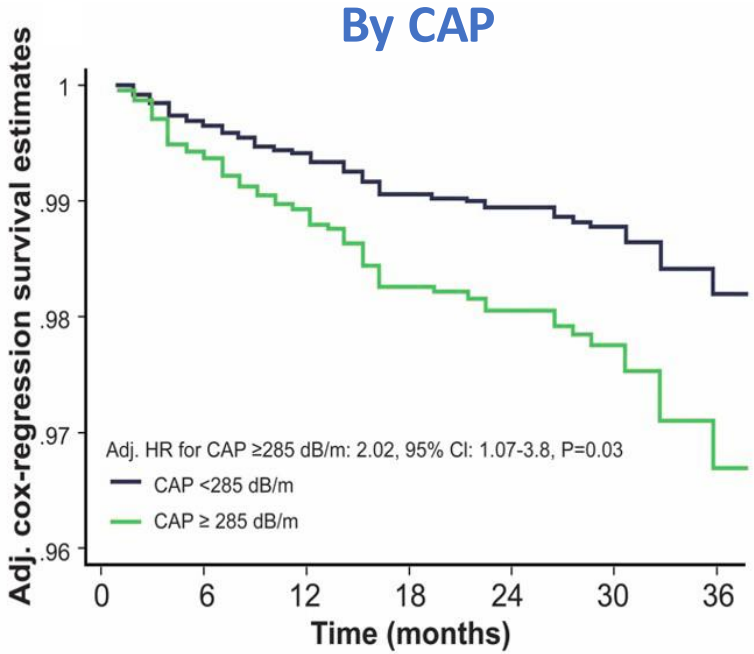
Adjusted cox-regression survival estimates

(N=4192 adults, NHANES 2017-2018)

By LSM cut-offs



By CAP



Associations with mortality

MASLD (CAP ≥285) **2.2x**

Advanced fibrosis (9.7-13.5 kPa) and **Cirrhosis** (LSM≥13.6 kPa) **SIGNIFICANTLY HIGHER CUMULATIVE MORTALITY**

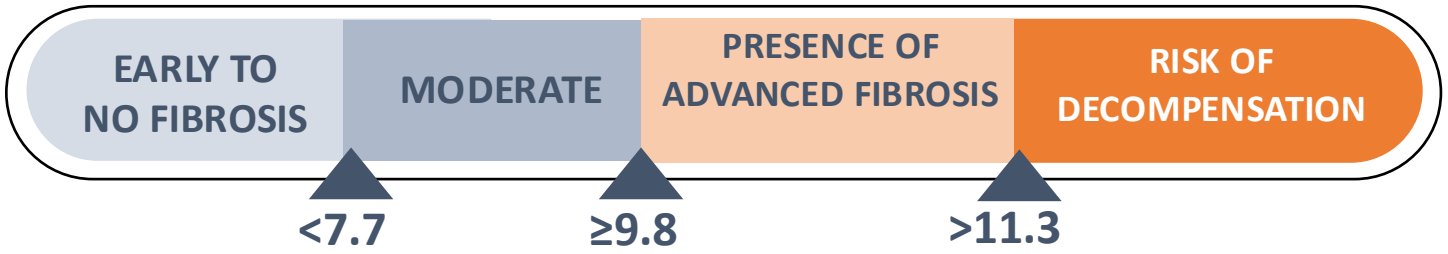
CAP and **LSM** **OVERALL MORTALITY**

CAP, controlled attenuation parameter; LSM, liver stiffness measurement.

Vilar-Gomez E et al. *Hepatology*. 2023;77(4):1241-1252.

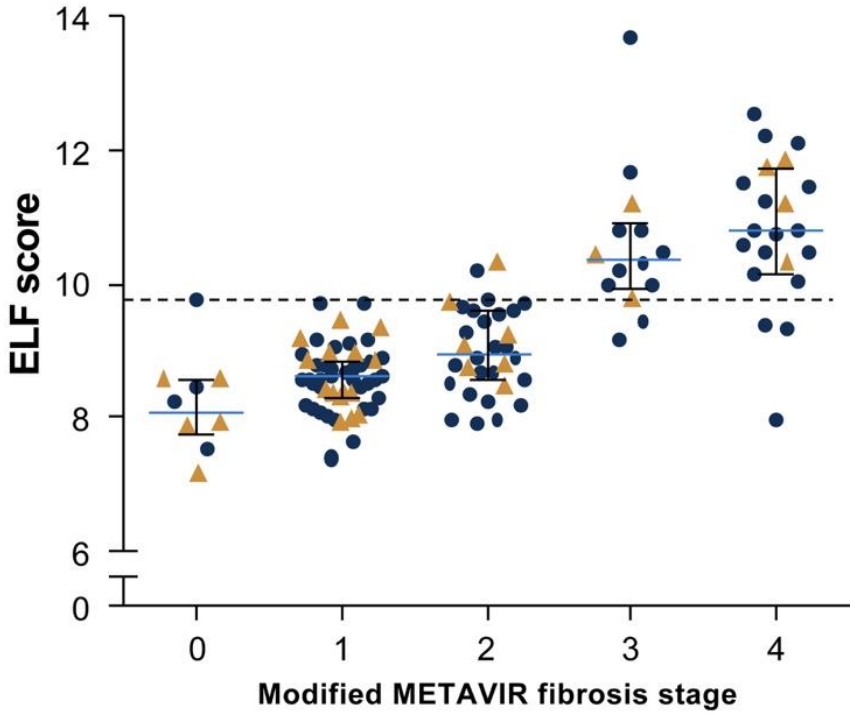
Enhanced Liver Fibrosis (ELF) Score: Staging

ELF cut-off scores and accuracy for measuring advanced fibrosis



ELF is a blood test that measures 3 biomarkers involved in collagen homeostasis (fibrosis): HA, PIIINP, and TIMP-1.

ELF score according to modified METAVIR fibrosis stage for patients with overweight/ obesity and steatosis on liver biopsy[2]



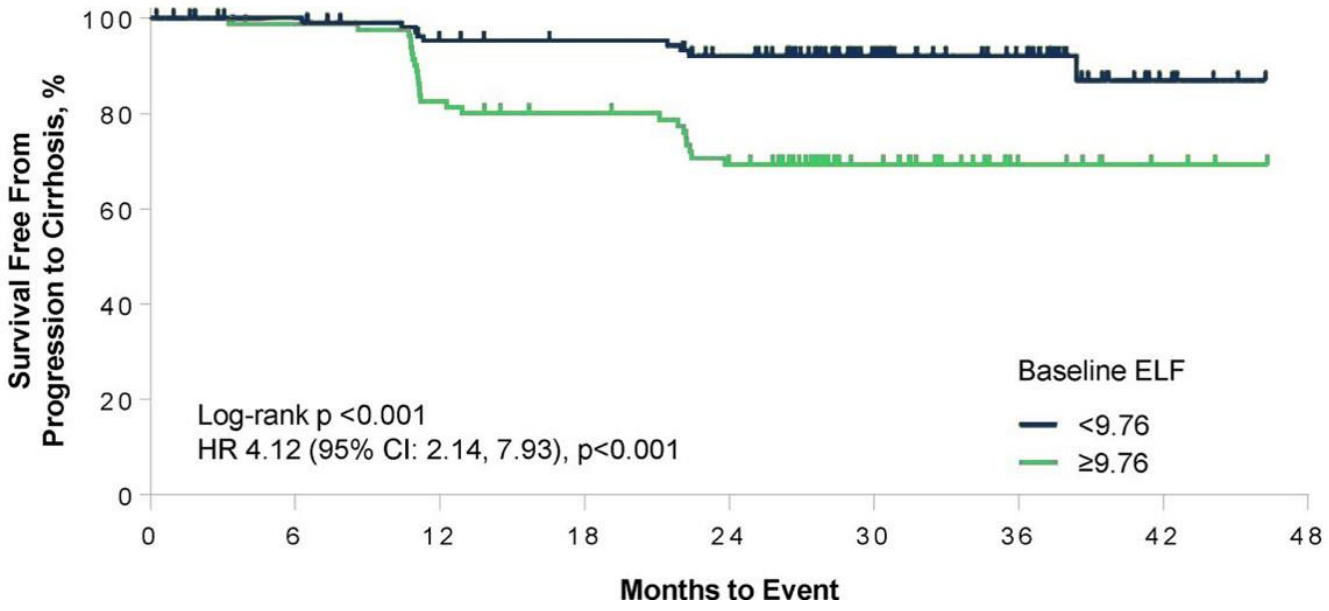
HA, hyaluronic acid; PIIINP, procollagen III amino terminal peptide; TIMP-1, tissue inhibitor of metalloproteinase.

1. Lichtinghagen R et al. *J Hepatol*. 2013;59:236–42. **2.** Fagan KJ et al. *Liver Int*. 2015;35:1673–81. **3.** Vali Y et al. *J Hepatology*. 2020;73(2):252-262. **4.** Day J et al. *J Appl Lab Med*. 2019;3(5):815-826.

ELF: Predicting Outcomes

Progression to cirrhosis in patients with bridging fibrosis by baseline ELF score

(N=217 paired histology and longitudinal serum samples)



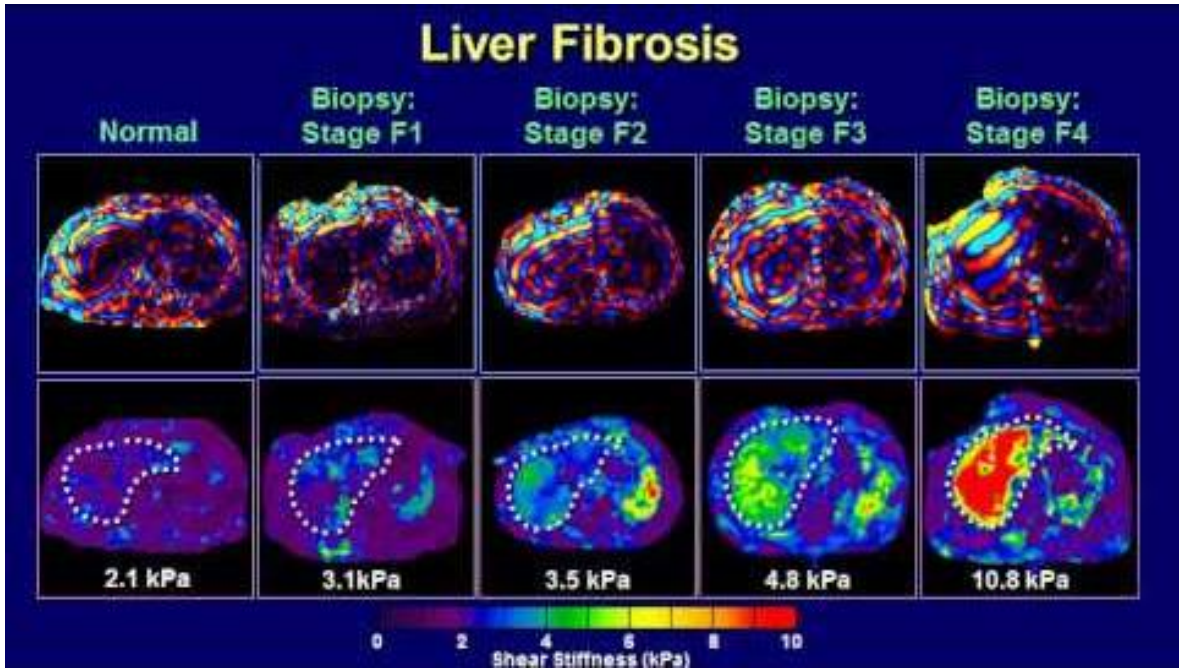
Higher baseline ELF score and increased ELF score compared with baseline were associated with progression to cirrhosis in patients with bridging fibrosis at baseline.

Parameter	HR (95% CI)	*P*-value
ELF baseline score	2.58 (1.96-3.38)	<0.001
Change from baseline in ELF score	1.64 (1.24-2.17)	<0.001

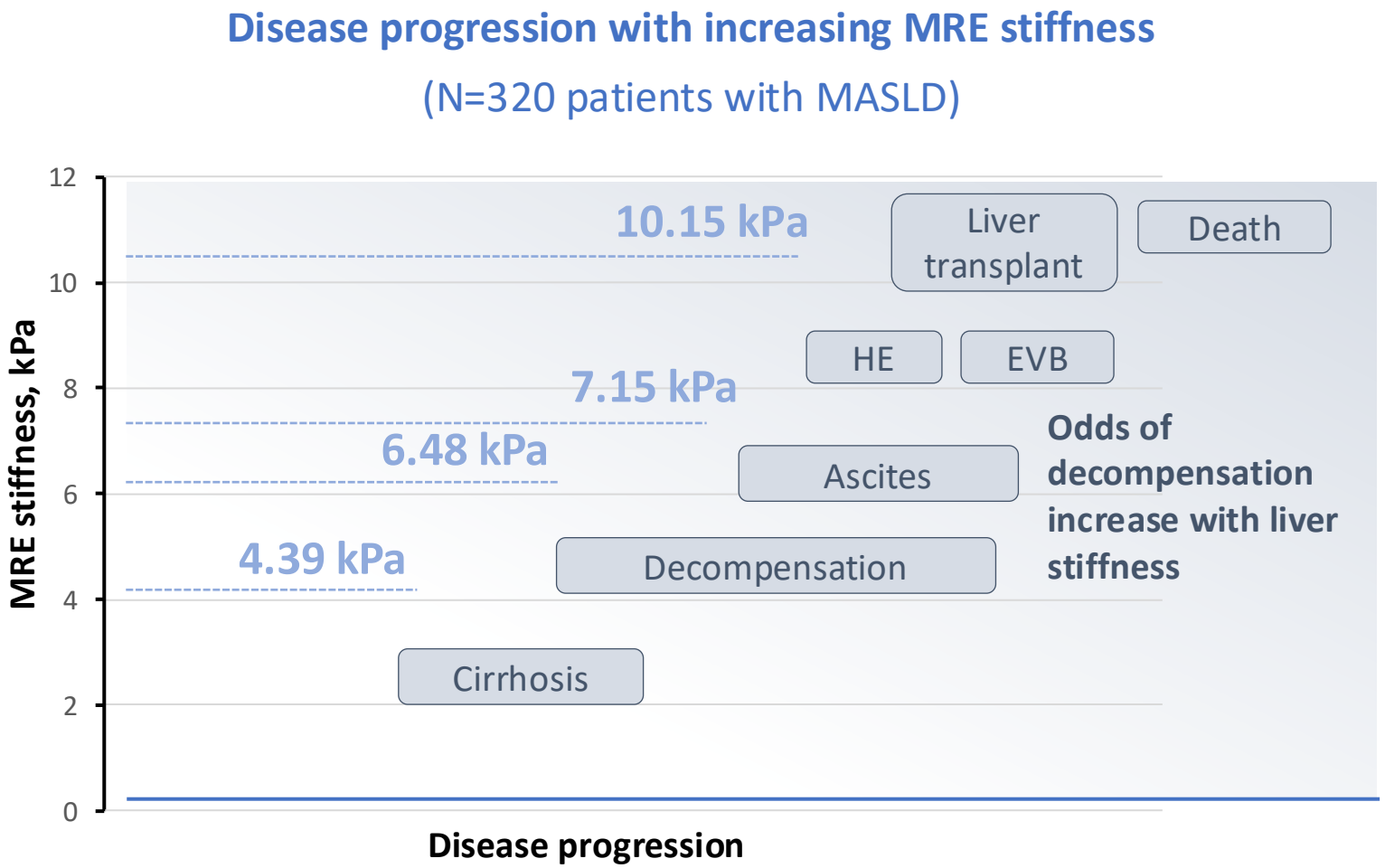
Analyses based on natural history data from two Phase 2b simtuzumab clinical trials in patients with bridging fibrosis.
Sanyal AJ et al. *Hepatology.* 2019;70:1913-1927.

MR Elastography

- Utilizes an external driver to produce hepatic shear waves
- Detected using MRI
- **Not impacted by hepatic steatosis, BMI**
- **Difficult to get insurance approval ($$$)**
- **Claustrophobia**



MRE: Predicting Outcomes



Thresholds for distinguishing cirrhosis from

4.39 kPa Noncirrhosis

6.48 kPa Decompensated cirrhosis

3.28 INCREASED RISK OF DECOMPENSATION with increasing liver stiffness (*P*<0.001)

Han MAT. *Liver Int.* 2020;40(9):2242-2251.

Overview of Noninvasive Parameters for Advanced Fibrosis

Detection of advanced fibrosis

	Test	Cut point: Likely	Cut point: Unlikely	Comments
Serum	FIB-4	≥2.67	<1.3	• No added cost • Not accurate in age < 35 years and lower rule-out threshold among high-risk individuals with high pre-test probability
Serum	ELF	≥9.8	<7.7	• Blood test sent to a reference lab • Cost
Imaging	VCTE	≥12 kPa	< 8 kPa	• Point of care
Imaging	MRE	≥3.63 kPa	<2.55 kPa	• MRE LSM ≥3.63 kPa (associated with advanced fibrosis, AUROC 0.93)

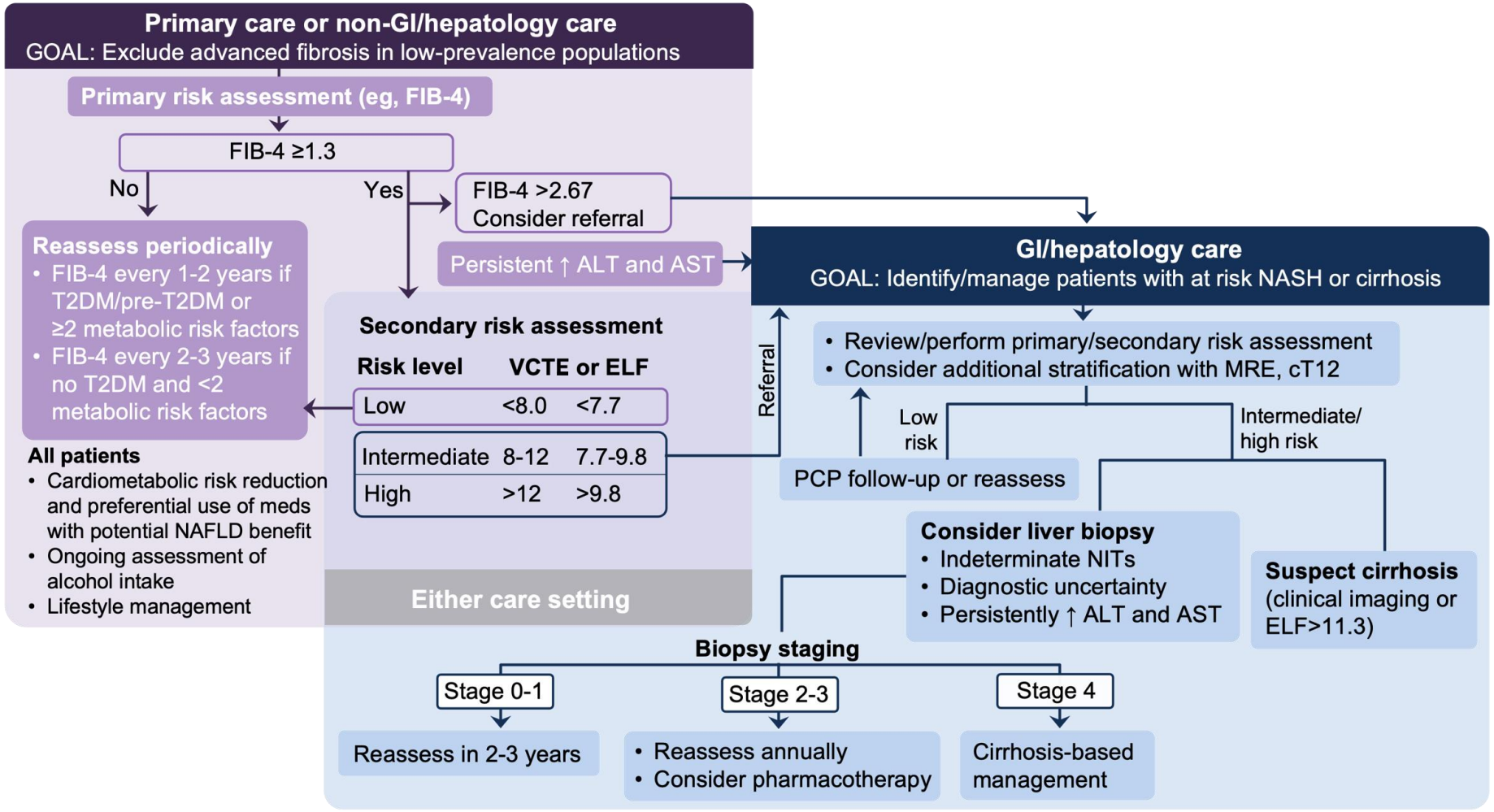
Diagnosis of cirrhosis (rule in or rule out)

	Test	Rule-in	Rule-out	Comments
Serum	FIB-4	≥3.48	<1.67	90% specificity cut-point for ruling-in and 90% sensitivity for ruling-out cirrhosis, respectively
Serum	ELF	≥11.3	<7.7	ELF ≥11.3 associated with increased risk of hepatic decompensation among patients with cirrhosis
Imaging	VCTE	≥20 kPa	<8 kPa	LSM by VCTE ≥20 kPa is associated with cirrhosis but for ruling out cirrhosis optimal cut-point is <8 kPa
Imaging	MRE	≥5 kPa	<3 kPa	LSM by MRE ≥5 kPa has very good (near 95%) specificity for diagnosis of cirrhosis and is associated with increased risk of incident hepatic decompensation

Rinella ME et al. *Hepatology.* 2023;77:1797-1835.

Who Should be Screened and Treated?

AASLD Recommends Non-invasive Tests (NITs) for Staging



AASLD recommends FIB-4 followed by ELF or VCTE

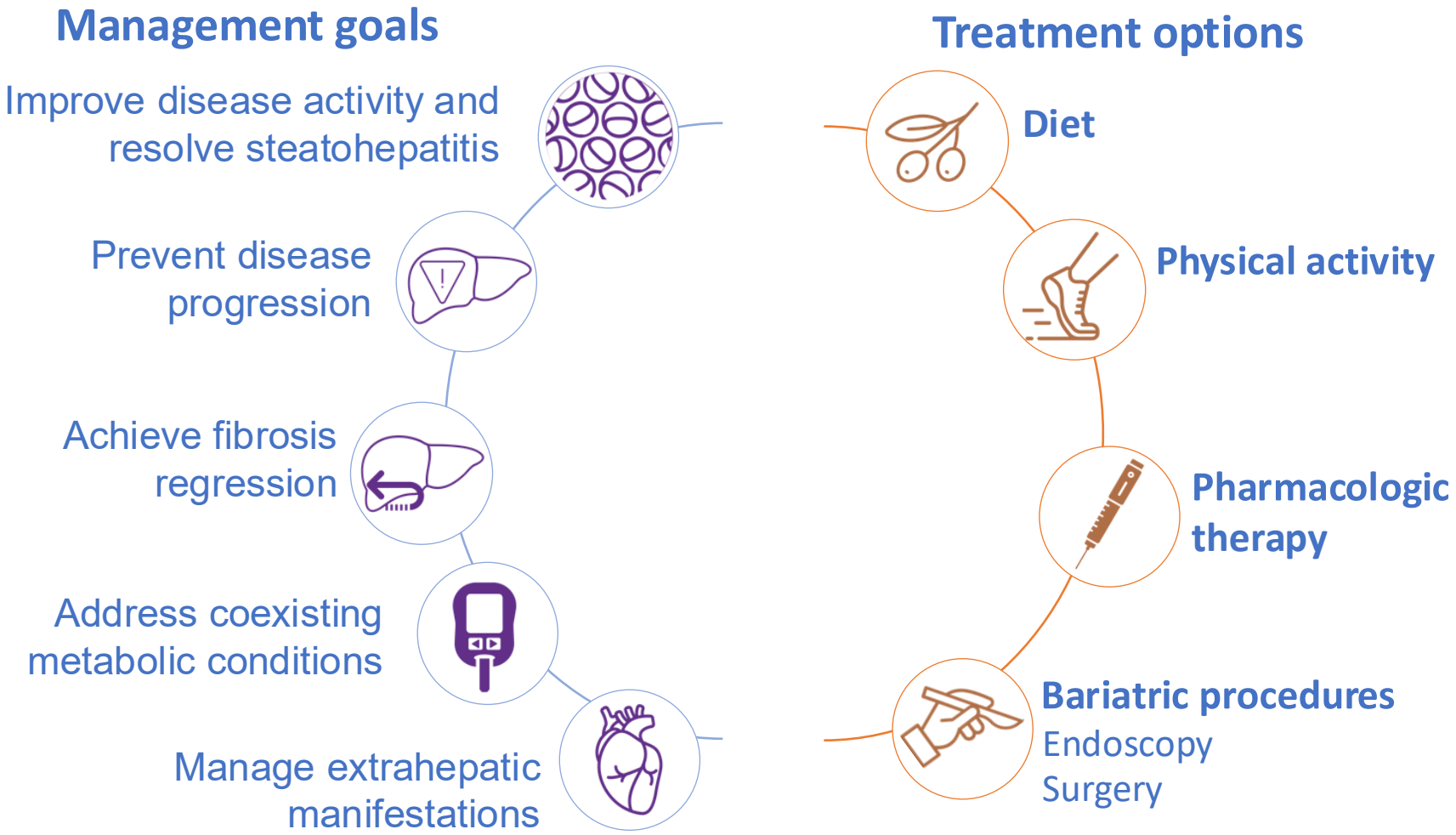
Note: Liver biopsy should be considered if there is diagnostic uncertainty.

Rinella ME et al. *Hepatology.* 2023;77:1797-1835.

Why Risk Stratification Matters

- MASLD affects 25-30% of the population
- Hepatology capacity cannot manage all patients
- Fibrosis stage is the dominant predictor of outcomes and mortality
- Need to triage and move along clinical pathway

Multidisciplinary Care



Achieving a functional multidisciplinary approach to management is essential

Summary

- The prevalence of MASLD is growing with ~1/3 of US adults having MASLD.
  - Prevalence of MASH is ~5%
- MASH is becoming the leading cause of cirrhosis and liver cancer.
  - MASH is among the leading indications for liver transplant in the US
- Significant fibrosis and multiple components of metabolic syndrome are risk factors for adverse outcomes and mortality.
- Multiple NITs are available to stage fibrosis in lieu of liver biopsy.
- Referring patients with fibrosis to liver specialists is important.