MASLD and Sarcopenia

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ZMY has received research funding and/or serve as consultant to Intercept, Cymabay, Boehringer Ingelheim, Ipsen, BMS, GSK, NovoNordisk, Siemens, Madridgal, Merck, Akero and Abbott.

Agenda

- Epidemiology
- Risk Stratification
- Treatment
- Extrahepatic manifestations
  - Sarcopenia
  - Epidemiology
  - Assessment
  - Treatment

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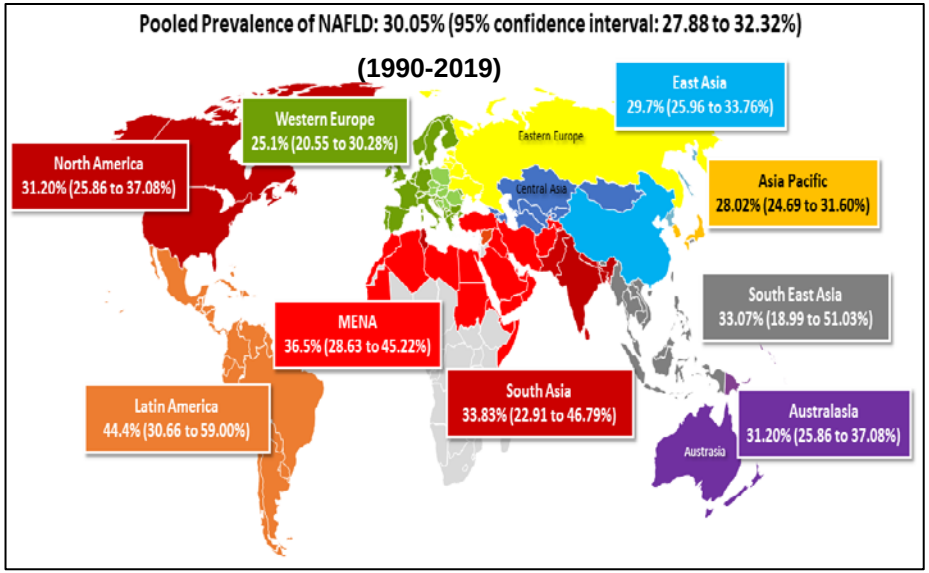
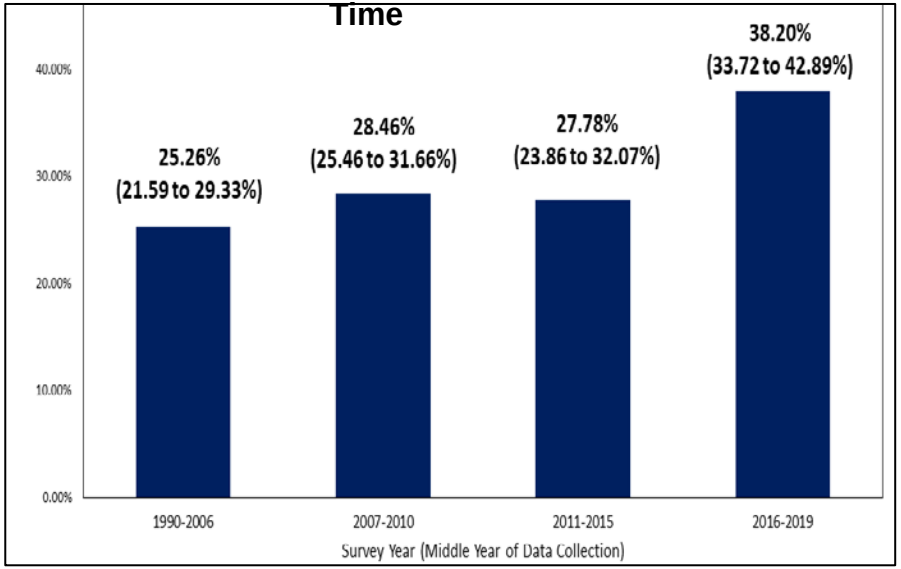
Global Prevalence of NAFLD/MASLD

The Global Prevalence of MASLD



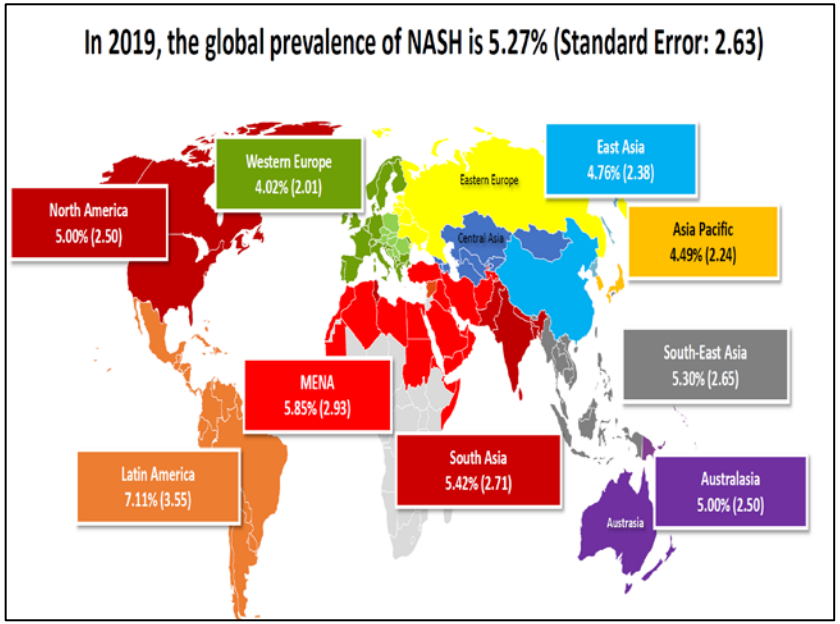
The Global Prevalence of MASLD over Time



Younossi ZM et al, Hepatology. 2023 Apr 1;77(4):1335-1347.

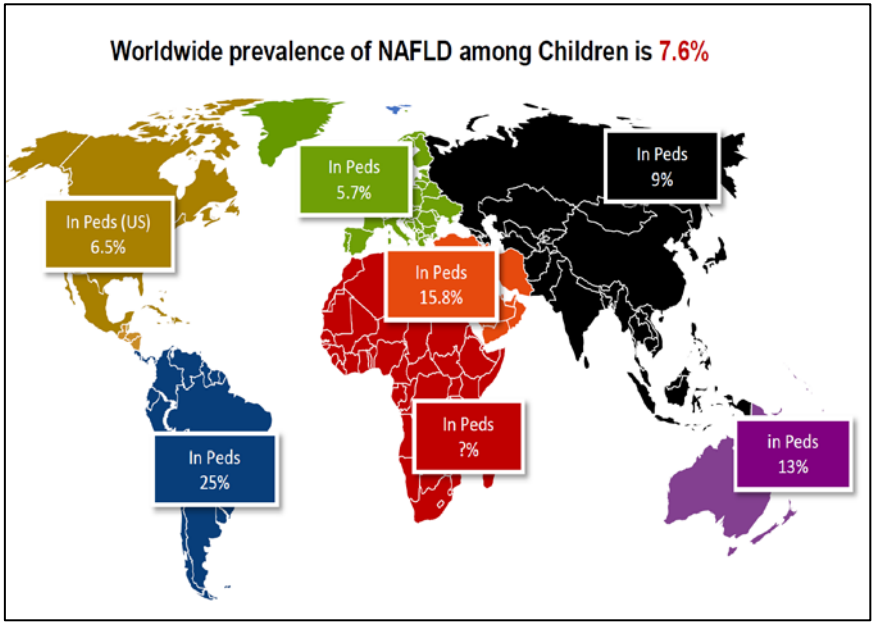
Global Prevalence of NAFLD/MASLD

The Global Prevalence of MASH



Younossi ZM et al, Hepatology. 2023 Apr 1;77(4):1335-1347.

The Global Prevalence of MASLD: Pediatrics



Schwimmer JB, et al. *Pediatrics*. 2006, Vos M et al. J Pediatr Gastroenterol Nutr. 2017

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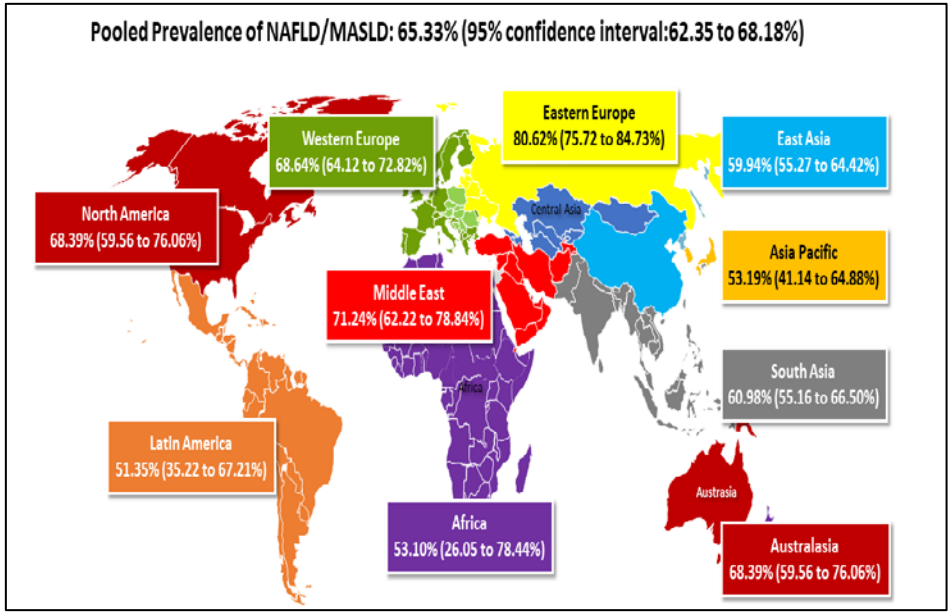
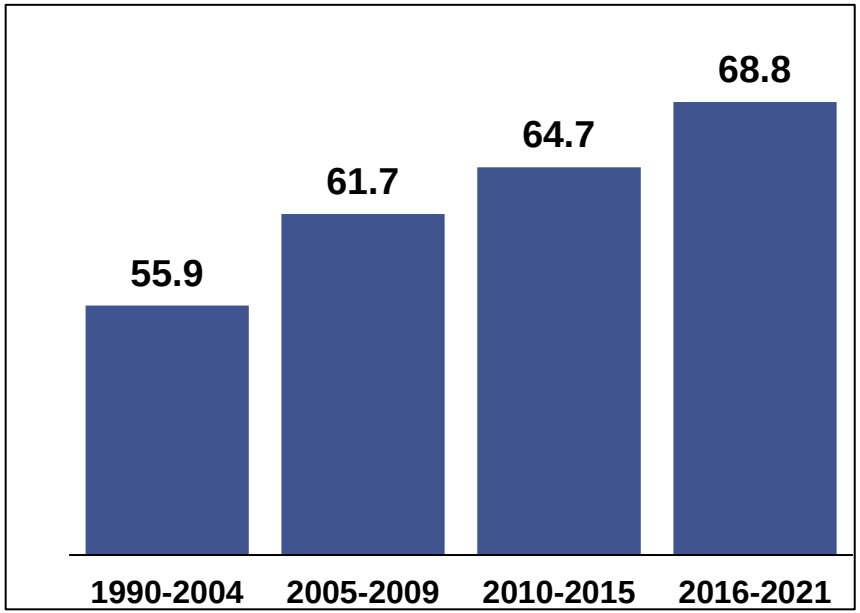
Global Prevalence of NAFLD/MASLD

The Global Prevalence of MASLD: T2D



Global Prevalence of MASLD over Time: T2D



Younossi ZM, et al. Clin Gastroenterol Hepatol. 2024 Mar 21:S1542-3565(24)00287-8

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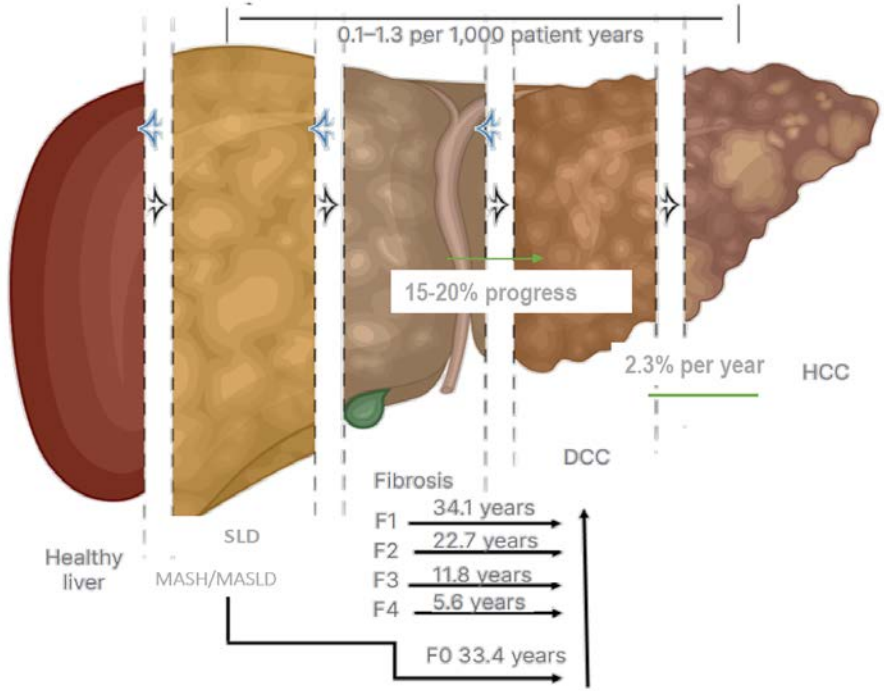
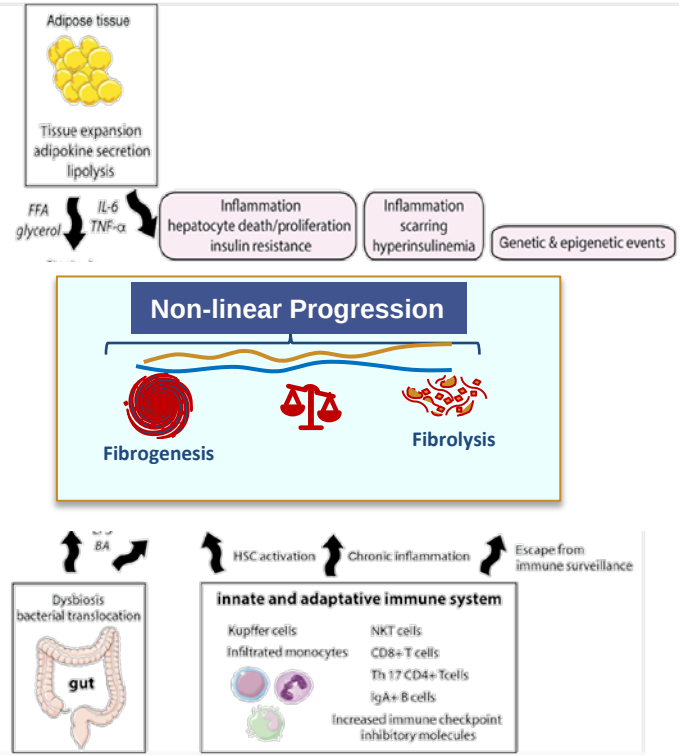
Natural History of MASLD and MASH





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

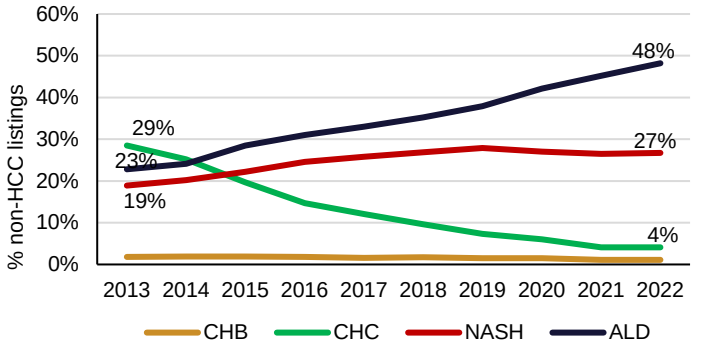
Consequences of NASH/MASH:
Cirrhosis, Liver Transplantation and Mortality

Cirrhosis

- Prevalence of MASH cirrhosis in the general population is 0.31 % (meta-analysis) and 1.84% (NHANES)
- Prevalence of MASH cirrhosis among MASLD (Meta-analysis): 5.05 % (95% CI 2.78-9.02)
- MASLD-cirrhosis mortality rate per 100 PY Overall: 7.46 (95% CI 3.67-14.56)

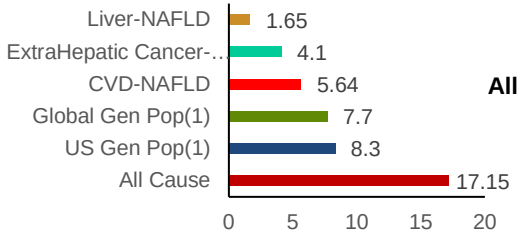
Owrangi S, Z Younossi DDW 2024

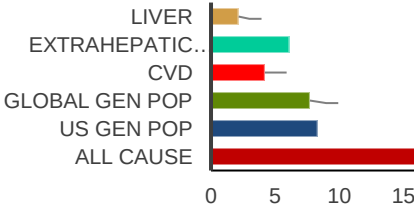
Liver Transplantation in the USA (Non-HCC)

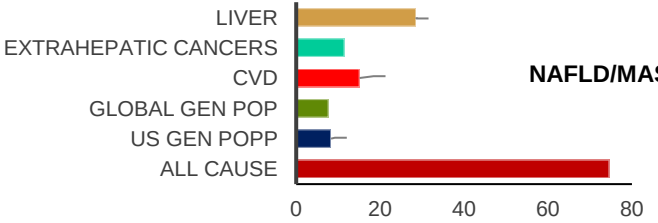


Younossi ZM, Hepatol Commun. 2023 Dec 22;8(1):e0352

Mortality (Per 1,000 person-yrs)







Younossi ZM et al, Hepatology. 2023 Apr 1;77(4):1335-1347, Younossi ZM. *Et al Clinical Gastro and Hepatology 2024,* Owrangi S, Z Younossi DDW 2024

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Global Consequences of MASLD:
Death from Liver Cancer and Cirrhosis (APC 2010-2019)

	Liver Cancer Death				Cirrhosis Death			
	NAFLD	ALD	HCV	HBV	NAFLD	ALD	HCV	HBV
Global	0.81	0.28	-0.61	-0.04	-0.12	-0.87	-0.86	-3.02
Region								
Australasia	1.21	0.17	1.28	0.27	-0.05	-0.49	-0.26	-0.12
High-income North America	1.54	2.59	0.96	1.25	1.51	-0.64	0.53	-1.97
High-income Asia Pacific	-1.71	-1.22	-2.53	-1.54	-1.26	-1.63	-3.04	-1.12
Southern Latin America	1.37	1.43	1.24	0.09	0.56	0.38	0.31	-4.00
Western Europe	0.25	-0.12	-0.13	-0.08	-1.24	-1.39	-1.64	-2.95
Central Europe	-0.65	-0.81	-1.20	-1.69	-1.31	-1.40	-1.62	-2.71
Eastern Europe	1.27	-0.03	0.55	-0.31	-0.24	-1.00	-0.66	-5.32
Central Asia	0.32	-0.05	-0.68	-1.01	0.15	-0.22	-0.35	-4.21
Southeast Asia	0.70	0.33	-0.15	-0.74	-0.36	-0.44	-0.83	-2.37
East Asia	1.66	1.83	0.10	0.22	-0.61	-1.80	-1.65	-6.62
Oceania	0.06	0.00	-0.27	-0.55	-0.20	-0.38	-0.47	-0.91
South Asia	-0.09	0.18	-0.19	-1.34	0.30	-0.20	-1.77	-2.72
Andean Latin America	0.87	0.46	-0.22	-0.30	-0.81	-0.98	-0.98	-4.10
Caribbean	1.84	1.79	1.09	1.27	1.39	1.38	1.16	0.16
Central Latin America	1.51	1.40	0.59	0.64	-0.29	-0.03	0.10	-0.34
Tropical Latin America	1.49	0.19	0.20	0.13	-0.03	-1.68	-1.87	-2.96
North Africa and Middle East	0.92	-0.35	-1.24	-0.08	-0.14	-0.57	-0.59	-2.51
Central Sub-Saharan Africa	0.38	0.35	-0.58	-1.25	0.25	-0.25	-0.14	-4.32
Eastern Sub-Saharan Africa	0.46	-0.22	0.15	-0.77	-0.32	-0.73	-0.51	-3.80
Southern Sub-Saharan Africa	-1.27	-1.74	-1.90	-2.02	-2.34	-2.37	-2.66	-4.19
Western Sub-Saharan Africa	0.04	-0.28	-0.62	-1.16	-0.94	-1.40	-1.38	-2.95

Improving Trend (APC≤ 0%)
Worsening Trend (APC> 0%)

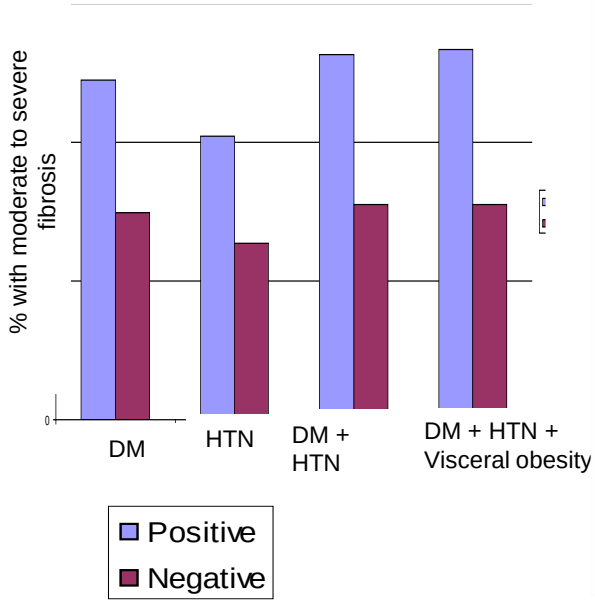
Paike J and Younossi Z Hepatology Communication 202

Clinical Predictors of Outcomes in MASLD:
Impact of Cardiometabolic Risks

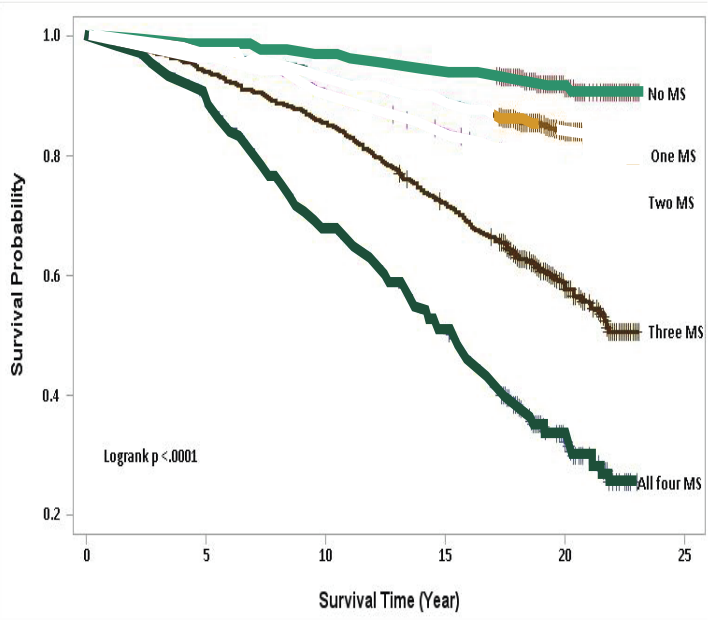
Long-Term Outcomes of Patients With T2D and NAFLD

- NAFLD & DM (n = 44) vs NAFLD alone (n = 88)
- Patients with NAFLD and DM have:
  - Higher rate of cirrhosis (25% vs 10.2, *P* = 0.04)
  - Higher liver-related mortality (RR = 22.83, *P* = 0.003)
  - Higher mortality (RR = 3.3, *P* = 0.00

Increasing Number of Metabolic Risks Are Associated With Advanced Fibrosis



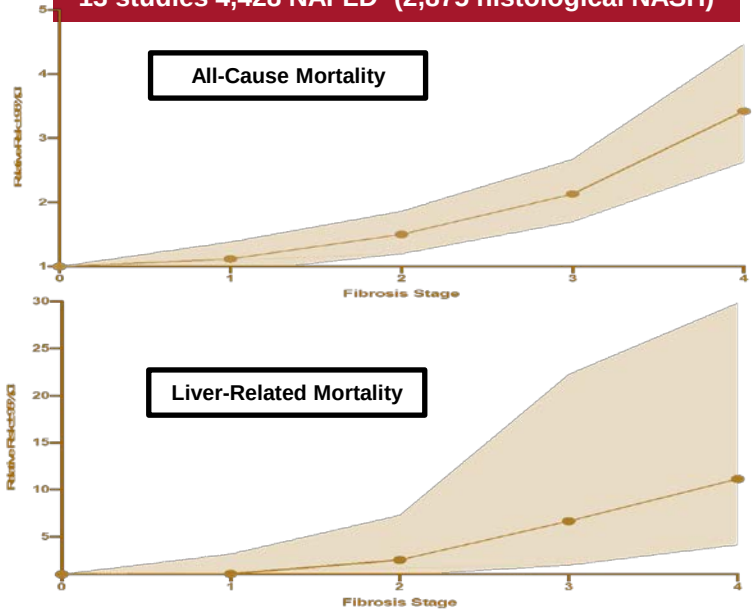
Increasing Number of Metabolic Risks Are Associated With Mortality



Younossi Z, et al. *Clin Gastroenterol Hepatol.* 2004;2(3):262–265., Hossain N, et al. *Clin Gastroenterol Hepatol.* 2009;7(11):1224-1229.e1-2., Golabi P, et al. *Medicine* 2018;97(13):e0214.

Histologic Predictors of MASLD Outcomes

13 studies 4,428 NAFLD (2,875 histological NASH)

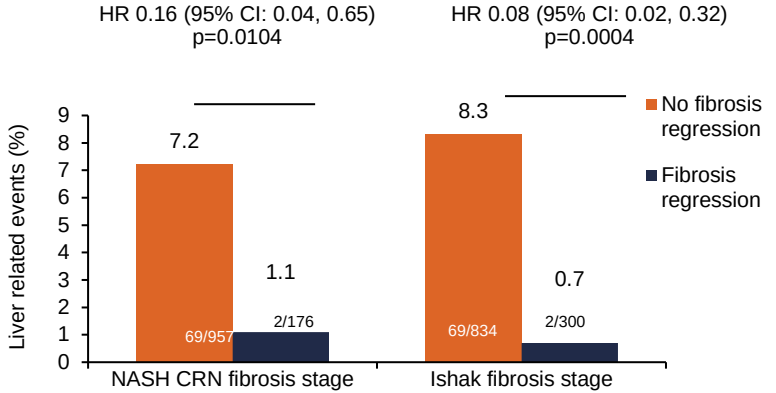


Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, Ishigami M, Toyoda H, Wai-Sun Wong V, Peleg N, Shlomai A, Sebastiani G, Seko Y, Bhala N, Younossi ZM, Anstee QM, McPherson S, Newsome PN. Gastroenterology. 2020May;158(6):1611-1625

Regression of Fibrosis Leads to Improvement of Clinical Outcomes

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

Fibrosis regression and liver-related events in NASH cirrhosis



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

Since liver biopsy to stage liver disease in clinical practice is no longer desirable, a number of non-invasive tests (NITs) such as FIB-4, TE, ELF and MRE are being used to risk stratify MASLD patients

Predictors of MASLD Outcomes

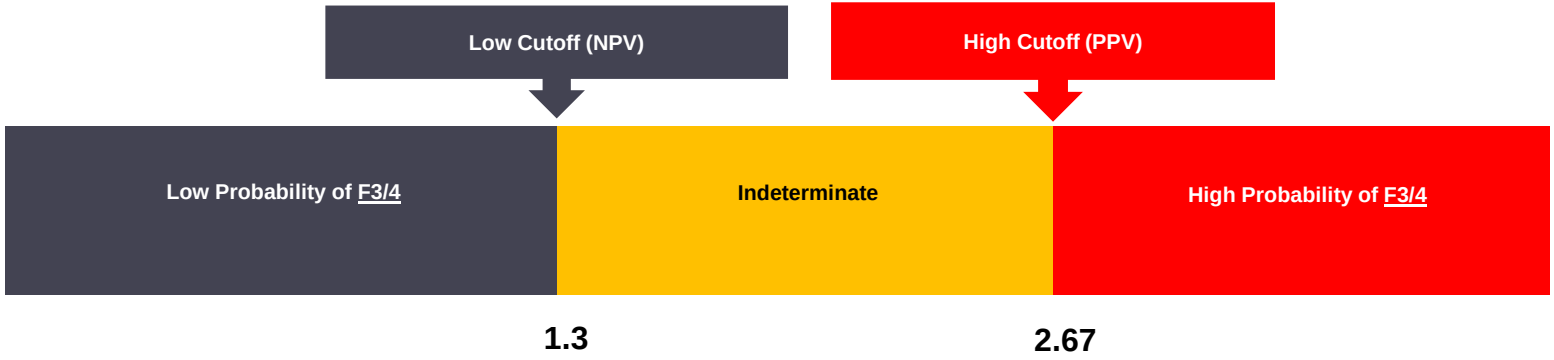
Risk Stratification

NITs Used to Identify High Risk MASH Patients

FIB-4 Index:

- Originally to predict advanced fibrosis in HIV/HCV coinfection
- FIB-4<1.3 No significant fibrosis
- FIB-4<1.45 F0–F2
- FIB-4>3.25 F3–F4

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}} =$$



Sterling et al. *Hepatology*. 2006, Eddowes et al. *Gastroenterology*. 2019. Vali et al. *J Hep*. 2020; Day J et al. *JALM*. 2019, Newsome et al; *Lancet Gastro Hep*. 2020

NITs Used to Identify High Risk MASH Patients

Liver stiffness

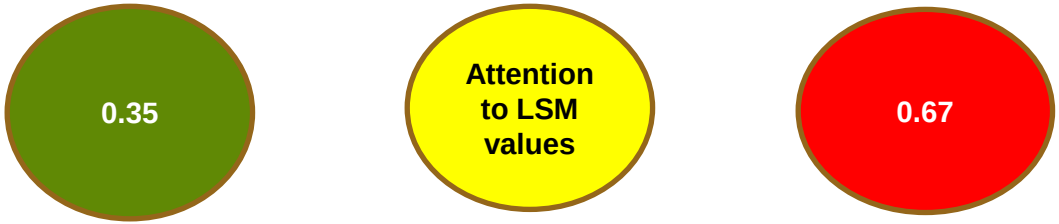
- Obtained through a VCTE measurement
- Correlated to extent of fibrosis

CAP

- Quantification of ultrasound attenuation obtained in VCTE measurement
- Correlated to liver steatosis

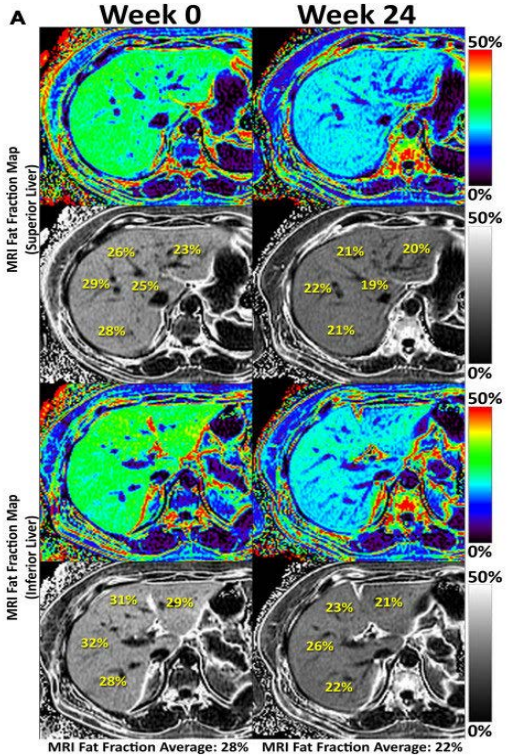
Stage	Threshold (kPa)	AUROC	Sensitivity	Specificity	PPV	NPV
F0-F1 vs ≥ F2	8.2	0.77	0.71	0.70	0.78	0.61
F0-F2 vs ≥ F3	9.7	0.80	0.71	0.75	0.63	0.81
F0-F3 vs F4	13.6	0.89	0.85	0.79	0.29	0.98

FAST: CAP+LSM+AST

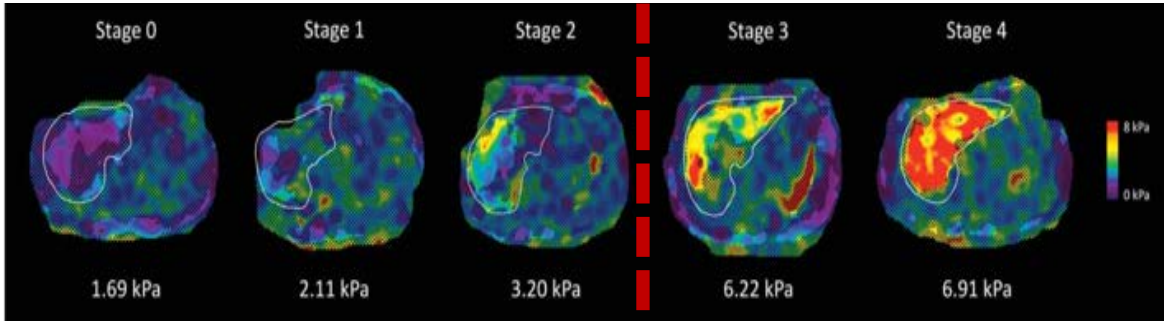


NITs Used to Identify High Risk MASH Patients

Imaging Technique: MRI-PDFF and MRE



- Modified phase-contrast pulse sequence to visualize rapidly propagating mechanical shear waves (~60 Hz)

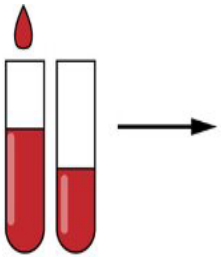


Cutoff for Detecting Advanced Fibrosis	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
MRE stiffness ≥ 3.64 kPa	0.86 (0.65-0.97)	0.91 (0.83-0.96)	0.68 (0.48-0.84)	0.97 (0.91-0.99)

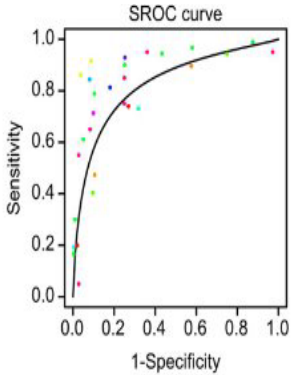
Noureddin. *Hepatology.* 2013, Loomba. *Hepatology.* 2015, Loomba *Hepatology*. 2014; Patel et al. *Ther Adv Gastroenterol*. 2016; Han, Noureddin. *Liver Int.* 2020..

NITs Used to Identify High Risk MASH Patients

- **Hyaluronic acid (HA)**
- **Procollagen III amino terminal peptide (PIIINP)**
- **Tissue inhibitor of metalloproteinase 1 (TIMP-1)**



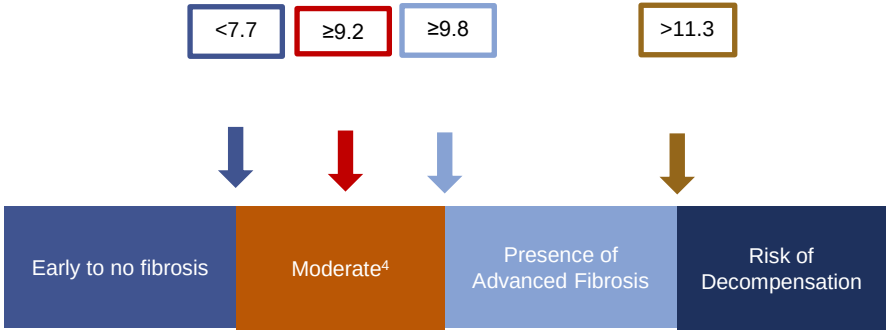
Enhanced Liver Fibrosis test; A blood based biomarker for diagnosis advanced fibrosis



Summary ROC Curve based on the multiple thresholds model using homogenized thresholds. Circles present information on sensitivity and specificity and each color corresponds to one study.

11 studies were included in the meta-analysis of advanced fibrosis
AUC: 0.83 (0.71, 0.90)
Sensitivity: 0.73 (0.60, 0.83)
Specificity: 0.80 (0.68, 0.88)

ELF cut-off scores and accuracy for measurement of Advanced Fibrosis[4]



Sensitivity of 85%
15% of patients with Advanced Fibrosis are missed

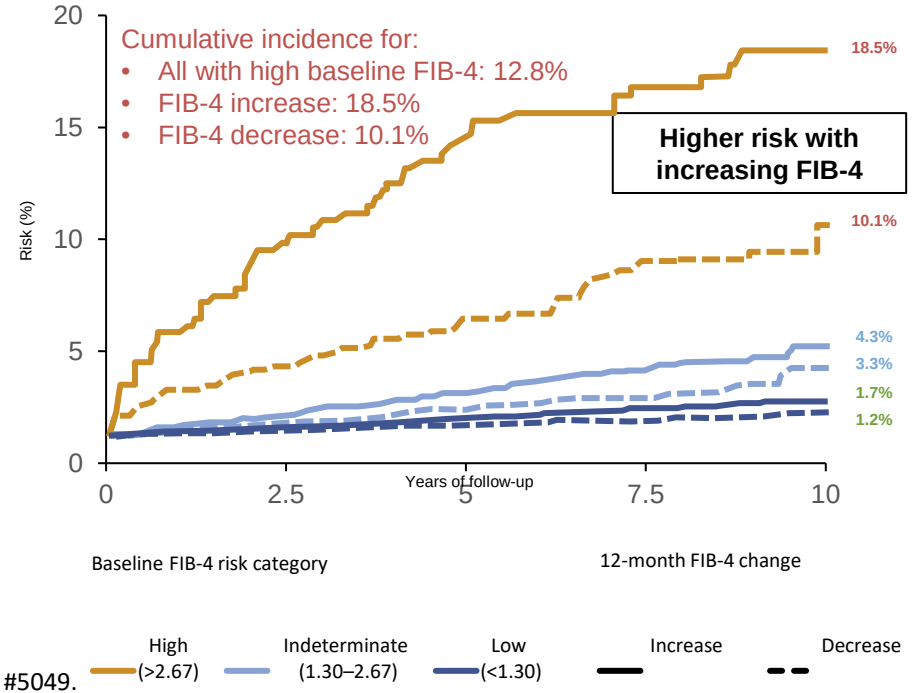
Sensitivity of 90%
10% of patients are wrongly diagnosed with Advanced Fibrosis

Vali et al. *J Hep*. 2020; Day J et al. *JALM*. 2019.

NITs Predicting Outcomes

FIB-4

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

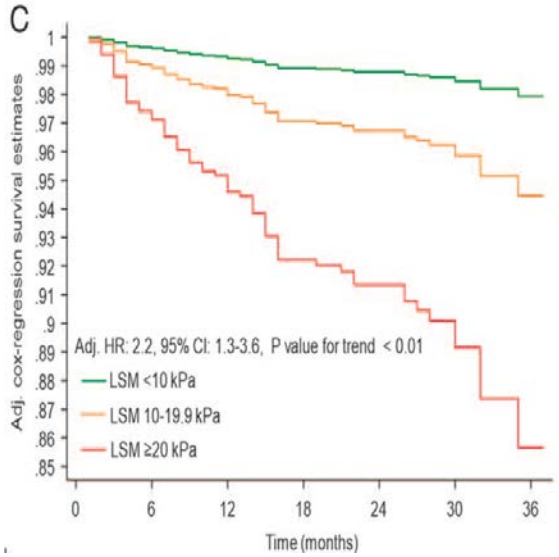


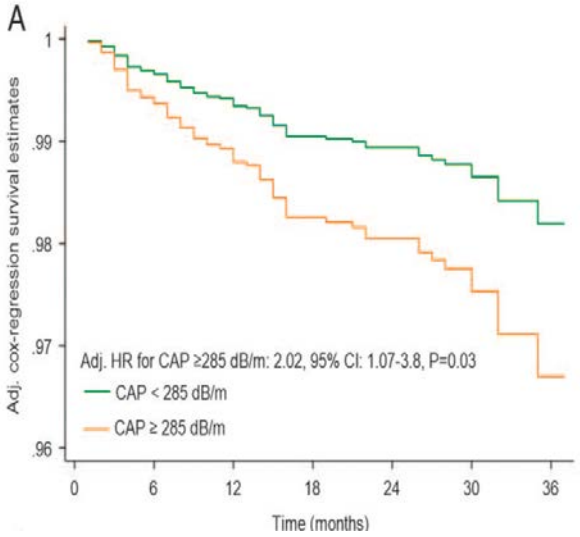
Anstee Q, et al. AASLD 2022. Late-breaking poster #5049.

NITs Predicting Outcomes

- 4192 adults NHANES (2017–2018)
- CAP (aHR: 1.01, 95% CI: 1.0–1.05), and LSM (aHR: 1.06, 95% CI: 1.02 1.11) associated with overall mortality.
- NAFLD by CAP ≥ 285 had a 2.2-fold (95% CI: 1.0–4.7) increased odds of mortality
- Cumulative mortality rates were significantly higher in participants with LSM of 9.7–13.5 (advanced fibrosis) and LSM ≥ 13.6 (cirrhosis)

VCTE



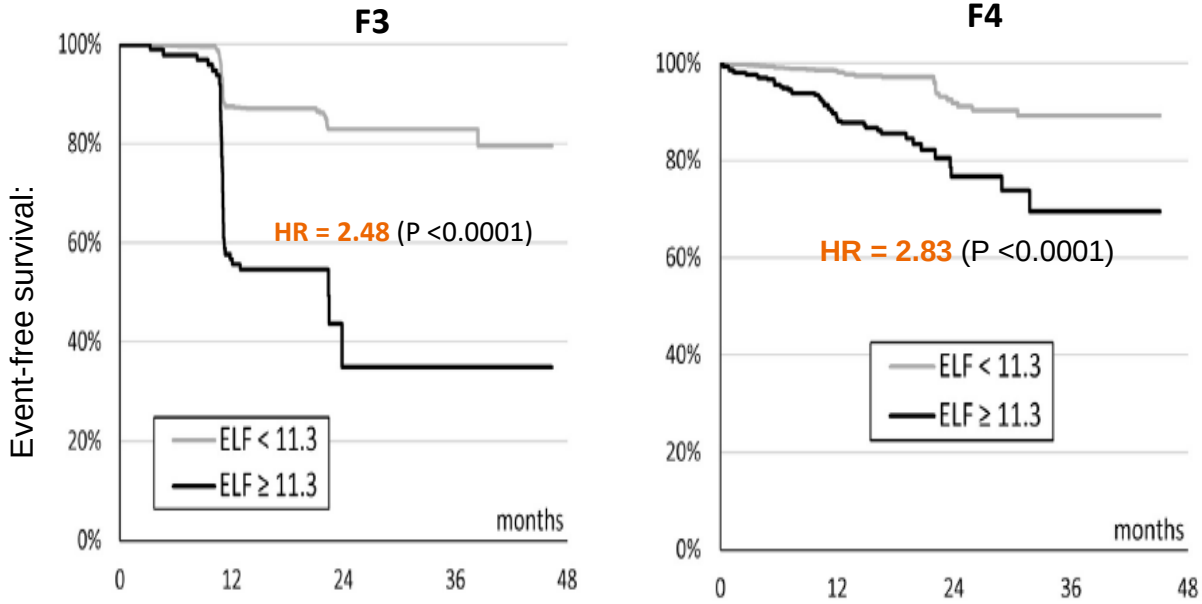


Vilar-Gomez E et al. Hepatology. 2023 Apr 1;77(4):1241-1252

NITs Predicting Outcomes

- Combined data from 4 clinical trials of SEL/SIM
- N = 2154 with advanced NASH
- 47.5% F3, 52.5% F4
- 72% had diabetes
- 60% Female, 40%, Male
- Mean follow-up = 16 months

ELF



Younossi ZM, et al. Gastro 2021;160:1608-19

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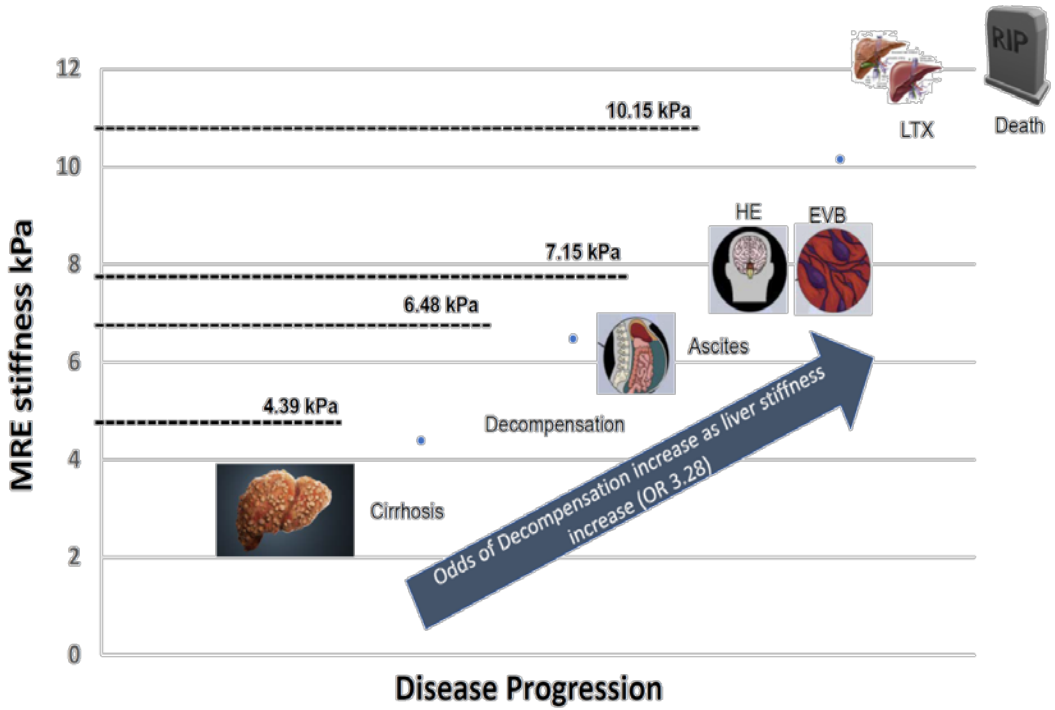
NITs Predicting Outcomes

MRE

- The study included 320 NAFLD patients with MRE.
- Threshold for distinguishing
  - -cirrhosis from NC: 4.39 kPa
  - -DCC: 6.48 kPa
  - -DCC odds with LS increase (OR 3.28) (*P* < .001).



Han MAT, Liver Int. 202040(9):2242-51.

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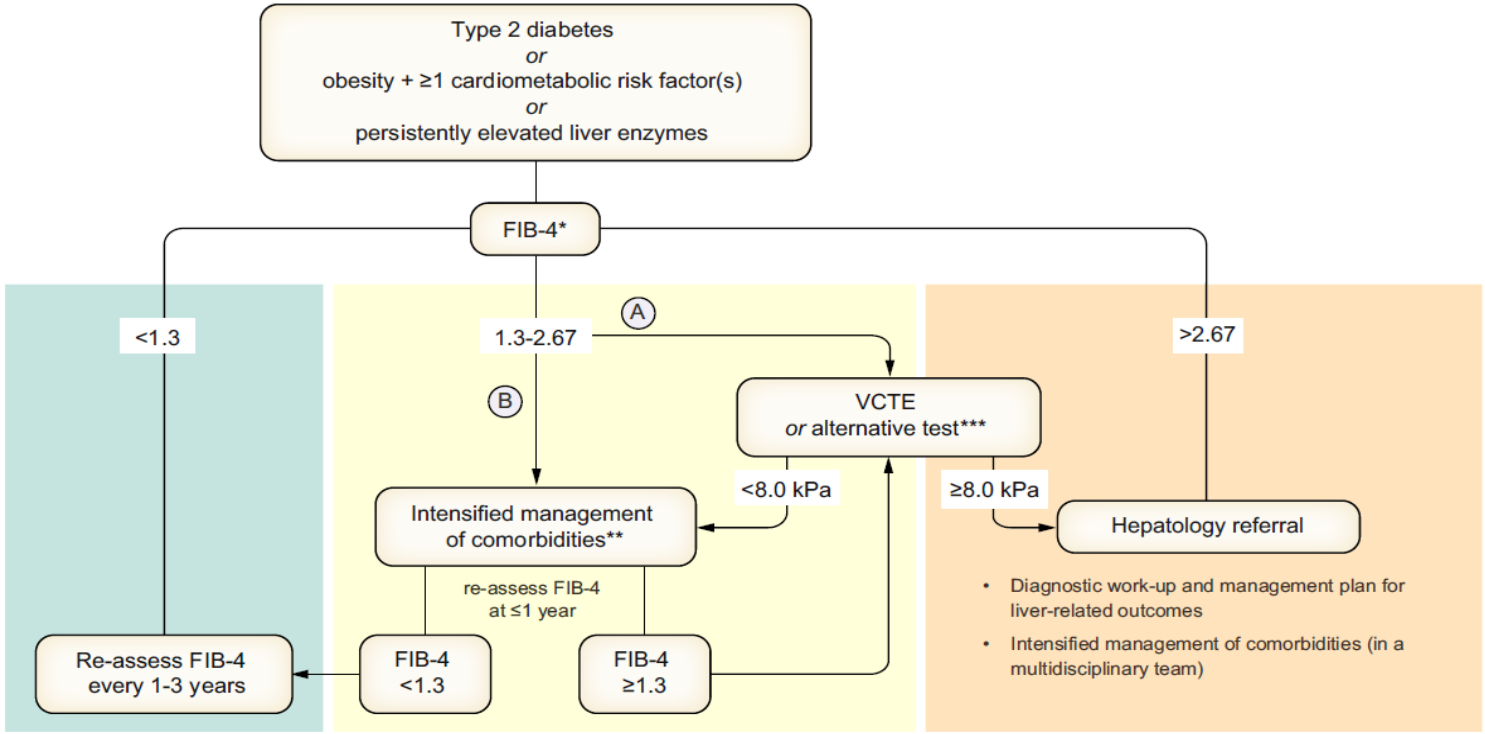
Algorithms for Risk Stratification:
2024 EASL–EASD–EASO Clinical Practice Guidelines on the management of MASLD



* 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

EASL, J of *Hepatology*. 2024.

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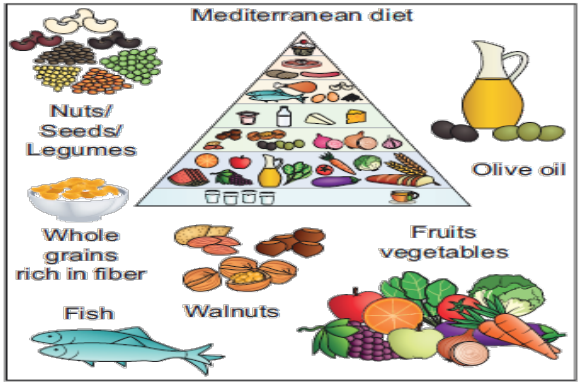
Lifestyle Recommendations for MASLD

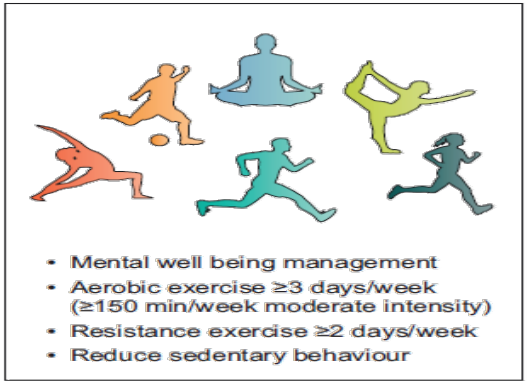
	Overweight/Obese MASLD	Non-Obese MASLD
Weight reduction	• The more severe the liver disease is, the higher the goals are in terms of weight loss • Healthy diet with caloric restriction tailored for your preferences	• 3-5% reduction of weight even within the normal BMI range (especially if recent weight gain occurred or if abdominal obesity is present)

Lifestyle advice for ALL patients with NAFLD

Recommended foods

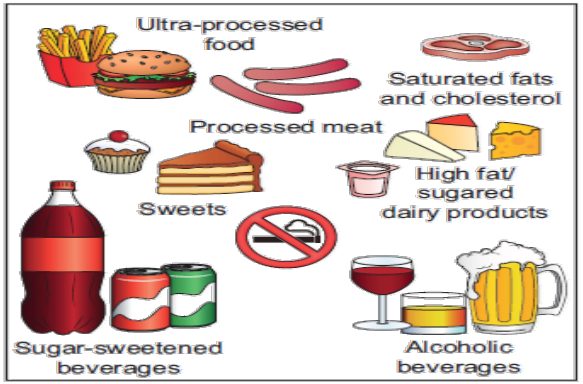


Recommended activity



- Mental well being management
- Aerobic exercise ≥3 days/week (≥150 min/week moderate intensity)
- Resistance exercise ≥2 days/week
- Reduce sedentary behaviour

Un-recommended foods/ Minimize consumption



- Reduce added sugar (*e.g.* by reducing sweets, processed foods, sugared dairy products, *etc.*)
- Avoid sugar-sweetened beverages
- Reduce saturated fat and cholesterol (*e.g.* by eating low fat meat and low fat dairy products)
- Increase n-3 fatty acids found in fish, and walnuts; prefer olive oil
- Minimize "fast food" and ultra-processed food
- Home-cooked meals are preferable
- Try to follow the Mediterranean dietary pattern

EASL patient guideline, Francque SM., JHEP Reports 2021

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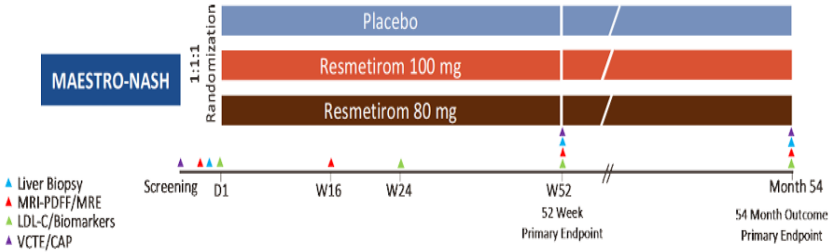
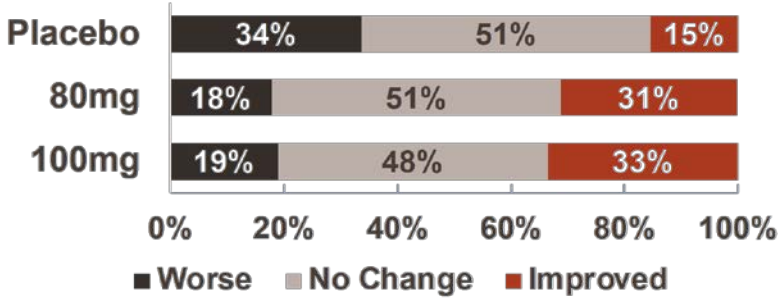
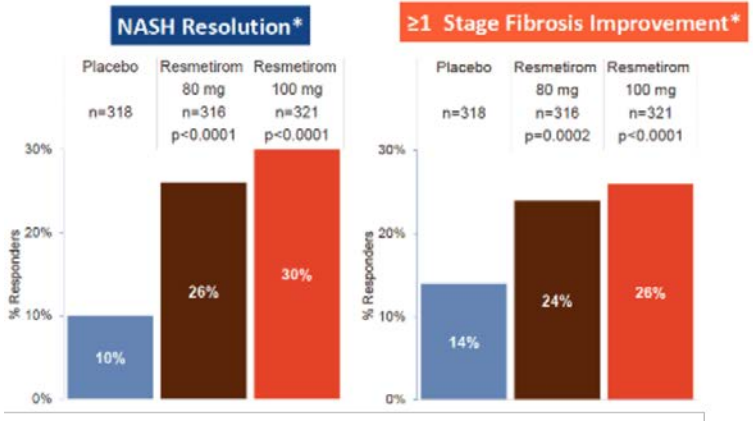
Treatment for NAFLD and NASH:
Current and Potentially Future Treatment Regimens (Phase 3)

	Agent	Mechanism		
STOP	Obeticholic acid	Lipotoxicity/oxidative stress (FXR agonist)	REGENERATE (n=2370, fibrosis stage 1–3) • Fibrosis improvement ≥1 stage without NASH worsening	Stopped after FDA Advisory
HOLD	Aramchol	Lipotoxicity (SCD1 inhibitor)	ARMOR (n=2000, fibrosis stage 2-3) • Reversal of NASH without worsening of fibrosis	
GO!	Resmetirom (MGL-3196)	Lipotoxicity (TRß agonist)	MAESTRO-NASH (n=966, fibrosis stage 2–3) • NASH resolution with at least a 2-point improvement in NAS without worsening of fibrosis	
	Semeglutide	GLP-1RA	Phase 2 complete	Phase 3: Ongoing 2025?
	Lanifibranor	Pan PPAR	Phase 2 complete	Phase 3: On going
	Efruxifermin	FGF19/FGF21	Phase 2 complete	Phase 3: SYNCHRONY Study
	Pegozafermin	FGF19/FGF21	Phase 2 complete	Phase 3: ENLIGHTEN Study

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

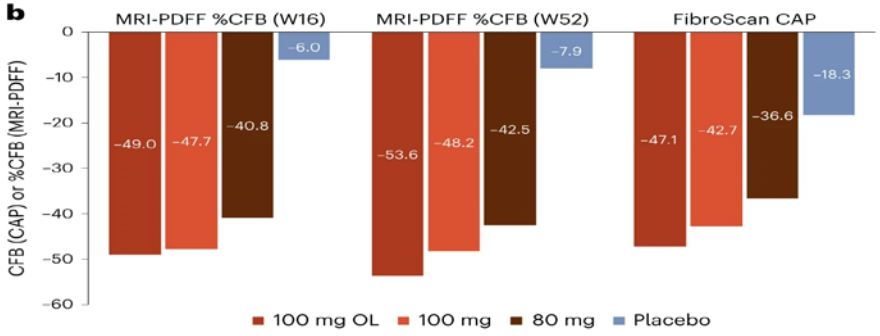






If NASH Resolution or Fibrosis improvement (> 1Stage), response is higher

- At week 52, more patients (>80%) on resmetirom improved or remained stable



Harrison S et al. *NEJM*. 2024.

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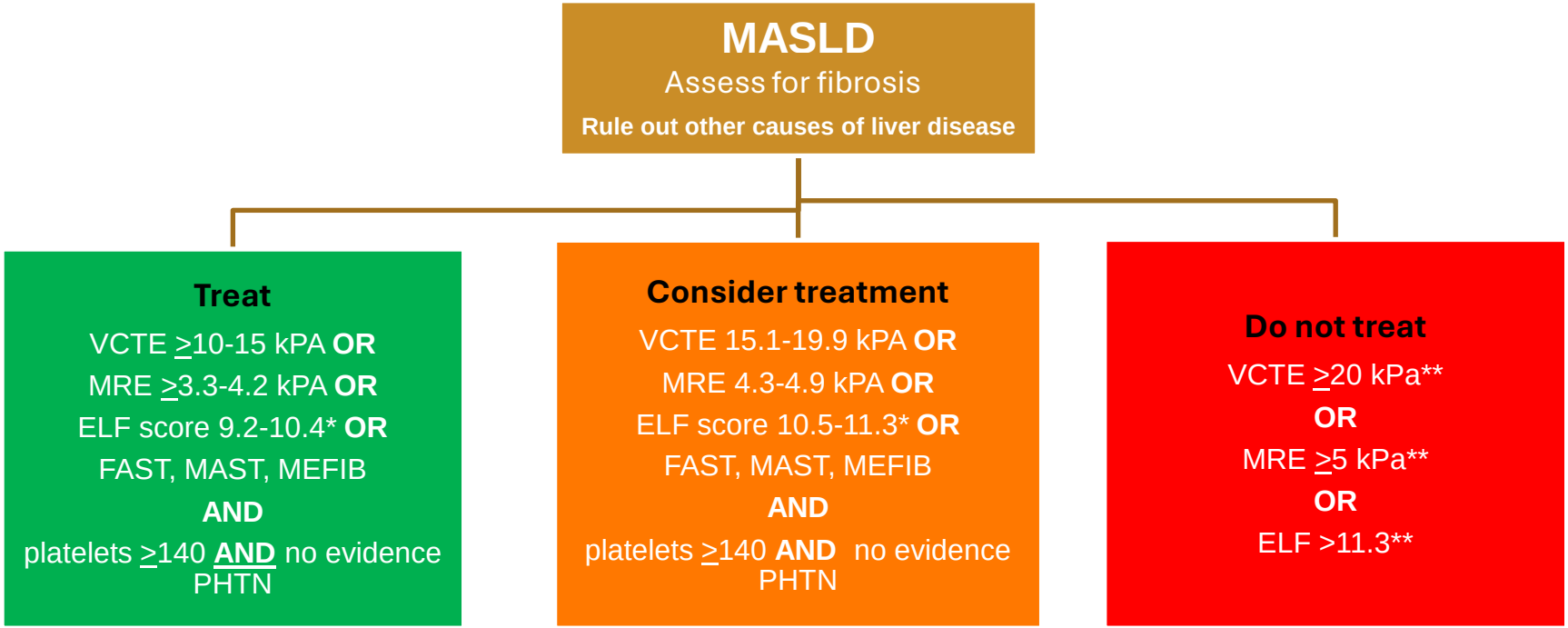
NITs to Select Patients for Treatment With Resmetirom



*To reduce false positives, we propose that two concordant blood based or liver stiffness above threshold values for VCTE or MRE that suggest the presence of significant/advanced fibrosis and not cirrhosis. In scenarios where only ELF is available in isolation, either a liver biopsy or a cutoff of 9.8 and higher is warranted. ** If biopsy is performed and liver histology demonstrates Stage 2 or 3 disease, treatment is appropriate, as long as there is no clinical or imaging evidence of portal hypertension (eg, ascites apparent on imaging, gastroesophageal varices, history of hepatic encephalopathy). PHTN: portal hypertension.

Noureddin M, et al Clin Gastroenterol Hepatol. 2024 Jul 20:S1542-3565(24)00667-0. doi: 10.1016/j.cgh.2024.07.003. Epub ahead of print. PMID: 39038768.

Assessment of Safety and Treatment Response on Resmetirom

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3 months

Start Resmetirom

Confirm safety
- Routine DILI parameters
- Tolerability

Common Adverse Reactions Reported with Resmetirom

Adverse Reaction	Placebo N=294 n (EAIR[1])	Rezdiffra 80 mg Once Daily N=298 n (EAIR[1])	Rezdiffra 100 mg Once Daily N=296 n (EAIR[1])
Diarrhea	52 (14)	78 (23)	98 (33)
Nausea	36 (9)	65 (18)	51 (15)
Pruritus	18 (4)	24 (6)	36 (10)
Vomiting	15 (4)	27 (7)	30 (8)
Constipation	18 (4)	20 (5)	28 (8)
Abdominal pain	18 (4)	22 (5)	27 (7)
Dizziness	6 (1)	17 (4)	17 (4)

*ALT improvement should be accompanied by improvement in imaging (≥ 30 reduction in MRI-PDFF or VCTE).

Assess safety and efficacy

Worsening of NITs* → **STOP**

No change in NITs* → Consider continuing, add-on or alternate approach

Treatment monitoring:
- ALT
- VCTE
- PDFF

Assess treatment response
- **ALT** >17 IU/L and/or >20% improvement* or normalization
- **VCTE** ≥30% drop in LSM
- **MRI-PDFF** ≥30% drop in liver fat

→ **Continue**

6 months

12 months

Noureddin M, et al Clin Gastroenterol Hepatol. 2024 Jul 20:S1542-3565(24)00667-0. doi: 10.1016/j.cgh.2024.07.003. Epub ahead of print. PMID: 39038768.

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Phase 3 Trials of Drugs for Treatment of MASH

Lanifibranor

Franque S et al. NEJM. 2021

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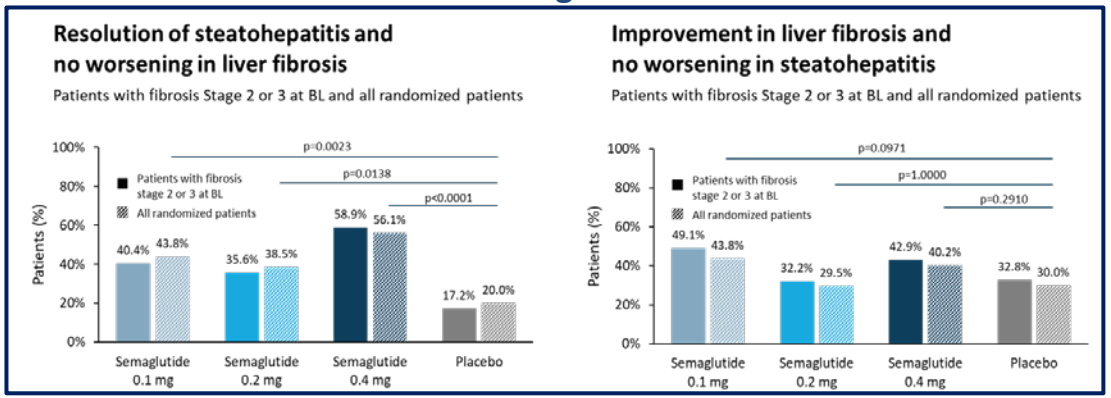
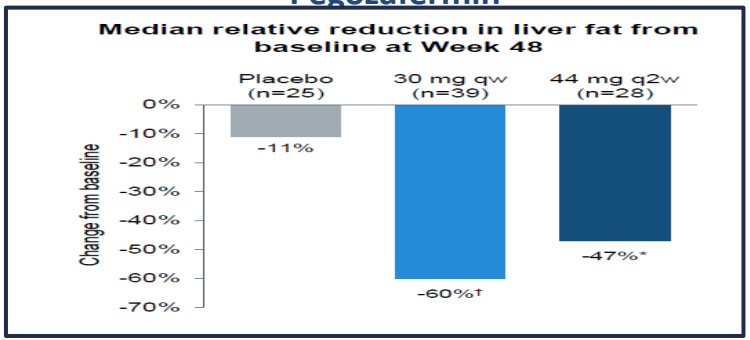
Semaglutide



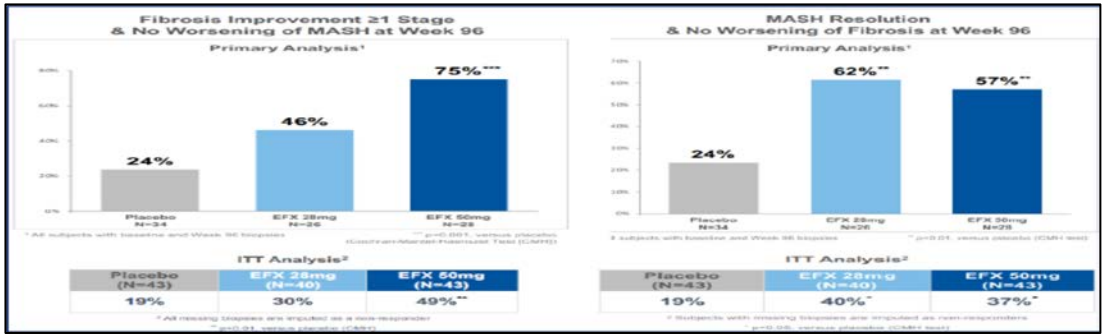
Newsome P, et al. NEJM 2021

Pegozafermin



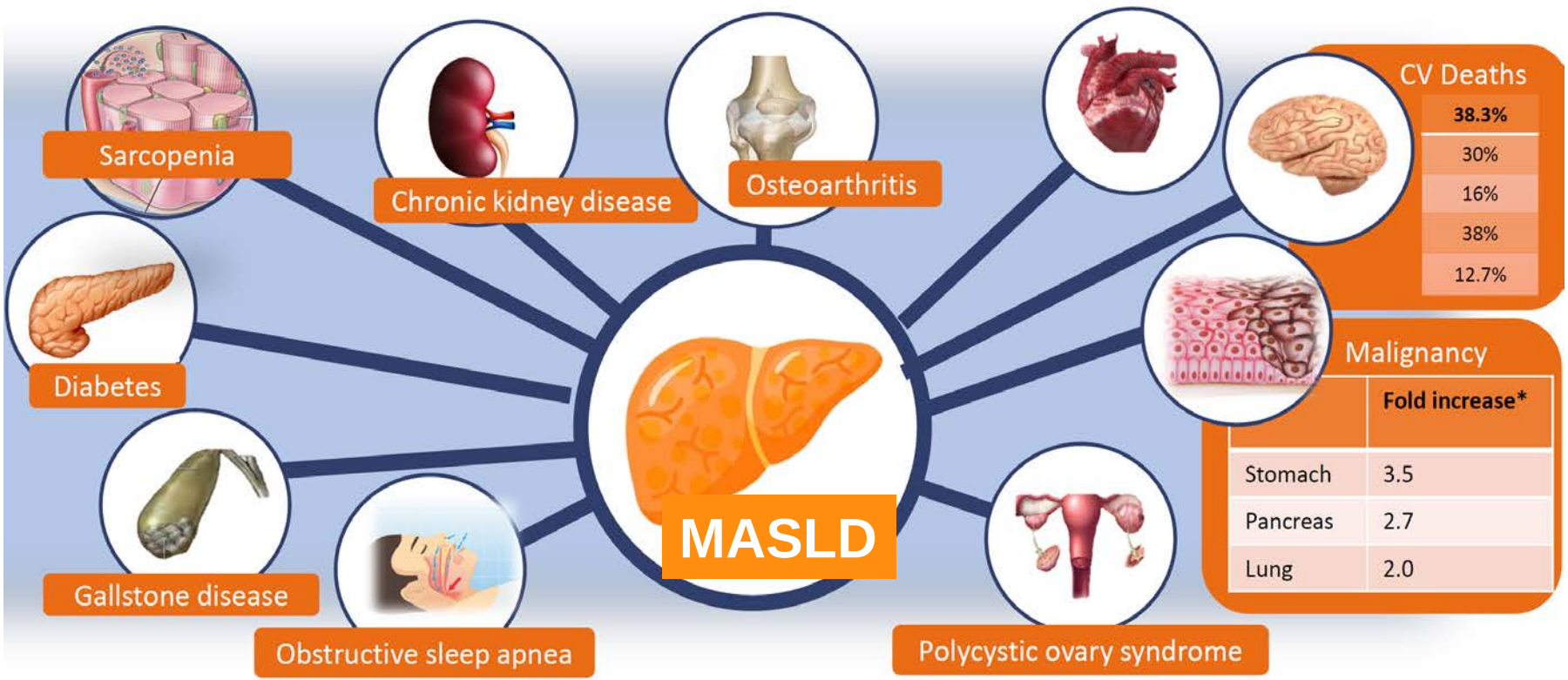
Loomba et al, ILC 2024

Efruxifermin



Harrison S, et al. Lancet Gastro & Hep. 2023

Extra-Hepatic Diseases Associated with MASH



Younossi Z et al 2020

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Sarcopenia: International Consensus

- A continuous process of loss of striated muscle mass and function, reducing locomotion, mobility and postural tonus
- In current definition of sarcopenia, **3 important aspects** are considered:
  - muscle strength,
  - muscle quantity and quality,
  - physical performance.
- Name derived from the Greek—**sarcopenia (ie, flesh loss).**
- Sarcopenia leads to **negative effects on function and clinical outcome.**
- "**no decline with age is more dramatic or potentially more functionally significant than the decline in muscle mass**"

Rosenberg IH, 1997

Differentiate from Other Similar Diseases

Condition	Definition	Measurements
Sarcopenia	Loss of muscle mass	DEXA MRI Computed tomography MAMC/Calf circumference Ultrasound Bioelectrical impedance * 13C-creatine dilution †
Kratopenia	Loss of force, ie, strength	Dynamometry (isometric) Isotonic or isokinetic strength tests
Dynapenia	Loss of power (Force 3 Velocity)	Walking speed Walking distance Stair climbing
Frailty	Increased risk of disability when stressed	CHS (Fried) criteria SOF criteria IANA criteria
Disability	Loss of function	Instrumental activities of daily living Activities of daily living Barthel Index Functional Index Measure

Morley JE, et al J Am Med Dir Assoc. 2011 Jul;12(6):403-9.

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Diagnostic Methods for Sarcopenia

Assessment	Test	Brief description	Sarcopenia cut off points (EWGSOP2)
Case finding	SARC-F questionnaire	5-item self report questionnaire	Score ≥ 4
Skeletal muscle strength	Grip strength	Standardized grip strength assessment by calibrated handheld dynamometer	<27 kg (men) <16 kg (women)
	Chair stand test	Amount of time needed for patient to rise five times from seated position	>15 sec
Skeletal muscle mass	ASMM by dual X-ray analysis (DXA)	ASMM assessed by DXA and corrected by height^2; weight or BMI	<7 kg/m^2 (men); < 5.5 kg/m^2 (women)
	ASMM by bioelectrical impedance analysis (BIA)	Estimates muscle mass based on whole-body electrical conductivity	< 7 kg/m^2 (men); < 5.5 kg/m^2 (women)
	Muscle cross-sectional area assessed by CT or MRI	Mid-thigh muscle area or lumbar L3 cross-sectional area assessed by CT or MRI	Not assigned
	US muscle assessment	Muscle thickness and cross-sectional area (e.g. quadriceps femoris)	Not assigned
Pshysical performance	Gait Speed	Usual gait speed assessment over a 6 m course	≤0.8 m/sec
	SPPB	Combination of balance, gait speed and TUG 5 times tests evaluated on a standardized score ranging from 0–12 points	≤8 point score
	TUG test	Time subjects to stand up form armchair walk 3 meters, navigate obstacle on floor and return to fully seated position	≥20 sec
	400 meter walk	Walk 10 laps of 40 m each as fast as possible	Non completion or ≥6 min for completion

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Diagnostic Methods for Muscle Loss

	Dual Energy X-ray Absorptiometry	Computed Tomography	Magnetic Resonance Imagery	Ultrasound	Bioelectrical Impedance *
Method	Measures attenuation of free muscle mass	Density of muscle area	Density of muscle area	Visualization of cross-sectional area	Indirect measure of muscle mass
Precision	1%–4%	1%–3%	1%–3%	2%	2%–4%
Radiation exposure	1 mrem (10 μSv)	15 mrem (150 μSv)	None	None	None
Availability	Readily available	Readily available	Readily available	Readily available	Available
Cost	Low	Medium	High	Low	Low
Technical difficulty	Minimum but needs standardization	Moderate	High	Moderate	Minimum
Examples of possible reference values for sarcopenia ¶	Males <7.26 kg/m^2 Females <5.45 kg/m^2	Males <55 cm^2/m^2 † Females <39 cm^2/m^2	Males <176 cm^3 Females <93 cm^3	Males <11 mm ‡ Females M10 mm	Males <14.6kg/m^2 § Females M11.4 kg/m^2

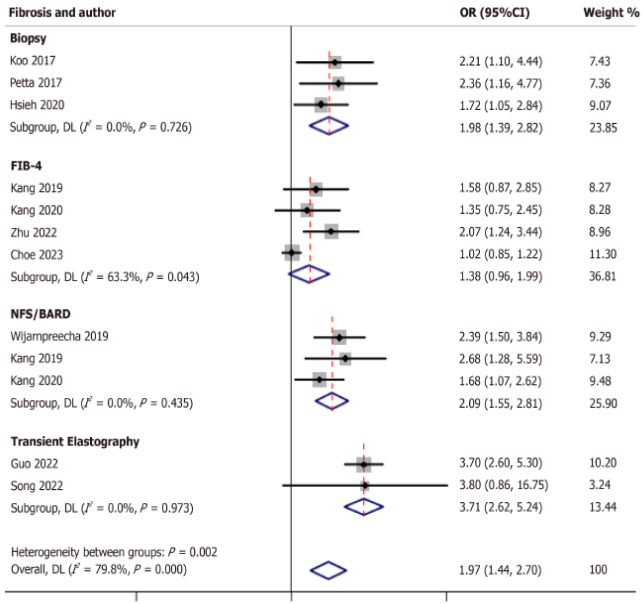
Morley JE, et al J Am Med Dir Assoc. 2011 Jul;12(6):403-9.

Sarcopenia and MASLD: Prevalence and Associations

Prevalence of sarcopenia in NAFLD

- Depends on diagnostic modality:
  - The overall prevalence varied significantly (1.6% MRI) to 63.0% (DEXA)
  - In DEXA studies, prevalence of sarcopenia ranged from 12.2% [ASM)/BMI) to 63.0% when using ASM/weight

Odds of advanced fibrosis with sarcopenia and NAFLD



Associations with Other Metabolic Diseases

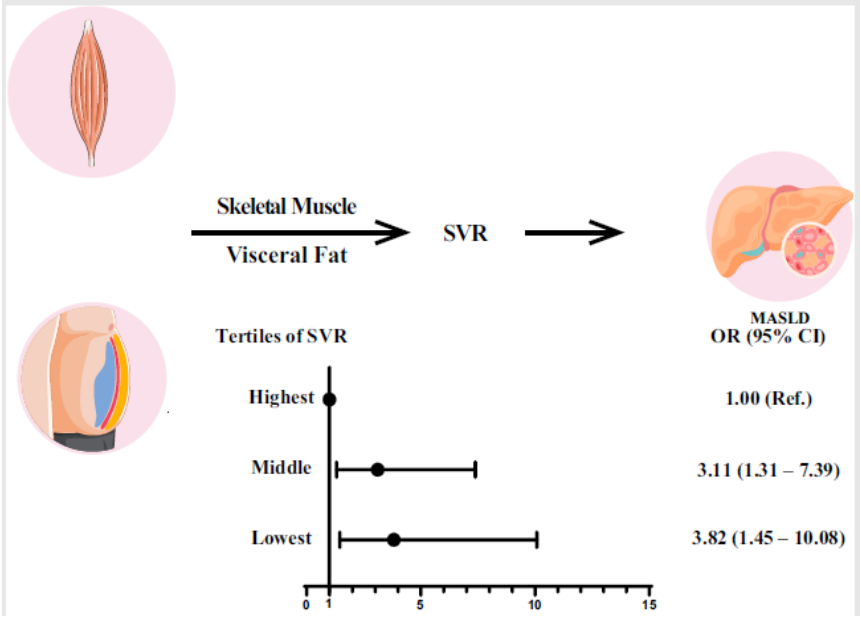
- Some association with increased intima-media thickness and carotid plaques
- Association with insulin resistance

*appendicular skeletal muscle mass (ASM)

Giri S, et al.. World J Gastrointest Pathophysiol 2024; 15(1): 91100

Association Of Skeletal Muscle Mass to Visceral Fat Area Ratio and MASLD

- The study uses the index skeletal muscle mass to visceral fat area ratio (SVR) to describe Sarcopenic Obese (SO)and its association with MASLD using NHANES (2017–2018) (N=2087)
- SVR was calculated according to the measurement of dual-energy x-ray absorptiometry and MASLD was diagnosed with CAP and CMR
- Significant association between SVR and MASLD was shown
  - **OR: 3.11, 95% CI: 1.31–7.39, p = .010 middle SVR**
  - **OR: 3.82, 95% CI:1.45–10.08, p = .007 lowest SVR)**

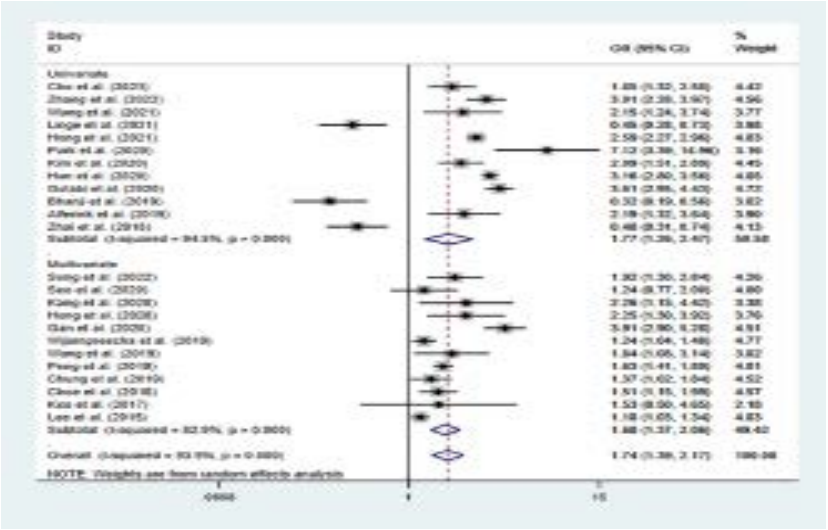


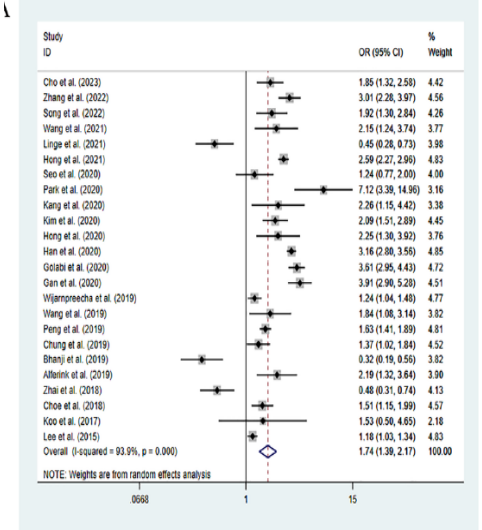
Mai Z et al. J of Diabetes 2024

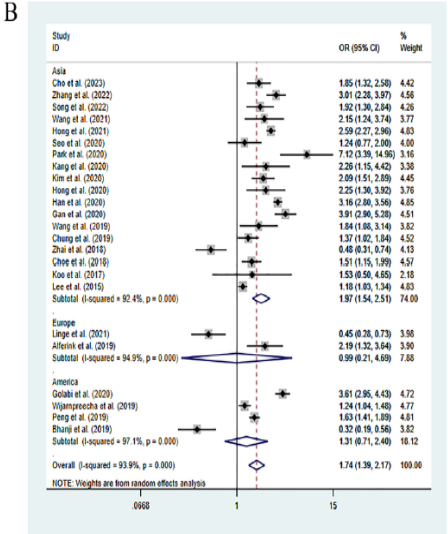
Is the Association only in Asian Patients?

- Systematic review of 24 studies (N=88 609 participants).
- Prevalence of sarcopenia higher in the NAFLD group than control (pooled OR 1.74, 95% CI 1.39 to 2.17).

- Regional analysis: Increased risk of sarcopenia (pooled OR 1.97, 95% CI 1.54 to 2.51) in the Asian group,
  - No significant association with the risk of sarcopenia
    - American (OR 1.31 (95% CI 0.71 to 2.40) or
    - European patients (OR of 0.99 (95% CI 0.21 to 4.69)





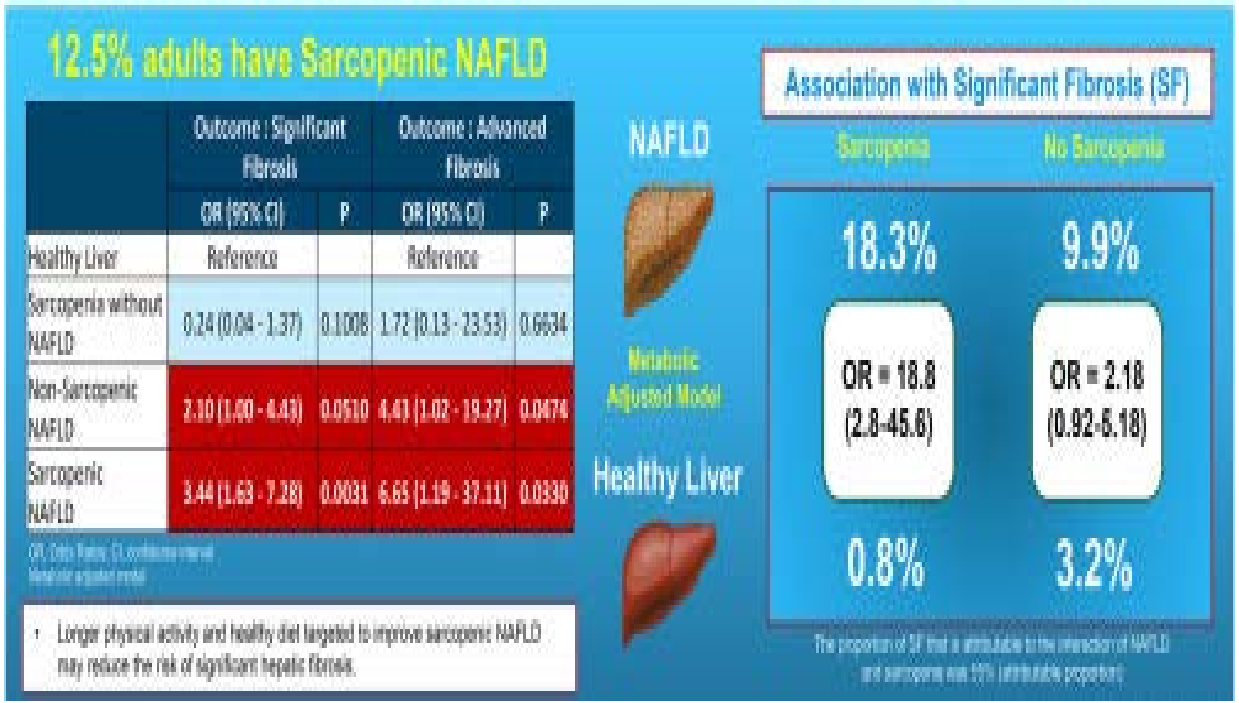


Deng C, et al. BMJ Open 2024;14:e078933. doi:10.1136/bmjopen-2023-078933

Sarcopenia in MASLD Is Associated With Advanced Fibrosis

- NHANES 2017-2018 (N=2,422)
- NAFLD: TE w/o other CLD
  - Significant=LS >8.0 kPa
  - Advanced= >13.1 kPa
- Sarcopenia by EWGSOP
- Sarcopenic NAFLD was associated with advanced fibrosis
- Association independent of demographics, socioeconomic status, and metabolic characteristics.
- Increased leisure time physical activity (>300 min/wk) is associated with a lower risk of sarcopenia.

NHANES 2017-2018 (N=2,422)



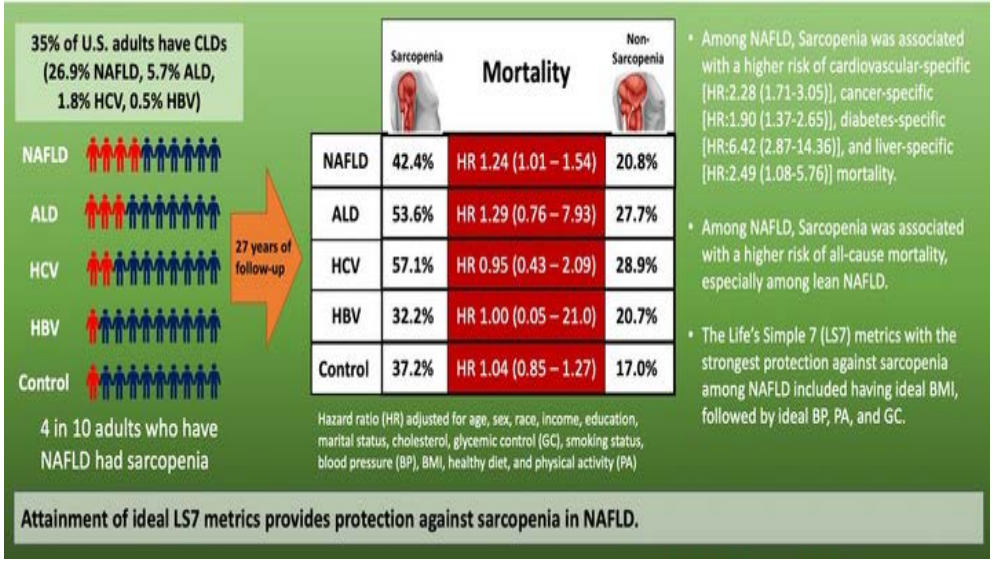
Harring M, Golabi P, Paik JM, Shah D, Racila A, Cable R, Srishord M, Younossi ZM.. Clin Gastroenterol Hepatol. 2023 Oct;21(11):2876-2888.e5..

Sarcopenia and Physical Inactivity Associations with Mortality in MASLD

- NHANES 1999-2004 (N=12,032) 34.9% w CLD
  - 0.5% HBV, 1.8% HCV, 5.7% ALD, 26.9% NAFLD and 65.1% controls
- Sarcopenia was more common among NAFLD than other CLDs
  - 40.7% in NAFLD, 27.2% in ALD, 22.4% in HCV, 16.8% in HBV, and 18.5% in controls; $p < 0.001$).
- NAFLD and ALD patients with sarcopenia were less likely to meet ideal LS7 metrics than without sarcopenia
- Mortality after 27 years of FU, HCV (35.2%), ALD (34.7%) and NAFLD (29.6%)
- Sarcopenia was associated with higher risk of all-cause mortality only among NAFLD (hazard ratio [HR] 1.24; 95% C] 1.01–1.54; $p = 0.04$).

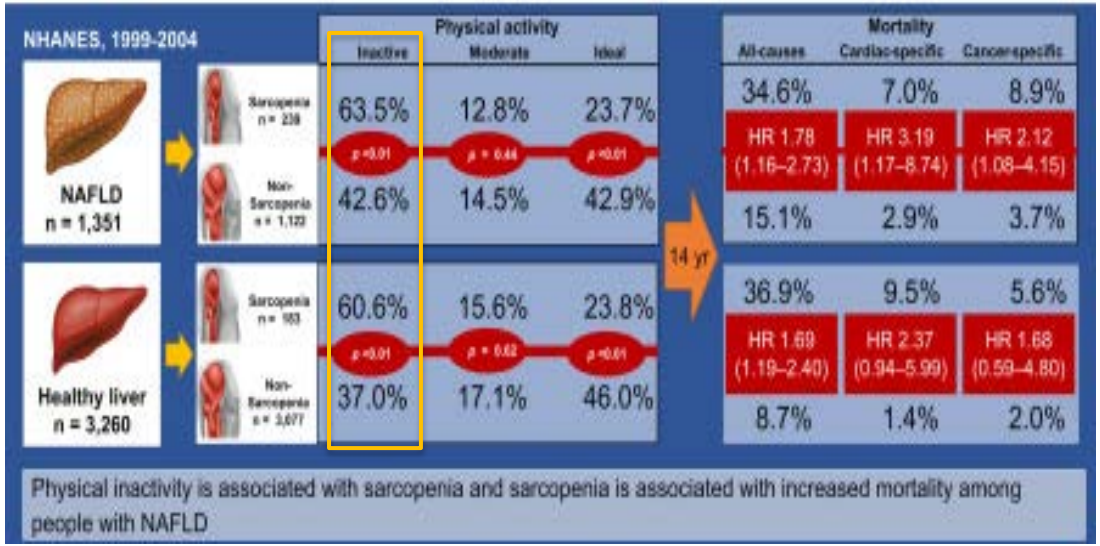
Van Dongen C, Paik JM, Harring M, Younossi Y, Price JK, Kabbara K, Golabi P, Younossi ZM. Hepatol Commun. 2022 Nov;6(11):3140-3153.

- In NAFLD, sarcopenia higher risk of CVM (HR 2.28 [1.71–3.05; $p < 0.01$]), cancer-specific (HR 1.90 [1.37–2.65]; $p < 0.01$) & LRM (HR 2.49 [1.08–5.76]; $p = 0.04$).
- MVA: Component of LS7 metrics (BMI, BP, physical activity, and glycemic control) provided strongest protection against sarcopenia in NAFLD



Sarcopenia Associations with Mortality in CLD

- NHANES (1999–2004)-Linked Mortality (N=4611)
- NAFLD by US FLI w/o other CLD (29.3%)
- Sarcopenia was defined using appendicular lean mass divided by BMI as defined by NIH (DEXA) (17.7%)
- Activity level was determined using standard self-reports.
- Sarcopenia inversely related to higher PA level,
  - NAFLD (OR= 0.45 [95% CI 0.30–0.69])
  - Non-NAFLD (OR = 0.51 [0.35–0.75]).

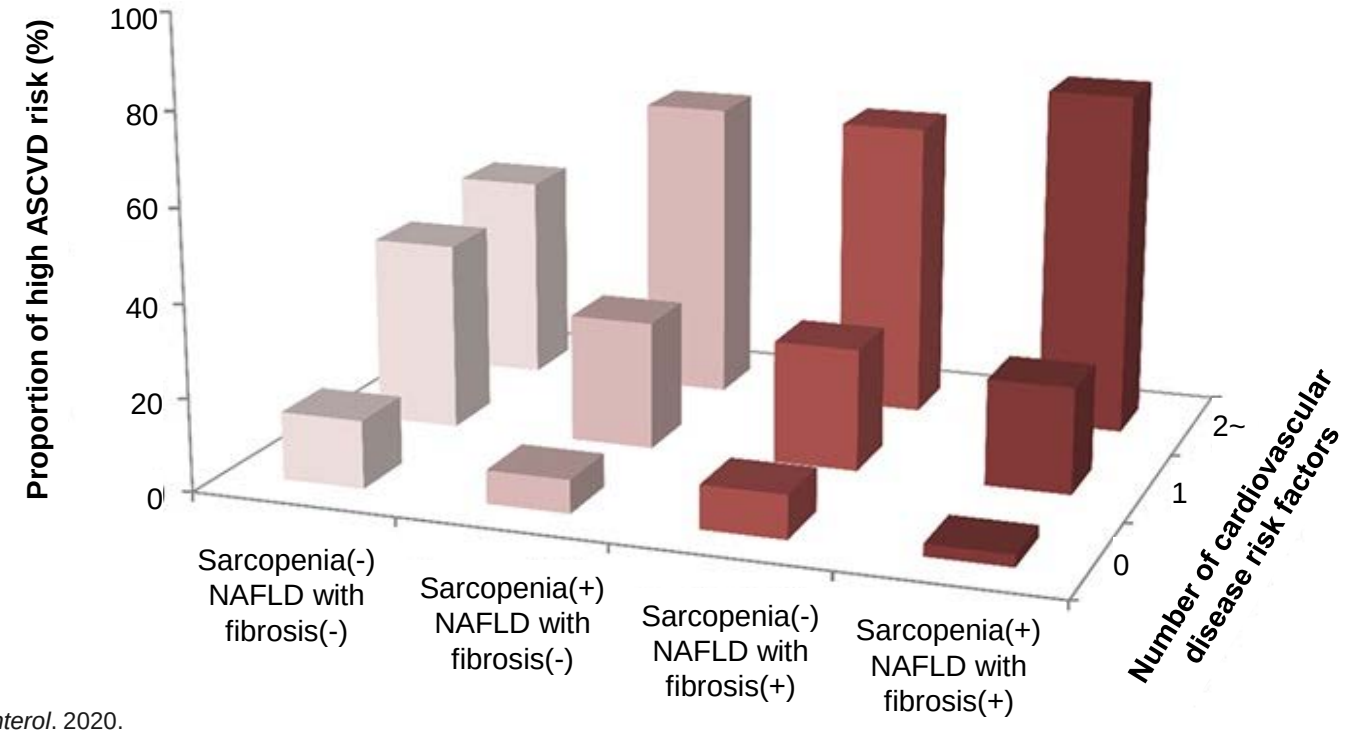


- Compared with NAFLD without sarcopenia, NAFLD with sarcopenia had higher risk of
  - All-cause HR = 1.78 [1.16–2.73])
  - Cardiac-specific (HR = 3.19 [1.17–8.74])
  - Cancer-specific mortality (HR = 2.12 [1.08–4.15]).

Golabi P, Gerber L, Paik JM, Deshpande R, de Avila L, Younossi ZM. JHEP Rep. 2020 Aug 15;2(6):100171.

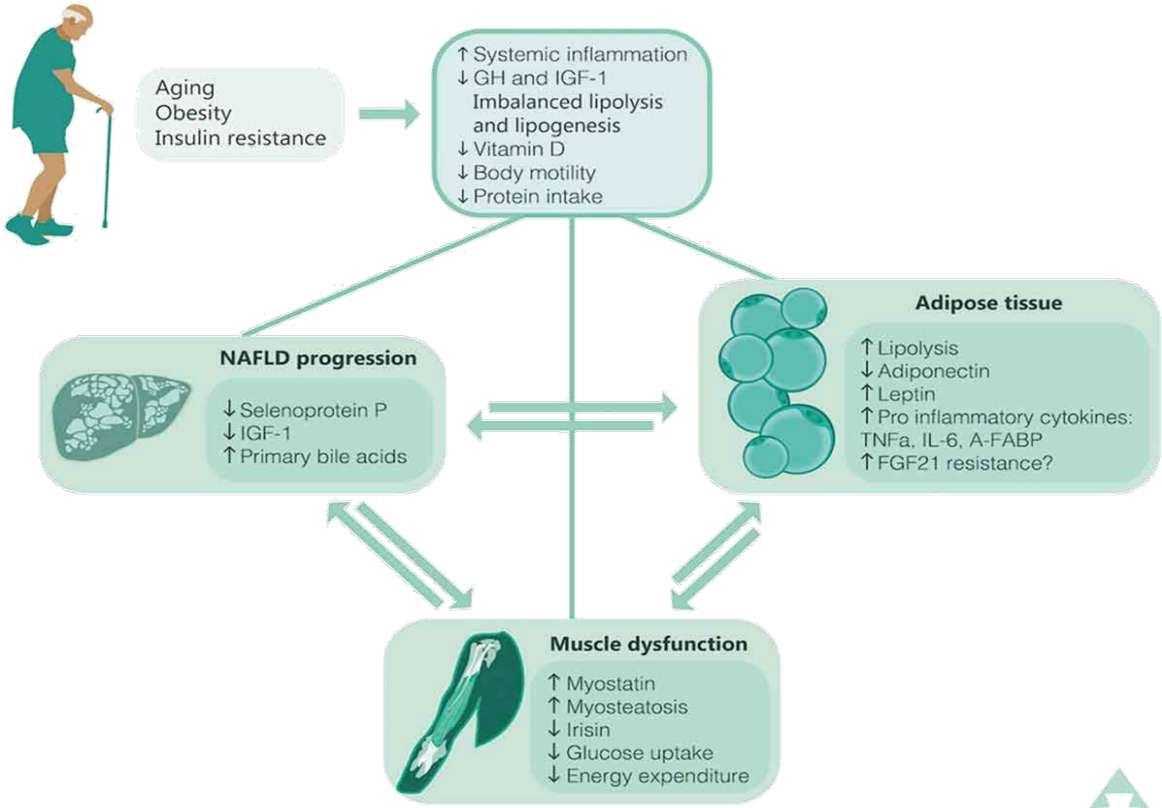
Sarcopenia and MASLD Association With Cardiovascular Risk

Korean National Health and Nutrition Examination Surveys database (n = 7,191) 2008-2011



Han E et al. *Am J Gastroenterol*. 2020.

MASLD and Sarcopenia



Fernández-Mincone T et al. NAFLD and sarcopenia: pathophysiological connections and therapeutic implications. *Expert Rev Gastroenterol Hepatol*. 2020.

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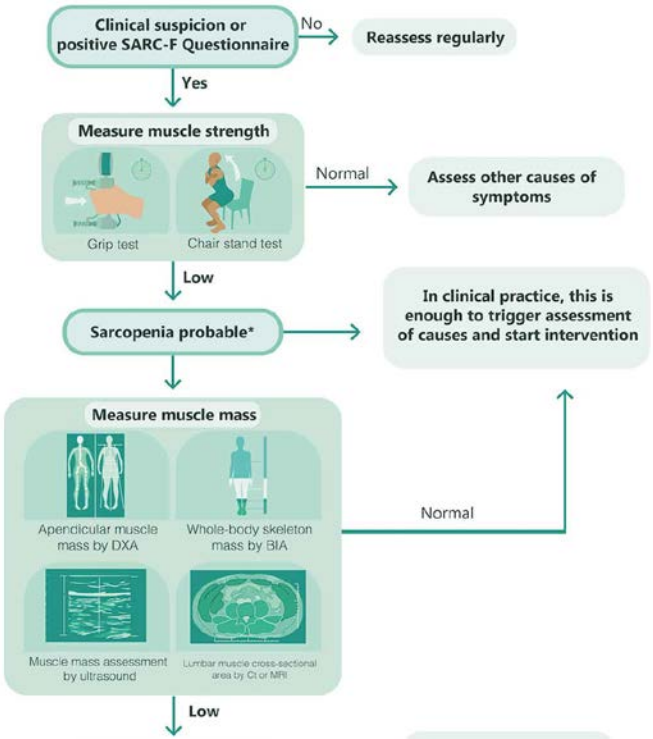
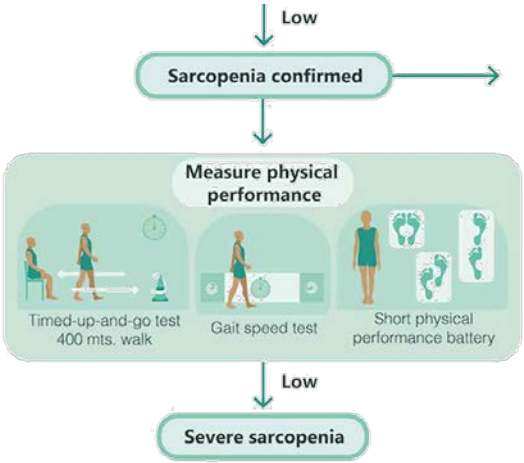
Clinical Assessment for Sarcopenia



1. screen: questionnaire

2. Diagnose with muscle strength

3. Confirm by measuring muscle mass



4. Grade severity by measuring physical performance

Fernández-Mincone T et al. Nonalcoholic fatty liver disease and sarcopenia: pathophysiological connections and therapeutic implications. *Expert Rev Gastroenterol Hepatol*. 2020.

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Management of Sarcopenia in MASLD

Treatment	Recommendations	Effects	ICFSR guidelines
Exercise	Type: Resistance, multiple exercise circuit training Intensity: moderate-high (50% to 80% of maximum repetition) Session: 35–40 minutes Frequency: 2–3 per week, nonconsecutive days Duration: 12–24 weeks	Muscle mass, strength and muscle capacity increase (1) Neuromuscular adaptations (2) Oxygen consumption increase Reduce liver enzymes (3) Reduce muscle mass loss (4) Improves body composition, decreases total fat mass, and increases leg fat free mass (5)	Strong recommendation; moderate certainty evidence
Diet	1.0–1.2 gr/kg of protein divided in meals (6) (1) In sarcopenic obese, reduce calorie intake (7) (6) Healthy fat/Omega-3, hydration and quality of calories ingested (processed vs non processed) assessment (1)	Weight reduction (8)(6) Improves body composition (8) Limited evidence for effect in muscle strength (9)(1,10)	Conditional recommendation, low certainty evidence
Nutritional Supplements	Leucine 10–15 g/d gr/d	Increase lean muscle protein synthetic rate, unclear effect on long term supplementation in muscle mass (11). Combined with exercise improves exercise capacity and HRQoL, and leg muscle mass in a small pilot study in cirrhosis (12)	No recommendation, very low certainty evidence
	Vitamin D 800 UI/d - 1000 UI/d	No clear additional effect to exercise intervention (13), daily doses in older frail subjects, with low baseline vitamin D values (11)	
	Creatine 3-20 gr/d	Associated with exercise improves muscle mass and strength (14)(15)(16)	
	B-hydroxy—b-methylbutiric acid (HMB) and amino acids supplementation (1.5-6 g/d)	Small and heterogenous trials show increase functionality and muscle strength used combined or not combined with exercise (17)	
	N-3 Polyunsaturated fatty acids (PUFA) > 2 g/day	Induce increment in muscle mass (4% increase by BIA) and functionality (2.3 kg in hand grip test) (18)	
Hormone supplementation	Testosterone (low physiologic dose)	Improvement in physical performance and muscle mass (19)(20). Important adverse effects reported Improvement in bone mass, hemoglobin, reduces fat mass and HbA1c in cirrhosis (21).	No recommendation, very low certainty evidence
	GH	Increase muscle mass, dissimilar results in muscle strength and performance (20)	

ICFSR, International Clinical Practice Guidelines for Sarcopenia; GH, growth hormone; GHRH, growth hormone release hormone, IGF-1, insulin-like growth factor 1.

Fernández-Mincone T et al. Nonalcoholic fatty liver disease and sarcopenia: pathophysiological connections and therapeutic implications*Expert Rev Gastroenterol Hepatol*. 2020.

Summary

- MASH is common and its global burden is growing
- NITs can be used to risk stratify MASH
- Treatment include management of co-morbidities with lifestyle and drugs
- The only approved drug in the US is resmetirom
- Other regimens are being developed
- Sarcopenia is relatively common in MASLD and associated with mortality
- Standard approach to screening and treatment must be considered in each patients with MASH