Metabolic Dysfunction-Associated Steatotic Disease and Steatohepatitis Liver Summit 2024

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Rinella ME, Neuschwander- Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease.
Hepatology. 2023;77:1797–1835. https://doi.org/10.1097/HEP.0000000000000323

What to know about the New Nomenclature :

- Steatotic Liver Disease **(SLD)** : Encompass the various etiologies of steatosis.
- **Steatohepatitis**: Will be retained due to the important pathophysiological concept.
- Metabolic Dysfunction-Associated Steatotic Liver Disease (**MASLD**): Encompasses patients with hepatic steatosis and have at least one of the five cardiometabolic risk factors (for Adult):
  - BMI ≥ 25 or WC >94 CM (M) 80 CM (F) or ethnicity adjusted.
  - FBS≥ 100 mg mg/dL or 2 hours postprandial glucose ≥140 mg mg/dL or HbA1C>5.7%,or Type II DM or on treatment.
  - BP>138/85 or on BP treatment.
  - Plasma Triglyceride ≥ 150 mg/dL or on treatment
  - HDL ≤ 40 mg/dL (M), ≤ 50 mg/dL (F).
- Metabolic Dysfunction-Associated Steatohepatitis (**MASH**): Replace NASH

- **MetALD** (Pronounce Met A-L-D): MASLD who use >140 g/week(F), 210 g/week (M).
- One standard drink has 14 gm of alcohol.
  - Wine 5 Oz/Glass
  - Beer 16 Oz
  - Liquor 1.5 Oz 40% (80 proof)
- **Cryptogenic SLD**: Those with no risk factor and no known cause

New Nomenclature of NAFLD
Hepatology ():10.1097/HEP.0000000000000520,
June 24, 2023. | DOI: 10.1097/HEP.0000000000000520

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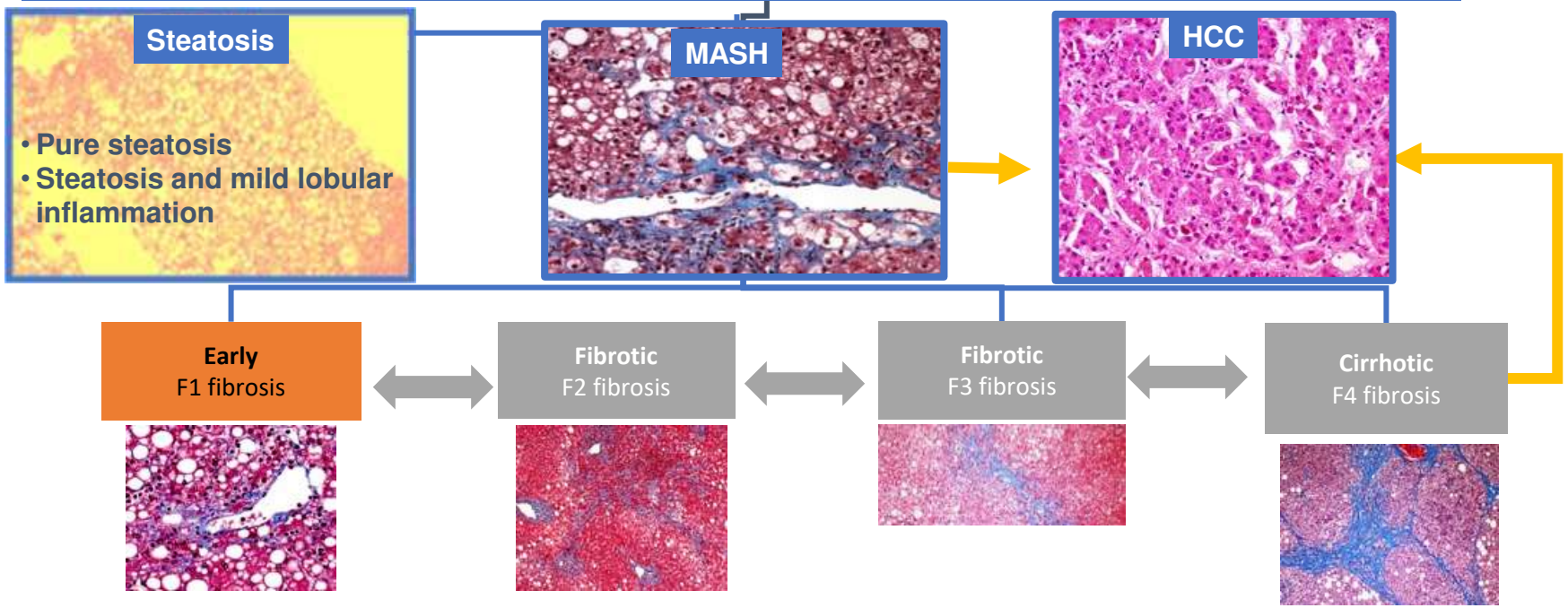
Defining MASLD

- **There must be**
  - **Evidence of hepatic steatosis, either by imaging or histology and**
  - **Lack of secondary causes of hepatic fat accumulation**
- **In most patients, MASLD is commonly associated with metabolic comorbidities such as**
  - **Obesity**
  - **Diabetes mellitus**
  - **Dyslipidemia**

- Chalasani N, et al. *Hepatology*. 2018;67:328-35.

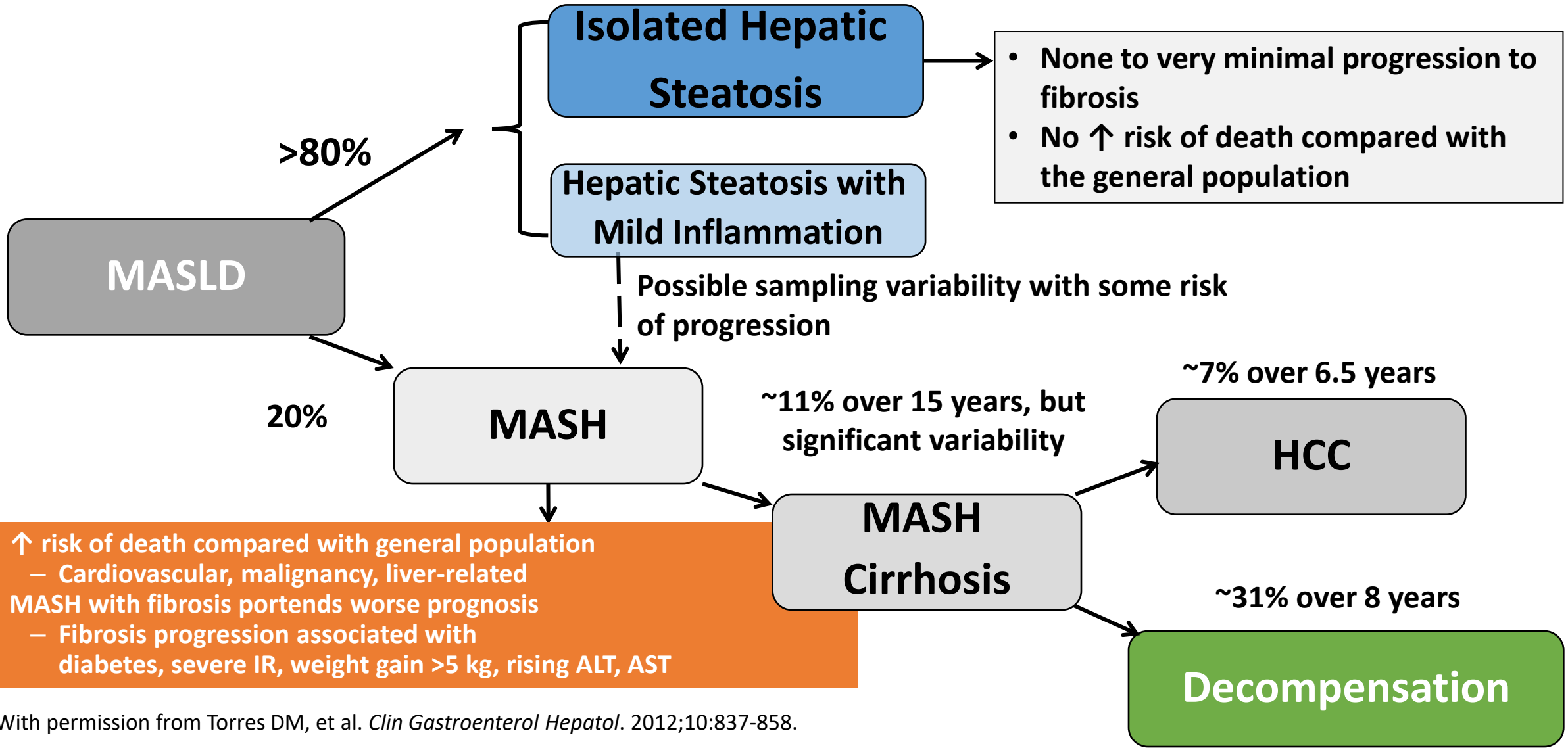
Let's Get the Terminology Correct: What Is MASLD and NASH and MASH?

- Steatosis in >5% of hepatocytes
- NASH requires specific pathologic criteria
- Exclusion of secondary causes and MASLD
- Risk factors are components of metabolic syndrome



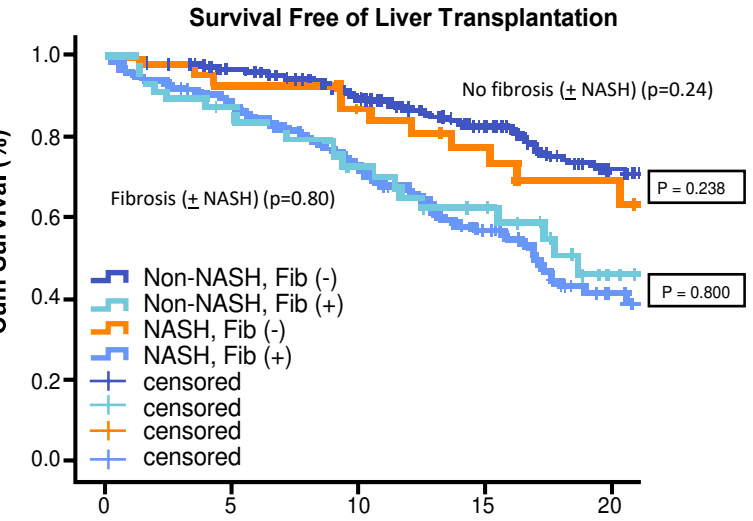
1. Younossi ZM. *Hepatology.* 2018;68(1):349-360; 2. Chalasani N, et al. *Hepatology*. 2018;67(1):328-35;
3. Younossi ZM, et al. *Hepatology*. 2011;53(4):1874-1882; 4. Younossi ZM, et al. *Hepatol Commun*. 2017;1(5):421-428;
5. Anstee QM, et al. *Gastroenterology*. 2016;150(8):1728-1744; 6. EASL–EASD–EASO CPG NAFLD. *J Hepatol.* 2016;64:1388–402.

Natural History of MASLD



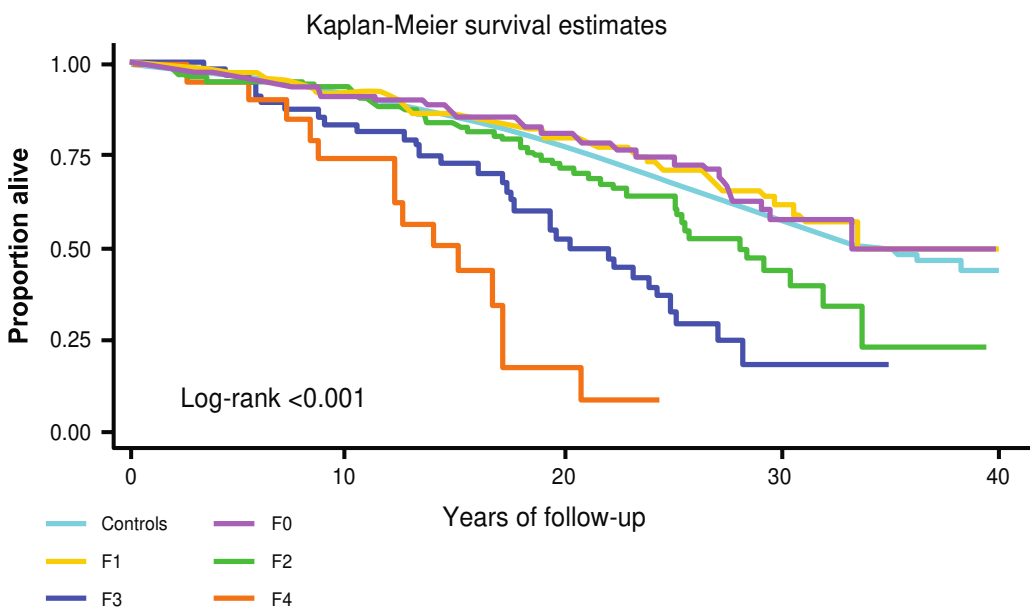
With permission from Torres DM, et al. *Clin Gastroenterol Hepatol*. 2012;10:837-858.

Histologic Features of MASH Predict Mortality

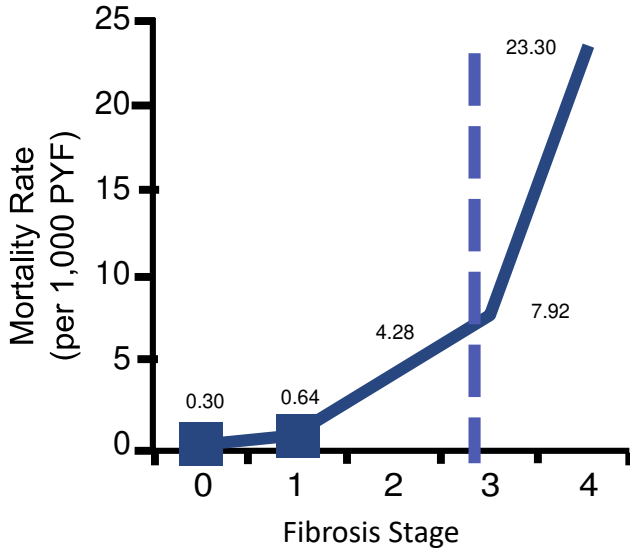


- *Fibrosis stage, but no other histologic features of steatohepatitis, were independently associated with overall lmortality, liver transplantation, and liver-related events*

Angulo P, et al. *Gastroenterology.* 2015; 149(2): 389–397.



Hagstrom H, et al. *J Hepatology.* 2017;67:1265-1273.



Systematic search of 5 studies of adult NAFLD cohort (N=1495) studies with mortality data and biopsy stage (0–4)

Dulai PS, et al. *Hepatology.* 2017;65(5):1557-1565.

Summary of common tests for determining fibrosis stage

Test	AUROC	Lower cut-off to rule out Advanced Fibrosis	Sensitivity for lower cut-off (%)	Upper cut-off to rule in Advanced Fibrosis	Specificity for upper cut-off (%)
Simple Scores					
FIB-4[1]	0.78	<1.3	82	≥2.67	93
NFS[1]	0.74	<-1.455	89	≥0.676	89
APRI[2]	0.76	<0.57	90	>0.84	65
Proprietary Serum Tests					
ELF™[3,4]	0.86†	<7.7	85	≥9.8	90
FibroSure®[5,6]	0.78	≤0.31	84	>0.58	83
Imaging Techniques					
FibroScan®[7]	0.93	<7.9 kPa	91	≥9.6 kPa	92
MRE[8]	0.93‡	<2.97 kPa	85	>3.62 kPa	83
Histological Tests					
Liver biopsy[9]	0.87	≤F2	85	≥F3	89

*For informational purposes only – not intended for comparison. All test cut-offs are based on NAFLD/NASH patient populations with the exception of FibroSure® (hepatitis C) and ELF™ (various etiologies).

†AUROC is for upper cut-off of ≥9.8 to detect patients with Advanced Fibrosis.[3]

‡AUROC is for upper cut-off of >3.62 kPa to detect patients with ≥F3 fibrosis.[8]

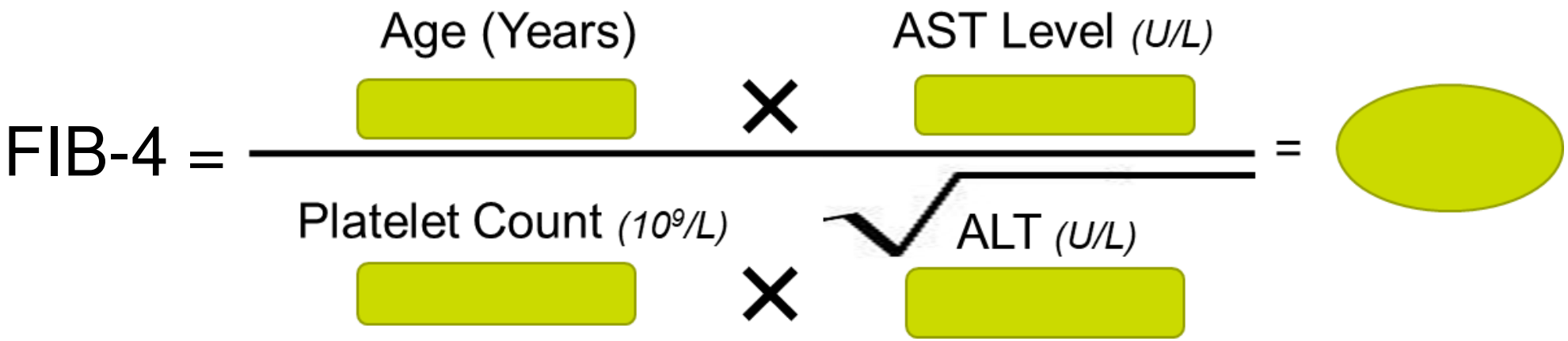
APRI, aspartate aminotransferase/platelet ratio; AUROC, area under the receiver operating curve; ELF, enhanced liver fibrosis; F2, stage 2 fibrosis; F3, stage 3 fibrosis; FIB-4, fibrosis-4; kPa, kilopascal; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease;

NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score.

1. Anstee QM, et al. *Hepatology.* 2019;70(5):1521–1530; 2. Siddiqui MS, et al. *Clin Gastroenterol Hepatol.* 2019;17(9):1877–1885; 3. Siemens Healthineers. ELF instructions for use. Available at: https://doclib.siemens-healthineers.com/rest/v1/view?document-id=728561. (Accessed October 2022); 4. Day J, et al. *J Appl Lab Med.* 2019;3(5):815–826; 5. Poynard T, et al. *Comp Hepatol.* 2004;3:8; 6. LabCorp NASH FibroSure sample report. Available at: https://files.labcorp.com/testmenu-d8/sample_reports/550140.pdf. (Accessed October 2022); 7. Wong VWS, et al. *Hepatology.* 2010;51(2):454–462; 8. Hsu C, et al. *Clin Gastroenterol Hepatol.* 2019;17(4):630–637.e8; 9. Ratzui V, et al. *Gastroenterology.* 2005;128:1898–1906.

FIB-4 can be easily calculated in office with a simple blood test and online calculators[1]

- Based on age, platelet count, ALT level and AST level[2]
- Simple Score that uses readily available patient data

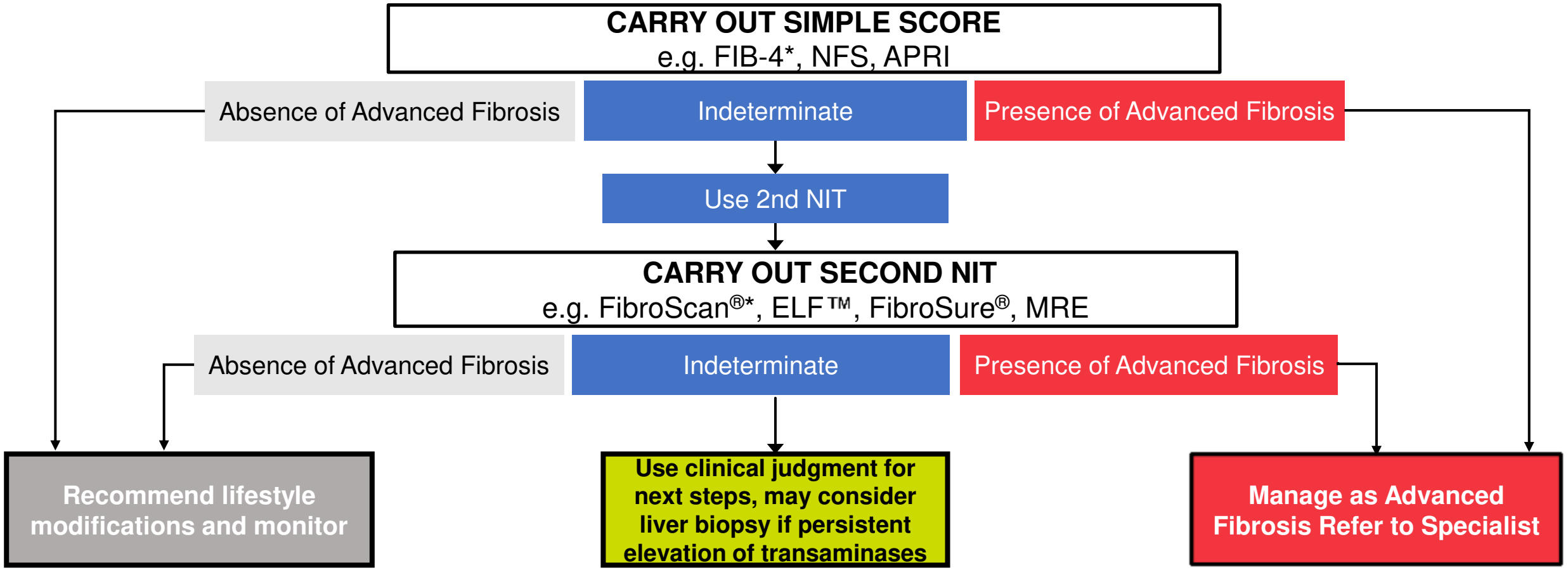


Calculator available at: https://www.mdcalc.com

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; URL, Uniform Resource Locator.

1. Fibrosis-4 calculator. Available at: https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis. (Accessed October 2022); 2. Alkhouri N, et al. *Gastroenterol Hepatol (N Y).* 2012;8(10):661–668.

Algorithmic approach for the screening of Advanced Fibrosis using two NITs[1–11]



***Most commonly recommended per clinical practice guidelines.[7–11]**

Not intended to be prescriptive. Clinical algorithms[1–3,5,7–11] have been published to guide screening of Advanced Fibrosis. Other NITs and combinations are possible.

APRI, aspartate aminotransferase to platelet ratio index; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; NIT, non-invasive test.

1. Patel PJ, et al. *Hepatol Commun.* 2018;2(8):893–905; 2. Festi D, et al. *Aliment Pharmacol Ther.* 2013;37:392–400; 3. Castera L, et al. *Gastroenterology.* 2019;156(5):1264–1281; 4. Anstee QM, et al. *Hepatology.* 2019;70(5):1521–1530; 5. Alkhouri N, et al. *Hepatol Commun.* 2019;3(5):605–613; 6. Younossi ZM, et al. Presented at: AASLD; November 9–13, 2018; San Francisco, United States; Abstract LB-10; 7. EASL Clinical Practice Guidelines. *J Hepatol.* 2021;75(3):659–689; 8. Kanwal F, et al. *Gastroenterology*. 2021;161:1657–1669; 9. Cusi K, et al. *Endocr Pract.* 2022;28(5):528–562; 10. Younossi ZM, et al. *Am J Gastroenterol.* 2020;116(2):254–262; 11. Rinella ME, et al. Hepatology. 2023. Online ahead of print.

Predictive Value of Liver Aminotransferases in MASLD

Serum ALT can be normal in up to nearly 60% of MSALD patients with MASH[1]

Serum ALT can be increased in up to 53% of MASLD patients with no MASH[2,3]

Therefore, serum ALT level alone is not predictive of MASH or fibrosis level[1-3]

- Normal ALT cannot rule out progression or MASH
- Increased ALT cannot predict MASH

Abbreviations: ALT, alanine aminotransferase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

1. Fracanzani AL, et al. *Hepatology*. 2008;48:792-798; 2. Verma S, et al. *Liver Int*. 2013;33:1398-1405;
3. Torres DM, et al. *Nat Rev Gastroenterol Hepatol*. 2013;10:510-511.

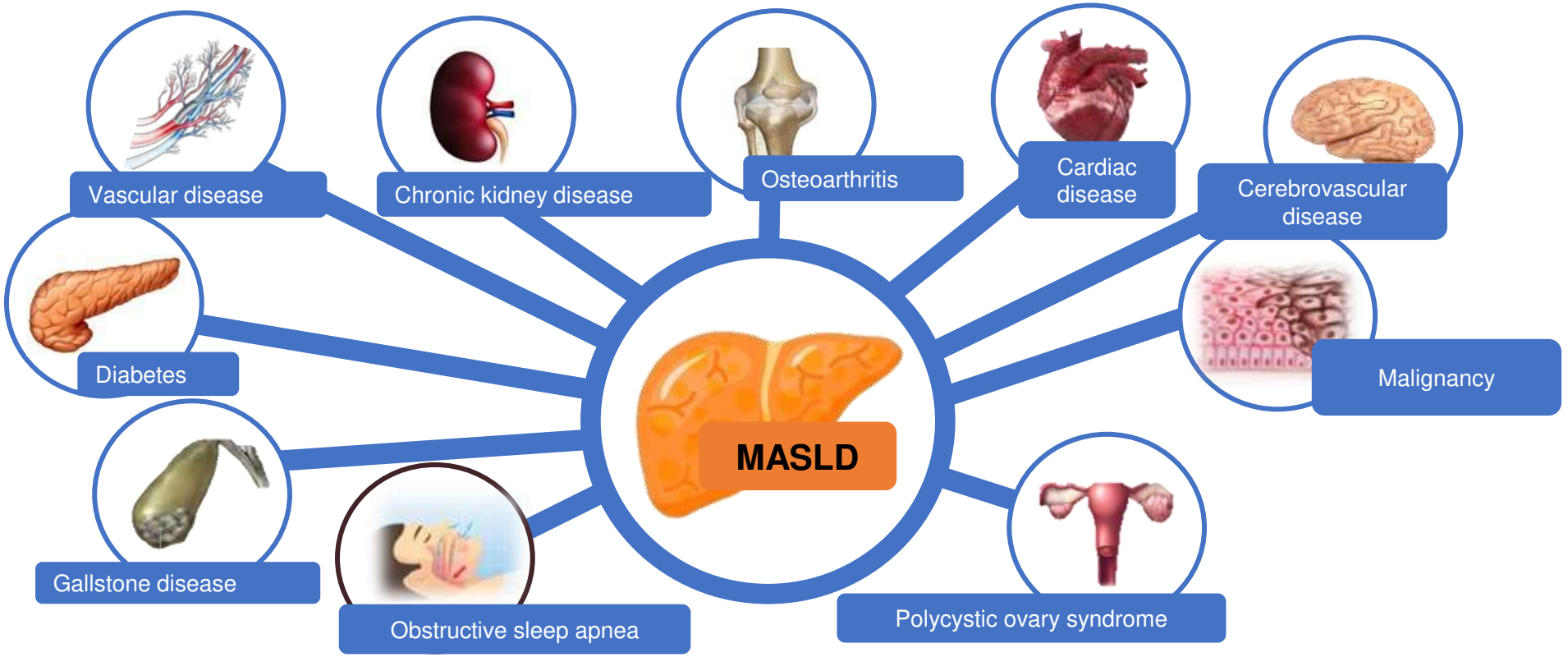
Drugs with potential risk for steatosis or steatohepatitis

- Amiodarone
- 5-FU
- Irinotecan
- Tamoxifen
- Methotrexate
- Corticosteroids

Current Treatment Options

- Resmetirom was recently FDA-approved medications for the treatment of MASLD.
  - **Resmetirom: Thyroid hormone receptor-beta agonist**.
  - Indicated for Adults with non-cirrhotic at-risk MASH,MASH with F2-F3 fibrosis.
- Semaglutide can be considered for its approved indications (T2DM/obesity) in patients with MASH, as it confers a cardiovascular benefit and improves MASH.
- Pioglitazone improves MASH and can be considered for patients with MASH in the context of patients with T2DM .
- Vitamin E can be considered in select individuals as it improves MASH in some patients without diabetes.
- Available data on semaglutide, pioglitazone, and vitamin E do not demonstrate an antifibrotic benefit, and none has been carefully studied in patients with cirrhosis.
- Metformin, ursodeoxycholic acid, dipeptidyl peptidase-4, statins, and silymarin are well studied in MASH and should not be used as a treatment for MASH as they do not offer a meaningful histological benefit.
- Do not forget weight reduction has been proven effective in reducing steatohepatitis and Fibrosis.

Not to Forget MASH Is a Part of a Multisystem Disorder



Angulo P, et al. *Gastroenterology*. 2015;149:389–397; Söderberg C, et al. *Hepatology*. 2010;51:595–602; Ekstedt M, et al. *Hepatology*. 2006;44:865–873;
Dam-Larsen S, et al. *Scand J Gastroenterol*. 2009;44:1236–1243; Rafiq N, et al. *Clin Gastroenterol Hepatol*. 2009;7:234–238;
Hicks SB et al. *J Hepatol* 2019;71:1229-1236.

Summary

- New Nomenclature has been developed to reduce stigmatization and better describe disease status.
- Increased morbidity and mortality has been associated with increased MASH prevalence.
- MASH is part of multi-system disease.
- Hepatic fibrosis is the driven factor which lead to cirrhosis and mortality.
- FDA has recently approved a medication for the treatment of non-cirrhotic at-risk F2-F3 MASH patients, Resmetirom.
- Early diagnosis and early intervention will render better outcome.