NAFL/NAFLD/NASH
(MASH)
Metablism Associated Steatohepatitis

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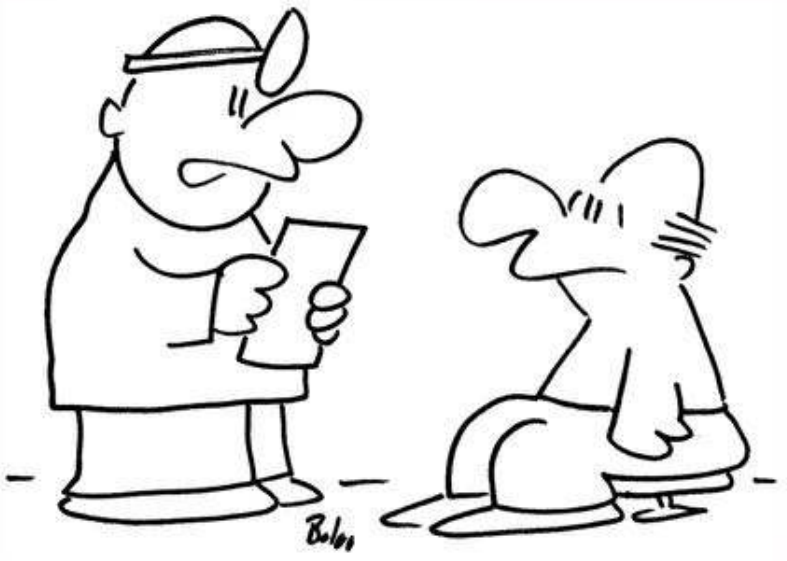
Harm Reduction ECHO: Hepatitis and Liver Health

Conflict of Interest

- I received honorarium from the following companies;
  - Intercept
  - Gilead
  - AbbVie
- I will not discuss off label usage of medications related to today's discussion.

Common Liver Issues in Daily Practice

1. Elevated liver transaminase during a routine office visit.
2. Abdominal Ultrasound reported increased echogenicity indicating fatty liver.
3. Increasing reports of bad outcome of fatty liver disease.



"Your liver has issues."

Non-Alcoholic Fatty Liver Disease(NAFLD)

Pickettt-Blakely O. et al Cell Mol Gastroenterol Hepatol 2018;451-462

- NAFLD is a systemic disorder of energy, glucose, and lipid homeostasis with hepatic manifestation.
- Perturbance of central signals involved in satiety and preference --->excessive consumption of obesogenic macronutrients.
- Deranged energy balance due to polymorphisms in metabolic regulatory genes-PNPLA3 etc (human patatin-like phospholipase domain-containing 3 gene (*PNPLA3*)

NAFLD : A Systemic disorder

- Cardiovascular disease.
- Malignancy
- Cerebrovascular disease
- Diabetic Mellitus
- Chronic Kidney Disease
- Obstructive sleep apnea
- Osteoarthritis
- Polycystic ovary syndrome
- Gall Stone

The PRELHIN Study—Prognostic Relevance of Liver Histology in NAFLD

- International study of NAFLD (N = 619; diagnosed between 1975 and 2005)
- Biopsies read centrally; median follow-up 12.6 years

Key Outcomes	**Death or OLT**	193 patients
	Death due to CV disease	74/193 (38.3%)
	Death due to nonliver cancer	36/193 (18.7%)
	Death due to complications of cirrhosis, HCC, or OLT	18/193 (9.3%)

Abbreviations: HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; OLT, orthotopic liver transplantation.

Angulo P, et al. *Gastroenterology*. 2015;149:389-397. (Dr. Jurgen Ludiwig 1980 – NASH)

Definitions of NAFLD, NAFL and NASH

Nonalcoholic fatty liver disease (NAFLD)

a. Evidence of hepatic steatosis by imaging or histology

b. Lack of secondary causes of hepatic fat accumulation

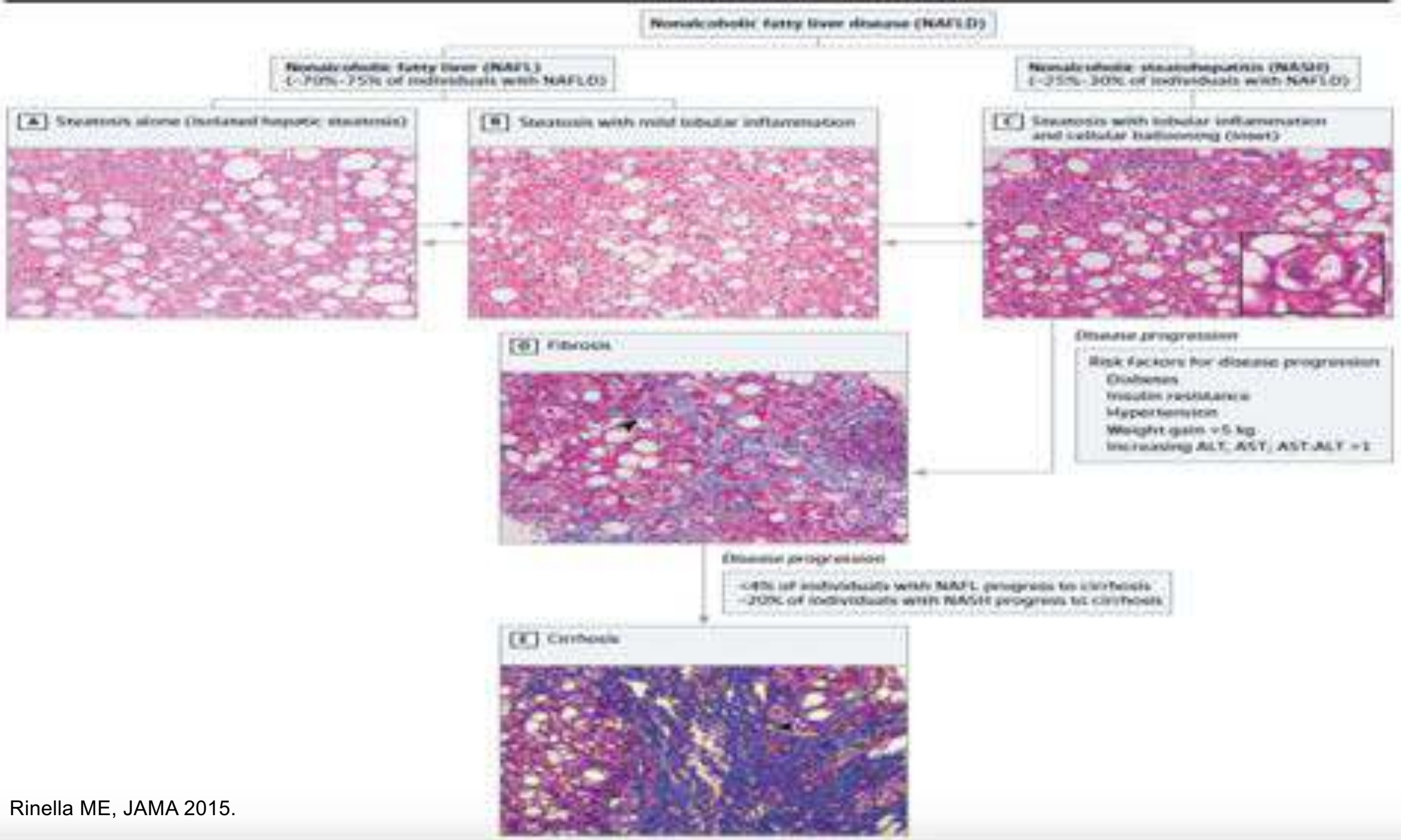
Nonalcoholic fatty liver (NAFL)

≥5% hepatic steatosis without evidence of hepatocellular injury in the form of hepatocyte ballooning

Nonalcoholic steatohepatitis (NASH)

≥5% hepatic steatosis and inflammation with hepatocyte injury (eg, ballooning), with or without any fibrosis

Chalasani N, et al. Hepatology. 2017. doi:10.1002/hep.29367



Rinella ME, JAMA 2015.

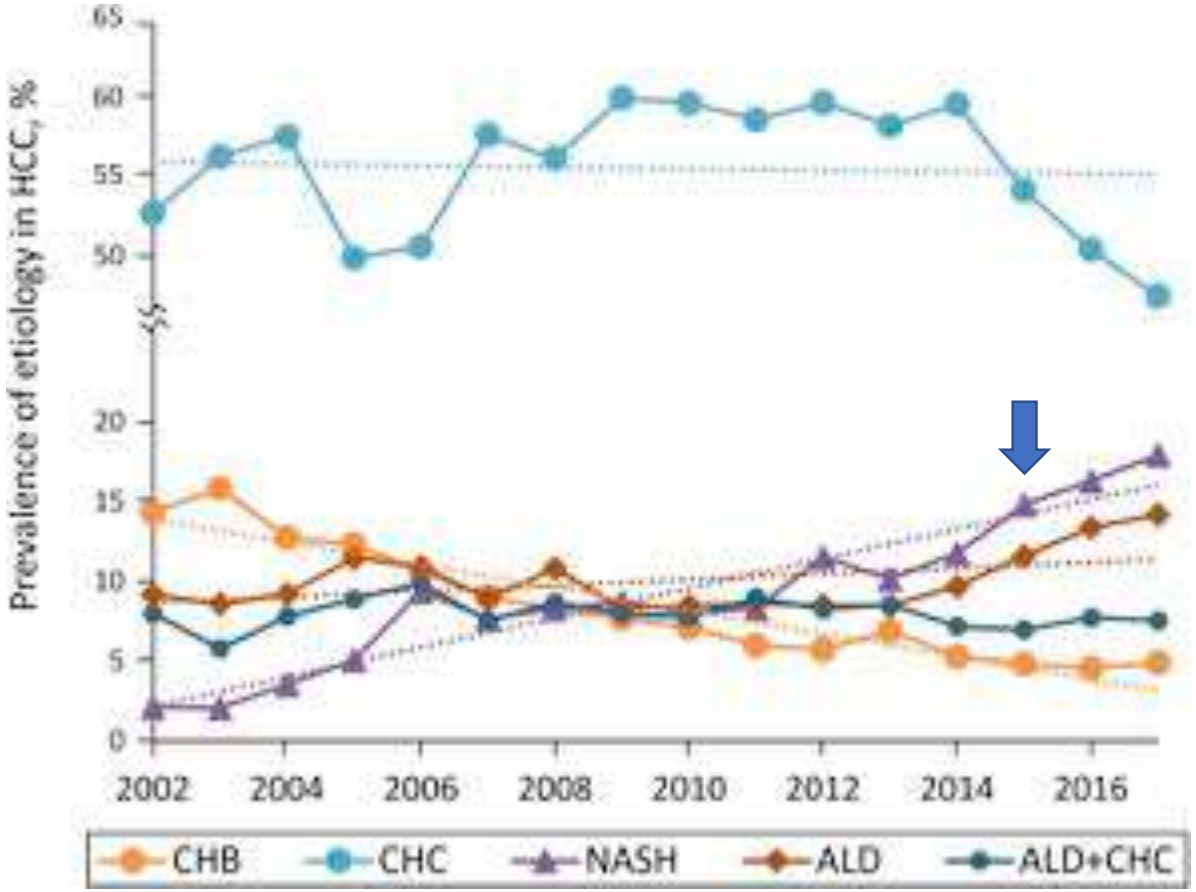
Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates (SRTR)

(Scientific Registra of Transplant Recipient) database

Zobair Younossi, Maria Stepanova, Janus P. Ong, Ira M. Jacobson, Elisabetta Bugianesi, Ajay Duseja, Yuichiro Eguchi, Vincent W. Wong, Francesco Negro, Yusuf Yilmaz, Manuel Romero-Gomez, Jacob George, Aijaz Ahmed, Robert Wong, Issah Younossi, Mariam Ziayee, Arian Afendy

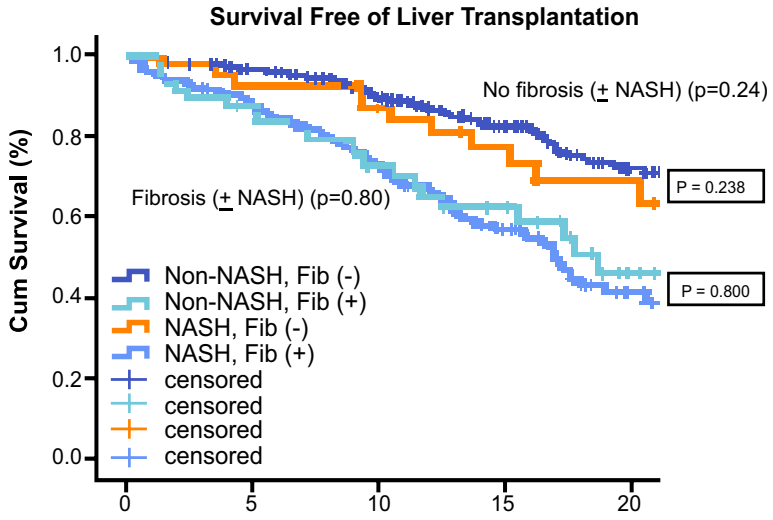
Clinical Gastroenterology and Hepatology
Volume 17, Issue 4, Pages 748-755.e3 (March 2019)
DOI: 10.1016/j.cgh.2018.05.057

Prevalence of etiology in HCC



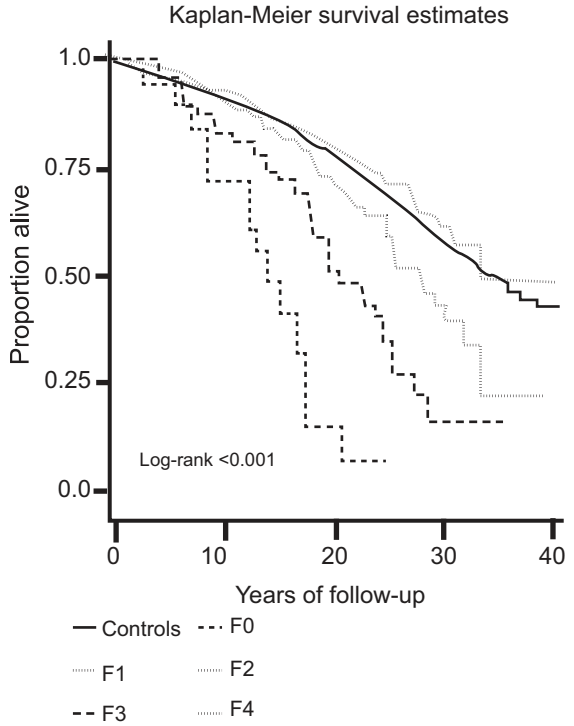
Z. Younozai, et al Clinical Gastroenterology and Hepatology March 2019

Liver Fibrosis, but No Other Histologic Features, Associates With Long-term Outcomes of Patients With NAFLD

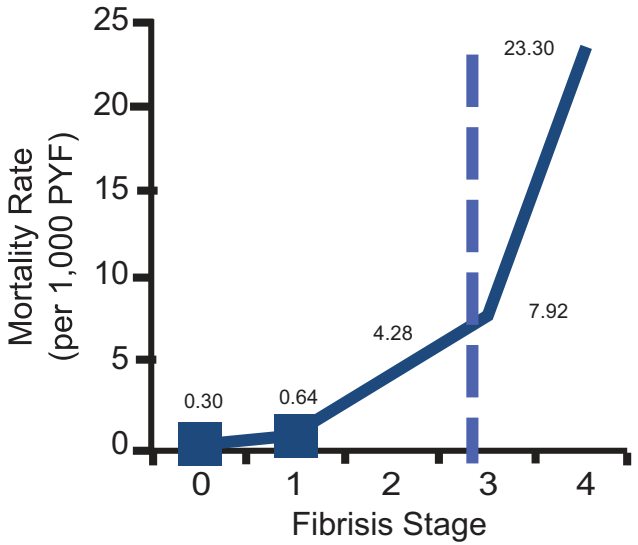


- *Fibrosis stage, but no other histologic features of steatohepatitis, were independently associated with overall lmortality, liver transplantation, and liver-related events*

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

Current Standard for NASH diagnosis is Liver Biopsy.

BUT

Is Liver Biopsy Necessary ?

Table 1. Summary of non-invasive scoring systems based on biochemical markers in NAFLD/NASH

Score	Components	Formula	AUROC	Cut-off values for advanced fibrosis
NAFLD fibrosis score (NFS)[12,37,38]	• Age • Hyperglycemia • BMI • Platelet count • Albumin • AST/ALT ratio	NFS = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet (×10^9/L) − 0.66 × albumin (g/dL)	0.81–0.85	NFS < −1.455 = F0–F2 NFS: 1.455 – 0.675 = indeterminate NFS > 0.675 = F3–F4
FibroTest[5,43]	• Bilirubin • GGT • α2-macroglobulin • Haptoglobin • Apolipoprotein A1	Proprietary formula	0.86	Fibrotest > 0.30: Advanced fibrosis (≥F3)
APRI[37,44,46,47]	• AST • Platelets	APRI = [AST/AST (ULN)]/ platelet (×10^9/L)	0.67–0.78	APRI > 1: Advanced fibrosis (≥F3)
FIB-4[47,55]	• Age • AST • ALT • Platelets	FIB-4 = (age (years) × AST (IU/L))/((PLT [109/L]) × (ALT (IU/L))^2)	0.80–0.82	FIB-4 < 1.30: F0-F1FIB-4 > 2.67: Advanced fibrosis (≥F3)
BAAT[55,56]	• BMI • Age • ALT • Triglycerides	Weighted sum of:B: BMI ≥ 28 = 1 A: Age ≥ 50 yrs = 1 A: ALT ≥ 2N = 1 T: Triglycerides ≥ 1.7 mmol/L = 1	0.67–0.84	BAAT > 2.86: Advanced fibrosis (≥F3)
BARD score[57–59]	• BMI • AST/ALT ratio • DM	Weighted sum of: B: BMI ≥ 28 = 1 point, AAR: AST/ALT ratio ≥ 0.8 = 2, DM = 1 point	0.67–0.87	BARD score > 2: Advanced fibrosis (≥F3)
ELF[63]	• P3NP • TIMP-1 • Hyaluronic acid	ELF = −7.412 + (ln(HA)*0.681) + (ln(P3NP)*0.775) +(ln(TIMP-1)*0.494).	0.90	ELF > 0.3576: Advanced fibrosis (≥F3)
FibroMeter for NAFLD[68]	• Age • Body weight • Glycemia • Platelets • AST • ALT • Ferritin	0.4184 glucose [mmol/L] + 0.0701 AST [U/L] + 0.00008 ferritin [μg/L] − 0.0102 platelet [g/L] − 0.0260 ALT [U/L] + 0.0459 body weight [kg] + 0.0842 age [years] + 11.6226	0.94	FibroMeter for NAFLD > 0.49: Significant fibrosis (≥F2)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; APRI, AST platelet ratio index; BAAT, BMI, age, ALT, triglycerides; BARD, BMI, AST/ALT ratio, DM; AUROC, area under receiver operating characteristic curve; BMI, body mass index; DM, diabetes mellitus; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transpeptidase; HA, hyaluronic acid; IFG, impaired fasting glucose; P3NP, procollagen 3 N-terminal peptide; TIMP-1, tissue inhibitors of metalloproteinase-1.

Table 2. Imaging-based assessment of fibrosis in NASH

Modality	Parameter assessed	Cut-off values for advanced fibrosis	AUROC	Comment
Transient elastography (VCTE)[74,75,101]	LSM using assessment of shear wave velocity	Fibroscan® LSM: <7.9 kPa (in NAFLD): No advanced fibrosis LSM: >9.6 kPa (in NAFLD): Advanced fibrosis	0.82–0.93	• Cheap • Reproducible • Use of XL probe may under-report LSM
Magnetic resonance elastography (MRE)[93,94]	LSM by shear wave measurement using MRI sequence with motion encoding gradient	MRE LSM: >4.15 kPa: Advanced fibrosis	0.90–0.95	• Expensive • Allows opportunistic assessment of LSM during MRI • Mitigates issues of obesity or presence of ascites
Acoustic resonance force impulse (AFRI)[99,102]	LSM integrating elastography and conventional B-mode ultrasonography	AFRI > 1.98 m/s for F4	0.74–0.85	• Cheap • Uses conventional ultrasound machines with modified algorithm
Supersonic shearwave imaging (SSI)[101,108]	LSM integrating elastography and conventional B-mode ultrasonography with simultaneous assessment of several shear waves of different velocity	SSI LSM > 8.3 kPa	0.83–0.92	• Cheap • Slightly higher reported accuracy for SSI for advanced fibrosis when compared with Fibroscan®

Abbreviations: AUROC, area under receiver operating characteristic curve; LSM, liver stiffness measurement.

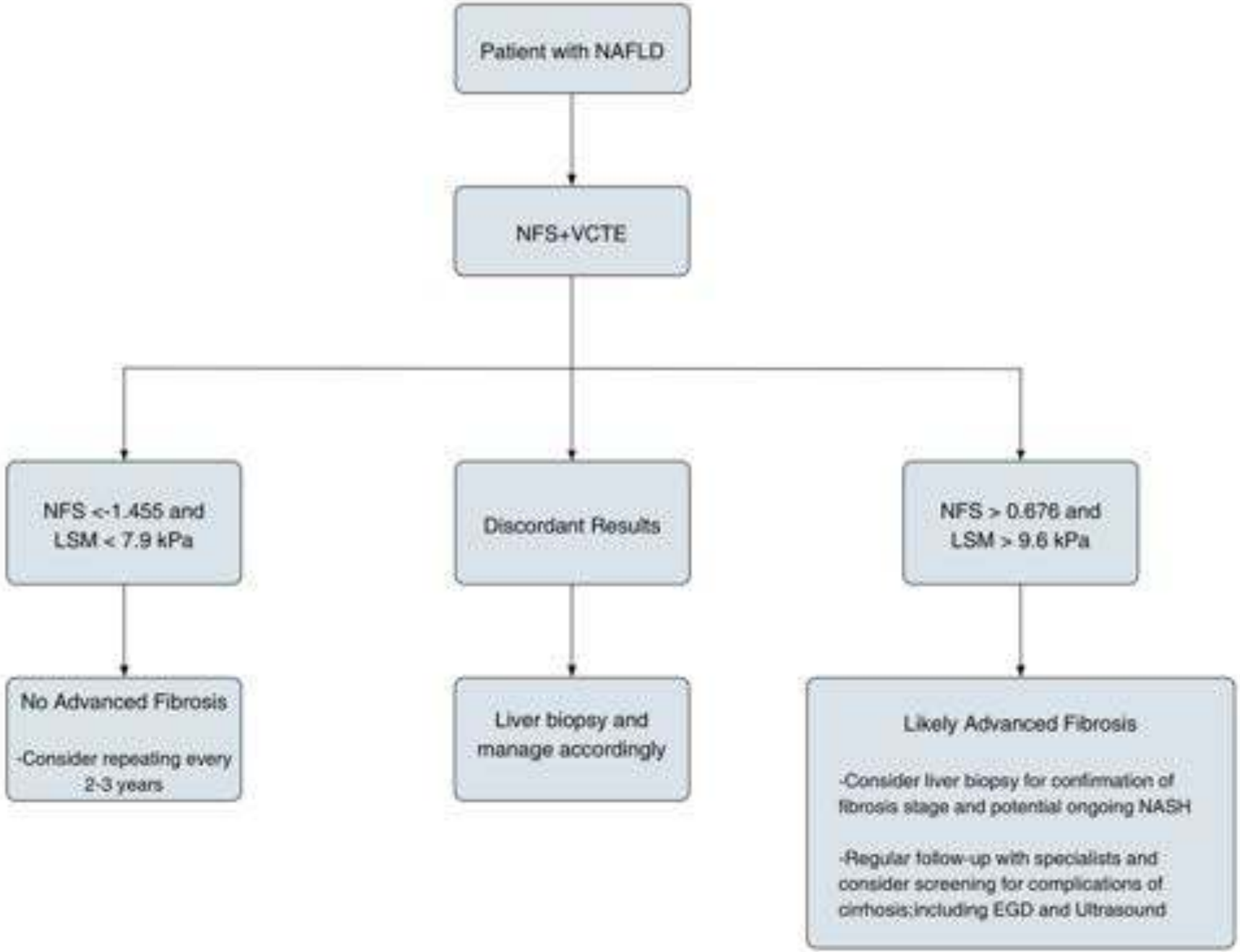
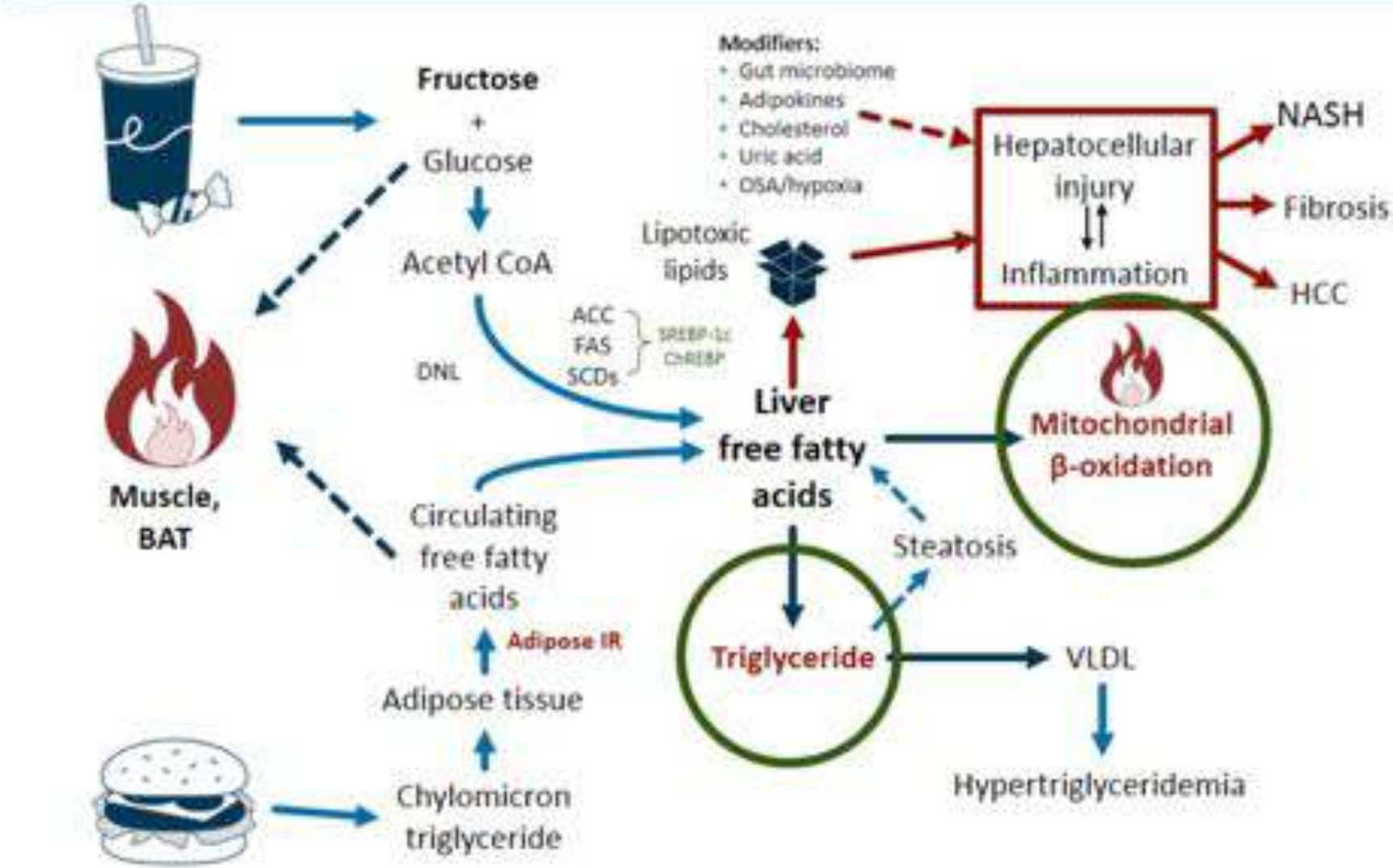


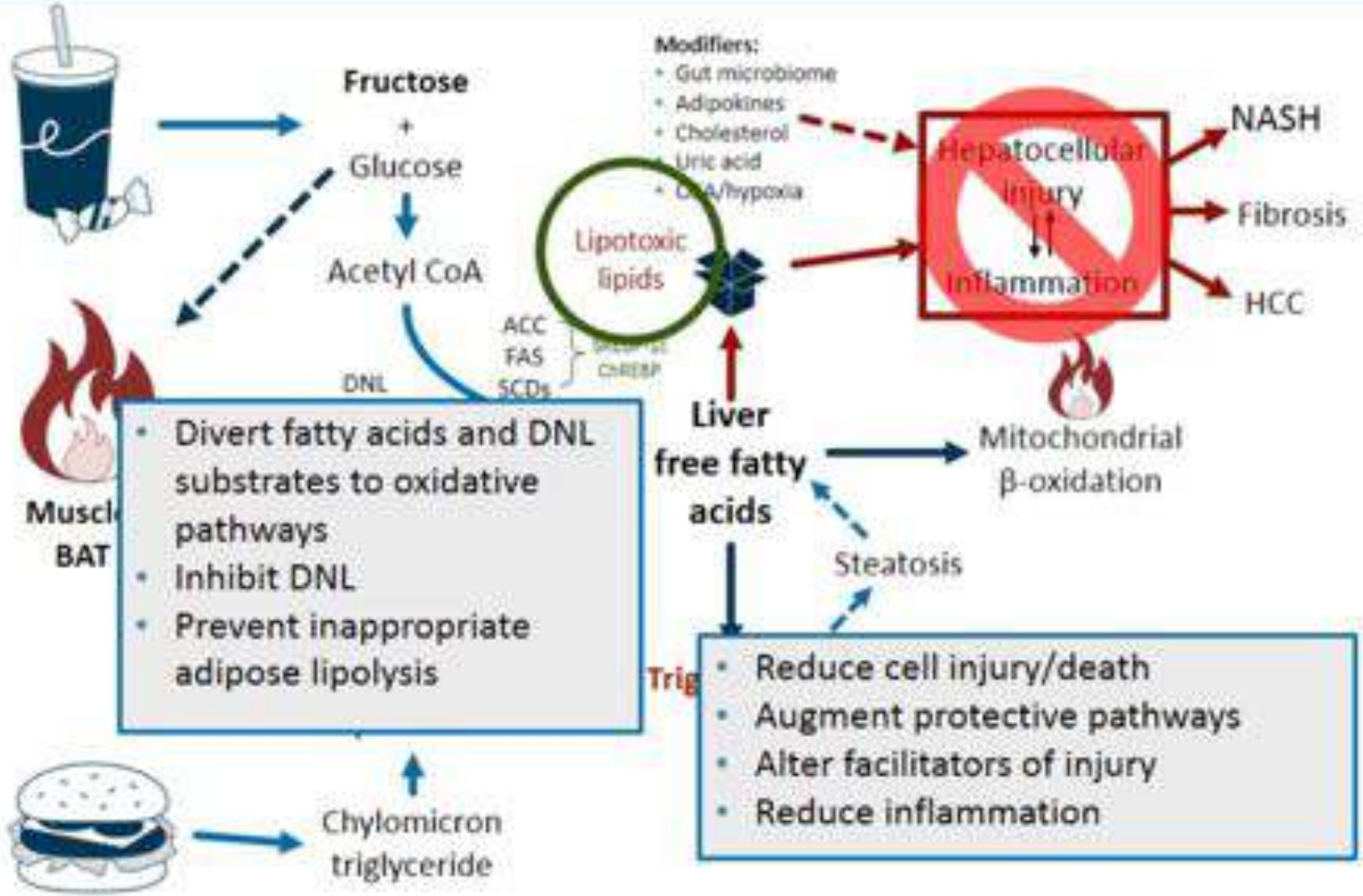
Fig. 1. Proposed algorithm for assessing NAFLD patients for advanced fibrosis.[100]

The Fates of Fatty Acids



Neuschwander-Tetri BA. *BMC Med*. 2017;15:45.

Targets of Therapy



Neuschwander-Tetri BA. *BMC Med*. 2017;15:45.

Treatment Options

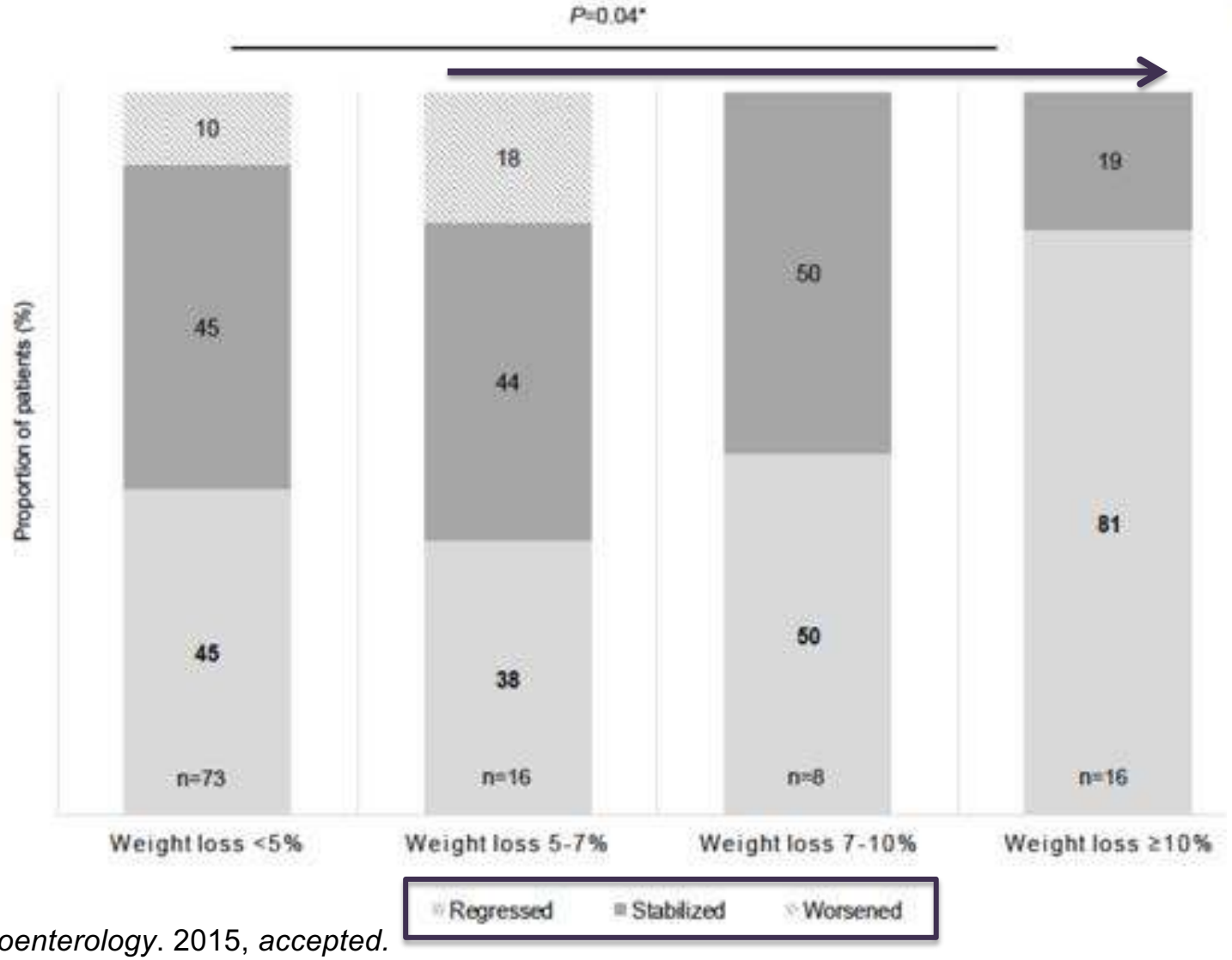
- Weight reduction:
  - Life style changes
  - Bariatric surgery
- Pharmacologic Treatment: (None FDA approved)
  - Current phase 2 and 3 trials showed no potential for NASH cure.
  - Need multiple targets interventions.
  - Strong placebo effects in clinical trials up to 10-15 %.

Weight Loss Works

- Prospective study 293 patients with histologically proven NASH who were encouraged to adopt recommended lifestyle changes to reduce their weight over 52 weeks
- 261 had paired biopsies
- 88 (30%) lost >5% body weight

Vilar-Gomez, et al. *Gastroenterology*. 2015.

Weight Loss Stabilizes or Reduces Fibrosis



Vilar-Gomez, et al. *Gastroenterology*. 2015, *accepted.*

Current Strategies in NASH Pharmacologic Treatment

- Metabolic Modification-Steatosis Reduction
- Anti-Inflammatory
- Anti-Fibrotic

My Recommendations:

- Determine Fibrosis stage
  - Biochemistry blood tests Score-NFS,FIB-4.
  - Fibroscan.
  - Liver biopsy (Conflicting results)
- Life style changes –Diet and Exercise.
- Risk factors modification- such as metabolic syndrome.
- Patients with F3-4, referred to specialists.
- Long term monitor for fibrosis progression.