MASLD in Type 2 Diabetes
Overview & Screening

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Learning Objectives

1. Identify risk factors for MASLD and MASH
2. Apply the updated ADA Standards of Care criteria to screen patients with risk factors for advanced fibrosis.
3. Incorporate non-invasive screening tests for patients with prediabetes or diabetes who are at risk for MASLD and MASH.

Pre-Question – which one answer is correct

The definition of MASLD requires

A. the association with at least one cardiometabolic risk factor associated with insulin resistance
B. the exclusion of other causes of liver disease
C. the exclusion of any or all alcohol ingestion
D. elevated liver tests (aminotransferases – ALT &/or AST)

Why the Current Focus on MASLD – Alarming Trends

- The burden of MASLD has dramatically increased worldwide, becoming the most common cause of chronic liver diseases.
  - The global prevalence of MASLD has risen from 25.3% (1990–2006) to 38.2% (2016–2019) & 7%–14% of children and adolescents [more recent estimates ~45%]
    - In North America, the National Health and Nutrition Examination Surveys from 2017–2018 reported an overall prevalence of 56.7%
  - MASLD has increased in parallel with the escalating rates of obesity, type 2 diabetes (T2D), and metabolic syndrome globally
  - MASLD is the most rapidly increasing contributor to the disease burden related to adverse liver outcomes, including cirrhosis, liver failure, and HCC
- Rates are much higher in people with type 2 diabetes with estimated prevalence of
  - ≥70% for MASLD
    - ~ 50% for MASH
    - ~20% for clinically significant fibrosis
    - 7% for MASLD-related cirrhosis

MASLD in People with Prediabetes

- prevalence between 37% and 50%.
- 8.5 times more likely to have significant fibrosis
- ~6 times more likely to have advanced fibrosis

Why the Current Focus on MASLD - Adverse Outcomes

- Increased risk of severe liver disease
  - MASLD with clinically significant fibrosis (stage ≥F2) raises the risk of cirrhosis, liver cancer (HCC), and overall liver-related mortality
- Leading cause for liver transplantation
  - Approximately one in five people with type 2 diabetes are at high risk of developing cirrhosis due to MASLD, making it one of the leading reasons for liver transplantation in the U.S.
- Higher likelihood of developing a broad spectrum of comorbidities
  - MASLD increases risk of
    - progression from prediabetes to type 2 diabetes
      - increased Insulin Resistance & more difficulty managing diabetes
    - development of cardiovascular disease
    - extrahepatic malignancies
- Increased risk of mortality
  - the highest risk of mortality with MASLD is among people with type 2 diabetes (4.0-fold increase in risk)
  - followed by those with prediabetes (3.4-fold increase in risk)

Why the Current Focus on MASLD - Lack of Awareness

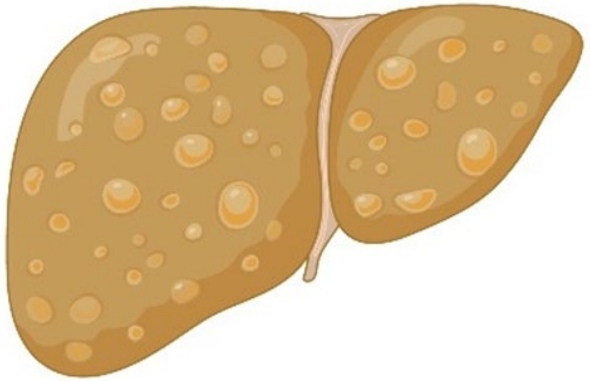
- *"Despite these alarming trends, a **significant lack of awareness** remains among both **people at risk and clinicians** regarding the health perils associated with MASLD and how best to manage it, often resulting in the condition being **overlooked and untreated**."* ADA Consensus paper
  - There is a pressing need for heightened awareness, early diagnosis, and comprehensive management.
  - Health care professionals must recognize that an early diagnosis is possible by using noninvasive tests (NITs) to stratify people for their risk of developing cirrhosis.
- *"A **timely diagnosis** can encourage the adoption of healthier lifestyle habits or the initiation of pharmacological treatments for obesity and type 2 diabetes, which can **prevent** disease progression and, ultimately, cirrhosis."*

*"Cirrhosis from MASLD is **preventable** in people with diabetes through early diagnosis, proper treatment, and long-term monitoring**, similar to the management of care for diabetes-related microvascular complications** (retinopathy, nephropathy, or neuropathy)"*

2023 Terminology Update

Metabolic Dysfunction – Associated Steatotic Liver Disease (**MASLD**) &

Metabolic Dysfunction- Associated Steatohepatitis (**MASH**)



replace

Nonalcoholic Fatty Liver Disease (**NAFLD**)

& Nonalcoholic Steatohepatitis (**NASH**)

MASLD definition

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined as the presence of **hepatic steatosis** (excess triglyceride storage in the liver) in conjunction **with at least 1 cardiometabolic risk factor***

*cardiometabolic risk factors associated with *insulin resistance*

- obesity/central (visceral) obesity
- prediabetes/diabetes (hyperglycemia)
- hypertension
- atherogenic dyslipidemia (elevated Triglycerides, low HDLc)

- Having multiple risk factors adds risk
- Family history of MASLD is a risk factor

- This is in the ***absence*** *of ongoing or recent consumption of* ***significant amounts of alcohol*** (defined as ingestion of < 21 standard drinks/<210 grams per week in men [<3 drinks/d] and <14 standard drinks/<140 grams per week [<2 drinks/d] in women over a 2-year period preceding evaluation)

The most common liver disease in the United States & globally
Potentially reversible & preventable

Definitions MASLD, MetALD vs NAFLD

- While NAFLD and MASLD generally refer to the same condition, a key distinction is that a *NAFLD diagnosis excludes other liver diseases*, whereas *MASLD is based on affirmative criteria*.
  - This affirmative method of diagnosis **now allows for the *coexistence of other liver diseases with MASLD***, such as autoimmune or viral hepatitis.

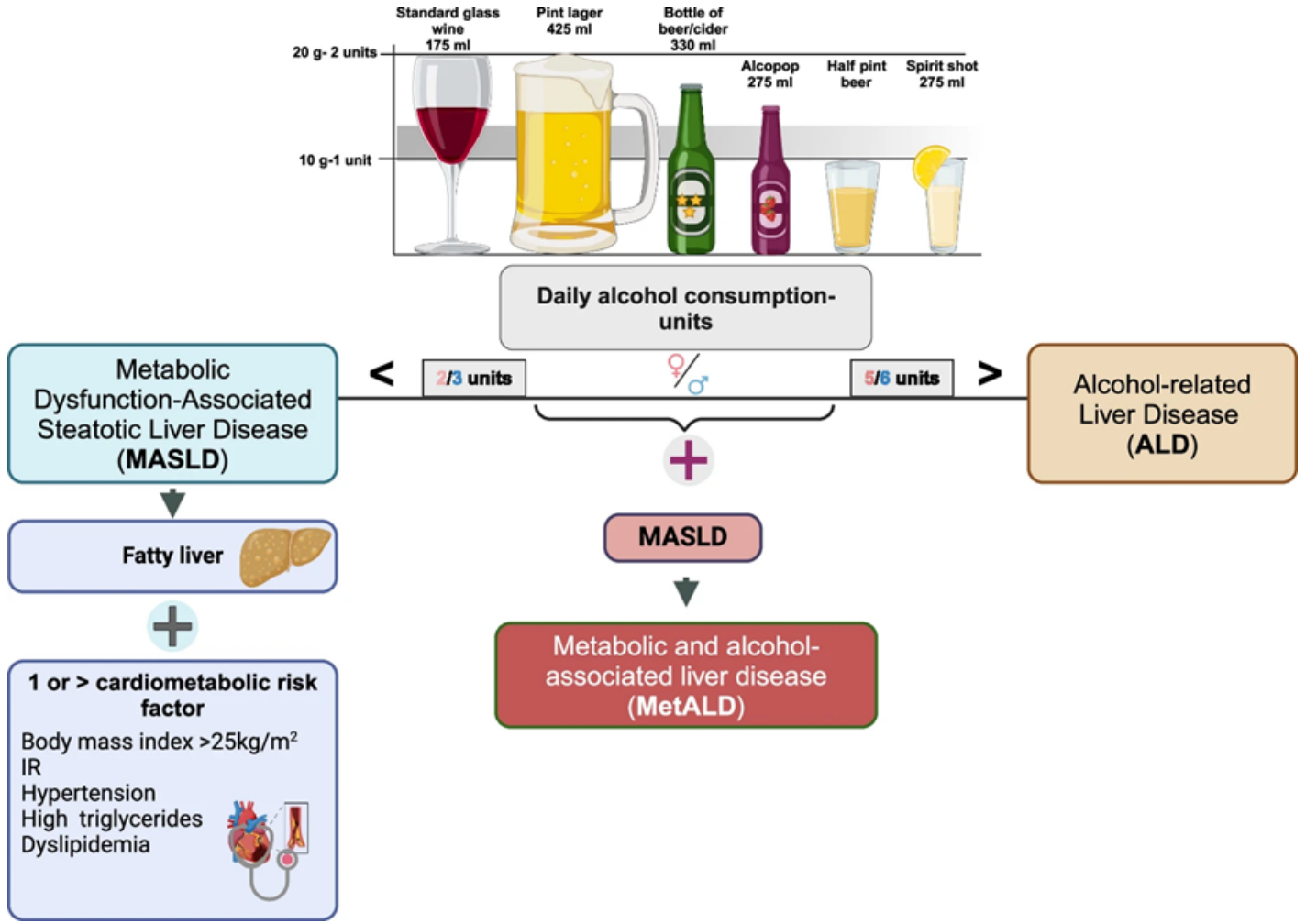
- The new nomenclature also introduces a diagnostic category, **metabolic dysfunction and alcohol-associated liver disease (MetALD)**, applying to individuals *meeting MASLD criteria with concurrent excessive alcohol intake*.
  - (MetALD) is defined as steatotic liver disease fulfilling the MASLD criteria in conjunction with an average alcohol intake of 20–50 g/day in women and 30–60 g/day in men (140–350 g/week in women and 210–420 g/week in men)

- Alcohol-Associated Liver Disease (ALD)- liver disease when alcohol intake is >50g/d in women or >60g/d in men

MASLD & Increased Alcohol Intake (MetALD)

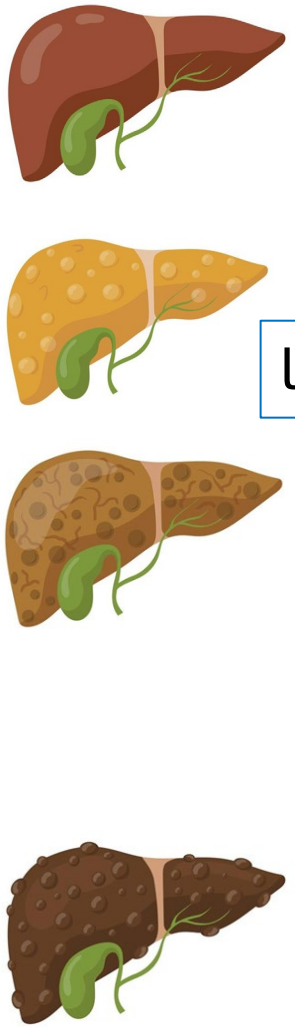
Spectrum

- MASLD - <20g (f)- <30g (m) alcohol/day [<2/3 drinks/day]
- **MetALD** (a new category) , describes *individuals with MASLD who consume moderate amounts of alcohol* (between 20-50g/day for females and 30-60g/day for males) - (on spectrum between MASLD & ALD)
- ALD -Alcohol-Associated Liver Disease – in individuals who consume more than 50g/day for females and 60g/day for males [≥ 5/6 drinks/day]



Types of MASLD

- Normal liver - <5% fat content
- MASLD – "fatty liver" (>5-10% fat content)
  - Mild – up to 1/3 of cells laden with fat droplets
  - Moderate – 1/3 to 2/3 cells w/ fat droplets
  - Severe – over 2/3 cells w/ fat droplets
- MASH – steatohepatitis (liver cell injury)
  - Fibrosis
    - F0, no fibrosis
    - F1, mild
    - F2, moderate (significant)
    - F3, severe (advanced)
    - F4, cirrhosis



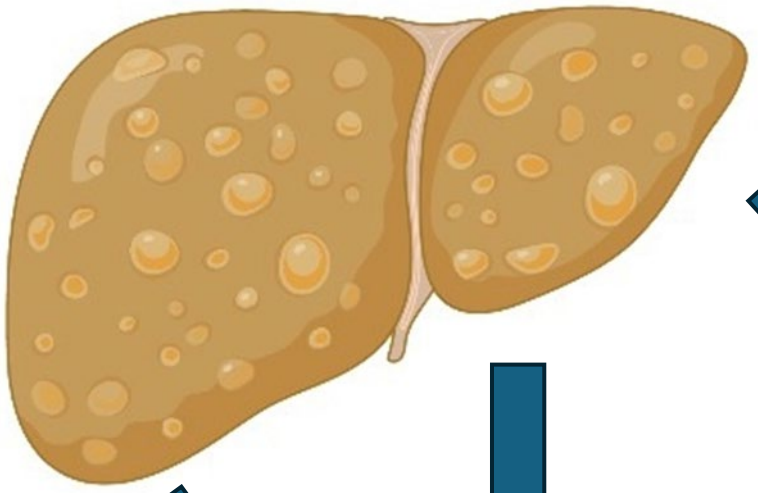
lipotoxicity

Excess calories, high sat fat, ~high HFCS intake → toxicity:

- saturated fatty acids (SFA)
- sphingolipids
- free cholesterol
- ceramides
- diacylglycerols (DAGs)
- long-chain acyl-CoAs
- acylcarnitines,
- lysophospholipids

The stage of fibrosis is the most important single predictor of significant morbidity and mortality in chronic liver disease

MASLD is associated with Increased Insulin Resistance & Increased CVD risk



Cardiovascular disease is reported to be the ***most common cause of mortality*** in patients with MASLD

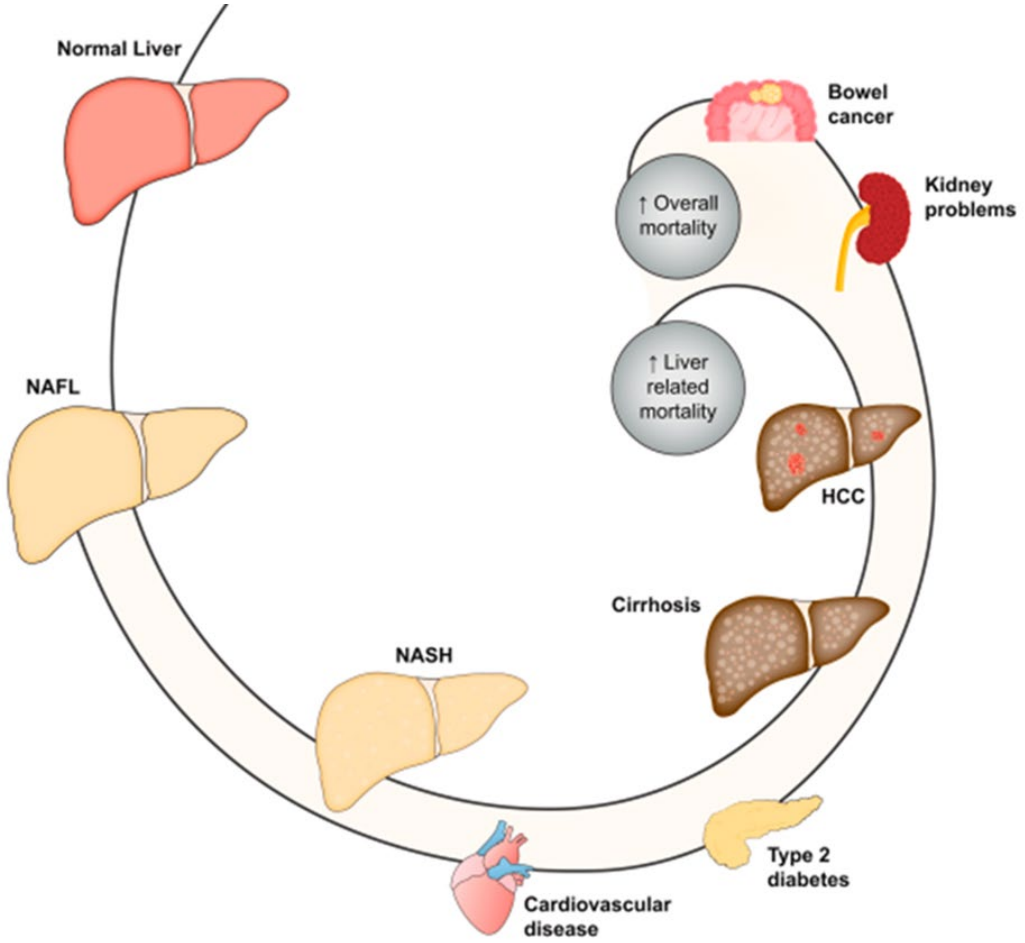
Insulin Resistance

Inflammation
Harmful Cytokines & Chemokines
Oxidate Stress
Endothelial Dysfunction
Plaque Formation

MASLD adds Additional Risk on to Risk

- Individuals with MASLD also are at a greater risk of developing **extrahepatic cancer** including
  - colorectal
  - breast
  - gastric
  - pancreatic & biliary
  - prostate
  - uterine
  - esophageal cancer
  - urinary/kidney
  - thyroid

- Emerging evidence suggests that MASLD increases the risk of **CKD** in people with type 2 diabetes, particularly when ***liver fibrosis*** is present



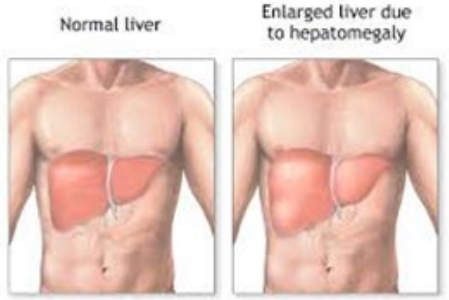
Diagnostics (Basel) 2020 Nov 7;10(11)

Example: Colorectal Cancer (CRC) Risk

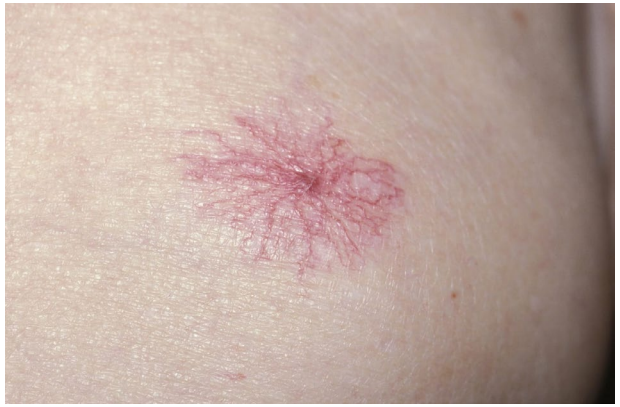
- **PwT2D** have 20-47% higher risk of developing CRC compared to those without diabetes. (OR 1.2-1.47)
- **MASLD** has been recognized as an independent risk factor for the development of colon polyps.
  - the risk of developing ***adenomatous colon polyps*** is three times that of the general population.
  - there are more likely to be *multiple polyps*, and they are more likely to be located in the *right or transverse colon* and present *high-grade dysplasia*
- In a study conducted in the USA in a cohort of 19,163 subjects, **MASLD** was associated with an ***increased risk of colon cancer*** (IRR 1.8; 95% CI, 1.1–2.8)
  - Over and beyond the increased risk from having T2D
- *" It is suggested that a **more rigorous colorectal cancer screening** protocol be implemented for MASLD patients."*

MASLD Signs & Symptoms

- Usually NO symptoms (until cirrhosis)
  - Occasional RUQ pain, abdominal fullness
  - Fatigue may be more common
- On exam may have an enlarged liver (hepatomegaly)
- Liver tests can be abnormal but are often normal
  - Use ALT or AST >30 for men and >20 for women as abnormal
- Fatty infiltration of the liver or “nodular” liver (cirrhosis) might be detected incidentally on other imaging
  - E.g., abdominal US, CT scan or MRI



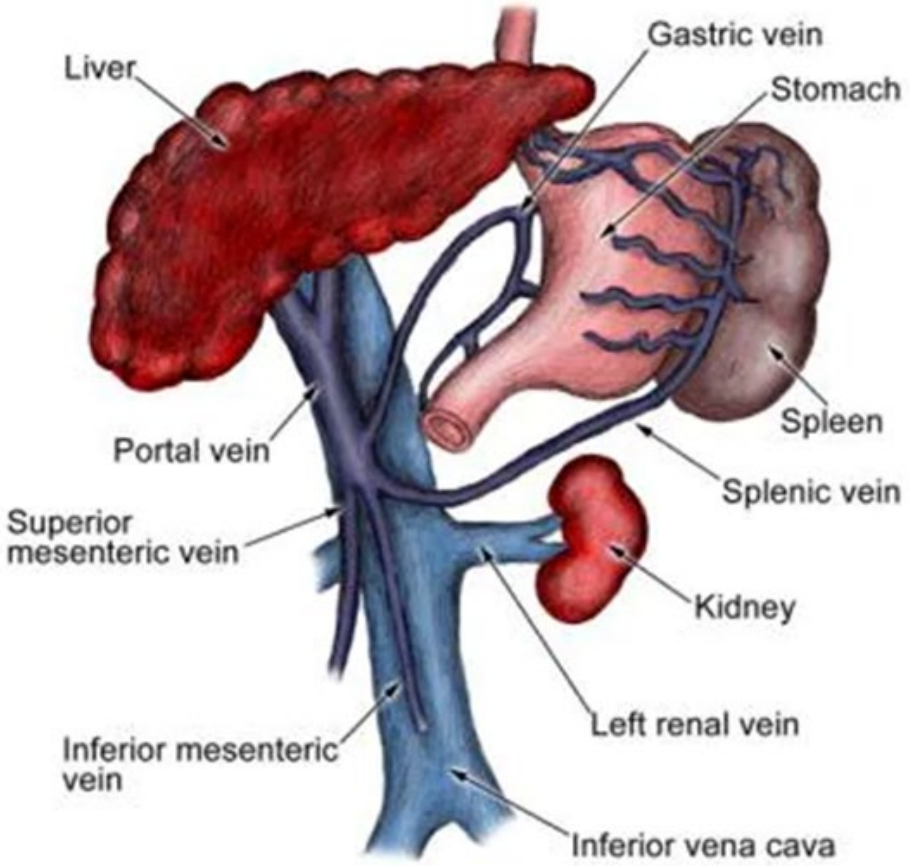
- Cirrhosis & decompensated cirrhosis
  - reduced platelets, AST/ALT ratio >1
  - hepatocellular carcinoma (HCC)
  - portal hypertension & splenomegaly
  - jaundice, spider angiomas, pruritis, sarcopenia
  - ascites, encephalopathy, GI bleeding (varices)



Compensated Cirrhosis

- **Cirrhosis** of the liver is a condition where ***healthy liver tissue is replaced by scar tissue***, hindering the liver's ability to function properly, and can lead to liver failure.
- In compensated cirrhosis, the liver is scarred, but it's ***still functioning at a level that allows the body to cope with the damage***.
  - People with compensated cirrhosis **may not experience any symptoms**, or they might have mild, **non-specific symptoms like fatigue or weight loss**.
  - This stage is characterized by the ***absence of complications*** like ascites (fluid buildup in the abdomen), variceal hemorrhage (bleeding from swollen veins), hepatic encephalopathy (brain dysfunction), or jaundice (yellowing of the skin and eyes).
- While compensated cirrhosis means the liver is still functioning well enough to mask the damage, the primary issue is that it's a **silent stage**, meaning there are no obvious symptoms, which ***can delay diagnosis and treatment until the condition progresses to decompensated cirrhosis***.

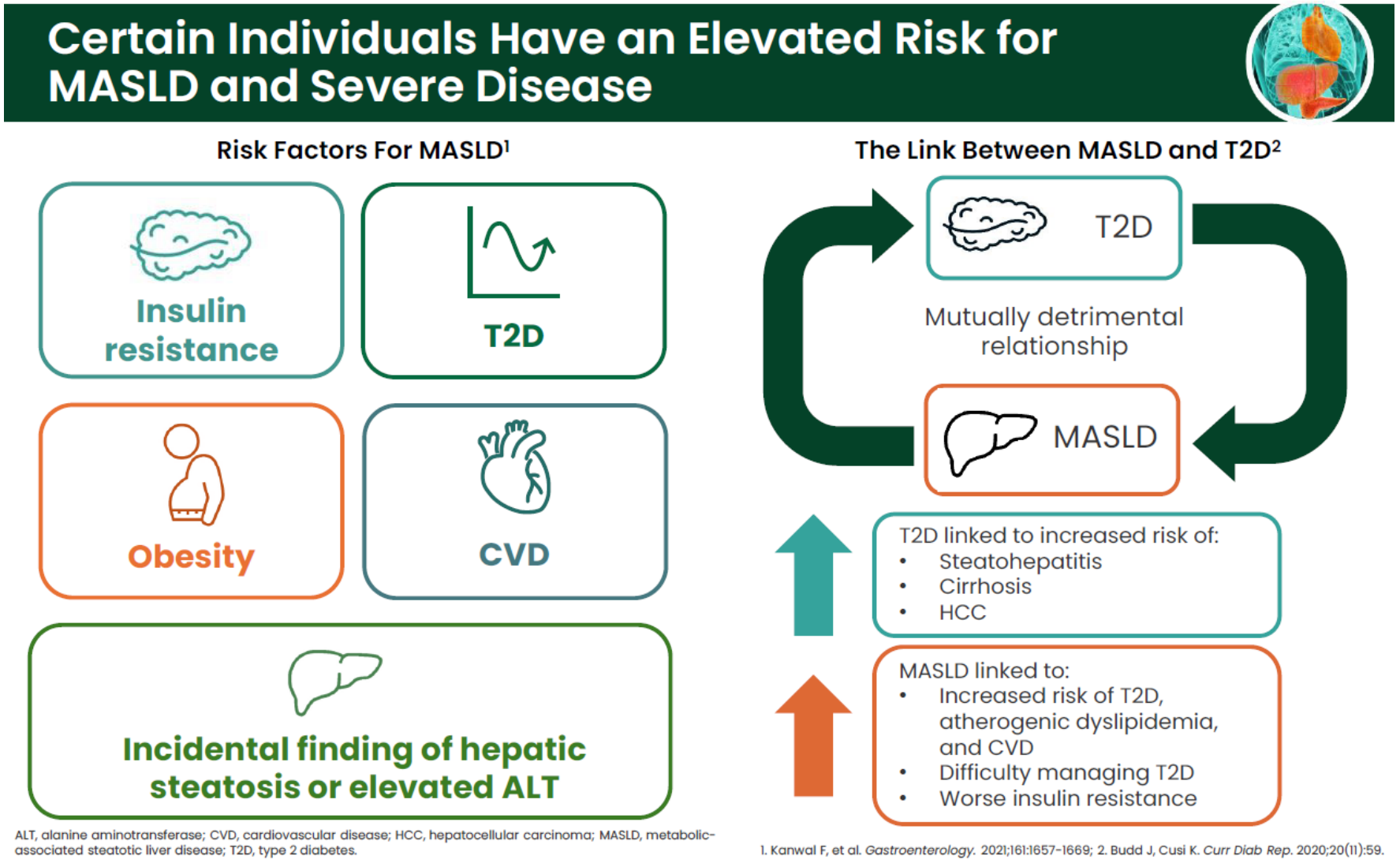
Decompensated Cirrhosis "Liver Failure"/ ESLD



- Portal Hypertension
  - Esophageal varices – hemorrhage
  - Splenomegaly – low platelets
  - Ascites / edema
- Reduced liver cell function
  - Manufacturing/clearing functions
    - Jaundice / high bilirubin
    - Low albumin & other proteins
      - Muscle wasting
      - Bruising (clotting factors)
    - Hyperestrogenism /male hypogonadism
    - Reduced thrombopoietin (TPO)
      - Reduced Bone Marrow production of platelets
  - Increased risk Hepatocellular Ca

Hepatocellular Carcinoma

- Cancer that develops from liver cells (hepatocytes) (a primary tumor of the liver)
- Usually develops on background of chronic liver disease and cirrhosis – most patients have cirrhosis
  - **MASLD is now a leading cause of HCC worldwide**, especially in western countries
  - A significant proportion of ***MASLD-related HCC* cases** (around one-third) occur in individuals at ***earlier stages of fibrosis*** **(i.e., without liver cirrhosis)** compared to other causes
- Hepatocellular carcinoma (HCC) is now the fifth most common cause of cancer worldwide & a major cause of cancer death - Five-year survival of HCC is 18%
  - Surgical resection if the tumor is small - high recurrence rate
  - Liver transplantation is associated with the removal of tumors and the potential for cure.
    - requires early detection
    - MASLD top reason for transplant due to HCC
- Patients with paraneoplastic features of HCC could present with
  - hypoglycemia (not due to extra Insulin – due to tumor glucose consumption/IGF2)
  - hypercalcemia (usually due to PTHrP production – hypercalcemia of malignancy)
  - erythrocytosis



ADA 2025 SoC: “Obesity in the setting of type 2 diabetes worsens insulin resistance and steatohepatitis, promoting the development of cirrhosis.”

Type 2 Diabetes is a risk factor for MASLD & a risk factor for MASH and Fibrosis

Risk Factors for MASLD

- Elevated body weight, such as with overweight or obesity
- Increased waist circumference
  - Visceral adiposity
- Insulin resistance, such as with:
  - Elevated fasting serum glucose levels
  - Elevated 2-hour post-load glucose levels
  - **Diabetes mellitus type 2**
  - Metabolic syndrome
  - Elevated blood pressure
  - Elevated plasma triglyceride levels

Risk Factors for Fibrosis/Cirrhosis

- Insulin resistance
- **Diabetes**
- Obesity (especially BMI $\geq$ 40)
- Weight gain > 5 kg (11 lbs)
- Hypertension

Over 70% of people with T2D have MASLD
(At least 80% if overweight/obese)

Over 50(66)% of people with T2D have MASH with or without fibrosis

ADA 2025 SOC
Screen for “at risk” MASH not for MASLD (“fatty liver”)

- *Presume* adult patients with T2D have MASLD – screen for risk of fibrosis
- 4.22a Screen adults with type 2 diabetes or with prediabetes, particularly those with obesity or other cardiometabolic risk factors or established cardiovascular disease, for their ***risk of having or developing cirrhosis*** related to metabolic dysfunction–associated steatohepatitis (MASH) using a calculated **fibrosis-4 index (FIB-4)** (derived from age, ALT, AST, and platelets [mdcalc.com/calc/2200/fibrosis4-fib-4-index-liver-fibrosis]), ***even if they have normal liver enzymes***.

- In the U.S., between 12% and 20% of people with type 2 diabetes have **“at-risk” MASH** (i.e., steatohepatitis with ***clinically significant fibrosis*** [≥F2] and at risk for cirrhosis)

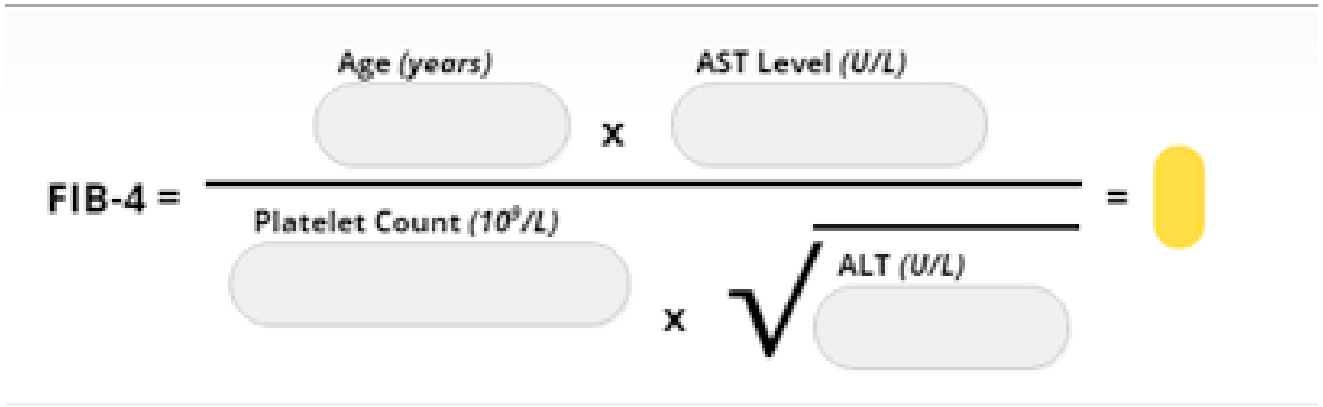
Determine Stage of Fibrosis

- The stage of fibrosis is the most important single predictor of significant morbidity and mortality in chronic liver disease .

- **Liver biopsy** remains the gold standard to evaluate liver fibrosis.
  - Invasive – pain, bleeding & infection risk (sampling of one site in liver)
  - Limited availability

- Use of **non-invasive tests (NITs)** to estimate risk of significant or advanced fibrosis
  - FIB4 – Fibrosis 4 Index
  - VCTE - Vibration-controlled Transient Elastography (Fibroscan) - LSM
  - ELF score - Enhanced Liver Fibrosis score

FIB4 formula



Less reliable at ages <35 or >65

Cut-off values for MASLD

- <1.3 unlikely to have significant fibrosis
  - If age 65+ use < 1.9-2.0*
- >2.67 – high risk of significant (advanced) fibrosis
- >1.3 and <2.67 – additional assessment of risk
  - If age 65+ use >1.9-2.0*

ADA Consensus paper recommends using 1.3 not 2.0 for PwT2D Age ≥ 65

*not all agree with <2.0 – reduces NPV meaning can miss people at risk & in need of additional assessment)

Liver Fibrosis & Low Platelet Count (PTC)

- Low platelet counts (thrombocytopenia) in liver fibrosis are primarily caused by **decreased platelet production** due to **reduced thrombopoietin (TPO)** production by the damaged liver
  - The liver plays a crucial role in producing Thrombopoietin (TPO), a hormone that stimulates the bone marrow to produce platelets.
  - In liver fibrosis, the liver's ability to produce TPO is impaired, leading to a decrease in platelet production in the bone marrow and consequently to a reduced number of platelets in the peripheral blood of patients with advanced-stage liver disease.

- Thrombocytopenia (platelet count < 150,000/µL)

Longitudinal decrease in platelet counts as a surrogate marker of liver fibrosis World J Gastroenterol. 2020

- The mean PTC decreased from 240,000/μL to 190,000/μL up to 15 years prior to cirrhosis diagnosis compared to controls whose PTC remained stable around the values of 240,000/μL.
  - In those who developed cirrhosis, FIB-4 increased gradually from 1.3 to 3 prior to cirrhosis diagnosis (Compared to controls whose values remained in the normal range)
  - In multivariable regression analysis, a *decrease of 50 units in PTC* was associated with 1.3 times odds of cirrhosis (95%CI: 1.25-1.35).

- This study indicates that **a progressive decline in platelet counts, within the normal range,** is associated with **a gradual increase in fibrosis scores, starting up to 15 years before the diagnosis of cirrhosis**.

Limitations to Reliability of FIB4 Index

- Age ≤35 – FIB4 underestimates risk of fibrosis
- Age ≥ 65 – FIB4 overestimates risk

- Type 2 diabetes – FIB4 can underestimate risk of fibrosis
  - *"With respect to misclassification, compared with those without diabetes, a higher proportion of **individuals with diabetes and advanced fibrosis had low FIB-4 <1.3** (4% vs. 13%, respectively)."*

- High alcohol intake (AST>ALT, lower platelets) – overestimate risk of fibrosis

- Another condition such as ITP that reduces platelet count
- Another condition such as myositis that elevates ALT & AST
- Co-existing liver condition
  - NIT cut-off values specific to liver condition – MASLD vs HCV vs PBC, etc.
  - Co-existing condition might predominate, exacerbate MASLD or progress while MASLD improves (e.g., autoimmune hepatitis with MASLD) – liver biopsy may be needed

If Intermediate FIB-4 Result – Additional Assessment

- 4.23 Adults with type 2 diabetes or prediabetes with a FIB-4 ≥1.3 should have ***additional risk stratification*** by
  - liver stiffness measurement (LSM) with transient elastography,

    or, if unavailable,
  - the enhanced liver fibrosis (ELF) test. B

- Guidelines:

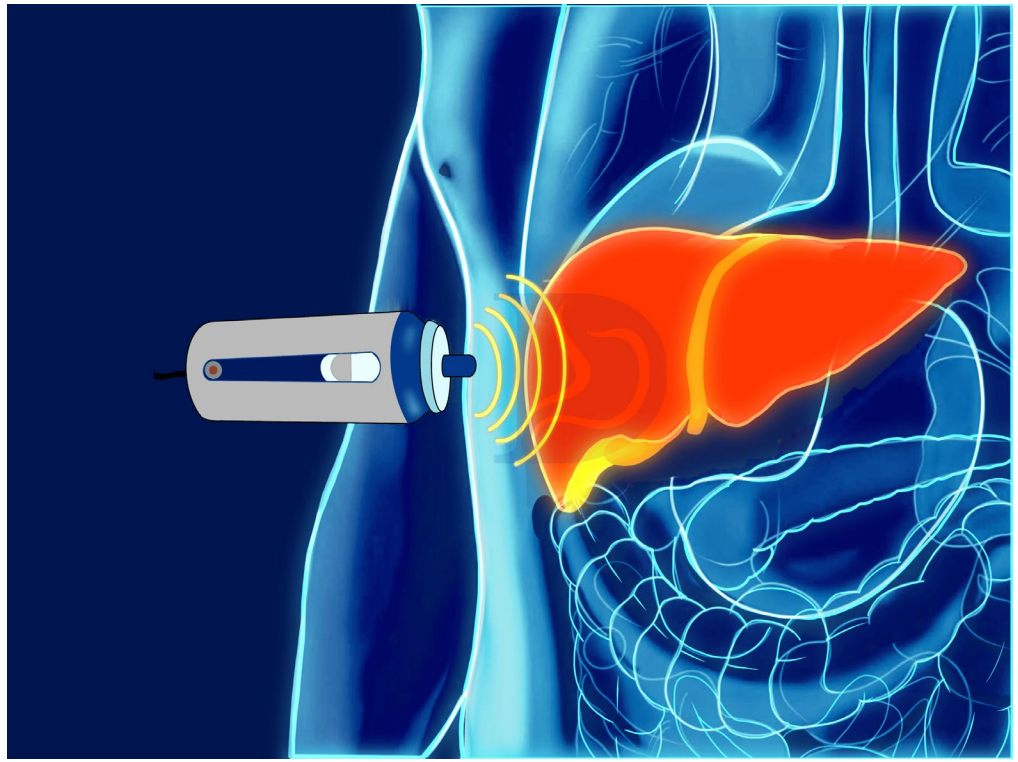
  > A value of >2.67 confers a high risk of having advanced fibrosis (F3–F4), and referral to the liver specialist is warranted without additional testing.

- Practice: Option to obtain additional NIT(s) to expedite care & more accurately stratify risk

Apply Clinical Judgement

- If the FIB4 score is **≥1.0 and ≤1.3** but patient with **T2D has multiple risk factors** – consider checking a secondary assessment test with VCTE or ELF test
  - ADA 2025 MASLD consensus report: ***"Clinically significant fibrosis may be present in some adults with type 2 diabetes and FIB-4 values between 1.0 and 1.3, especially when type 2 diabetes is associated with obesity and multiple cardiometabolic risk factors."***
    - "Therefore, a FIB-4 score cutoff of <1.3 should be taken as a general guidance for assessment of having a lower risk of advanced fibrosis, but it does not replace clinical judgement."
  - Case finding with eventual **additional testing may be justified with a FIB-4 score between 1.0 and 1.3 in people with type 2 diabetes with obesity or other traditional cardiometabolic risk factors.**
    - For these cases transient elastography (Fibroscan) may also be of benefit as part of risk assessment [or ELF test if Fibroscan not available]

Vibration-controlled transient elastography (VCTE)
Liver Stiffness Measurement (LSM)
Fibroscan (specific brand of device that performs VCTE)



Liver Stiffness Measurement (LSM) in VCTE:

- Normal Range: 2 to 7 kPa.
- Fibrosis: Higher values indicate increased liver stiffness and potential fibrosis.
- Cirrhosis: Values generally >12-14 kPa

- VCTE can also detect steatosis using the controlled attenuation parameter (**CAP score**) - Values >280 dB/m are highly likely indicative of having steatosis.

FIB-4 followed by LSM helps stratify people with diabetes by risk level and minimize specialty referrals ADA 2025 SoC

- Transient elastography (LSM) is the best-validated imaging technique for fibrosis risk stratification, and it predicts future cirrhosis and all-cause mortality in MASLD – *ADA Standards of Care suggest cutoff of 8.0 kPa*

- An LSM value of **<8.0 kPa** has a good negative predictive value to exclude advanced fibrosis (≥F3–F4) and indicates lower risk for clinically significant fibrosis.
  - Such individuals with prediabetes or type 2 diabetes can be followed in nonspecialty clinics with repeat surveillance testing every ≥2 years (the precise time interval remains to be established).
- If the LSM is **≥8.0 kPa**, the risk for advanced fibrosis (≥F3–F4) is higher and such individuals should be *referred to the hepatologist* within the framework of an interprofessional team

kPa = Pascal or kilopascal - a derived unit of pressure

Conditions that can affect FibroScan results

- Obesity - body mass index (BMI) > 30 (Asian >25)
  - class 3 obesity was strongly linked to the overestimation of fibrosis by at least 2 stages by Fibroscan *Journal of Clinical Gastroenterology*
- Ascites
  - Fluid build up in the belly.
- Biliary obstruction
- Scar tissue around/outside of the liver
  - Scar tissue from previous surgeries or radiation therapy near the liver can interfere with the ultrasound waves.
- Liver inflammation or congestion:
  - Liver inflammation, either caused by recent liver illness or drinking alcohol, or liver congestion (when the liver is too full of blood or other fluids) can lead to inaccurate readings.
- Liver tumors:
  - Both benign and cancerous tumors in the liver can also affect the accuracy of the test.

FibroScan discordance with liver biopsy significantly overestimates advanced fibrosis and cirrhosis in MASLD subjects with class 3 obesity: J Clin Gastroenterol. 2025. Velji-Ibrahim J, et al

- Overestimation of fibrosis by at least 2 stages:
  - class 3 obesity 38.6% of patients
  - class 2 obesity 24.6% of patients
  - class 0 to 1 obesity 18.4% of patients

- Among patients with class 3 obesity, FibroScan suggested the presence of cirrhosis in 57.9%, whereas liver biopsy confirmed cirrhosis in 24.2%.

- *"Given the prevalence of class 3 obesity and its impact on FibroScan accuracy, in the absence of clinical, biochemical, or imaging support for cirrhosis, a second noninvasive test should be used before proceeding with liver biopsy or excluding individuals from novel liver-directed therapy."*
- Consider the New *XL* probe for VCTE or Magnetic Resonance Elastography (MRE)
  - Often recommend MRE if BMI >40

If LSM is not available or accurate → the ELF score

- The Enhanced Liver Fibrosis (ELF) score - A blood sample is taken to measure the levels of three *serum biomarkers*:
  - hyaluronic acid (HA)
  - procollagen III N-terminal peptide (PIIINP)
  - tissue inhibitor of matrix metalloproteinase-1 (TIMP-1)
- Quest, LabCorp, some health system labs, some regional reference labs

- *The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values* J Hepatol. 2013
  - Identified three cut-off values:
    - 7.7 for a high sensitivity exclusion of fibrosis
    - 9.8 for a high specificity identification of fibrosis (sensitivity 69%, specificity 98% for moderate fibrosis),
    - 11.3 to discriminate cirrhosis (sensitivity 83%, specificity 97%)

Given the lack of widespread availability of LSM, the ELF test is a good alternative ADA 2025 Standards of Care

- Individuals with **ELF <9.8** are considered at low risk for adverse liver outcomes.*
- Individuals with **ELF ≥9.8** are considered at high risk of having MASH with advanced liver fibrosis (≥F3–F4) and therefore are at risk for adverse liver outcomes.
  - They should be referred to a gastroenterologist or hepatologist.

- The optimal cutoff for clinical use of ELF in primary care and endocrinology settings is evolving:
  - *An ELF <9.8 suggests an individual is at low risk of advanced liver fibrosis and may be followed in the nonspecialty clinic with repeat testing in ≥2 years but may need repeat testing more often if ELF is between 9.2 and 9.7.

  - No interference by age, diabetes, obesity - males usually measure higher ELF than females

Referral for Further Evaluation & Management

- 4.24 Refer adults with type 2 diabetes or prediabetes at higher risk for significant liver fibrosis (i.e., as indicated by FIB-4, liver stiffness measurement, or ELF) to a gastroenterologist or hepatologist for further evaluation and management. B
  - FIB4 ≥2.67*
  - FIB4 ≥1.3** + LSM ≥ 8
  - FIB4 ≥1.3** + ELF ≥ 9.8

- *Consider ordering a LSM (Fibroscan) and/or ELF test to expedite referral and improve accuracy of risk status
- **FIB4 ≥1.0 + LSM >8 or ELF≥ 9.8 in PWT2D & multiple risk factors
- If FIB4 >1.3 but LSM <8.0 or ELF <9.8 – manage in primary care

Interpreting/Explaining Non-Invasive Test (NIT) Results

- “Since NITs have significant interindividual variability and overlapping confidence intervals across fibrosis stages, it is best to consider results in the context of having a ***“probability” of a given liver disease stage*** rather than the certainty that only a liver biopsy can provide.”
  - E.g., FIB4 >2.67 has a 60-80% range of a positive predictive value for clinically significant fibrosis in patients with MASLD

- Different cut off levels for NITs for different liver conditions (e.g., HCV, PBC, autoimmune hepatitis, etc.)

From: **4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2025**

Diabetes Care. 2024;48(Supplement_1):S59-S85. doi:10.2337/dc25-S004

Diagnostic Algorithm for the Prevention of Cirrhosis in People With Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

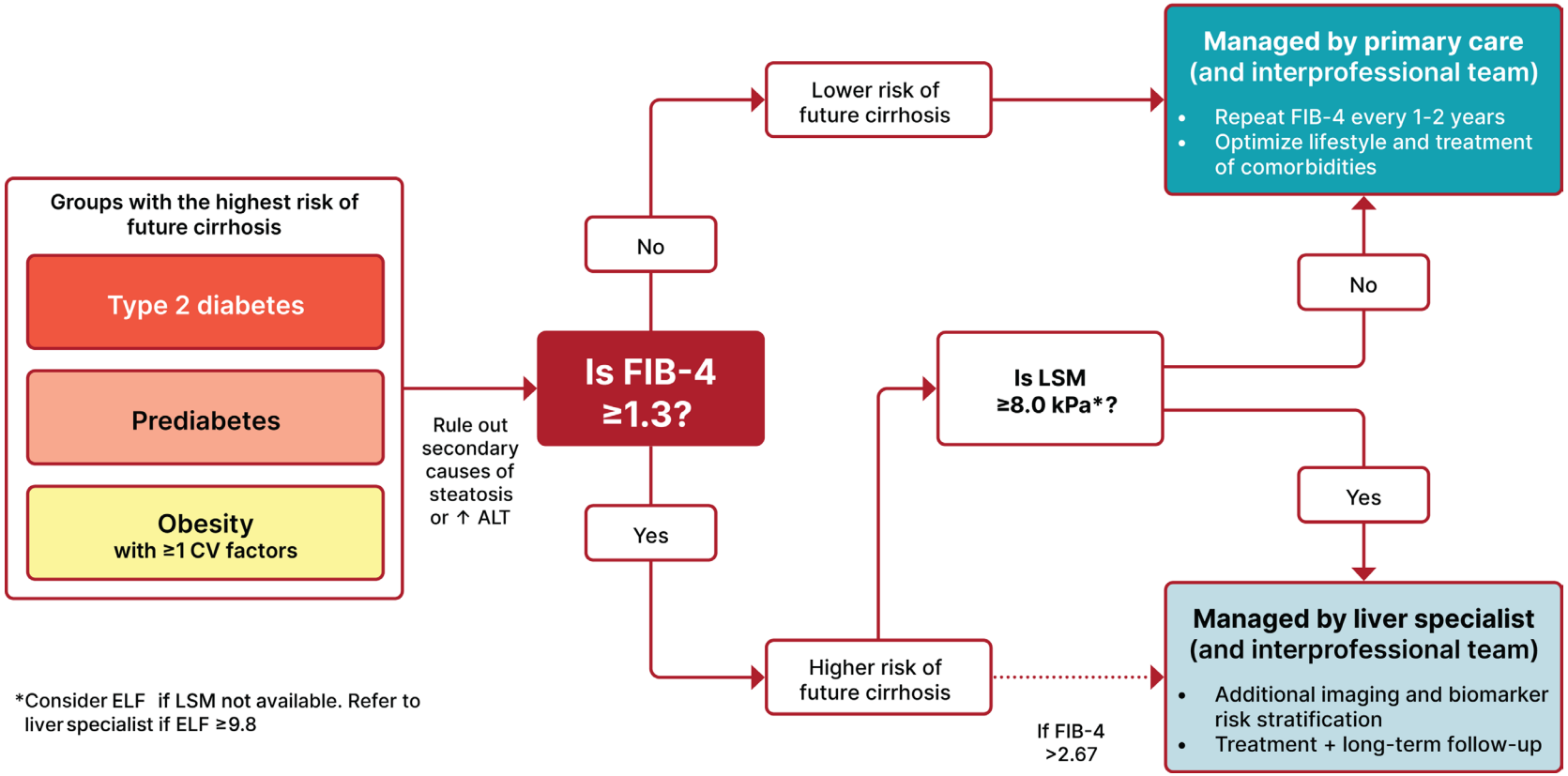
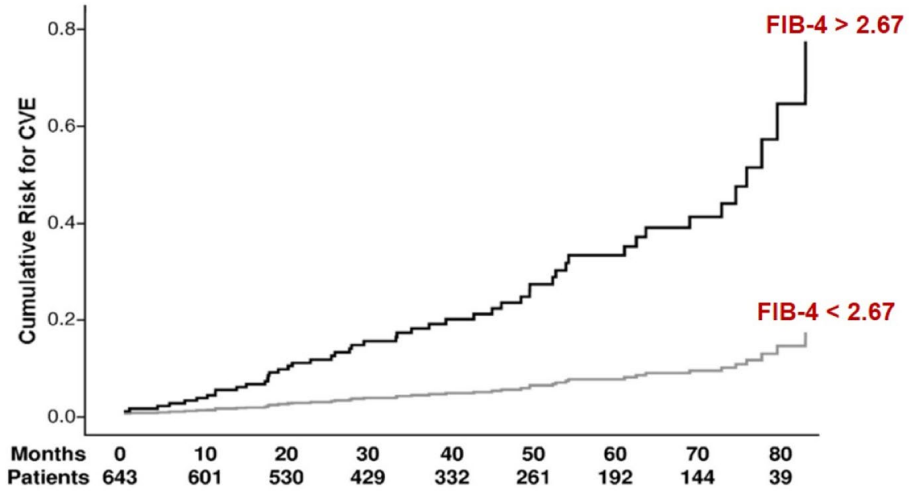


Figure Legend:

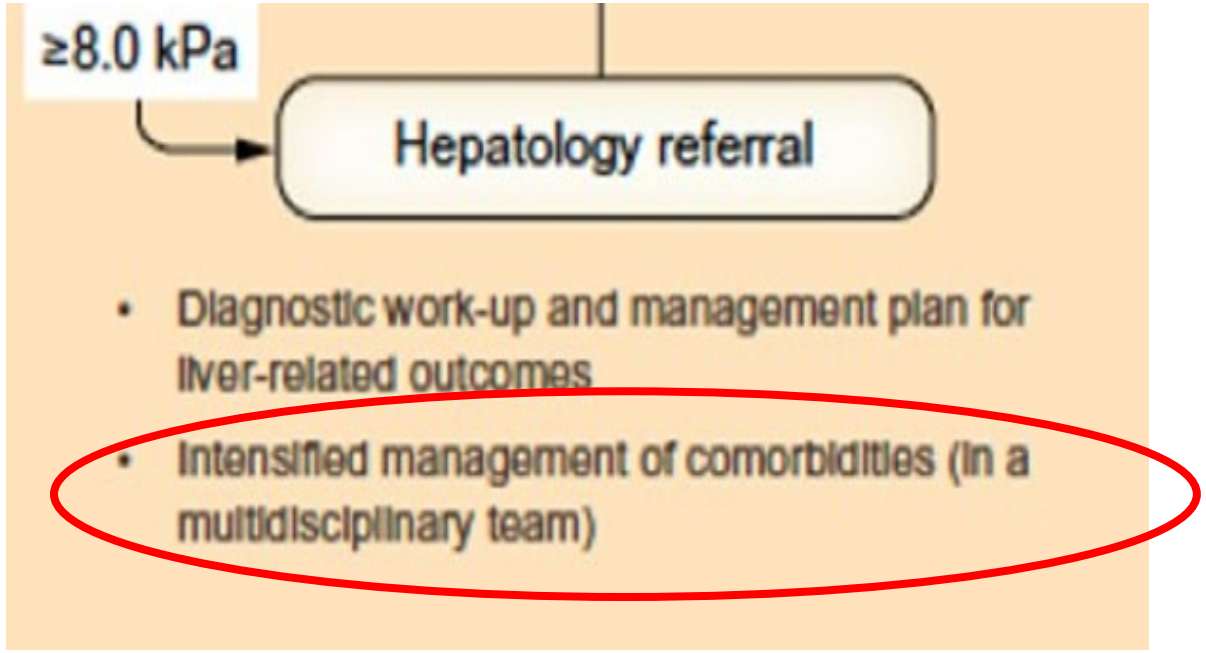
Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with metabolic dysfunction–associated steatotic liver disease (MASLD). CV, cardiovascular; ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement, as measured by vibration-controlled transient elastography. *In the absence of LSM, consider ELF a diagnostic alternative. If ELF ≥9.8, an individual is at high risk of metabolic dysfunction–associated steatohepatitis with advanced liver fibrosis (≥F3–F4) and should be referred to a liver specialist.

Elevated FIB4 /Advanced Fibrosis Increases the Risk of CVD, CKD & Non-hepatic Cancers as well as Liver Complications – Ongoing Role for Primary Care to Intensify Management for these Comorbidity Risks

FIB-4 Predicts CV Risk



CVE, cardiovascular event.
Baratta F, et al. Clin Gastroenterol Hepatol. 2020;18:2324-2331.e4.



Goal of Screening with FIB-4

- The goal of this screening is to identify people with at-risk MASH to prevent future cirrhosis, HCC (hepatocellular carcinoma), liver transplantation, and all-cause mortality (including CVD & malignancy)
  - In people with T2D - 3x risk for HCC

- This risk of liver complications is higher in people who
  - have central obesity and cardiometabolic risk factors or insulin resistance,
  - are >50 years of age, and/or
  - have persistently elevated plasma aminotransferases (AST and/or ALT >30 units/L for >6 months)*
    - ADA Standards of Care recommend the upper limits of normal for ALT level: 29-33 units/L for men, 19-25 units/L for women

*Need to evaluate for **alternative or co-existing liver conditions** if elevated liver tests or steatosis on imaging – even if low risk FIB4

- The definition of MASLD allows for co-existing conditions (vs NAFLD – required the absence of other causes of steatosis/abnormal liver function)

If elevated liver tests/steatosis on imaging – evaluate for Alternative or Co-existing Liver Conditions

- Alcoholic Liver Disease: (AST-ALT ratio often >2), social history
  - Phosphatidylethanol (PEth)
- Hemochromatosis: Ferritin, transferrin saturation test, HFE gene testing
- Chronic viral hepatitis: HCVAb, HBsAg, etc.
- Celiac disease: tTG-IgA (tissue transglutaminase immunoglobulin A) and total IgA.
- Autoimmune liver disease: ANA, anti-smooth muscle AB test
- Alpha 1- Antitrypsin deficiency: alpha 1 Antitrypsin phenotyping
- Drug-induced liver injury: e.g. Methotrexate, amiodarone, tamoxifen, corticosteroids, 5-fluorouracil, Irinotecan, etc.
  - https://www.ncbi.nlm.nih.gov/books/NBK547852/ (Liver Tox)

More details in
"Extra Slides" section

Summary – Key Points

- MASLD & MASH replace the NAFLD & NASH terminology along with some differences to the definition
  - At least one Cardiometabolic risk factor associated with insulin resistance
  - Allows for co-existence of other liver conditions
- MASLD is the most common liver disease in the USA
- MASLD increases the risk of CVD, cancers & CKD as well as the risk of liver complications
- >70% of people with T2D have MASLD and >50% have MASH, therefore the ADA recommends presuming the presence of MASLD & screening for the risk of fibrosis in all patients (even with normal liver tests) using FIB4 index
  - To identify those who need special attention/referral to prevent liver complications
  - Secondary NITs such as Fibroscan (LSM) and ELF test can help further stratify risk
- Efforts to reverse MASLD are important for all people with MASLD (i.e., most people with T2D)

Post-Question – which one answer is correct

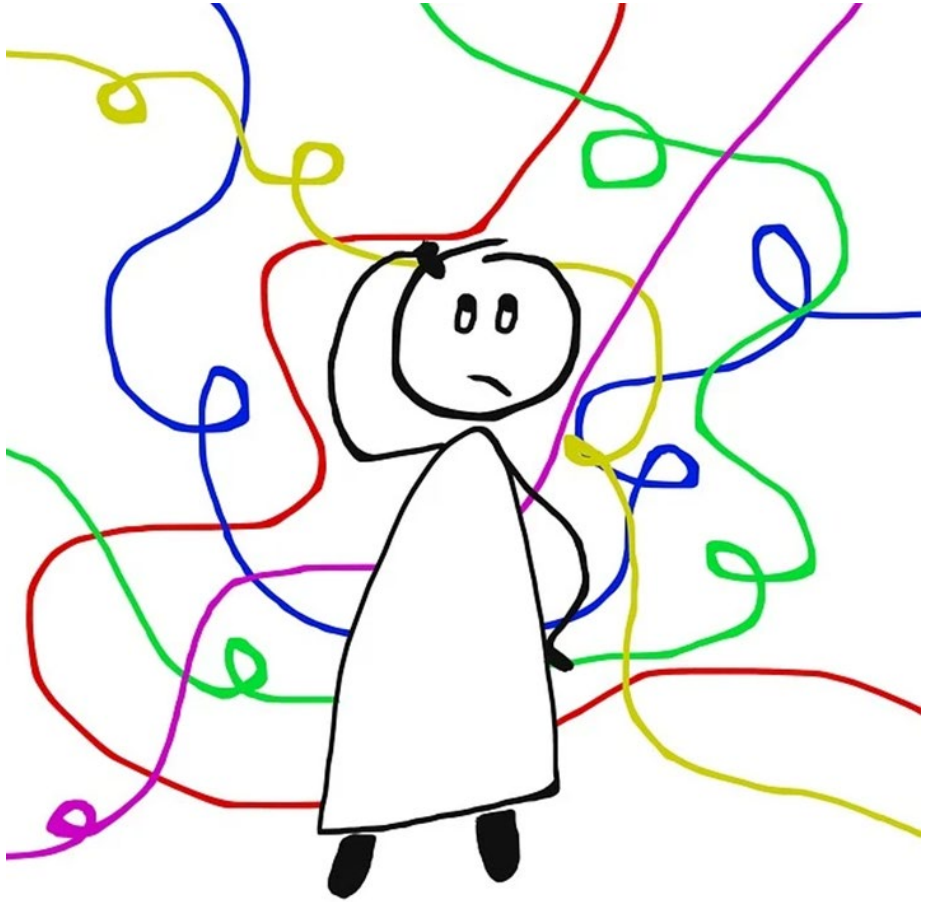
The definition of MASLD requires

A. the association with at least one cardiometabolic risk factor associated with insulin resistance
B. the exclusion of other causes of liver disease
C. the exclusion of any or all alcohol ingestion
D. elevated liver tests (aminotransferases – ALT &/or AST)

Next Steps – next 2 weeks on management

- We want to *prevent or reduce* liver fat & inflammation & any fibrosis in all our patients [not just those screening at risk for liver complications]
  - Steatosis is a critical factor that influences its development, severity, and progression of MASH - Managing and reducing steatosis is therefore a primary goal in treating and preventing MASH.
- For all patients – even those with low-risk FIB4/NITs & those waiting for referral:
  - Exercise (even 10 minutes) /reduce sedentary time!!
  - Food choices – in addition to reduced calories
    - avoid alcohol
    - avoid/reduce high sugar & High-Fructose Corn Syrup (HFCS) food items
    - reduce saturated fats
    - encourage coffee intake – 3 to 4 cups/day including both caffeinated and decaffeinated varieties
  - Glycemic management/Weight loss – GLP1 RA or Dual GLP1/GIP RA medications
    - Not if decompensated cirrhosis – only insulin & avoid weight loss
  - Pioglitazone

Questions, Comments, Clarification



Are you routinely screening patients with T2D with FIB4 index?
Are you able to get a LSM/Fibroscan result for your patient?

What is your experience of getting patients referred in with a liver team?

Extra Slides

- https://www.echosens.com/en-us/find-a-fibroscan-map/

Magnetic Resonance Elastography (MRE) - if BMI >40 or need further evaluation

- While MRE may not be the initial choice for risk stratification due to cost and access considerations, it can serve as a valuable tool in specialty clinics, especially in cases of uncertainty or unreliable VCTE results.
  - VCTE-derived LSM >10 kPa and MRE-derived LSM >3.5 kPa suggest advanced fibrosis (i.e., liver fibrosis stages 3 [F3] and 4 [F4])
  - a value >15 kPa and MRE values >4.4 kPa are consistent with a high probability of cirrhosis (i.e., stage F4).\
  - VCTE-derived LSM >25 kPa (99), VCTE-derived LSM >20 kPa with platelet counts ≤150,000/mm3, and MRE-derived LSM >5.7 kPa are all reflective of likely having clinically significant portal hypertension

- Superior Diagnostic Accuracy: MRE has consistently demonstrated higher diagnostic accuracy across all stages of liver fibrosis, particularly in detecting early fibrosis (F0-F2) where VCTE may be less sensitive.
- Effectiveness in Obese Patients: Obesity is a common comorbidity in MASLD, and VCTE's accuracy can be compromised in these patients due to limitations in ultrasound wave transmission. MRE, on the other hand, performs well in assessing liver stiffness even in the presence of obesity.
- Broader Liver Coverage: MRE evaluates the entire liver, unlike liver biopsy which only samples a small portion, according to the Mayo Clinic. This allows for a more comprehensive assessment of fibrosis distribution.

Diagnosing MASLD / “Fatty Liver”

- Because having obesity and prediabetes or type 2 diabetes is associated with a high pretest probability of hepatic steatosis (>70%), one may proceed directly to fibrosis risk assessment without an ultrasound to confirm steatosis.
- Steatosis can be diagnosed with the controlled attenuation parameter (CAP score) from a vibration-controlled transient elastography (VCTE) examination. Values >280 dB/m are highly likely indicative of having steatosis.
- MRI is the gold standard for confirmation of steatosis
- While a liver ultrasound has in the past been widely used to diagnose hepatic steatosis, the presence of an echogenic liver itself is not highly specific, as its diagnosis is operator dependent and ultrasound has poor sensitivity for mild steatosis (not reliably detected until 30% fat or more)

Secondary causes of hepatic fat accumulation which may be differential diagnoses for metabolic dysfunction-associated steatotic liver disease (MASLD):

- Excessive alcohol consumption, such as > 2 drinks/day in female patients and 3 drinks/day in male patients, in the absence of other potential causes of liver injury (see Alcohol-Related Liver Disease)
- Chronic hepatitis C virus (genotype 3)-associated steatotic liver
- Wilson disease
- Disorders of lipid metabolism, including inborn errors of metabolism, such as:
  - Hypobetalipoproteinemia
- Pfeifer-Weber-Christian syndrome, which is an idiopathic disorder with nonsuppurative nodular panniculitis that can affect lipid metabolism and is reported to be associated with MASLD (Clin Med Insights Case Rep 2020;13:117954762091795 8)
- Lysosomal acid lipase deficiency, such as with Wolman disease or cholesteryl ester storage disease
- Lipodystrophy, which is genetically inherited or induced by highly active antiretroviral therapy (HAART)

Secondary causes of hepatic fat accumulation which may be differential diagnoses for metabolic dysfunction-associated steatotic liver disease (MASLD) continued:

- Mauriac syndrome (rare complication of growth failure involving cushingoid appearance and hepatomegaly in young patients with diabetes mellitus type 1 described in Endocrinol Nutr 2013 May;60(5):245)
- Nutrient deficiency/malnutrition, including carnitine or choline deficiency due to anorexia, short bowel syndrome, or bypass surgery
- Parenteral nutrition
- Celiac disease
- Pregnancy associated etiologies such as hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, or acute onset of steatotic liver disease during pregnancy
- Endocrine diseases, such as:
  - Hypothyroidism
  - Polycystic ovary syndrome (PCOS)
  - Growth hormone deficiency (see Growth Hormone Deficiency in Adults and Growth Hormone Deficiency in Children)
  - Panhypopituitarism (primary or secondary)

Other causes of elevated liver enzymes which may be differential diagnoses for MASLD:

- **Alcohol-related liver disease (ALD**), which is associated with steatosis and a positive history of excessive alcohol use, may cause elevated liver enzymes. ALD and MASLD are considered overlapping conditions along a continuum across which the contribution of MASLD and ALD will vary, which is called MASLD and increased alcohol intake (MetALD) (see also Determination of Alcohol Consumption in Alcohol-Related Liver Disease) (Hepatology 2020 Jan;71(1):306 and Ann Hepatol 2024 Jan-Feb;29(1):101133).\
- **Autoimmune hepatitis**, which is not associated with steatosis, may have a history of diabetes mellitus type 1, Graves disease, ulcerative colitis, vasculitis, or Sjogren syndrome and may be ruled out by liver biopsy.4
- **Hepatitis B or hepatitis C virus infections** cause elevated liver enzymes, but only hepatitis C genotype 3 is associated with liver steatosis. Risk factors for viral hepatitis include injection drug use, risky sexual behaviors, and blood transfusions (4 and Med Clin North Am 2014 Jan;98(1):1).
- **Drug-induced liver injury** is associated with increased transaminase levels after starting a medication which resolve when the medication is discontinued (Eur J Intern Med 2016 Mar;28:9).
- **Hemochromatosis**, which is not associated with steatosis, may be associated with increased skin pigmentation, hepatomegaly, testicular atrophy, decreased libido, fatigue, and cardiomyopathy. Patients may have elevated transferrin saturation and serum ferritin levels (Hepatology 2011 Jul;54(1):328).

Medications, that can cause drug-induced liver disease and may be ruled out by liver biopsy, such as:

- 5-fluorouracil (5-FU)
- Acetylsalicylic acid
- Amiodarone
- Amphetamines
- Corticosteroids
- Irinotecan
- Lomitapide
- Methotrexate
- Tamoxifen
- Tetracyclines
- Valproate

Newer Criteria for Alcohol Ingestion – US Dietary Guidelines

https://www.niaaa.nih.gov/alcohols-effects-health/alcohol-drinking-patterns

Risk Factors for MASLD

- Risk factors for metabolic dysfunction-associated steatotic liver disease (MASLD) include:
  - Elevated body weight, such as with overweight or obesity
  - Increased waist circumference
  - Insulin resistance, such as with:
  - Elevated fasting serum glucose levels (in children, can include elevated serum glucose)
  - Elevated 2-hour post-load glucose levels
  - Diabetes mellitus type 2
  - Metabolic syndrome
  - Elevated blood pressure
  - Elevated plasma triglyceride levels
  - Elevated high-density lipoprotein (HDL) cholesterol

Most (60–80%) but not all individuals with type 2 diabetes have MASLD.
Those without MASLD have been suggested to have diabetes subtypes that are not as closely linked to the metabolic syndrome but remain classified as type 2 diabetes.

Reference - Ann Hepatol 2024 Jan-Feb;29(1):101133

Risk Factors for Progression to Severe Liver Disease

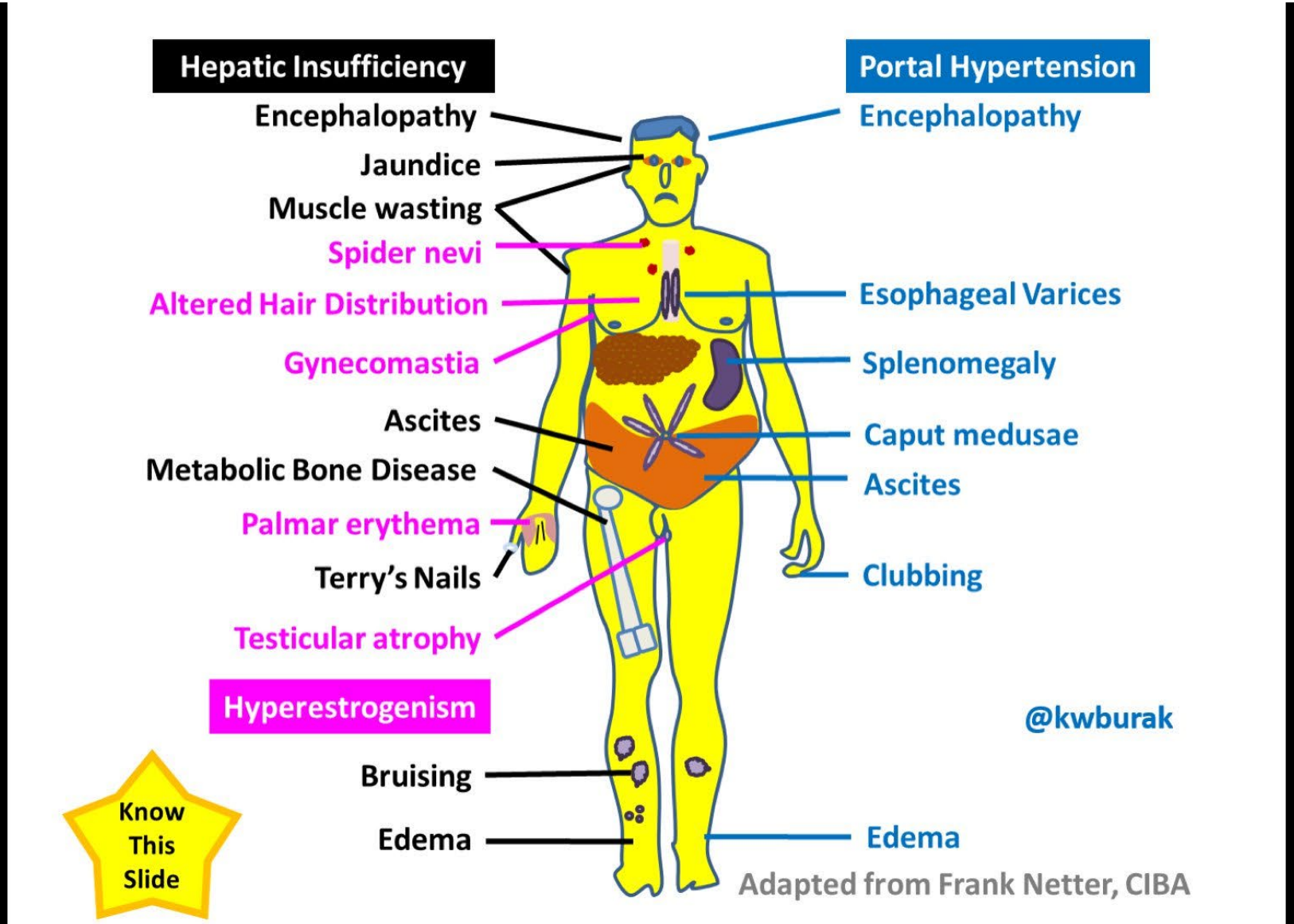
- Risk factors for more severe liver disease include:
  - Hyperglycemia
  - Diabetes
  - Evidence of metabolic syndrome, such as arterial hypertension
  - Obesity
  - Weight gain (especially if >11 pounds)
  - Older age
  - Aspartate aminotransferase : alanine aminotransferase (AST:ALT) ratio > 1

Reference - Clin Liver Dis (Hoboken) 2018 Apr;11(4):81

Compensated Cirrhosis

- Why is it a Problem?
- Lack of Symptoms: The asymptomatic nature of compensated cirrhosis means that people may not realize they have a serious liver problem until the disease progresses to a more advanced, symptomatic stage.
- Delayed Diagnosis and Treatment: Because there are no obvious symptoms, people with compensated cirrhosis may not seek medical attention until the liver damage becomes severe, leading to a delay in diagnosis and treatment.
- Progression to Decompensated Cirrhosis: Compensated cirrhosis can progress to decompensated cirrhosis, where the liver is no longer able to function properly, leading to serious complications and a poorer prognosis.
- Risk of Complications: Even in the compensated stage, individuals are still at risk for developing complications like portal hypertension (high blood pressure in the portal vein), varices (swollen veins in the digestive system), and liver cancer.
- What to Do?
- Regular Checkups: People at risk for liver disease (e.g., those with a history of alcohol abuse, viral hepatitis, or other liver conditions) should undergo regular checkups to monitor liver health.
- Early Intervention: If cirrhosis is diagnosed early, even in the compensated stage, treatment can focus on addressing the underlying cause of the liver damage and preventing progression to decompensated cirrhosis.
- Lifestyle Changes: Adopting a healthy lifestyle, including a balanced diet, regular exercise, and avoiding alcohol and other harmful substances, can help slow down the progression of liver disease.

Decompensated Cirrhosis



Screening
ADA 2025 Standards of Care

- 4.22a Screen adults with type 2 diabetes or with prediabetes, particularly those with obesity or other cardiometabolic risk factors or established cardiovascular disease, for their risk of having or developing cirrhosis related to metabolic dysfunction–associated steatohepatitis (MASH) using a calculated fibrosis-4 index (FIB-4) (derived from age, ALT, AST, and platelets [mdcalc.com/calc/2200/fibrosis4-fib-4-index-liver-fibrosis]), even if they have normal liver enzymes. B

- 4.22b Adults with diabetes or prediabetes with persistently elevated plasma aminotransferase levels for >6 months and low FIB-4 should be evaluated for other causes of liver disease. B

- 4.23 Adults with type 2 diabetes or prediabetes with a FIB-4 ≥1.3 should have additional risk stratification by liver stiffness measurement with transient elastography, or, if unavailable, the enhanced liver fibrosis (ELF) test. B

- 4.24 Refer adults with type 2 diabetes or prediabetes at higher risk for significant liver fibrosis (i.e., as indicated by FIB-4, liver stiffness measurement, or ELF) to a gastroenterologist or hepatologist for further evaluation and management. B

“Apply Clinical Judgement”
ADA 2025 MASLD consensus report

- ADA MASLD 2025 consensus report: Clinically significant fibrosis may be present in some adults with type 2 diabetes and FIB-4 values between 1.0 and 1.3, especially when type 2 diabetes is associated with obesity and multiple cardiometabolic risk factors.
  - For instance, in a recent large *phase 3 study* with recruitment of people with MASLD with fibrosis stages F2 and F3, often with obesity and type 2 diabetes, the mean ± SD of the FIB-4 score was 1.4 ± 0.7 .
    - This indicates that for some individuals with at-risk MASH FIB-4 score may be <1.3, especially in the context of obesity and type 2 diabetes.
  - Therefore, a FIB-4 score cutoff of <1.3 should be taken as a general guidance for assessment of having a lower risk of advanced fibrosis, but it does not replace clinical judgement.
- Case finding with eventual additional testing may be justified with a FIB-4 score between 1.0 and 1.3 in people with type 2 diabetes with obesity or other traditional cardiometabolic risk factors.
  - For these cases transient elastography may also be of benefit as part of risk assessment.

Apply Clinical Judgement

- FIB4 has potential for *underestimation of fibrosis severity* in individuals with T2D

- If the FIB4 score is **≥1.0 and <1.3** but patient with ***T2D has multiple risk factors*** – consider checking a secondary assessment test with VCTE or ELF test
  - The risk of developing MASLD, MASH and fibrosis/cirrhosis has been independently associated with
    - insulin resistance
    - weight gain
    - obesity
    - cardiometabolic risk factors
    - family history (genetic risk)

FIB4 Examples - Impact of Drop in Platelet Count

- MASLD with normal ALT/AST levels
  - 50 yo/ALT 18/AST 18/PTC 240,000 = 0.88
  - 50 yo/ALT 18/AST 18/PTC 200,000 = 1.06
  - 50 yo/ ALT 18/AST 18/PTC 150,000 = 1.41 – (estimate F0-1)
  - 50 yo/ALT 18/AST 18/PTC 100,000 = 2.12 – (estimate F2-3)
- MASLD with abnormal ALT/AST levels
  - 50 yo/ALT 49/AST 44/PTC 200,000 = 1.57
  - 50 yo /ALT 49/AST 44/PTC 150,000 = 2.46 (estimate F2-3)
- MASLD with AST>ALT level
  - 50 yo/ALT 39/AST 54/PTC 150,000 = 2.88
  - 50 yo/ALT 39/AST 54/PTC 100,000 = 4.82 (estimate F4+) - cirrhosis