EthNoHep

ESIM
ETHIOPIAN SOCIETY OF
INTERNAL MEDICINE

MAFLD

Ethio Health Exhibition
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Project ECHO®
St. Paul's Hospital Millennium Medical College

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St. Paul's Hospital Millennium Medical College

DISCLOSURE

- I disclose that I have no conflict of interest

Diagnosis of MAFLD

OUTLINE

- MAFLD Introduction
- MAFLD Vs NAFLD
- Diagnosis of MAFLD
- Case presentation
- Summary of treatment options

CASE

- Mr. X
- Age:- 65 years
- Sex: Male
- Weight: 80 kg, Ht=170 cm; BMI= 27.7 kg/m2
- Comorbidity: Type 2 DM,
- Medications: Insulin, Metformine

CASE

- **History:**
- Fatigue, Abdominal swelling, jaundice, a single episode of hematemesis

- **Examination:**
- Icteric Sclerae
- Moderate pallor
- Ascites ++
- Peripheral edema +

CASE

- **Hgb=9gm/dl,** Bil (T)=0.91, Sodium=136, **paletlet=86**, **INR=2.03**, **Vitamin D=16**, calcium=9.6, **AST=55**, ALT=33,**ALb=3.3**, ALP=284 (0-270), creatinine=0.88,
- HBsAg=Neg; HCVAb=Neg,
- **MELDNa= 17**

- Abdominal US: Cirrhosis,Ascites, splenomegaly (mild)
- EGD: Large Varices
- Further assessment of this patient?

NAFLD

Definition

- NAFLD:- Hepatic steatosis - - - Steatohepatitis - - - Cirrhosis
    - Exclusion 2ry causes
- NASH:- ≥5% hepatic steatosis with inflammation and hepatocyte injury (also known as hepatocyte ballooning), +/- liver fibrosis.
- NAFLD is a diagnosis of exclusion

MAFLD

Definition

- The presence of hepatic steatosis with at least one of the following:
    - Obesity
    - Type 2 DM
    - Metabolic disease

MAFLD is not a diagnosis of exclusion

MAFLD

Definition

Hepatic steatosis in adults

Overweight/obesity **Type 2 diabetes** **Lean/ normal weight**

+

Presence of at least two of the following metabolic risk abnormalities:

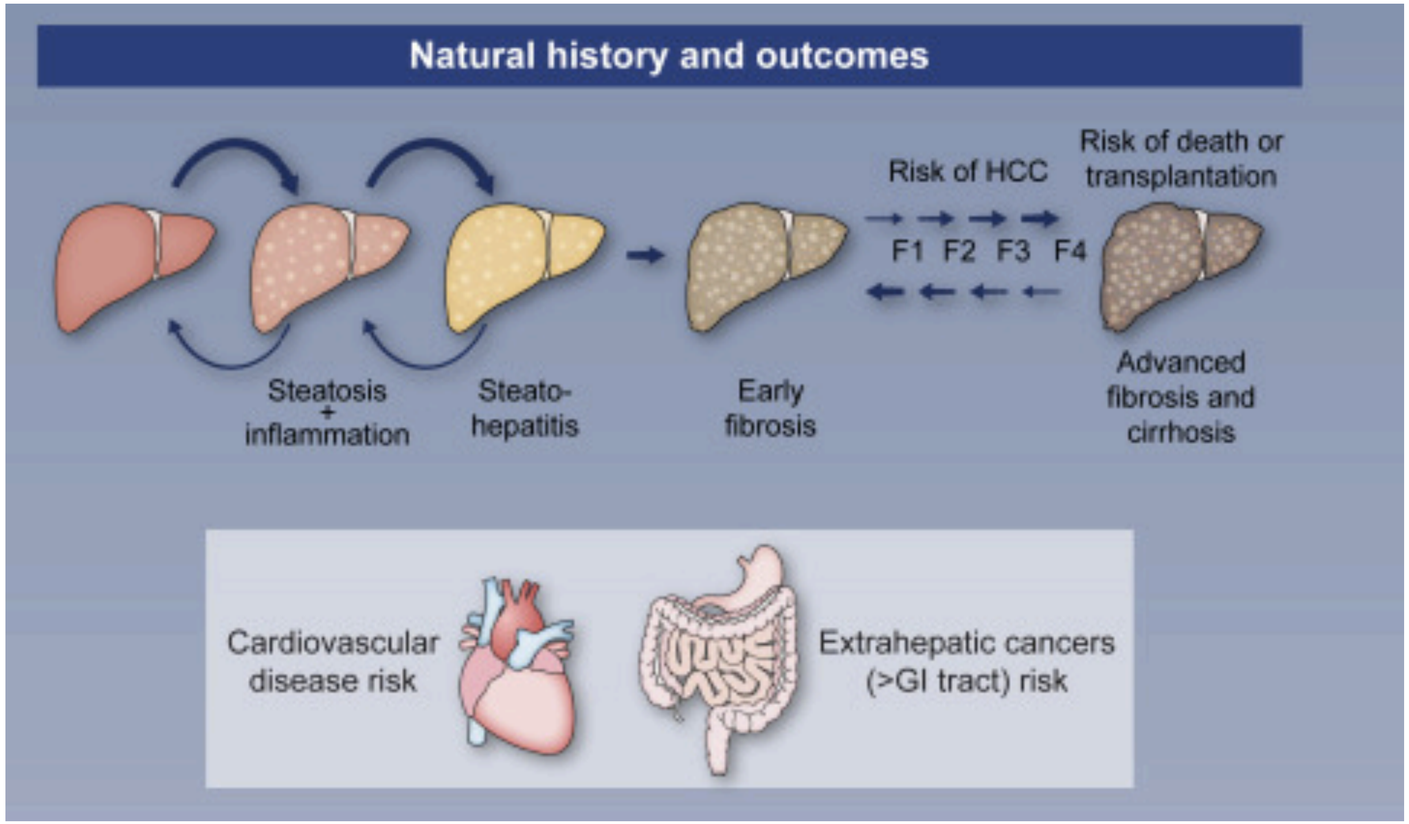


1. Waist circumference ≥ 102 cm in Caucasian men and ≥ 88 cm in women (or ≥ 90 in Asian men and ≥ 80 in Asian women)
2. Blood pressure ≥ 130/85 mmHg or hypertension drug treatment
3. Plasma triglicerydes ≥ 150 mg/dL (≥ 1.70 mol/L) or its drug treatment
4. Plasma HDL-cholesterol < 40 mg/dL (< 1.0 mmol/L) for men and < 50 mg/dL (< 1.3 mmol/L) for women or its drug treatment
5. Prediabetes
6. Homeostasis model assessment of insulin resistance (HOMA-IR) score ≥ 2.5
7. Plasma high – sensitivity C-reactive protein level > 2 mg/L

Fouad Y.Liv Int

THE CONTINUUM

Insulin-resistant adipose tissue	Compensated Steatosis	SH “Decompensated steatosis”	Fibrosis



J HEP, 2022

NAFLD

Secondary causes of steatosis

Excessive alcohol consumption
Hepatitis C (genotype 3)
Lipodystrophy
Acute weight loss
(bariatric surgery and starvation)
Malnutrition
Parenteral nutrition
Abetalipoproteinemia
Reye syndrome
Pregnancy associated
- HELLP syndrome
- Acute fatty liver of pregnancy

Medications
- corticosteroids, Mipomersen, Lomitapide, Amiodarone
- Methotrexate, Tamoxifen
- Valproate, ARV Medications

Other causes
- Autoimmune hepatitis
- A1AT deficiency
- Wilson syndrome ...

NAFLD

Lab evaluation: Secondary causes of steatosis

Hepatitis C

HCV antibody with reflex testing HCV RNA

Additional tests to consider:

Hepatitis B: HBsAg, ~~HBsAb~~, and HBcAb

ANA

AMA

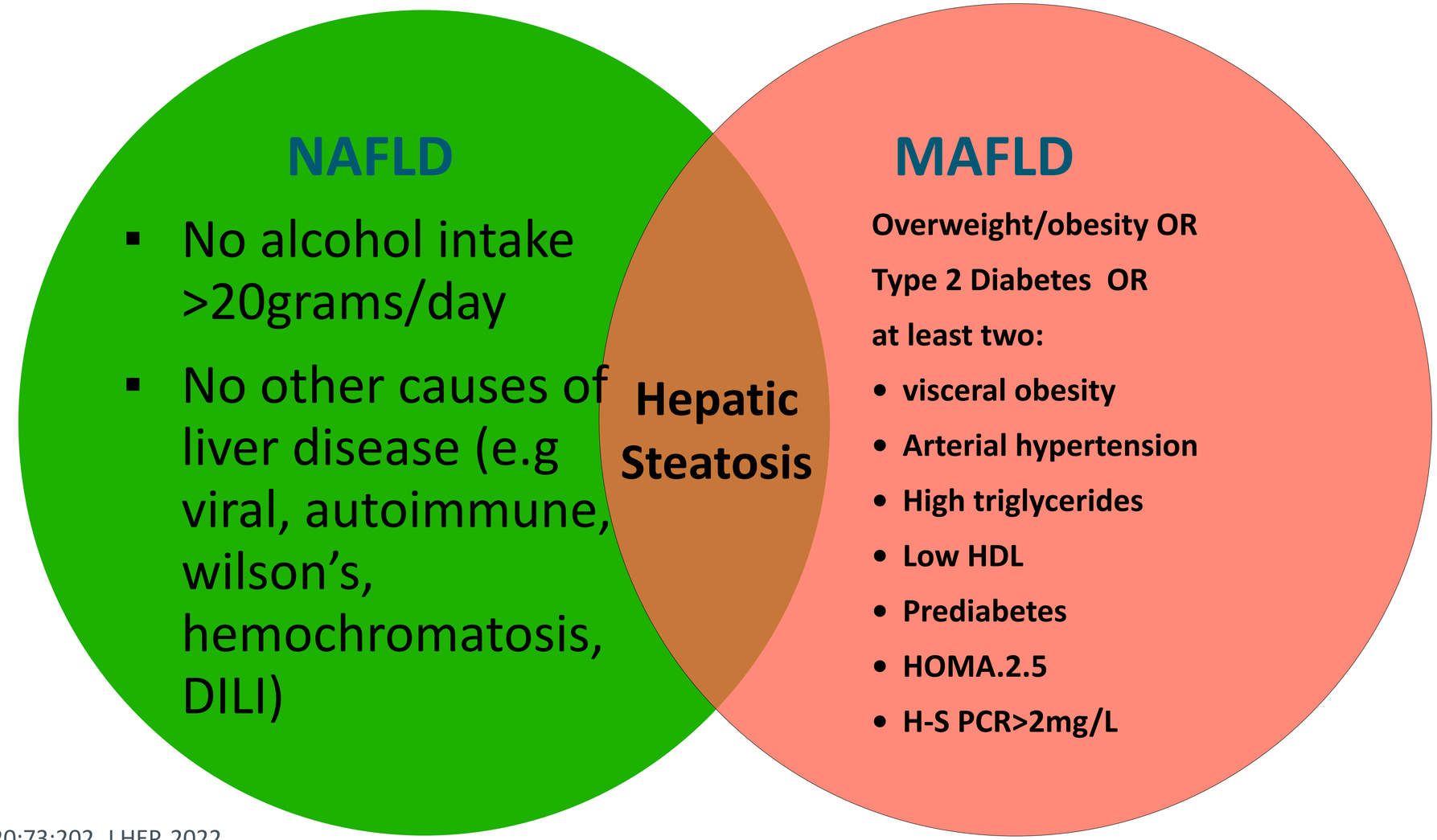
ASMA

Immunoglobulins

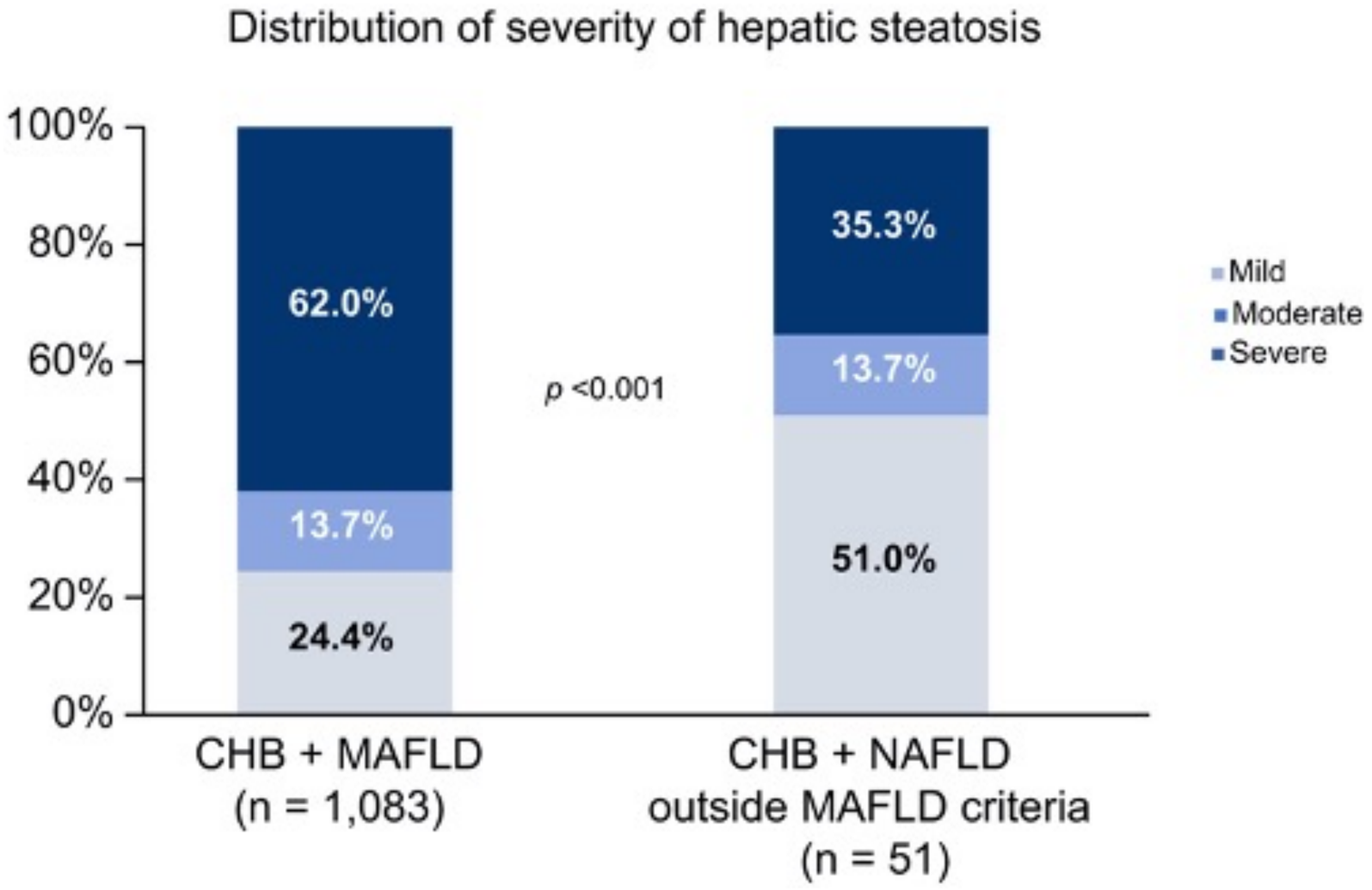
Ferritin

A1AT

From NAFLD to MAFLD



Eslam. J Hepatol. 2020;73:202. J HEP, 2022



Lung Et al. Journal of Hepatology,2020

Which adults with NAFLD should be considered at “high risk” of clinically significant fibrosis (stages F2-F4) and at risk of cirrhosis?

- Persons with obesity and/or features of metabolic syndrome
- Prediabetes or T2D, and
- Those with hepatic steatosis on any imaging study and/or
- Persistently elevated plasma aminotransferase levels (over 6 months)

- High risk patients should be screened for NAFLD and advanced fibrosis

Association of MAFLD and Extrahepatic Manifestations

- **Obesity**
- **Diabetes - Type 2, Type 1***
- **Hypertryglyceridemia**
- **Metabolic syndrome**
- CVD
- CKD
- Extrahepatic Malignancies (e.g. Colorectal cancer)
- PCOS

- Sleep Apnea
- Sarcopenia
- Osteoporosis
- Psoriasis
- Hypothyrodism
- Hypopituitarism

1. Andrew. Gut Liver. 2020;14:168. 2. Filip. Clin Interv Aging. 2018;13:1879.
3. Andrew. Clin Liver Dis. 2020;16:73. 4. Umbro. World J Gastroenterol. 2020;26:2669.

Should all persons with diabetes mellitus be screened for clinically significant fibrosis (stages F2-F4) associated with NAFLD?

- In persons with Type 2 DM
    - Liver enzymes
    - FIB-4
- In type 1 DM
    - Patients with risk factors such as obesity, features of metabolic syndrome, elevated plasma aminotransferase levels (>30 U/L), or hepatic steatosis on imaging.

Guideline Recommendations: Who Is at Risk for NASH and Advanced Fibrosis?

AASLD[1]

In type 2 diabetes, **suspect NAFLD and NASH** and determine patient's risk of advanced fibrosis

Increasing number of metabolic diseases = **increasing risk of progressive liver disease**

"There should be a high index of suspicion for NAFLD and NASH in patients with T2DM," but did not recommend systematic screening for NAFLD

EASL-EASD-EASO[2]

NAFLD **screening recommended** in persons at high CVD risk, including type 2 diabetes or metabolic syndrome

ADA[3]

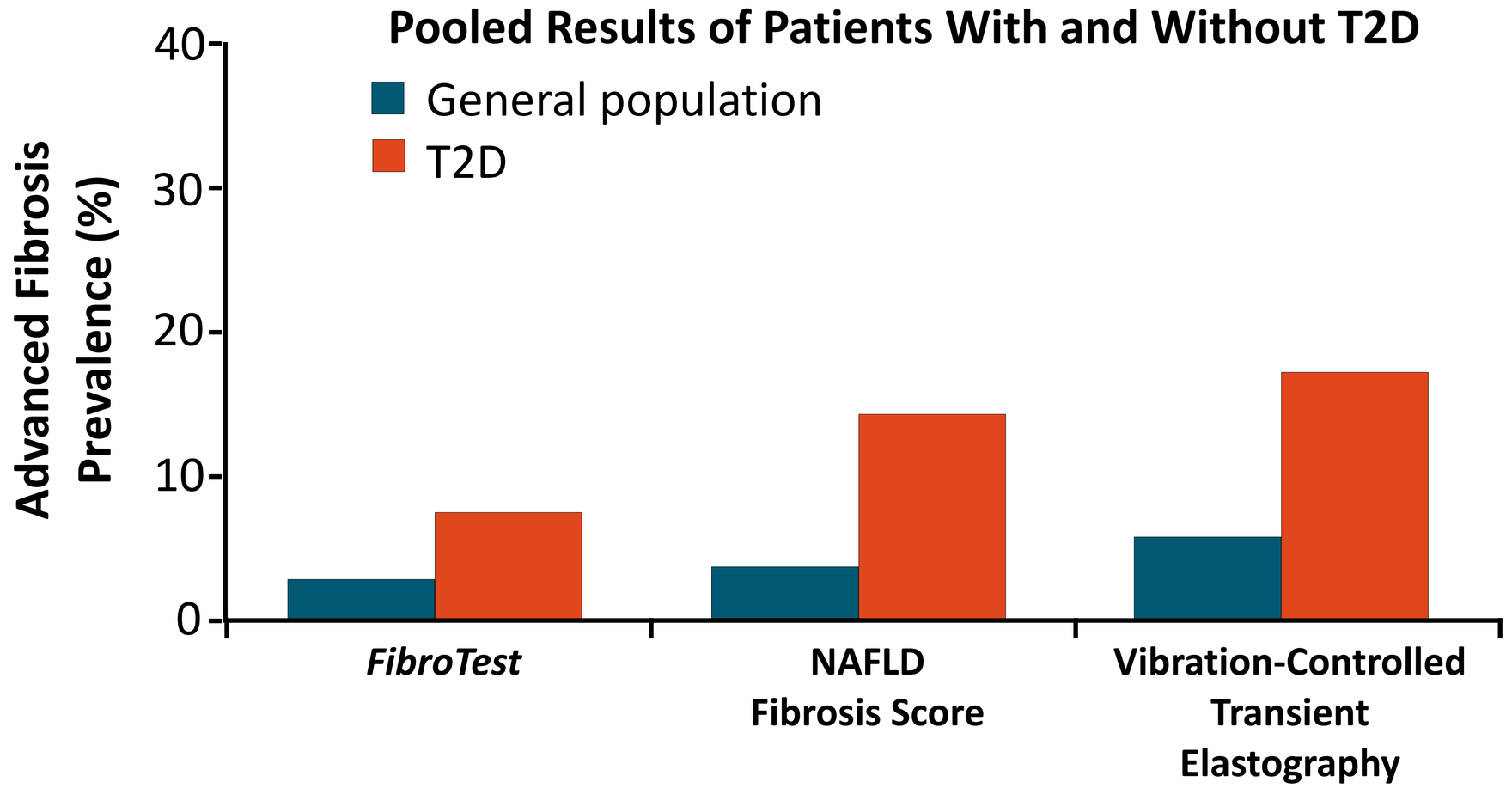
NASH and fibrosis **screening recommended** in persons with type 2 diabetes or prediabetes and elevated ALT or fatty liver

1. Chalasani. Hepatology. 2018;67:328.
2. EASL, EASD, EASO. J Hepatol. 2016;64:1388.
3. ADA. Diabetes Care. 2019;42:S34.

Kwok R,Gut. 2016 Aug;65(8):1359-68. doi: 10.1136/gutjnl-2015-309265.

T2D as a Risk for Advanced Fibrosis (by Diagnostic Approach)

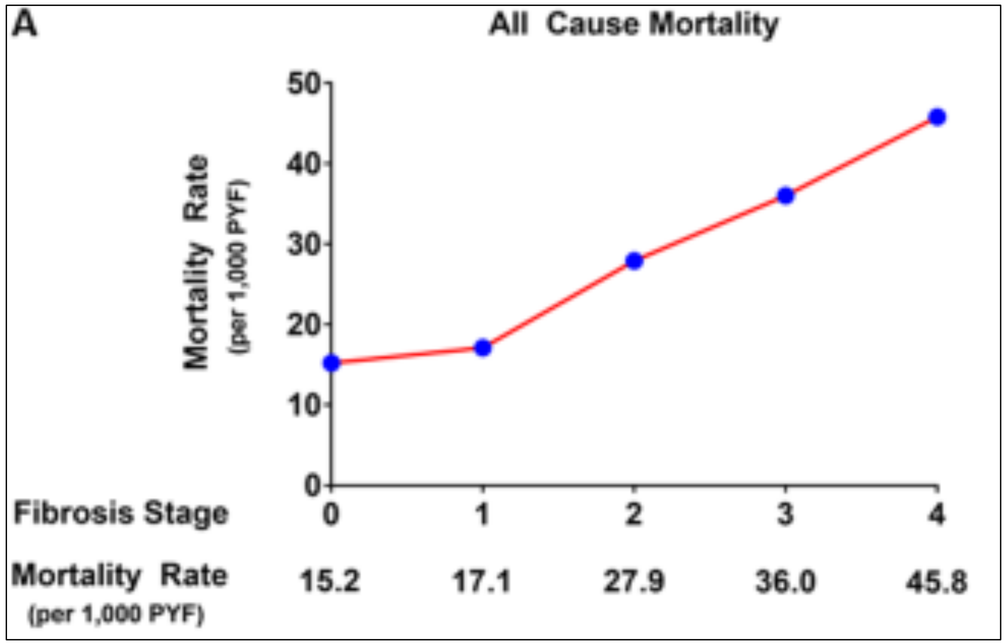
- Meta-analysis (N = 3229)

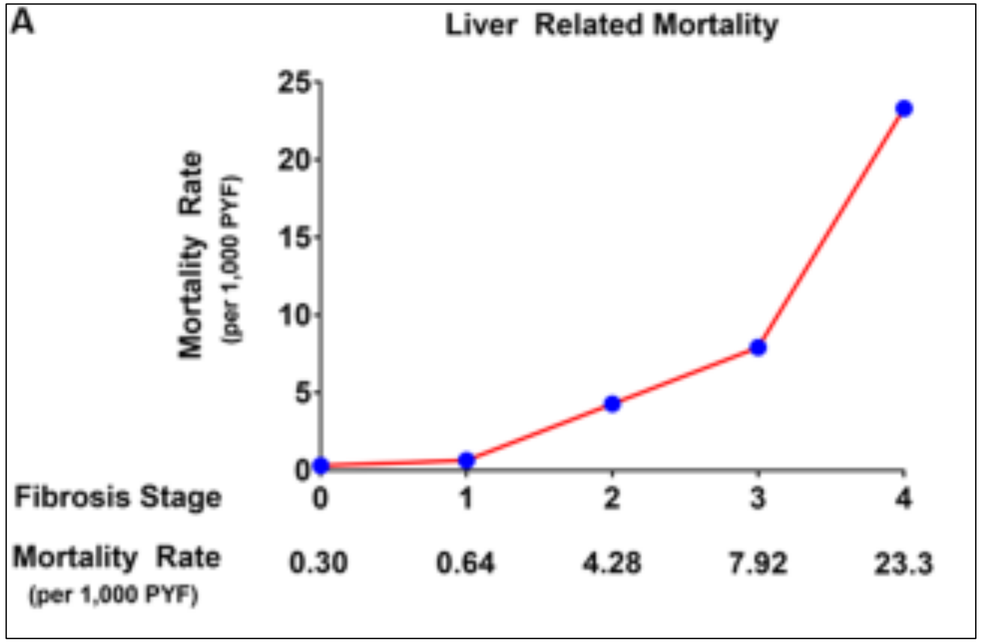


Bril. Diabetes Care. 2017;40:419.

Why do we Assess Fibrosis?

Increase Fibrosis stage is associated with significant Mortality





Meta Analysis of 5 studies with 1,495 NAFLD patients and 17,452 patient years

Dulai et al. *Hepatology* 2017

Non-invasive scoring algorithms to assess fibrosis

FIB-4 index

$$\textbf{FIB-4} = \frac{\text{Age (yrs)} \times \text{AST (U/L)}}{\text{Plts } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

NAFLD fibrosis score

NFS = -1.675 + 0.037 x age [yrs] + 0.094 x BMI (kg/m^2) + 1.13 x IFG/DM (yes = 1, no = 0)
+ 0.99 x AST/ALT – 0.013 x plts (10^9/L) – 0.66 x albumin (g/dL)

NAFLD Score	Correlated Fibrosis Severity
< -1.455	F0-F2
-1.455 – 0.675	Indeterminant score
> 0.675	F3-F4

Role of Liver Enzymes

- ALT: considered liver specific markers
  - Used in both FIB-4; NFS with AST
- ALT is non-specific in NAFLD/NASH (Normal > 50% NASH; 80% NAFLD), can be elevated in NAFLD with out NASH
- The ratio of AST/ALT usually is less than 1 (unless in advanced cases)
- Abnormal ALT may warrant work up for NAFLD
- Alkaline phosphatase may be elevated up to twice the upper limit of normal;
  - γ-glutamyltransferase (GGT) also may be elevated.

Common Imaging Tests for Hepatic Fibrosis

Vibration-controlled transient elastography – *FibroScan*

- Can be point of care
- **Most reliable in ruling out advanced hepatic fibrosis (great NPV)**

MR elastography/MR spectroscopy/ liver multiscan

- Requires radiology referral
- **Most accurate** of the imaging modalities

2D shear wave elastography

- May require radiology referral but can be point of care with minimal training

These imaging tests measure liver stiffness, which is an indirect measure of hepatic fibrosis and not hepatic fat content

Example of a Proposed Sequence of Testing in NAFLD

- If NAFLD, rule out low risk with either:
  - **Serum biomarker/algorithm** (FIB-4, NFS, ELF) or
  - **Imaging** (VCTE, MRE, or shear wave elastography)
- If low risk not ruled out, use the other modality to confirm intermediate or high risk

- NAFLD
  - US, CT, MRI, VCTE
- NASH
  - Liver biopsy

- Advanced fibrosis
  - FIB4, APRI, proprietary panels
  - VCTE/ARFI
  - MR elastography
  - Liver biopsy

Younossi. Am J Gastroenterol. 2020;00:1.

Commonly Used Noninvasive Tests

Clinical or Laboratory Scores

Simple

- Fibrosis-4 (FIB-4)[1,2]
- NAFLD fibrosis score[1,2]
- AST/platelet ratio index[1]

Proprietary

- Enhanced Liver Fibrosis Test[1]
- NIS4
- ADAPT/Pro-C3[3]
- *FibroSure*[1]
- Hepascore

Imaging

Elastography

- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]
- Corrected T1 (*Liver MultiScan*)[5,6]
- MRI-PDFF[7]
- FAST score[8]

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

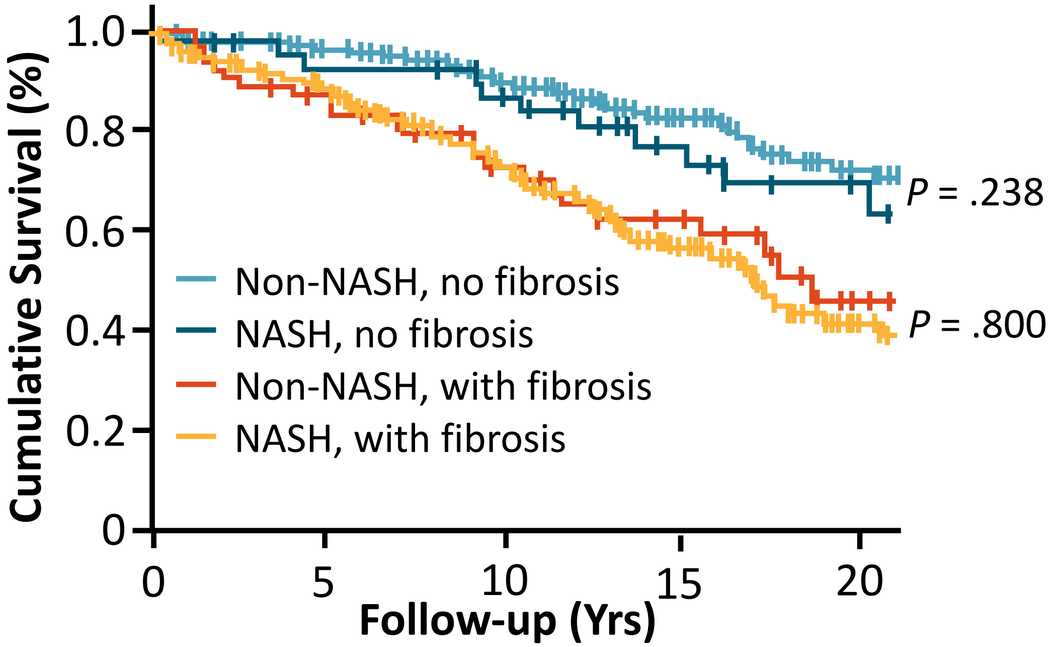
Diagnosis of Fibrosis

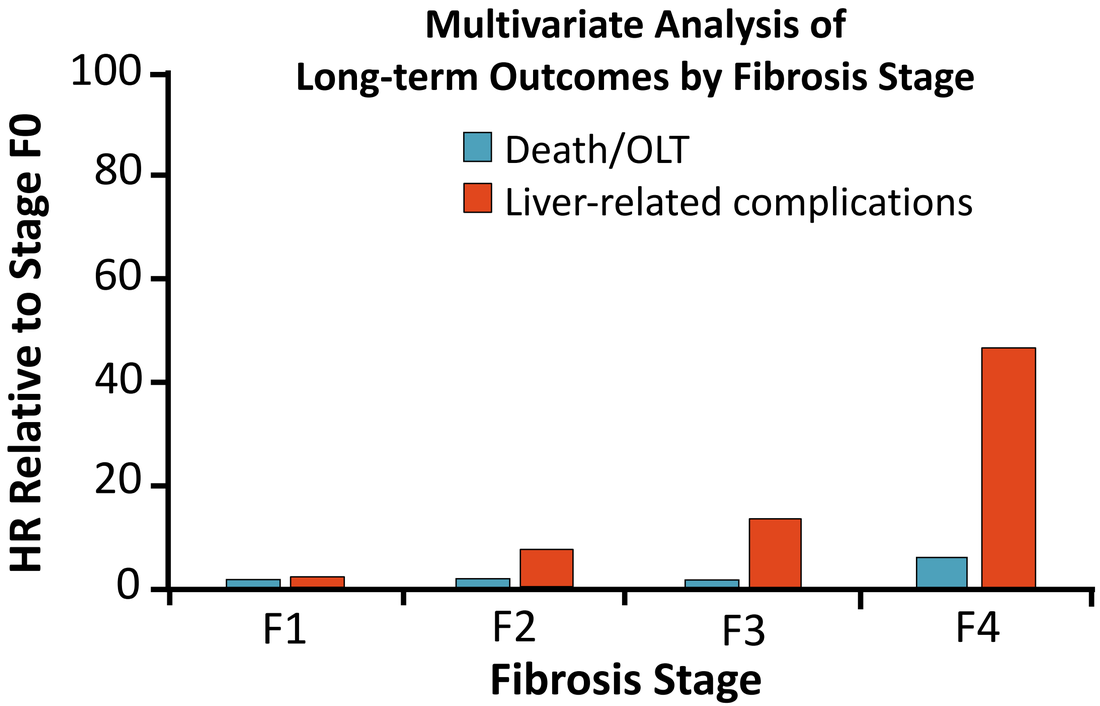
- Diagnosis of Fibrosis is important as it is associated with long term outcomes
- US can identify fatty liver (steatosis), but cannot distinguish steatosis Vs NASH Vs Fibrosis (Early Cirrhosis)

- Simple tests (FIB-4, NFS, APRI)
  - Good NPV
  - Easily applicable

PRELHIN Study: Hepatic Fibrosis Associated With Long-term Outcomes in Patients With NAFLD

- Retrospective analysis in patients with NAFLD (N = 619); median follow-up: 12.6 yrs (range: 0.3-35.1)





Only fibrosis stage was associated with overall mortality, OLT, and liver-related events. Presence of NASH, NAS (or any of its components) had no independent prognostic effect.

Angulo. Gastroenterology. 2015;149:389.

Noninvasive Tests Exclude or Determine Advanced Hepatic Fibrosis

- FIB-4 recognized by AASLD as useful in identifying patients with a higher likelihood of F3 or F3-F4[1]

Cutoff Scores for Measurement of Advanced Hepatic Fibrosis[2,3]

FIB-4: ≤ 1.3 NFS: < -1.455	FIB-4: ≥ 2.67 NFS: > 0.675
↓	↓
Absence of Advanced Fibrosis	Presence of Advanced Fibrosis

1. Vallet-Pichard. Hepatology. 2007;46:32. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Shah. Clin Gastroenterol Hepatol. 2009;7:1104.

Noninvasive Tests Exclude or Determine Advanced Hepatic Fibrosis

- FIB-4 recognized by AASLD as useful in identifying patients with a higher likelihood of F3 or F3-F4[1]

Patients with advanced cirrhosis usually have a very low platelet count

FIB-4 Score < 1.3 NPV >95%

Rules out advanced fibrosis

FIB-4 Score >2.67 NPV 75%

Rules in advanced fibrosis

A low FIB-4 score indicates there is no advanced fibrosis and that liver biopsy is not needed

Vibration-Controlled Transient Elastography

- Measures 1D velocity of low-frequency shear wave
- Directly related to tissue stiffness (fibrosis)
  - The stiffer the liver, the faster the shear wave propagates
- Quick, bedside test (~ 5 mins)
- Limited by obesity, food intake, operator experience





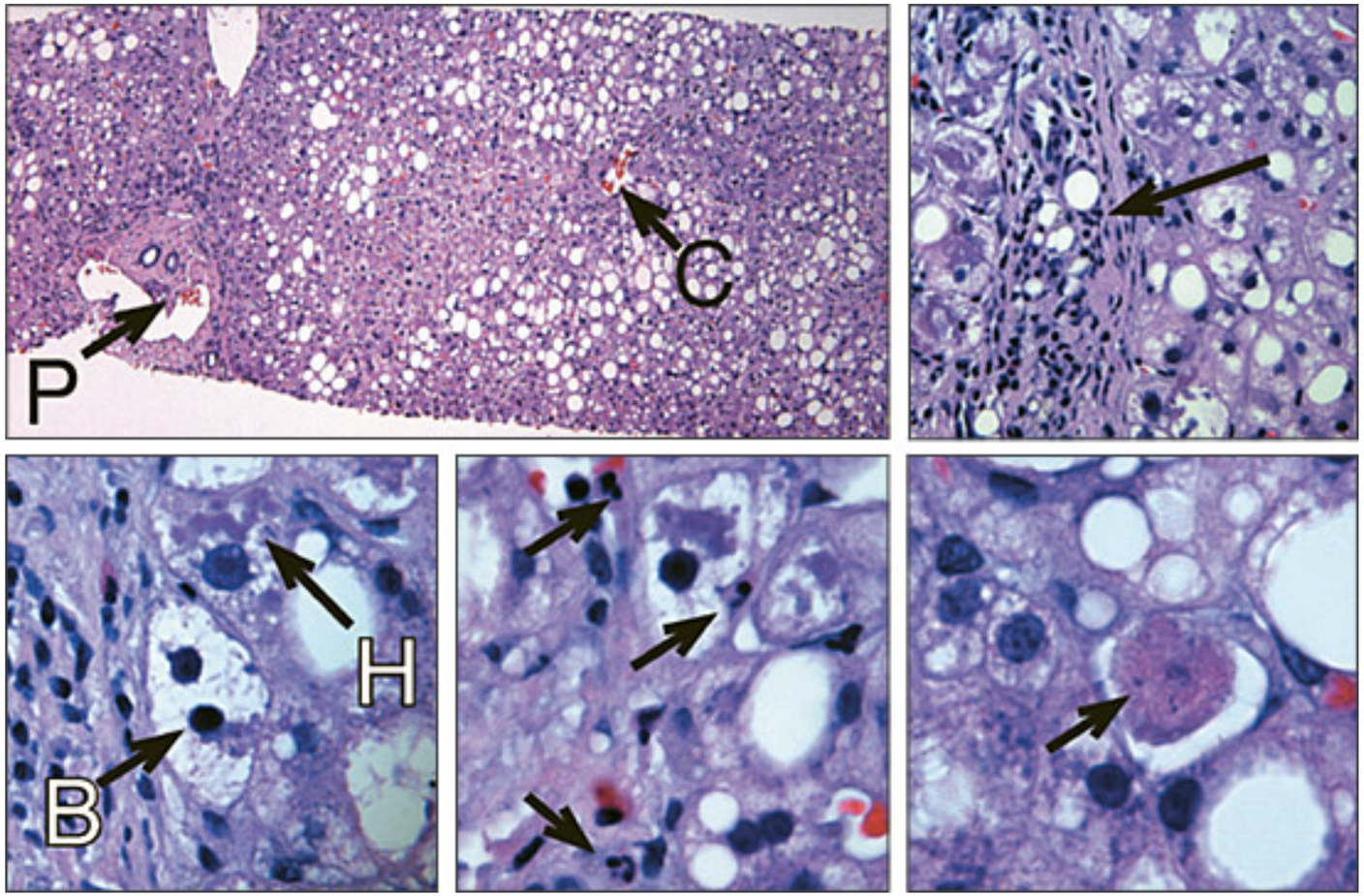
Sigrist. Theranostics 2017;7:1303.

Liver Biopsy

Indications

- Liver biopsy remains the gold standard for differentiating NAFL from NASH and staging liver fibrosis.
- Proceed with liver biopsy if:
- (1) suspicion for NAFLD advanced fibrosis
- (2), or concern for coexisting or competing etiology of chronic liver disease (B2).

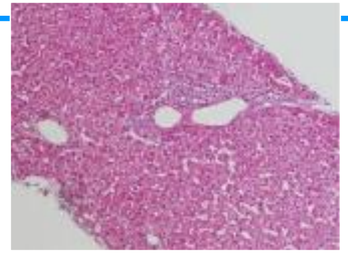
LIVER BIOPSY



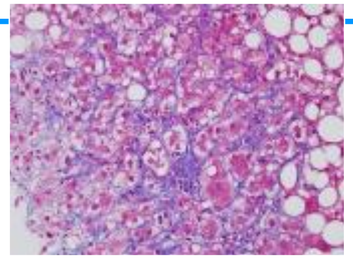
P: lipogranuloma
H: Mallory body
B: Balloon cell
Middle: PMNs
Bottom right: acidophil bodies

Liver Histology Grades

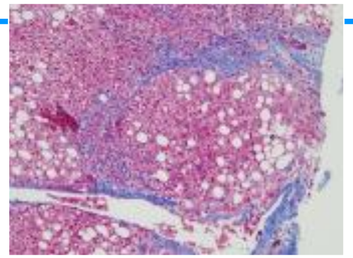
Fibrosis Stage



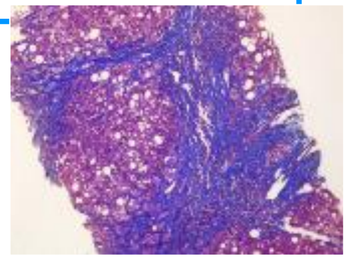
F0: Normal



F1/2: Perisinusoidal ± Portal



F3: Bridging Fibrosis



F4: Cirrhosis

With VCTE:

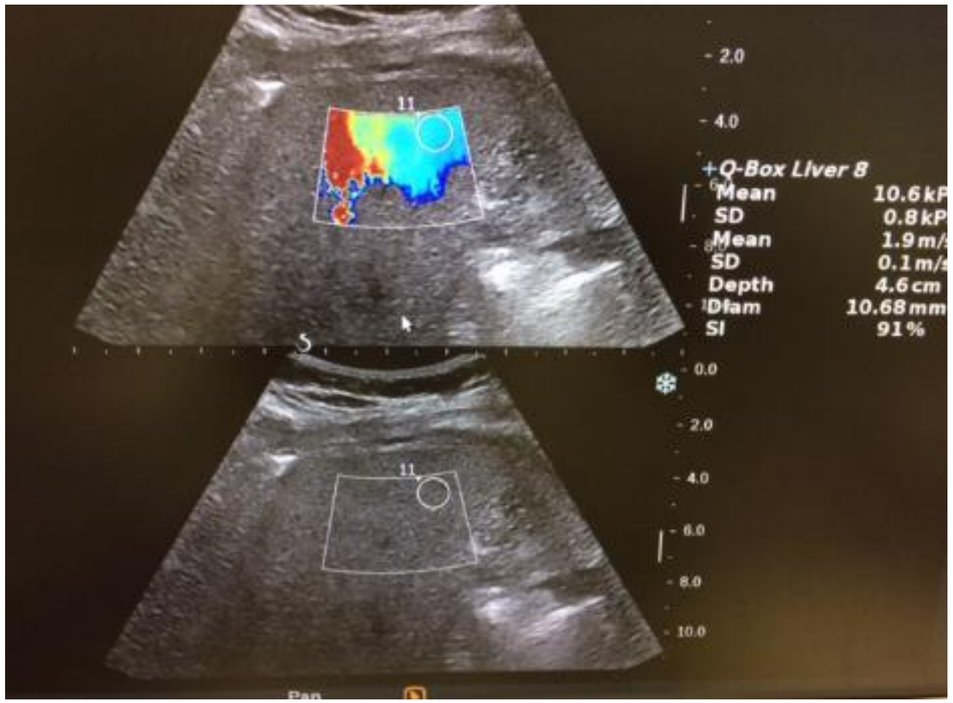
Fibrosis unlikely with low value (< 6 kPa)

Higher levels: Hepatitis, cholestasis, liver congestion, obesity, HCC

Good correlation with portal pressure (20+ Kpa)

2D Shear Wave Elastography

- Ultrasound system, using real-time SWE map of liver elasticity to determine liver stiffness
  - 2D SWE color-coded map superimposed on B-mode image confirms readings are in liver, not in nearby vessels or kidneys
- May require radiologist/sonographer
- Liver elasticity measurements can be obtained in challenging cases of obesity

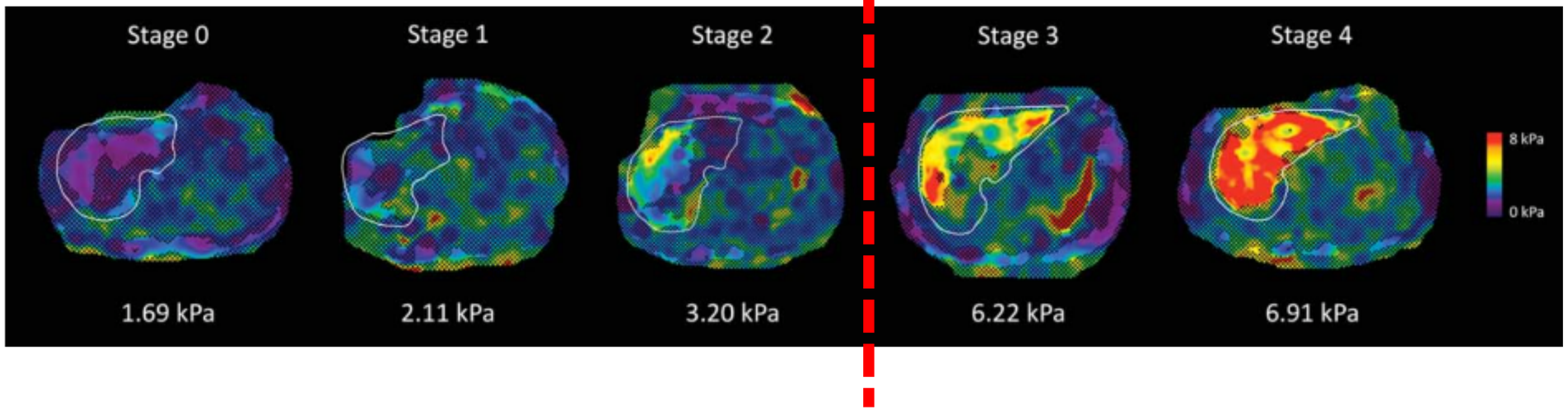


Cutoff for Detecting Advanced Hepatic Fibrosis ≥ F3 in HCV[2]	Sensitivity	Specificity	AUROC
2D-SWE stiffness > 8.7 kPa	.973	.951	.98

1. Sigrist. Theranostics 2017;7:1303. 2. Ferraiolo. Hepatology 2012;56:2125.

MRE: Detecting Advanced Hepatic Fibrosis in NAFLD

- Prospective, cross-sectional analysis of 2D MRE in N = 117 patients with biopsy-proven NAFLD



Cutoff for Detecting Advanced Hepatic Fibrosis ≥ F3	Sensitivity	Specificity	AUROC
MRE stiffness > 3.63 kPa	.86	.91	.924

Loomba. Hepatology. 2014;60:1920.

Diagnostic accuracy of non-invasive methods of fibrosis assessment

Diagnostic Test	Area under the Receiver Operating Curve (AUROC) for detection of moderate fibrosis	AUROC for detection of advanced Fibrosis
NAFLD Fibrosis Score	0.82	0.86
FIB-4 Index	0.83	0.86
FibroScan	0.82	0.88
MR elastography	0.91	0.89

Imajo et al. *Gastroenterology* 2016;150:626–637

Acute MI in the young ; Lipid accumulation

LAL D

- Early identification
- Supportive care
  - Low fat diet
  - Statins
  - Evaluate for liver transplantation
- Enzyme replacement therapy with sebelipase alfa

Children and Adolescents

- Who should be screened for NAFLD and comorbidities?
    - Obesity or Type 2 DM
    - Adolescent females with polycystic ovary syndrome
- Diagnostic Approach
    - Screening using ALT
    - Next step:- Imaging (US / MRI - PDFF)
    - Liver Biopsy in unclear cases and exclusion of other cause:
        - Wilson syndrome, mitochondrial disease, and medications.

Diagnosis of MAFLD

Risk factor + Diagnosis + CSPH + Complications

- Complications
  - Ascites
  - Variceal bleeding
  - Encephalopathy
  - HCC

N.B. HCC in NAFLD can occur in the absence of cirrhosis

MEDICATIONS
NASH

- **VITAMIN E:**
  - NASH without T2DM or cirrhosis
  - Liver related: improves steatosis,NASH resolution? No proven benefit on fibrosis
  - S/Es: Hemorrhagic stroke, risk of prostate cancer?
  - No cardiac benefit

MEDICATIONS
NASH

- **Pioglitazone 30-45 mg po/day**
  - T2DM (FDA); NASH with and without T2DM
  - Liver related: improves steatosis, activity and NASH resolution, fibrosis improvement?
  - Non liver related: improves insulin sensitivity, prevention of diabetes, CV risk reduction, and stroke prevention
  - S/Es: weight gain, risk of heart failure exacerbation, bone loss in postmenopausal women
  - Has cardiac benefit

MEDICATIONS
NASH without cirrhosis

- **Liraglutide 1.8 mg SC daily (T2DM) 0.6-3mg SC daily (obesity)**
  - T2DM, Obesity (FDA); NASH without cirrhosis
  - Liver related: improves steatosis, no proven impact on fibrosis
  - Non liver related: improves insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease
  - S/Es: gastrointestinal, gallstones (related to weight loss), pancreatitis
  - Has cardiac benefit

MEDICATIONS
NASH without cirrhosis

- **Semaglutide 0.4 mg SC daily, 0.25-2.4 mg SQ weekly**
  - T2DM, Obesity (FDA); NASH without cirrhosis
  - Liver related: improves steatosis, NASH resolution, no proven impact on fibrosis (may slow)
  - Non liver related: improves insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease, stroke prevention
  - S/Es: gastrointestinal, gallstones (related to weight loss), pancreatitis
  - Has cardiac benefit

MEDICATIONS

T2DM or obesity with NAFLD

- **Tirzepatide**
  - T2DM (FDA)
  - Liver related: improves steatosis on imaging
  - Non liver related: improves insulin sensitivity, significant weight loss,
  - S/Es: gastrointestinal, gallstones (related to weight loss), pancreatitis
  - Unknown cardiac benefit

MEDICATIONS

T2DM or obesity with NAFLD

- **SGLT-2i**
  - T2DM (FDA)
  - Liver related: improves steatosis on imaging
  - Non liver related: improves insulin sensitivity, CV and renal outcomes; modest weight loss; benefit in heart failure
  - S/Es: genitourinary yeast infection, volume depletion, bone loss
  - Cardiac benefit

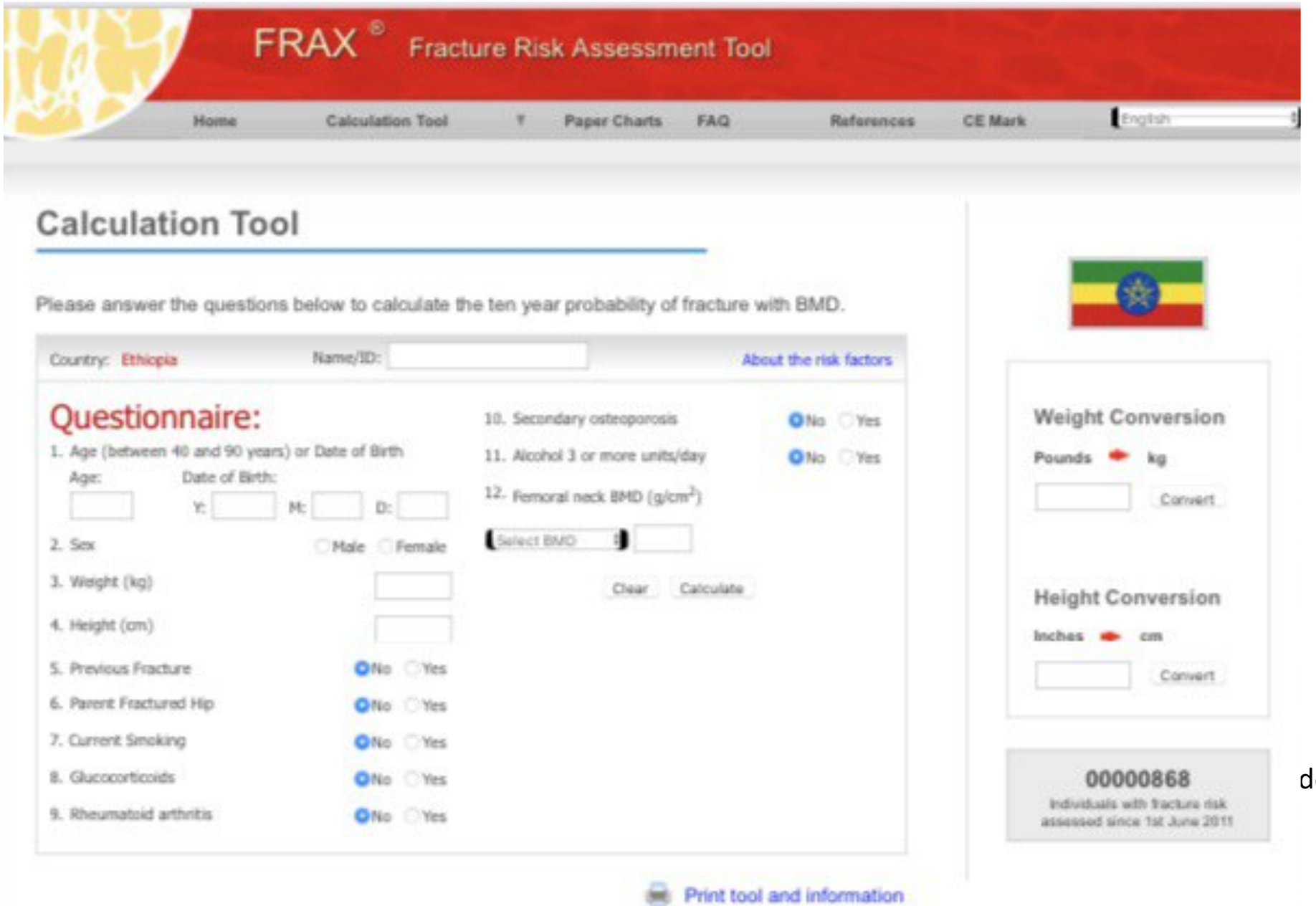
Diagnosis of MAFLD

Risk factor + Diagnosis + CSPH + Complications

- Complications
  - Ascites
  - Variceal bleeding
  - Encephalopathy
  - HCC

N.B. HCC in NAFLD can occur in the absence of cirrhosis

FRAX: FRACTURE RISK ASSESSMENT: BACK TO THE PATIENT



docr Pract. 2020;26(suppl 1):1

FRAX: FRACTURE RISK ASSESSMENT

Additional History:
- Previous Fracture
- Parent Fracture Hip
- Current smoking
- Glucocorticoid
- Rheumatoid Arthritis
- Secondary osteoporosis

Additional History:
- Alcohol 3 or more units per day
- Femoral neck BMD

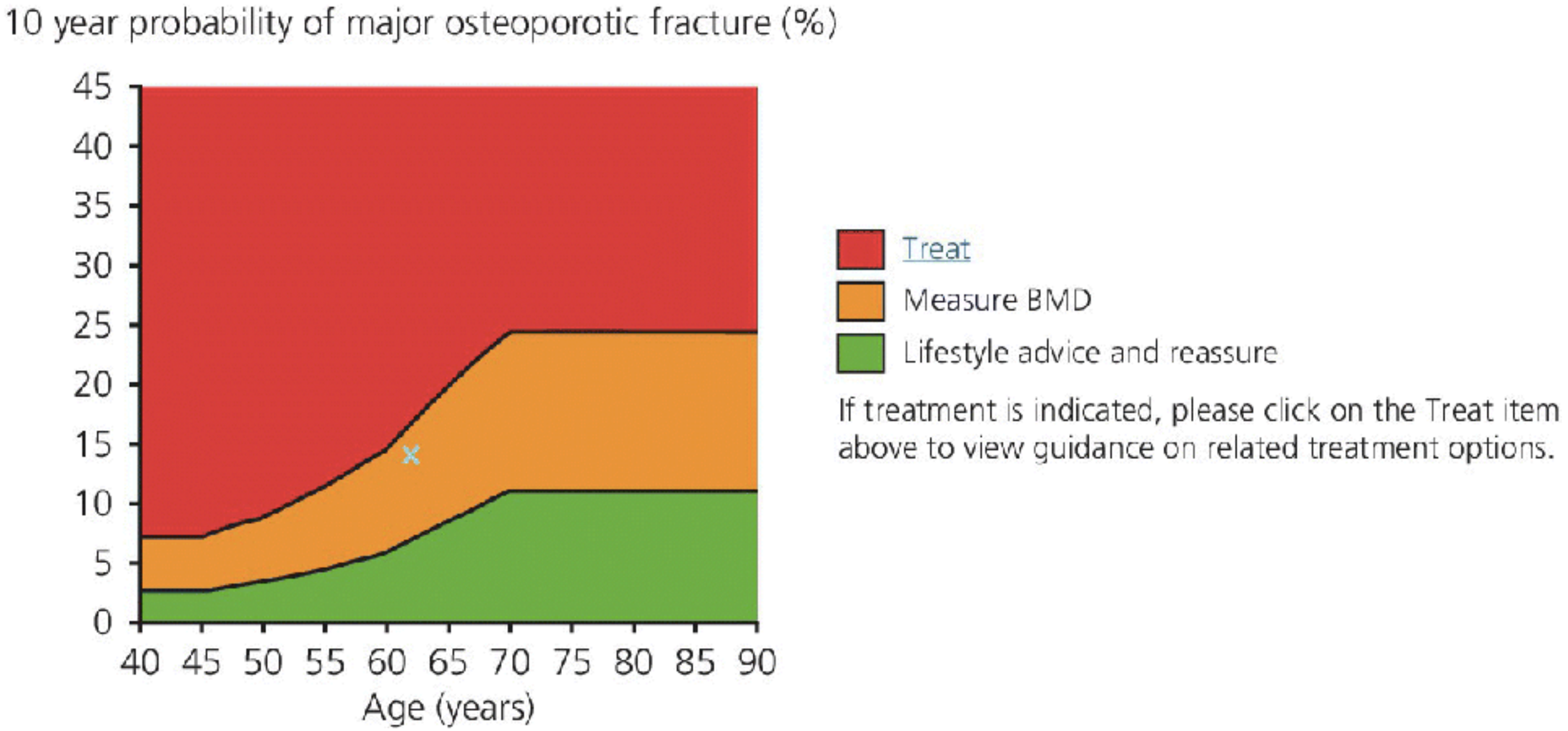
10 year risk:

Major osteoporotic 3.8%

Hip fracture 1.6%

What is next?

FRAX: FRACTURE RISK ASSESSMENT



https://musculoskeletalkey.com/11-osteoporosis-and-metabolic-bone-disease/

SUMMARY

- Identify high risk individuals for screening of MAFLD
- If patient has NAFLD/NASH, stratify based on the degree of Fibrosis
- patients with Advanced Hepatic Fibrosis can quickly progress to Cirrhosis, HCC, Need of liver transplant, and poor Outcome
- FIB-4 marker considered as an initial NIT to assess for degree of fibrosis
- Aim for weight reduction
- New drugs in the horizon

THANK YOU

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https://t.me/SSA_GastroVirtualClinic
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