Hepatic Steatosis: NASH vs NAFLD vs MAFLD

Robert Aran, DO

Objective/ Disclosures

- No Disclosures

- Objectives
  - Identify patients with nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis and initiate therapies that can reduce risk of serious liver damage.
  - Describe treatment options for managing patients with metabolic-associated fatty liver disease.
  - Summarize lifestyle and dietary interventions that can be key factors associated with successfully reducing risk in patients with NAFLD.

Case

55 year old female, named Lisa.

She has a past medical history of HTN on one hypertensive medication, “pre-diabetes”, GERD

Her visit today is to establish care with a PCP. She recently moved from Texas, and works as a lawyer for an oil company. She was referred to you by your spouse, who has know Lisa since college.

Case

-Heart rate 82 bpm
-blood pressure was 132/84
-O2 % saturation 95%
-Calculated BMI 31

- WBC 4.9
- Hgb 14
- MCV 87
- PLT 198

- Na 136
- K+ 4.2
- Cr 1.0
- Glucose 104

- AST 60
- ALT 72
- Alk Phos 134
- Total Bili 1.0
- Albumin 3.4

Patient encounter

-Oh gosh! Look at my liver! Does this mean I have cirrhosis?

-I'm not ready to diagnosis your with cirrhosis and there are test we need to order for an accurate diagnosis.

-Let me start with a few questions. Do you drink alcohol?

-Well no? I mean , I have a few cocktails here and there.. but I'm not an alcoholic or anything!

- So I bet every primary care / ER doc / surgeon has this conversation weekly, if not daily.
  - -Maybe the conversations starts because of steatosis seen on an unrelated CT scan…
- Patients tend to associate liver disease with alcohol abuse, and our history gathering reinforces that thought.
  - Be careful and clear with your questions
  - Explain why you are asking these questions
  - Try not to sound accusatory.

Alcohol Associated Liver Disease

Alcohol associated liver disease

- Active or history of;
  - more than 21 standard drinks per week in men
  - more than 14 standard drinks per week in women.
- Typically we see over a decade of heavy drinking, but there are several factors that might accelerate liver disease with less than a decade of heavy alcohol use…

Vilar-Gomez & Chalasani 2022

Definition: NAFLD

Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD)

- The presence of hepatic steatosis, either from imaging or histology in the absence of secondary causes of fatty liver (e.g., excessive alcohol consumption) or other chronic liver diseases.
- Fatty liver infiltration, affecting at least 5% of hepatocytes, with no evidence of hepatocyte injury

Vilar-Gomez & Chalasani 2022

Risk factors

- Obesity
- Diabetes
- Hypertension
- Polycyclic ovarian syndrome
- Obstructive sleep apnea
- Age
- Sex
- Ethnicity

NASH vs NAFLD

- Both are disease with fat infiltration of the liver, but NASH is causing inflammation
- Need a biopsy for the diagnosis of NASH
  - NAFLD Activity Score (Nas). Histologically scoring system. Not very useful clinically, but used in research
    - Steatosis (0-3)
    - Ballooning (0/2)
    - Lobular inflammation (0-3)

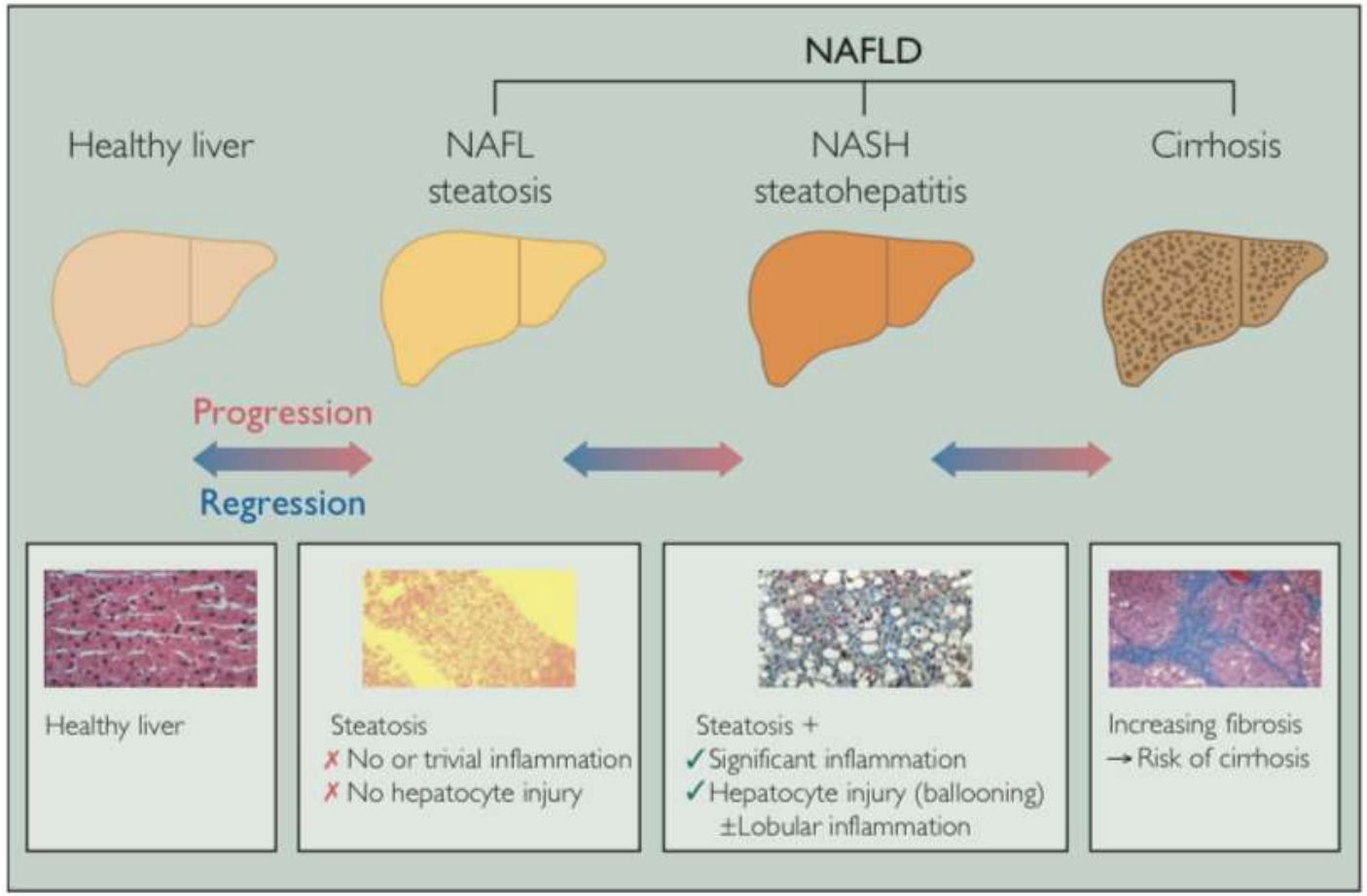
NASH

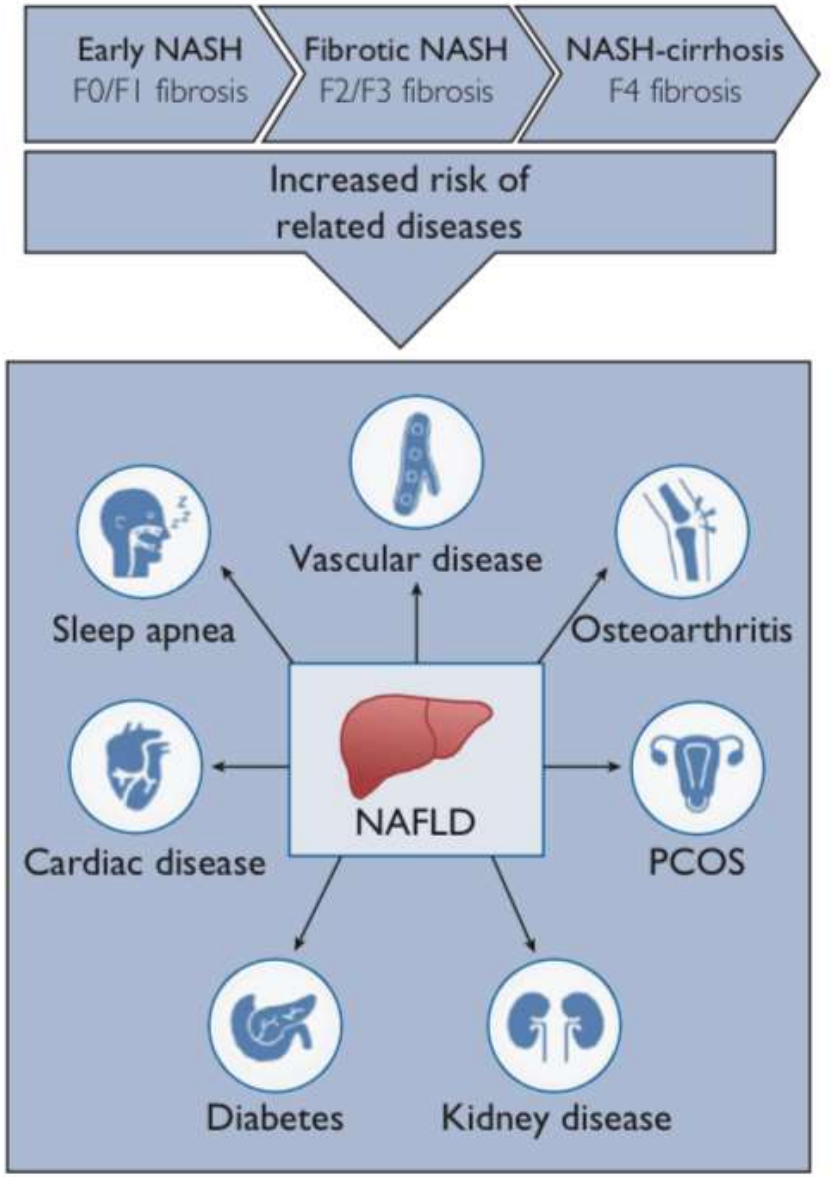
Non alcoholic steatohepatitis

- Non-alcoholic steatohepatitis (NASH): the presence of necroinflammation with or without fibrosis in a background of fatty liver.
- This is a histological diagnosis.
  - Emphasis for appropriate charting/ documentation purposes
  - I don't use the as an official diagnosis unless there is biopsy, but I've defiantly put "likely NASH related cirrhosis"

NAFLD prevalence
Global: 25.2% (33.5% by 2030)
United States: 24.1% (~100M adults by 2030)

NASH prevalence
Global: 1.5%–6.45%





Basu et al 2022

MAFLD
Metabolic associated fatty liver disease
or

MASLD
Metabolic dysfunction associated steatotic liver disease

Metabolic associated fatty liver disease (MAFLD)

- Hepatic steatosis is the hepatic manifestation of metabolic syndrome.

- Defined by the presence of hepatic steatosis with diabetes, obesity, or at least two minor metabolic abnormalities.
  - Waist circumference 102 cm [size 40] men or 88cm [34] in women
  - HbA1c 5.7–6.4%,
  - Blood pressure ≥130/85 mmHg
  - Lipid abnormalities

Younossi et al 2016

MAFLD-

Metabolic associated fatty liver disease

- Takes into account that alcohol may have some contribution to disease, as part of a constellation of other factors
- Clinically, this is the easiest way to describe what you're seeing if you don't spend the 2-5 minutes discussing EtOH use history
- It also places an emphasis on the patient's global metabolic issues, and not to a relationship with or without alcohol.

Case

- Work up negative (negative Hep panel, medication list review etc)
- A1c 5.8
- INR 1.2
- Liver Ultrasound
  - Mild hepatomegaly
  - Increased echogenicity
  - No masses, normal CBD
  - Pancreas obscured by intestinal gas

Patient encounter

-Hey Doc, so how bad is my liver?

-Well, it depends. I don't think you're actively dying of liver disease, and it's possible whatever damage we see now is reversable

-OK so what comes next? We need to figure out what's going on because I'm NOT an alcoholic!?

Obesity and NAFLD

- NALFD association 51%
- NASH association 82%
- Obesity prevalence in US is ~40%, and expected to reach 50% by 2030
  - 33% estimated having metabolic syndrome

Vilar-Gomez & Chalasani 2022

Diabetes and NAFLD

- Estimated 70% of individuals with type 2 diabetes, have nonalcoholic fatty liver disease (NAFLD)

Lomonaco et al 2021

Patient encounter

MyChart Message

- Hi Doctor, I was discussing our visit with my husband, and he asked what my life expectancy was? We have a cruise planned for next summer and I'm wondering if I should cancel that trip?

-Lisa,

I am not concerned at all about you making your trip. In fact, you should take an extra week to enjoy yourself

Life expectancy

- Future-oriented patients will ask you something like this. You need to be able to risk stratify and objectively classify the disease severity.
- Up to 1 in 5 patients with NAFLD have NASH
  - considerable morbidity and mortality, increase for cirrhosis and hepatocellular carcinoma (HCC)

Long et al 2022

Life expectancy

- NAFLD can double risk for all cause mortality
- Estimated loss of up to 6 years of life expectancy

Shang et al 2021

Patient encounter

Hey Doc,

-I was watching Oprah, and she was interviewing a liver specialist. Do you think I should go see that lady to make sure we aren't missing anything?

Lisa

-I feel that we have everything under control, but you are due for your next screening colonoscopy. Why don't I send you to a local gastroenterologist for your colonoscopy and they can talk to you a little more about your liver.

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

ELSEVIER

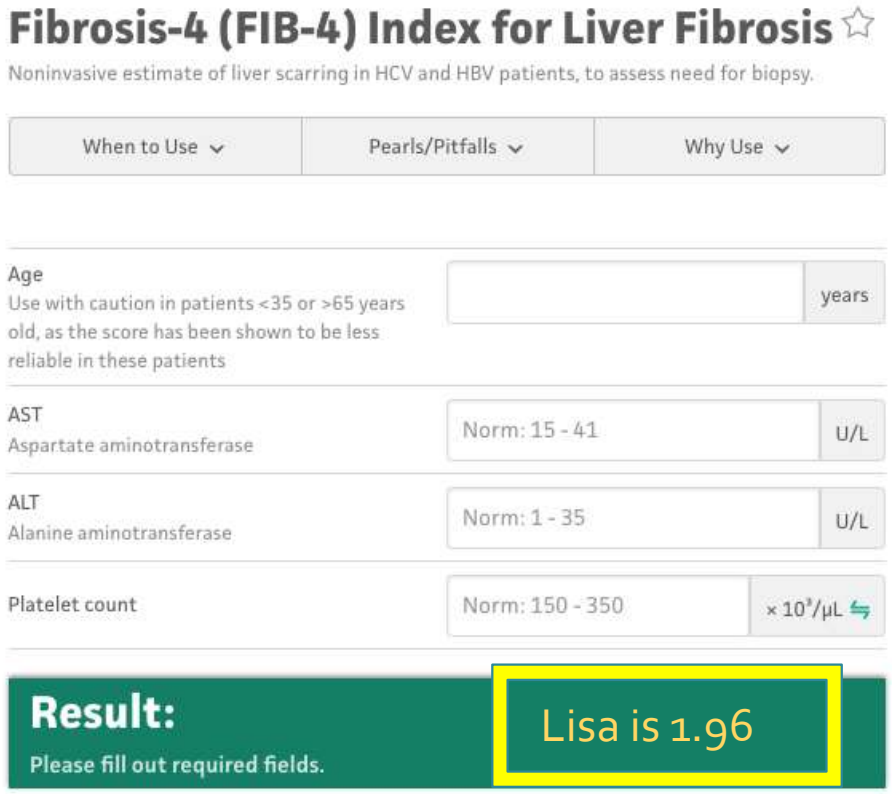
aga

t al 2021

FIB-4

LOW RISK
FIB-4 < 1.3 or
LSM < 8 kPa or
liver biopsy F0-F1

- FIB4 index < 1.30 had a 90% negative predictive value for advanced liver disease
- A FIB 4 >2.67 had an 80% positive predictive value for advanced liver disease
- * young patients will have lower scores, old patient will have higher scores.



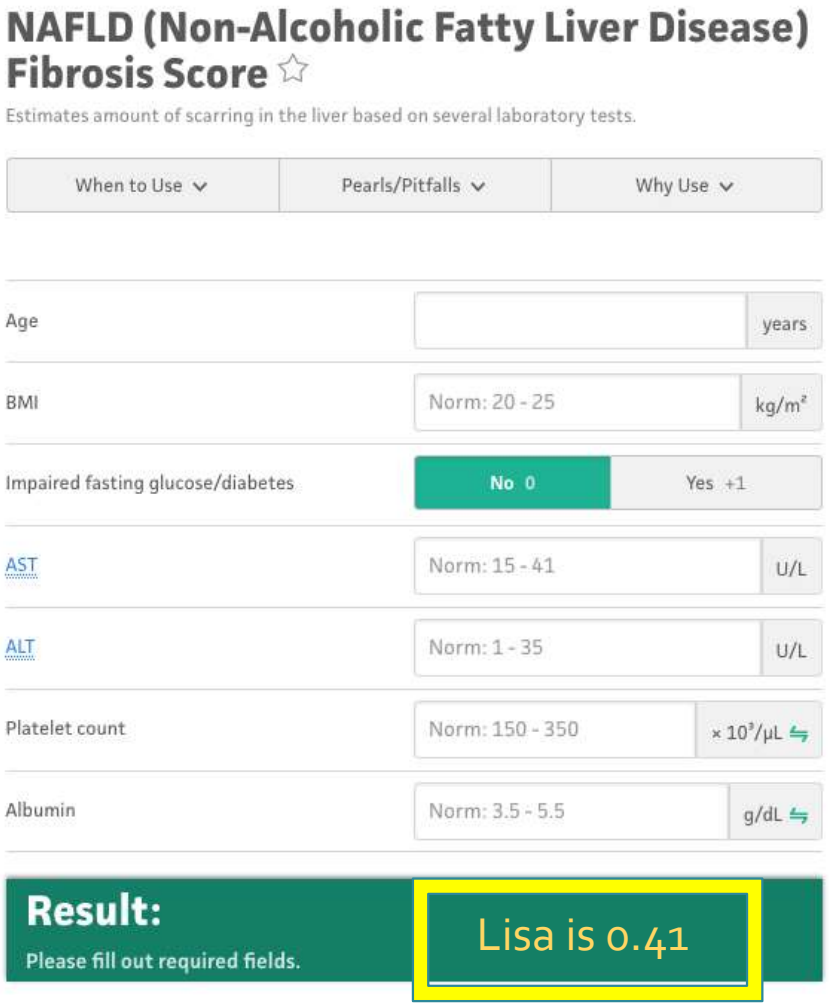
Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease

Amy G Shah [1], Alison Lydecker, Karen Murray, Brent N Tetri, Melissa J Contos, Arun J Sanyal; Nash Clinical Research Network

Shah et al 2009

NAFLD fibrosis score

- NAFLD score < -1.455 Fo- F2 disease (~90% negative predictive value)
- NAFLD score -1.455- 0.675 Indeterminate
- NAFLD score > 0.675 F3- F4 (~96% positive predictive value)



LOW RISK

FIB-4 < 1.3 or
LSM < 8 kPa or
liver biopsy F0-F1

LSM- Liver Stiffness Measurement

- Non invasive imaging to determine liver stiffness, thus fibrosis.
- Several methods
  - MRI- elastography
  - Shear-wave elastography (SWE)
  - Vibration-controlled transient elastography

- Typically reported in kilopascals (kPa)
- Normal between 2-7 kPa
- >10 -13 kPa usually correlates between F2 and F3
- >13 typically seen with cirrhosis.
- >Esophageal varices seen around 20 kPa

Vibration Controlled Transient Elastography

Liver biopsy

- Trichrome stain to evaluate fibrosis.
- Batts-Ludwig Scoring System
- Stage 1- peri-sinusodial / portal fibrosis
- Stage 2- Fibrosis extends beyond portal tracts, beginning of "bridges" and septae
- Stage 3-bridging fibrosis , septae formation
- Stage 4-cirrhosis; regenerative nodules, fibrous bands, entire liver

Fibrosis on Biopsy

LOW RISK

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LSM < 8 kPa or
liver biopsy F0-F1

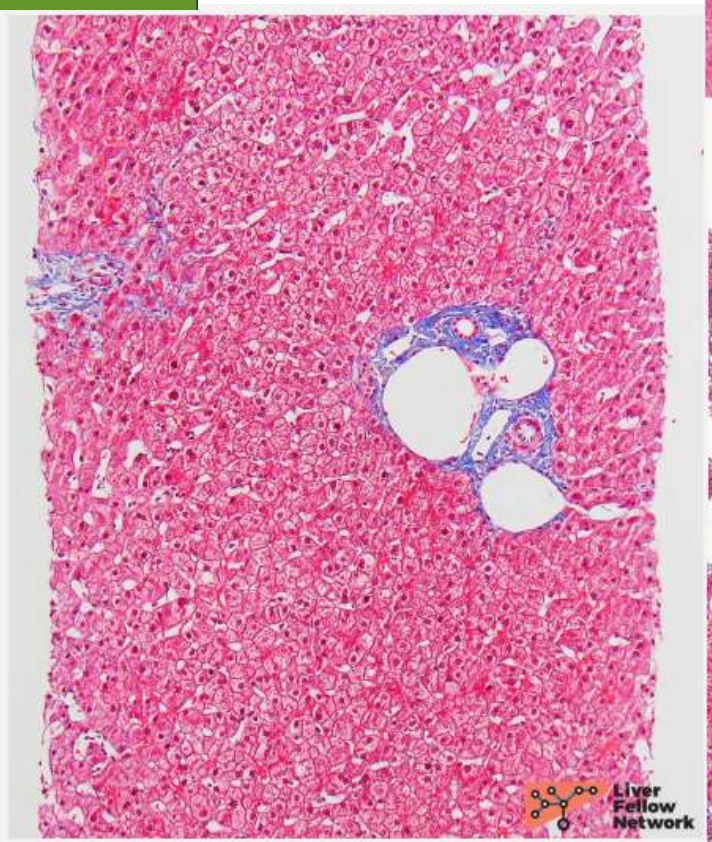
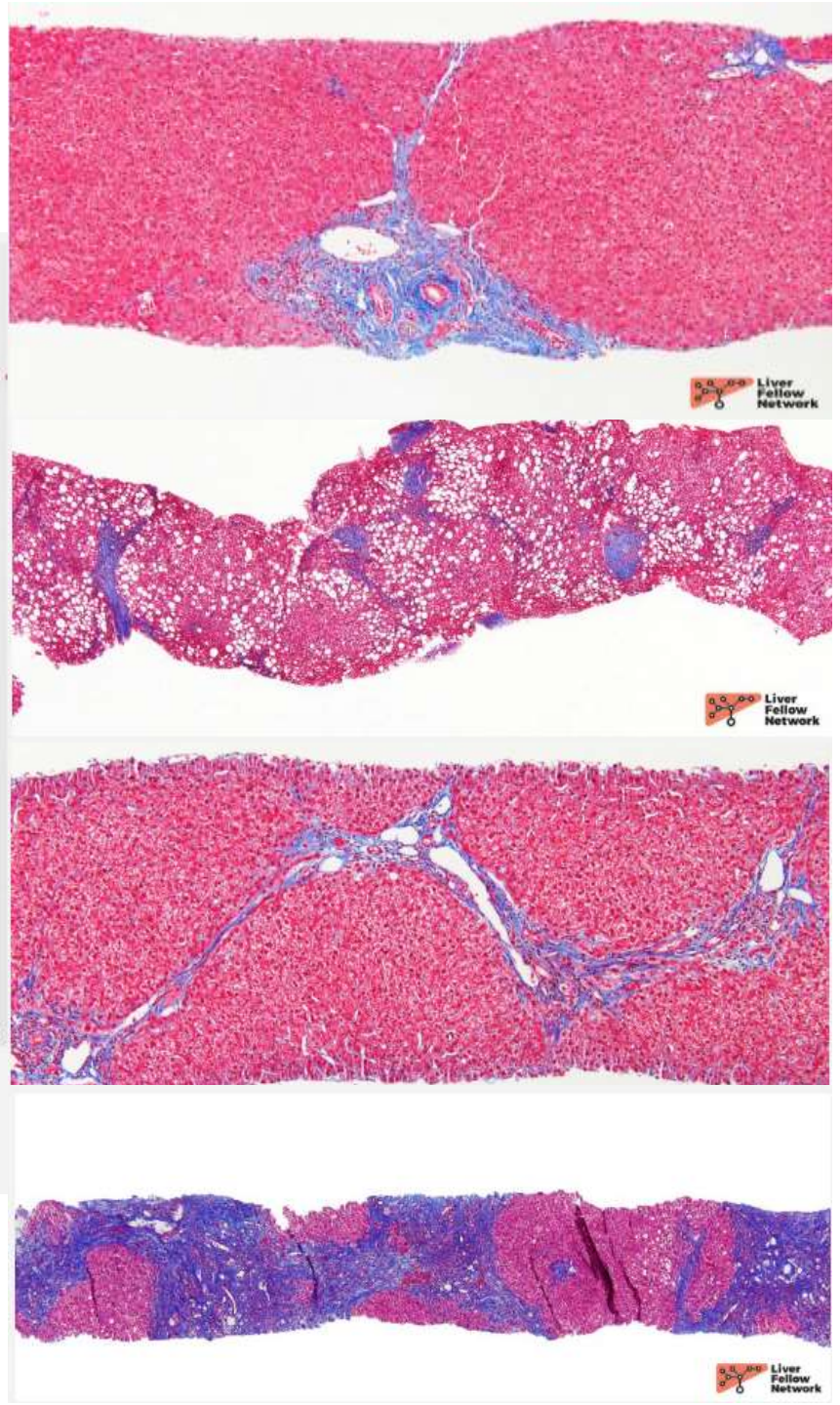
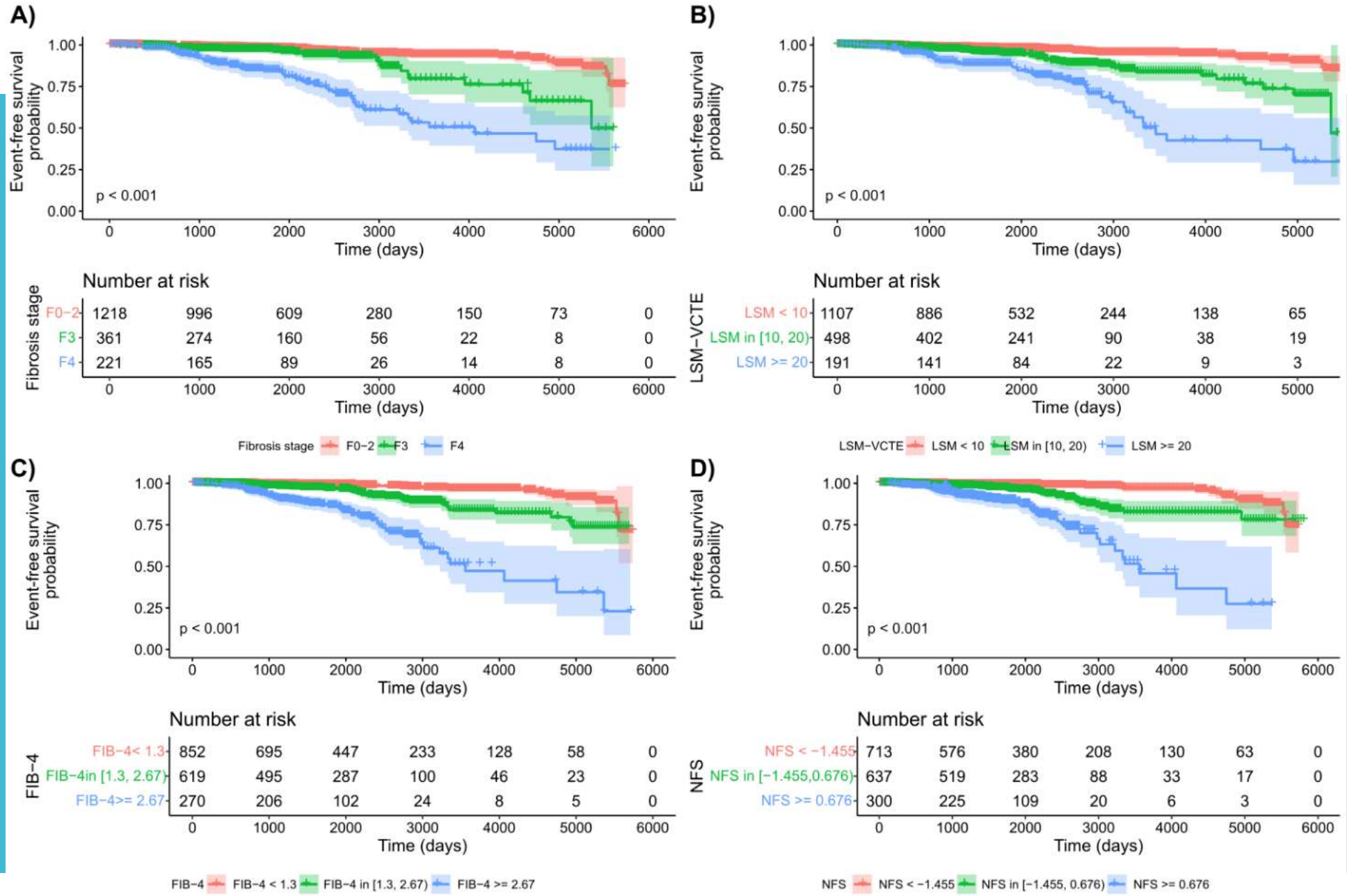


Figure 2. Trichrome stain showing normal collagen deposition (blue) in a portal tract.



https://liverfellow.org/

Biopsy vs non-invasive evaluation of prognosis



Mozes- unpublished 2023

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Kanwal et al 20

Indeterminate risk

The Grey Zone

- This is the patient population the field is focusing on to reduce morbidity and mortality
- Nash leads to cirrhosis in about 20% of patients
- Cardiovascular event is more like to cause death in this patient population than due to direct liver-related event (bleeding, cancer etc)

FDA approved therapy for NASH

- No FDA approved treatments for NASH

What Medication Can You Use?

Vitamin E

- Indications are for people with biopsied proven NASH
- Give 800 IU/ day
- Not recommended for patients with diabetes and cirrhosis.
- Concerns for all cause mortality and possible prostate cancer in men.
- Can improve steatohepatitis but not fibrosis.

Kanwal et al 2021

Basu et al 2022

What Medication Can You Use?

- Metformin
  - Not recommended, did not have good histological improvement
- Pioglitazone
  - Can be used off label with biopsy proven NASH (with or without T2DM) and will help inflammation and ballooning but wont improve fibrosis. Side effects are weight gain and heart failure?
- GLP-1 & SGLT2
  - Semaglutide: in 2021 NEJM article also showed NASH resolution but did not show improvement to fibrosis.
  - risk: cholelithiasis, pancreatitis, delayed gastric emptying

Kazemi et al 2012

Newsome et al 2021

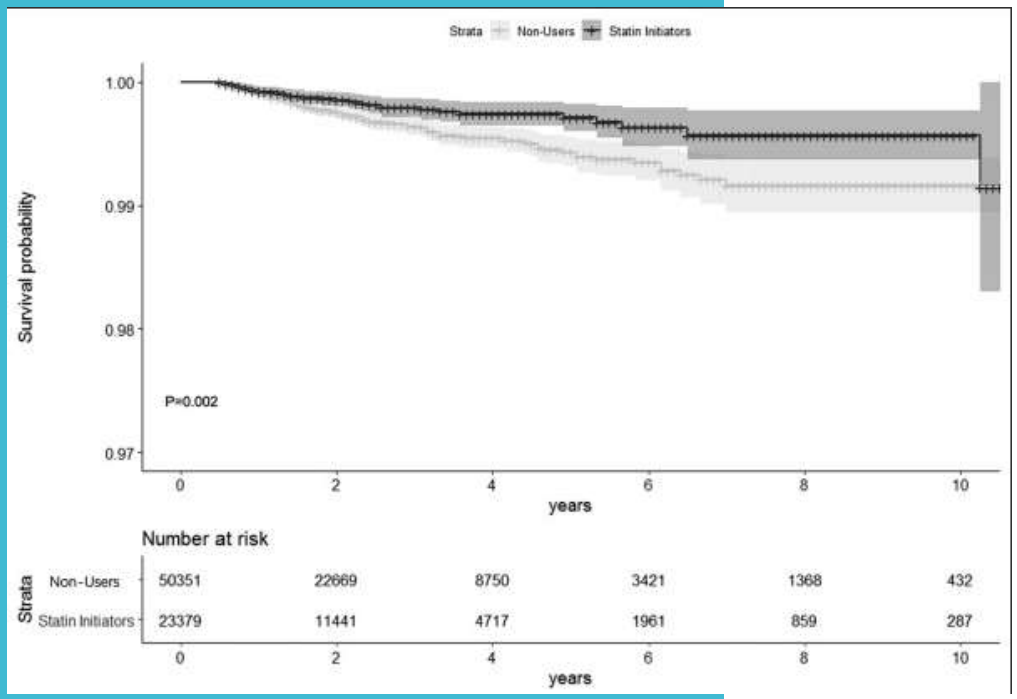
What Medication Can You Use?

Statins

- Not officially recommended to treat NASH.. but not contraindicated either

Statin Use and Reduced Hepatocellular Carcinoma Risk in Patients With Nonalcoholic Fatty Liver Disease

Biyao Zou • Michelle C. Odden • Mindie H. Nguyen



- 272,431 adults with NAFLD diagnosis, which consists of 73,385 statin initiators and 199,046 nonusers.
- NAFLD patients with statin use associated with 56% hazard reduction in developing HCC, with better reduction in risk with cumulative doses

Zou et al 2023

Hepatocellular carcinoma

- The incidence rate of hepatocellular carcinoma (HCC) has been increasing for the last 3 decades, and we can treat hep C…
- NAFLD expected to become the leading cause of HCC in developed countries

Hepatocellular carcinoma

- Based on epidemiological studies, drinking coffee may reduce the risk of hepatocellular carcinoma.
  - 2-3 cups / day ~40% risk reduction compared to non drinkers.

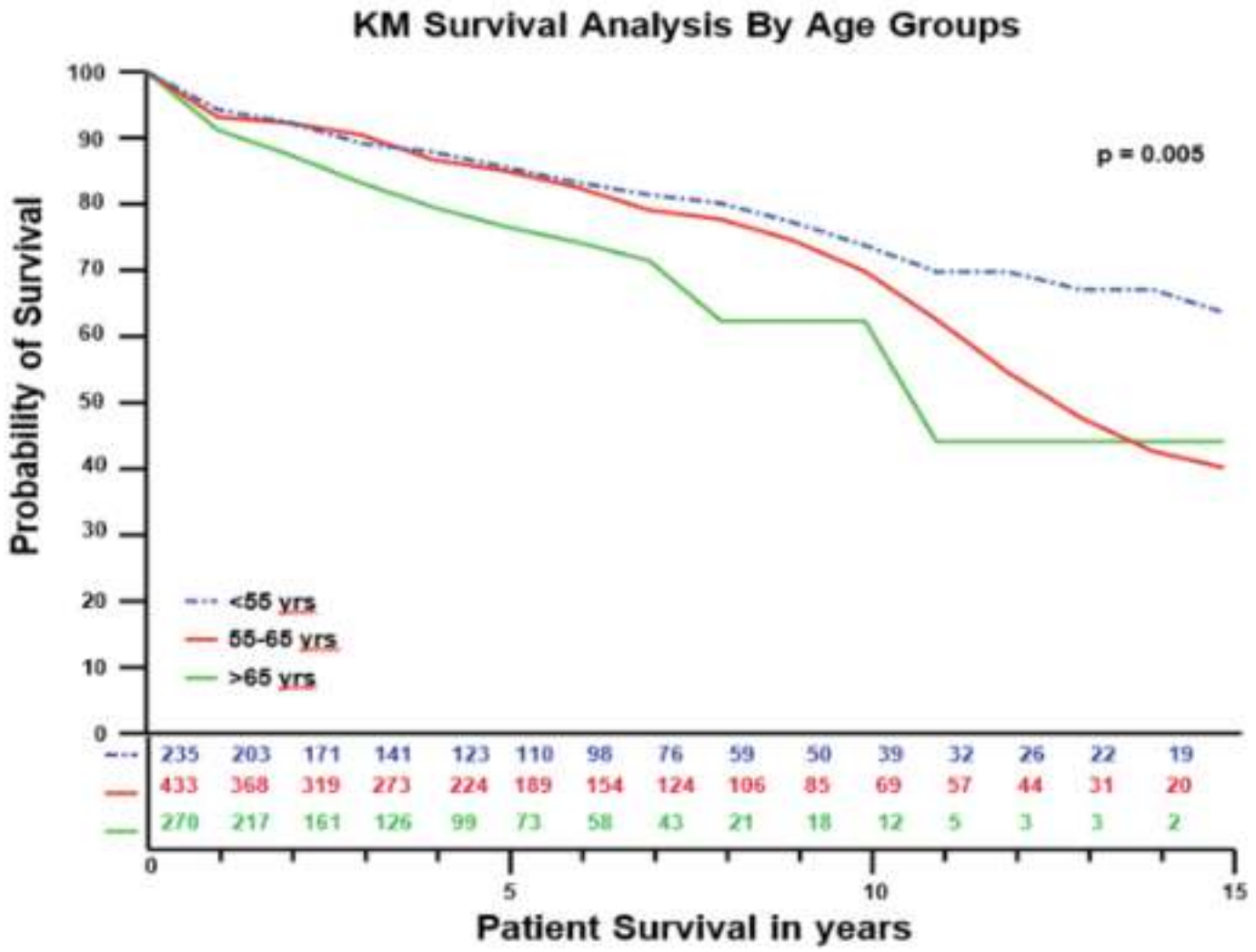
Setiawan et al 2015

Transplant- What You Should Know

- Nonalcoholic steatohepatitis (NASH) is the leading indication for liver transplant (LT) in women and the elderly
- The 1-, 3-, 5-, 10-, and 15-year survival of the cohort was 93%, 88%, 83%, 69%, and 46%, respectively
- 3 most common causes of death were CVD 36 (18%), infection-related 38 (19%), and cancer 34 (17%)
- Recurrent NASH cirrhosis in 20%

Rinella et al 2023

Survival After Transplant



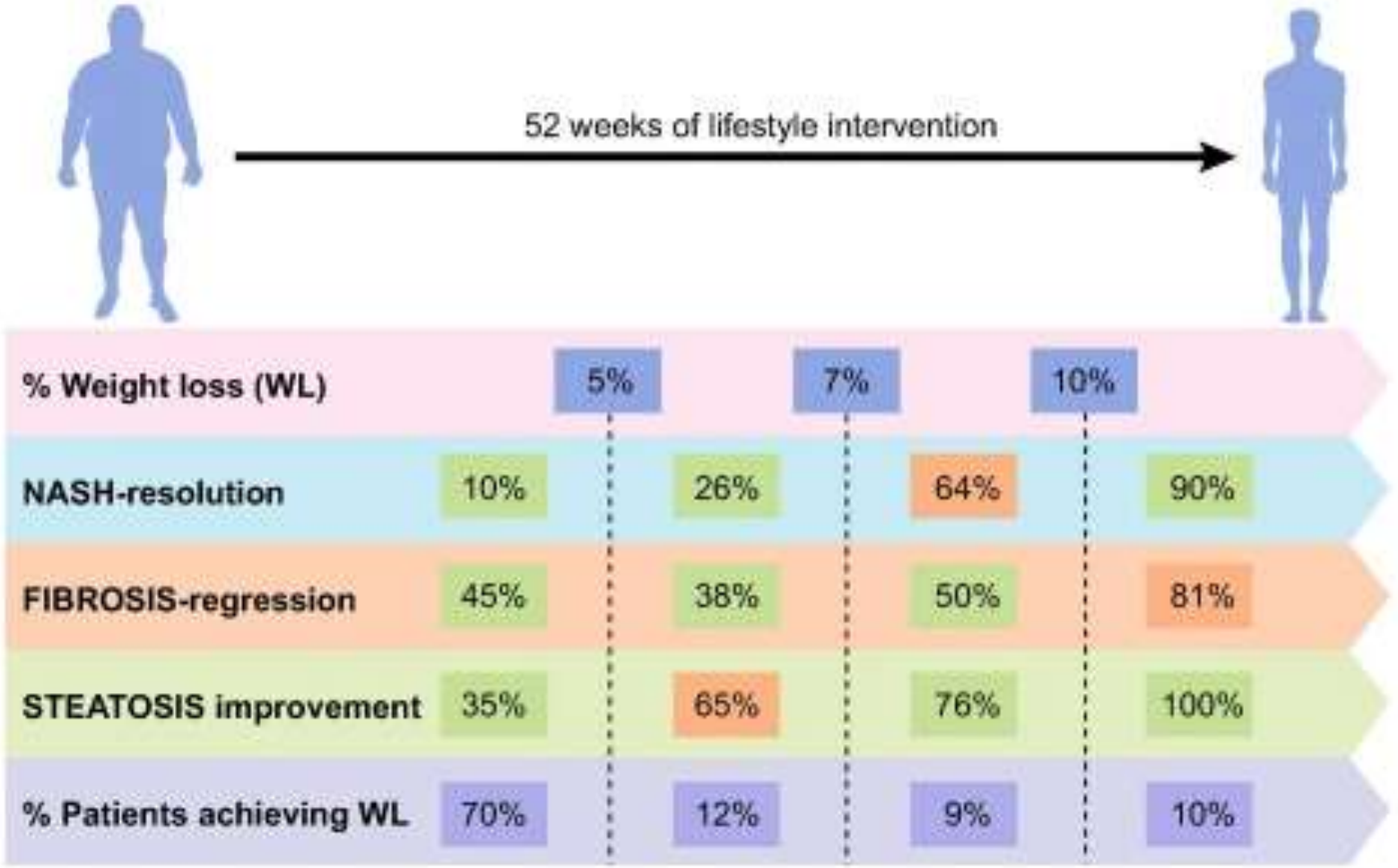
Rinella et al 2023

Patient encounter

-Good morning Doctor,
I appreciate the discussion about medications we can start for my liver disease. I've been doing a lot of my own research and would like to try a natural approach. Apart from the Vitamin E, what else can I consider?

-The most proven thing we can do is try and achieve >10% total body weight loss. We can do this by cutting calories, eating healthy (I recommend Mediterranean diet) and exercise >150 minutes per week

Weight loss and NASH Resolution



Vilar-Gomez & Chalasani 2022

Diet

- Patients should follow a Mediterranean diet; associated with a decrease in hepatic steatosis, improved insulin sensitivity, and lower mortality- Recommended by EASL
  - Wine? We'll get to that..
- Randomized controlled trials suggest snacking is an independent risk factor in hepatic steatosis.
- Limit refined carbohydrates and sugar intake

Koopman et l 2014

Kanwal et al 2021

Exercise

- London (UK) bus drivers, who spend most of their day sitting, were 3x as likely to have a coronary heart disease than bus conductors, who spend most of the day physically active collecting tickets on double-decker buses
- Exercise alone can yield a 20–30% relative reduction in intrahepatic lipid (weight loss can reach 80%)
- No "liver guidelines" for exercise, so I recommend 150 minutes of moderate exercise that the CDC recommends.

Hashida et al 2017

Morris et al 1953

Koutoukidis et al 2019

Bariatric surgery

- NASH/ NAFLD is not a contraindication to surgery, and if the patient qualifies, they should be considered.
  - BMI > 35 kg/m^2
  - BMI > 30 kg/m^2 with T2DM, OR who were not successful in nonsurgical weight loss methods.
- In general, the field is moving away from gastric banding, and toward Roux en Y and sleeve gastrectomy

American Society for Metabolic and Bariatric Surgery

Repeat testing

- If initially low risk, repeat FIB-4 in 2-3 years
  - Recommended in T2DM studies, 12% of patients had >30% increase in kPa in 3 years
- Follow weight- lowest total body weight is achieve around 6 months, with many patients regaining weight after 2 years.
  - 3 month in clinic follow up for 3 visits?
- Look AHEAD study study for T2DM
  - 5,145 participants
  - 1 hour group sessions x3/week for 6 months, weekly personal trainers. Years 2-8 > 200 minutes exercise / week
  - Structured meal plans 1200-1800 kcal/day
  - >5% weight loss in 50% of participants

Look AHEAD 2014

Vilar-Gomez & Chalasani 2022
Romero-Gomez et al 2017

Patient encounter

Hey Doc,
I was thinking, my mom always had stomach issues, and my sister needed her gallbladder removed. Can my liver disease be genetic? Should they get screened too?

-There isn't a specific genetic test, but metabolic syndrome can run in families, especially the ones that don't.

Genetic factors to NAFLD

- PNPLA3- most prevalent in Hispanics (49%), less common in non-Hispanic Europeans (23%), and the least common in African Americans (17%)
  - TM6SF2 probably the second most cited gene
- Valenti et al (2010) reported that the PNPLA3 variant was associated with hepatic steatosis and NAFLD severity (per liver biopsy) independent of age, body mass index (BMI), or diabetes.
- Patients with the CG and GG genotype did not respond as well to lifestyle modification at reducing haptic steatosis.

Romero-Gomez et al 2017

Valenti et al 2010

Krawczyk et al 2020

PNPLA3

Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease

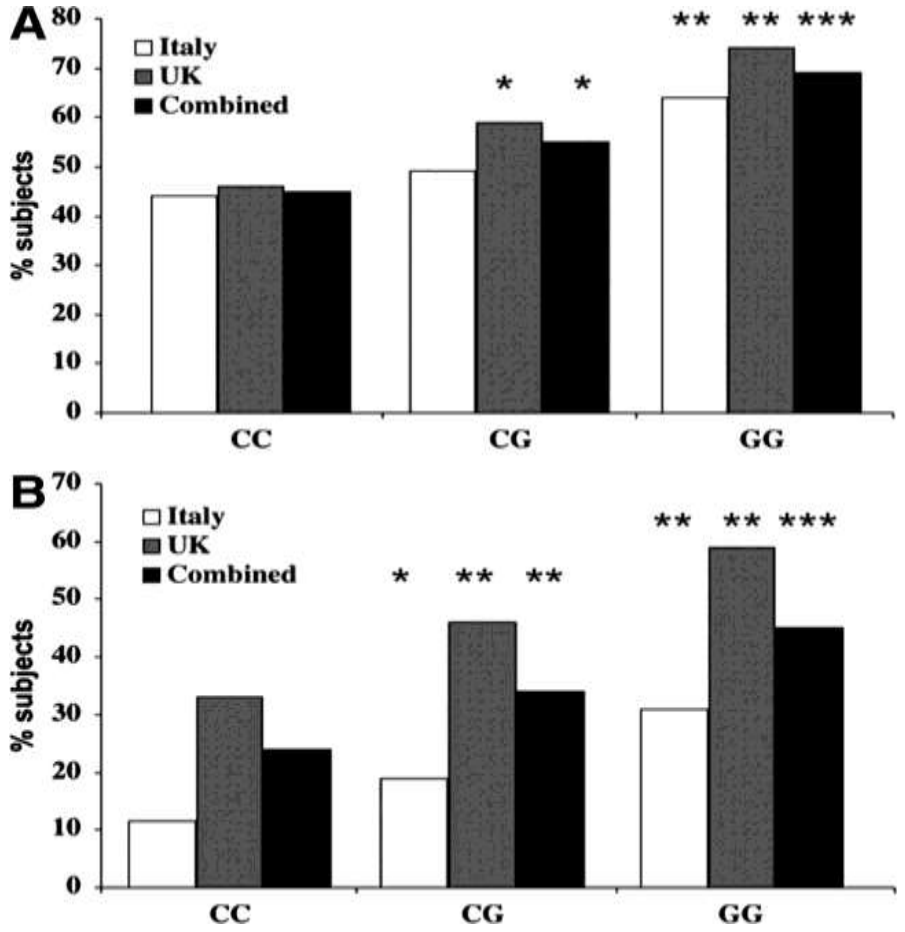


Figure 1
Open in figure viewer
PowerPoint
Prevalence of (A) NASH and (B) fibrosis in 591 biopsied patients with NAFLD subdivided according to the adiponutrin rs738409 C→G genotype (encoding for I148M) and the referral center. (A) P = 0.0002 at chi-squared for trend for the prevalence of NASH across the adiponutrin genotypes in the combined series. (B) P < 0.0001 at chi-squared test for trend for the prevalence of fibrosis >1 across the adiponutrin genotypes in the combined series. *P < 0.05, **P < 0.005, ***P < 0.0001 versus CC genotype

Hepatology, Volume: 51, Issue: 4, Pages: 1209-1217, First published: 26 March 2010, DOI: (10.1002/hep.23622)

Valenti et al 2010

Patient encounter

MyChart Message

What about alcohol? My gas station attendant told me wine is actually good for your liver!

Thanks,

-Lisa

Well, I'm sure your friend has good resources, but that isn't the whole truth. There is a study showing 2-3 glasses of wine per week is associated with a lower ALT. But clinically it doesn't seem to "help" your liver, and I recommend you completely stop drinking alcohol.

Can I drink Alcohol?

Modest Wine Drinking and Decreased Prevalence of Suspected Nonalcoholic Fatty Liver Disease

Winston Dunn[1], Ronghui Xu[2], Jeffrey B. Schwimmer[3]

[1]Division of Gastroenterology, Department of Medicine, University of California, San Diego, San Diego, CA

- Cross sectional study done between 1988 and 1994
- Included 21 yo, white, black and Mexican with <2 drinks per day
- NAFLD was defined by anyone with elevated ALT that didn't have other liver disease
  - (etoh abuse, hepatitis, iron sat >50%, or drug use that is associated with DILI)
- When adjusted for age, sex, education, income and location- Wine had consistently and significantly lower levels of ALT than non drinkers. NAFLD seen in 14% of non drinkers, and 8.5% in wine drinkers

Dunn et al 2008

Alcohol

Alcohol Use

Even low alcohol intake is associated with increased risks for advanced liver disease, and cancer, in individuals with NAFLD

- averaging more than 1 drink per day doubles the risk for adverse liver-related outcomes compared with lifetime abstainers

Åberg et al 2020

Take Home Points

- NALFD and NASH are a spreading epidemic associated with significant morbidity.
- NASH is the aggressive stage of NAFLD
- NASH with evidence of advanced fibrosis should be the target population we focus on for intervention.
- Non invasive testing has become the norm to risk stratify patients.

References

- Naga Chalasani, MD, FACG , Zobair Younossi, MD, FACG, Joel E. Lavine, MD, PhD, Anna Mae Diehl, MD, Elizabeth M. Brunt, MD, Kenneth Cusi, MD, Michael Charlton, MD , Arun J. Sanyal, MD. The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. AGA| VOL 42, ISSUE 7, P1592-1609, 2012
- Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology. 2006 Oct;44(4):865-73. doi: 10.1002/hep.21327. PMID: 17006923.
- Vilar-Gomez, Eduardo,MD; Chalasani, Naga MD. Therapeutic management of NAFLD. GI&Hepatology News. August 2022
- Basu R, Noureddin M, Clark JM. Nonalcoholic Fatty Liver Disease: Review of Management for Primary Care Providers. Mayo Clin Proc. 2022 Sep
- Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. statel evel prevalence of adult obesity and severe obesity. N Engl J Med. 2019
- Krawczyk M, Liebe R, Lammert F. Toward genetic prediction of nonalcoholic fatty liver disease trajectories: PNPLA3 and beyond. Gastroenterology. 2020;158(7):1865-1880.e1.
- Valenti, L., Al-Serri, A., Daly, A.K., Galmozzi, E., Rametta, R., Dongiovanni, P., Nobili, V., Mozzi, E., Roviaro, G., Vanni, E., Bugianesi, E., Maggioni, M., Fracanzani, A.L., Fargion, S. and Day, C.P. Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. Hepatology, 51: 1209-1217. 2010
- Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and out-comes. Hepatology. 2016;64:73–84
- Long MT, Noureddin M, Lim JK. AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review. Gastroenterology. 2022
- Mary E. Rinella, Sanjaya K. Satapathy,Danielle Brandman,Coleman Smith,Sal Elwir,Jonathan Xia,Meg Gibson,Carlos Figueredo,Mounika Angirekula,Jason M. Vanatta,Raiya Sarwar,Yu Jiang,Dyanna Gregory,Tandy Agostini,JimIn Ko,Pradeep Podila,Grace Gallo et al. Factors Impacting Survival in Those Transplanted for NASH Cirrhosis: Data From the NailNASH Consortium. Clinical Gastroenterology and Hepatology. vol 21, 2, P445-455, Feb 2023
- Lomonaco R., Godinez Leiva E., Bril F.et al. Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient setting: the need for systematic screening.Diabetes Care. 2021

References

- Fasiha Kanwal, Jay H. Shubrook, Leon A. Adams, Kim Pfotenhauer, Vincent Wai-Sun Wong, Eugene Wright, Manal F. Abdelmalek, Stephen A. Harrison, Rohit Loomba, Christos S. Mantzoros, Elisabetta Bugianesi, Robert H. Eckel, Lee M. Kaplan, Hashem B. El-Serag, Kenneth Cusi . Clinical Care Pathway for the Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease . Gastroenterology. Volume 161 Issue 5 Pages 1657-1669 (November 2021)
- Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009
- Kazemi R, Aduli M, Sotoudeh M, Malekzadeh R, Seddighi N, Sepanlou SG, Merat S. Metformin in nonalcoholic steatohepatitis: a randomized controlled trial. Middle East J Dig Dis. 2012
- Åberg F, Puukka P., Salomaa V. et al. Risks of light and moderate alcohol use in fatty liver disease: follow-up of population cohorts. Hepatology. 2020;
- Koutoukidis D.A., Astbury N.M., Tudor K.E. et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. JAMA Intern Med. 2019; 179: 1262-1271
- Manuel Romero-Gómez, Shira Zelber-Sagi, Michael Trenell. Treatment of NAFLD with diet, physical activity and exercise. Journal of Hepatology. Vol 67, Iss 4 May 2017
- Dunn W., Xu R., Schwimmer J.B. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. Hepatology. 2008
- Koopman K.E., Caan M.W, Nederveen A.J., Pels A., Ackermans M.T., Fliers E.. Hypercaloric diets with increased meal frequency, but not meal size, increase intrahepatic triglycerides: a randomized controlled trial.. Hepatology. 2014;
- Setiawan V.W., Wilkens L.R., Lu S.C, Hernandez B.Y., Le Marchand L., Henderson B.E. Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. Gastroenterology. 2015
- Morris J.N., Heady J.A., Raffle P.A., Roberts C.G., Parks J.W. Coronary heart-disease and physical activity of work. Lancet. 1953
- Hashida R.Kawaguchi T. Bekki M.Omoto M.Matsuse H.Nago T. Aerobic *vs.* resistance exercise in non-alcoholic fatty liver disease: A systematic review. *J Hepatol.* 2017
- Look AHEAD Research Group. Eight years weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity. 2014
- Shang Y, Nasr P, Widman L, Hagstrom H. Life expectancy and risk of cardiovascular disease in non-alcoholic fatty liver disease: a population-based cohort study. EASL International Liver Congress, June 23-26, 2021