MASLD-related Hepatocellular Carcinoma: Controversies and Challenges

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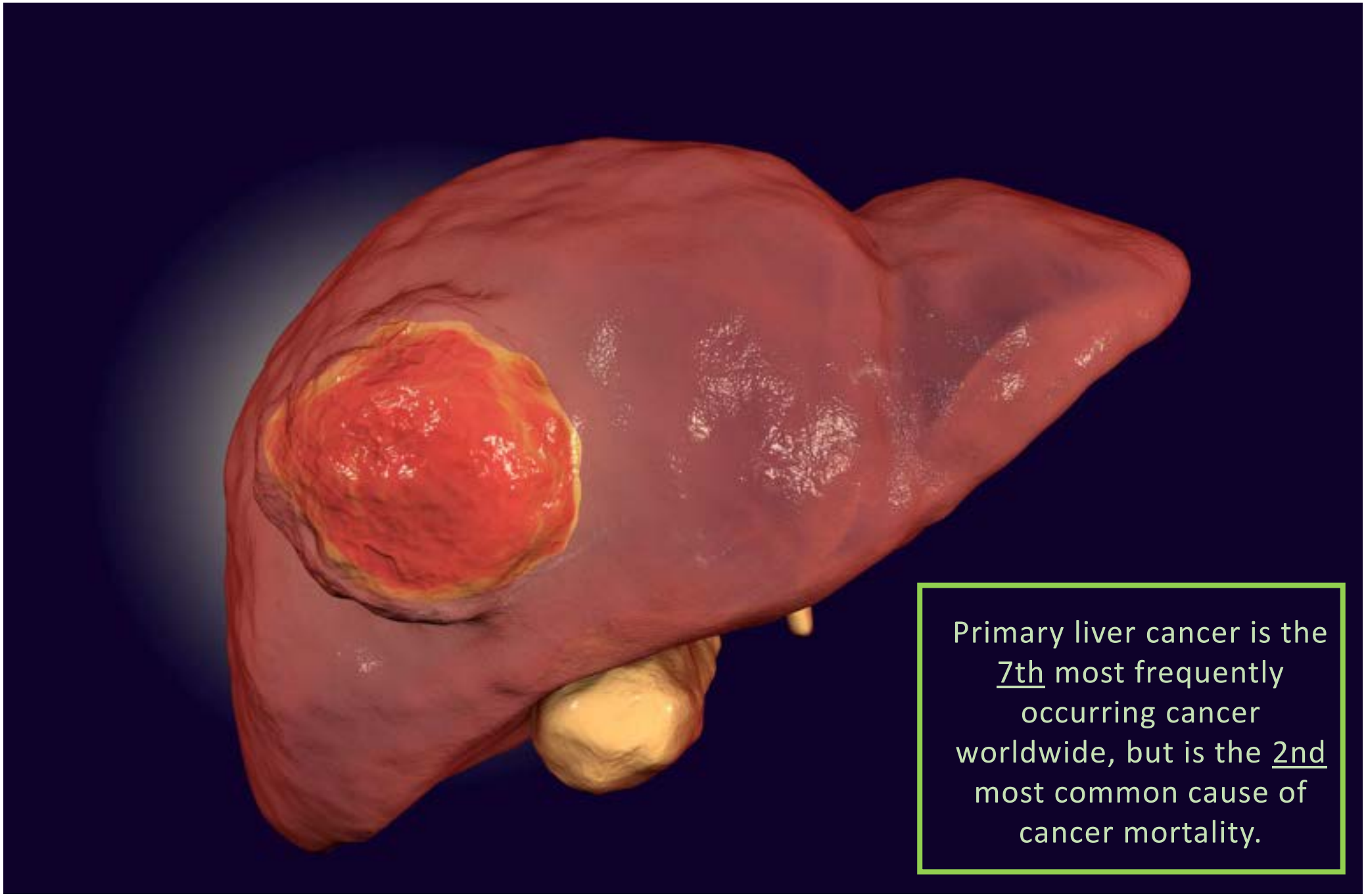
Learning Objectives:

- Understand challenges applying the new nomenclature for steatotic liver disease.
- Understand patient characteristics that increase risk for HCC
- Describe individualized approaches to screening and challenges with screening.

Burden of Hepatocellular Carcinoma



Primary liver cancer is the 7th most frequently occurring cancer worldwide, but is the 2nd most common cause of cancer mortality.

Between 41,000-42,000 individuals are diagnosed each year with cancer of the liver or intrahepatic bile ducts.

80% have HCC

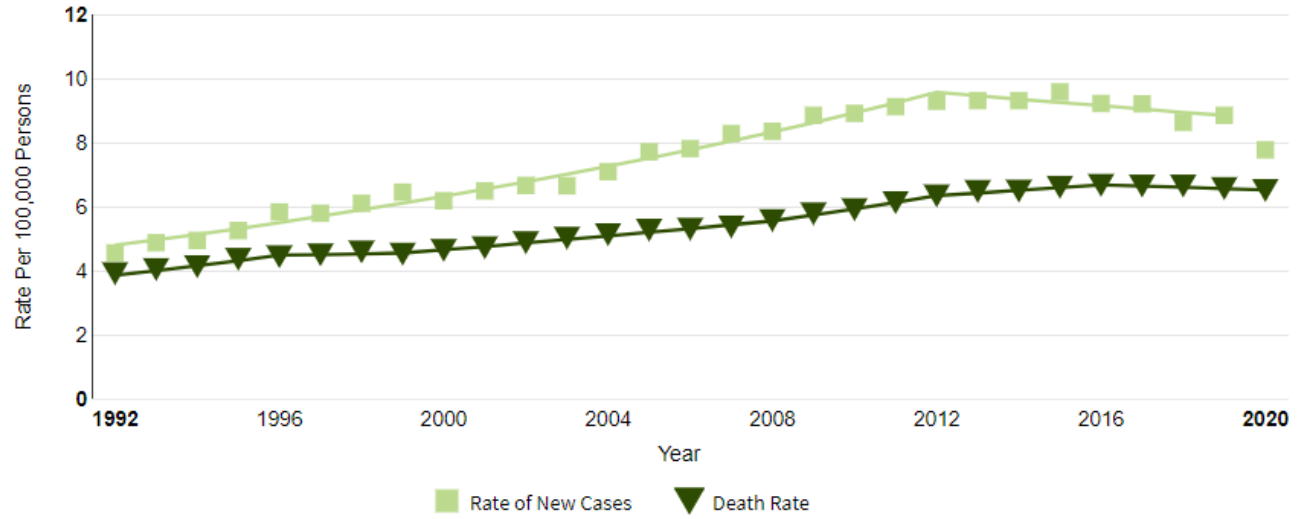
Estimated New Cases in 2023	41,210
% of All New Cancer Cases	2.1%

Estimated Deaths in 2023	29,380
% of All Cancer Deaths	4.8%

5-Year Relative Survival

21.6%

2013–2019

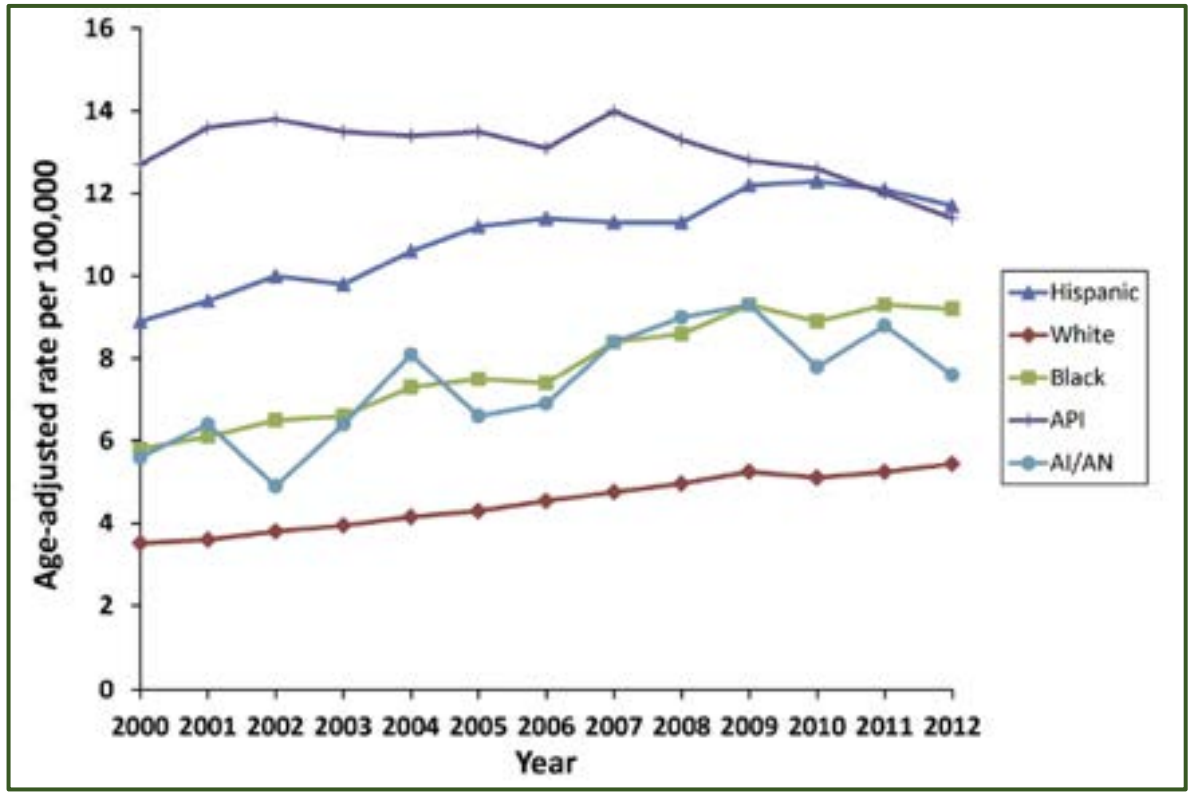


New cases come from SEER 12. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Trend Analysis Software.
The 2020 incidence rate is displayed but not used in the fit of the trend line(s). Impact of COVID on SEER Cancer Incidence 2020 data

New cases are also referred to as incident cases in other publications. Rates of new cases are also referred to as incidence rates.

https://seer.cancer.gov/statfacts/html/livibd.html

Racial and Ethnic Disparities in HCC Incidence

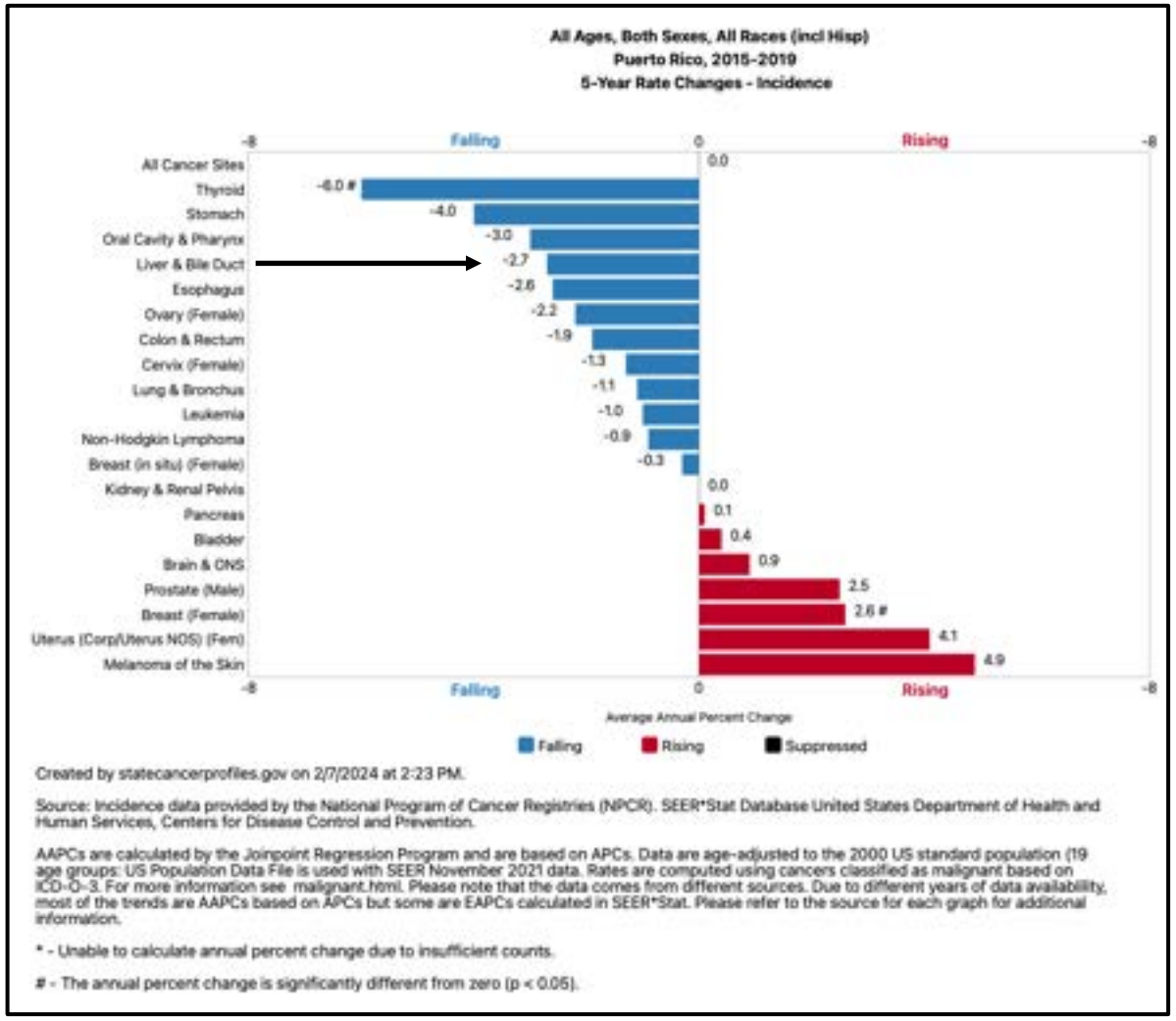


White DL et al. Gastroenterology. 2017 Mar; 152(4):812-820.e5

Race/Ethnicity	Incidence (%)
American Indian/Alaskan Native	11.4
Hispanic	9.8
Asian/Pacific Islander	9.1
Non-Hispanic Black	8.1
Non-Hispanic White	4.6

McGlynn KA et al. *Hepatology*. Jan 2021;73 Suppl 1:4-13. doi:10.1002/hep.31288

Liver Cancer Incidence is Decreasing.



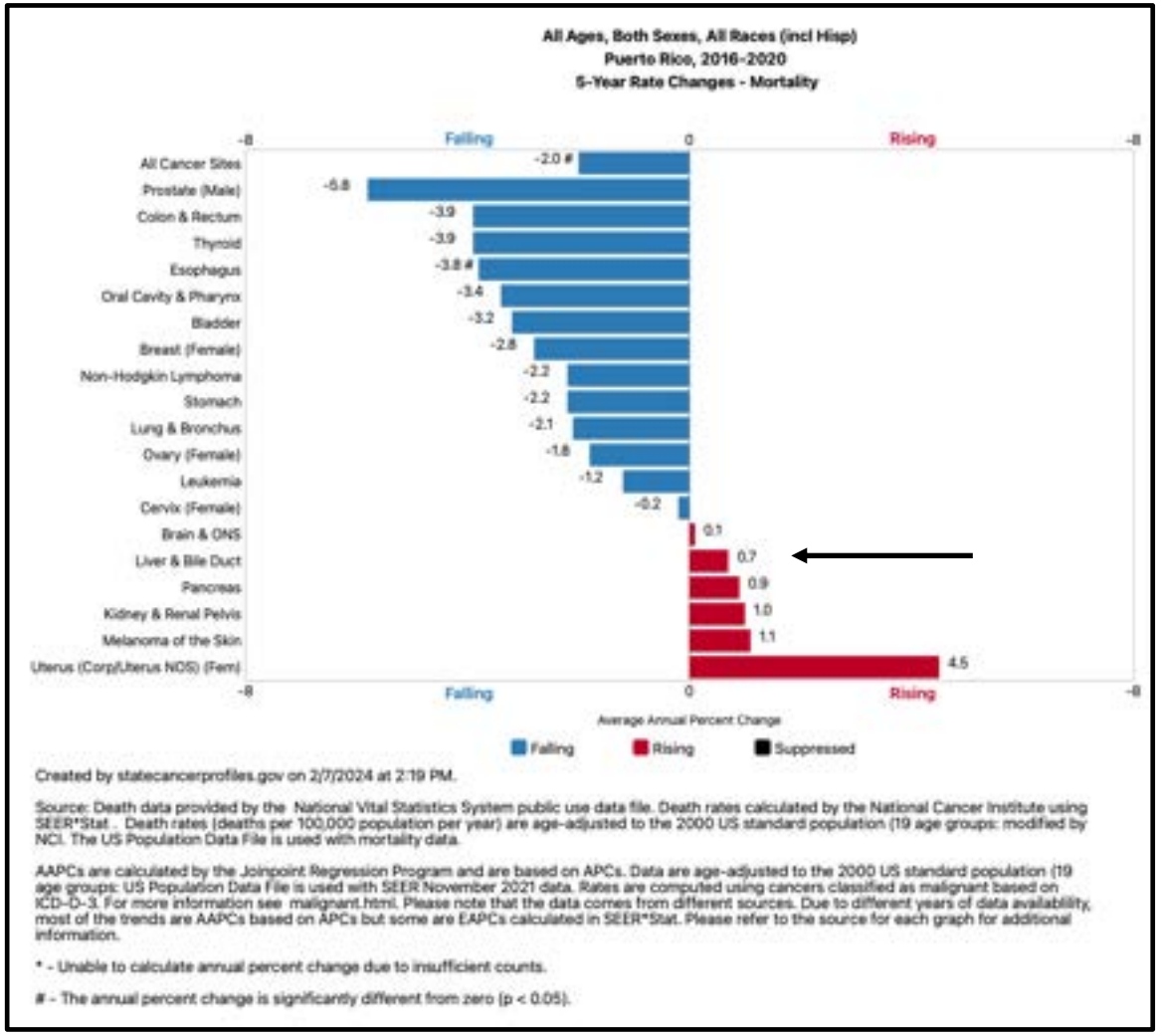
Created by statecancerprofiles.gov on 2/7/2024 at 2:23 PM.

Source: Incidence data provided by the National Program of Cancer Registries (NPCR). SEER*Stat Database United States Department of Health and Human Services, Centers for Disease Control and Prevention.

AAPCs are calculated by the Joinpoint Regression Program and are based on APCs. Data are age-adjusted to the 2000 US standard population (19 age groups: US Population Data File is used with SEER November 2021 data. Rates are computed using cancers classified as malignant based on ICD-O-3. For more information see malignant.html. Please note that the data comes from different sources. Due to different years of data availability, most of the trends are AAPCs based on APCs but some are EAPCs calculated in SEER*Stat. Please refer to the source for each graph for additional information.

* - Unable to calculate annual percent change due to insufficient counts.

- The annual percent change is significantly different from zero ($p < 0.05$).



Created by statecancerprofiles.gov on 2/7/2024 at 2:19 PM.

Source: Death data provided by the National Vital Statistics System public use data file. Death rates calculated by the National Cancer Institute using SEER*Stat . Death rates (deaths per 100,000 population per year) are age-adjusted to the 2000 US standard population (19 age groups: modified by NCI. The US Population Data File is used with mortality data.

AAPCs are calculated by the Joinpoint Regression Program and are based on APCs. Data are age-adjusted to the 2000 US standard population (19 age groups: US Population Data File is used with SEER November 2021 data. Rates are computed using cancers classified as malignant based on ICD-O-3. For more information see malignant.html. Please note that the data comes from different sources. Due to different years of data availability, most of the trends are AAPCs based on APCs but some are EAPCs calculated in SEER*Stat. Please refer to the source for each graph for additional information.

* - Unable to calculate annual percent change due to insufficient counts.

- The annual percent change is significantly different from zero ($p < 0.05$).

Mortality Related to Liver Cancer is Increasing.

https://statecancerprofiles.cancer.gov/quick-profiles/index.php?statename=puertorico

The Etiology of Liver Disease leading to HCC has Changed

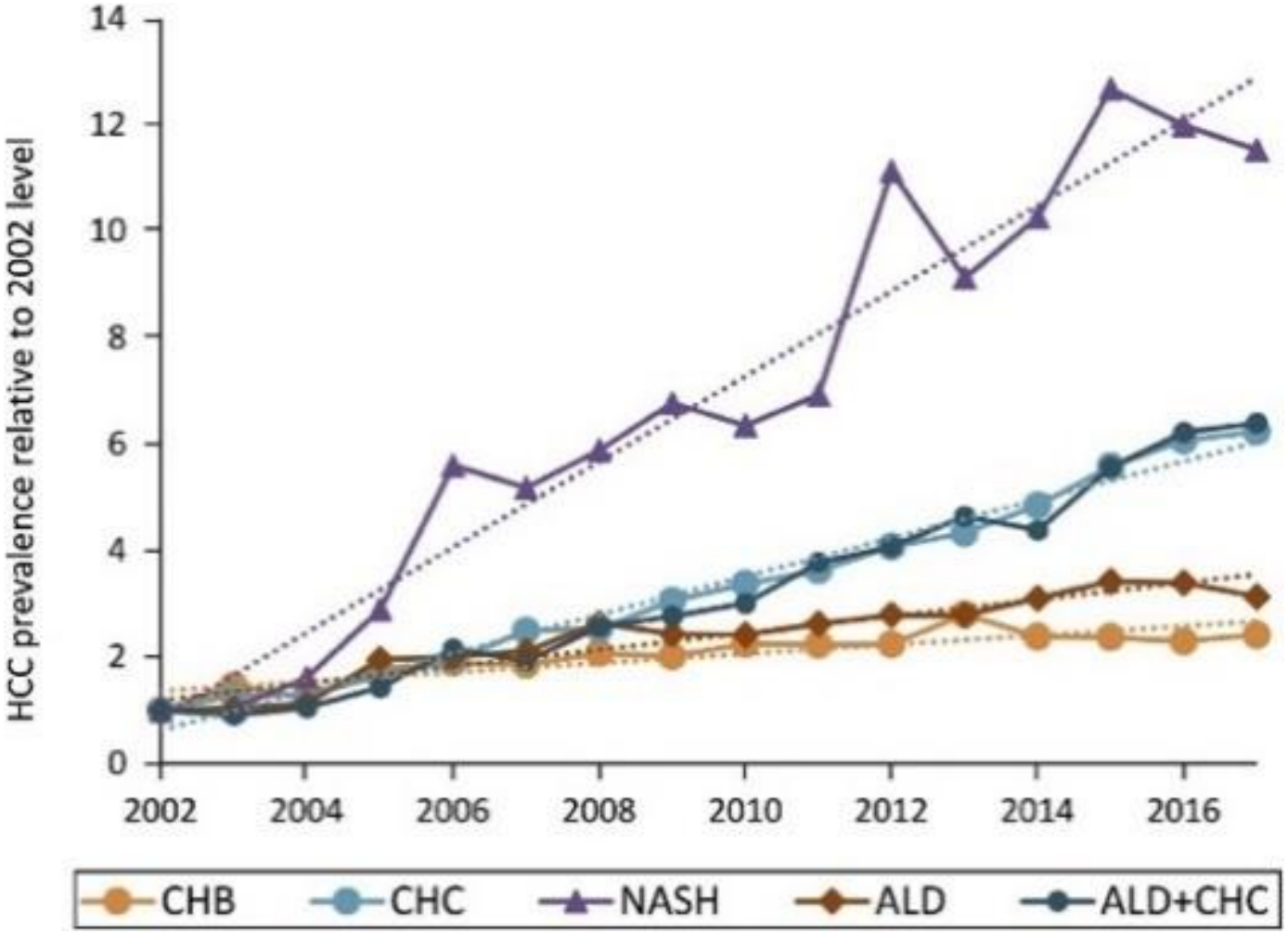


Figure 1. Prevalence of HCC in waitlisted candidates by etiology relative to that in 2002 *Dotted lines* represent linear trends. [7]

Younossi Z et al. *Clin Gastroenterol Hepatol*. 2019;17(4):748-55 e3. Epub 2018/06/17. doi: 10.1016/j.cgh.2018.05.057. PubMed PMID: 29908364.

Case Presentation

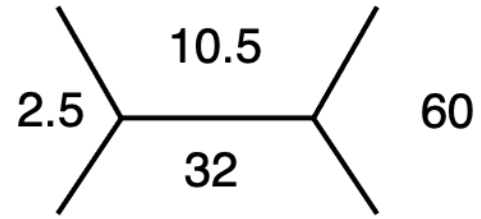
- 67 year-old man was referred for a liver mass.
  - Unaware that he had liver disease
- He has had chronic GI upset but recently has severe abdominal pain whenever he eats.
- Ultrasound revealed a large heterogenous liver with an ill-defined focal hypoechoic area in the right hepatic lobe (3.4 x 3.1 x 3.7 cm). The liver demonstrates cirrhotic morphology.
- MRI demonstrated a large mass with **arterial hyperenhancement and corresponding washout.**

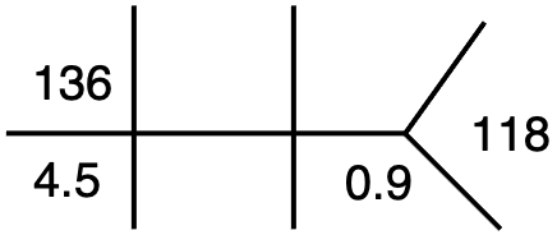
Case Presentation

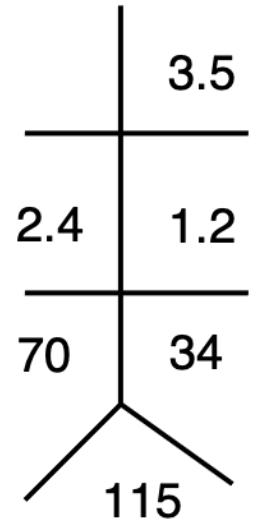
- Previously unaware that he had liver disease
  - Drinks 11 alcoholic drinks/week.

- **Past Medical History:**
  - Hyperlipidemia
  - Hypertension
  - Obesity
  - Prostate cancer

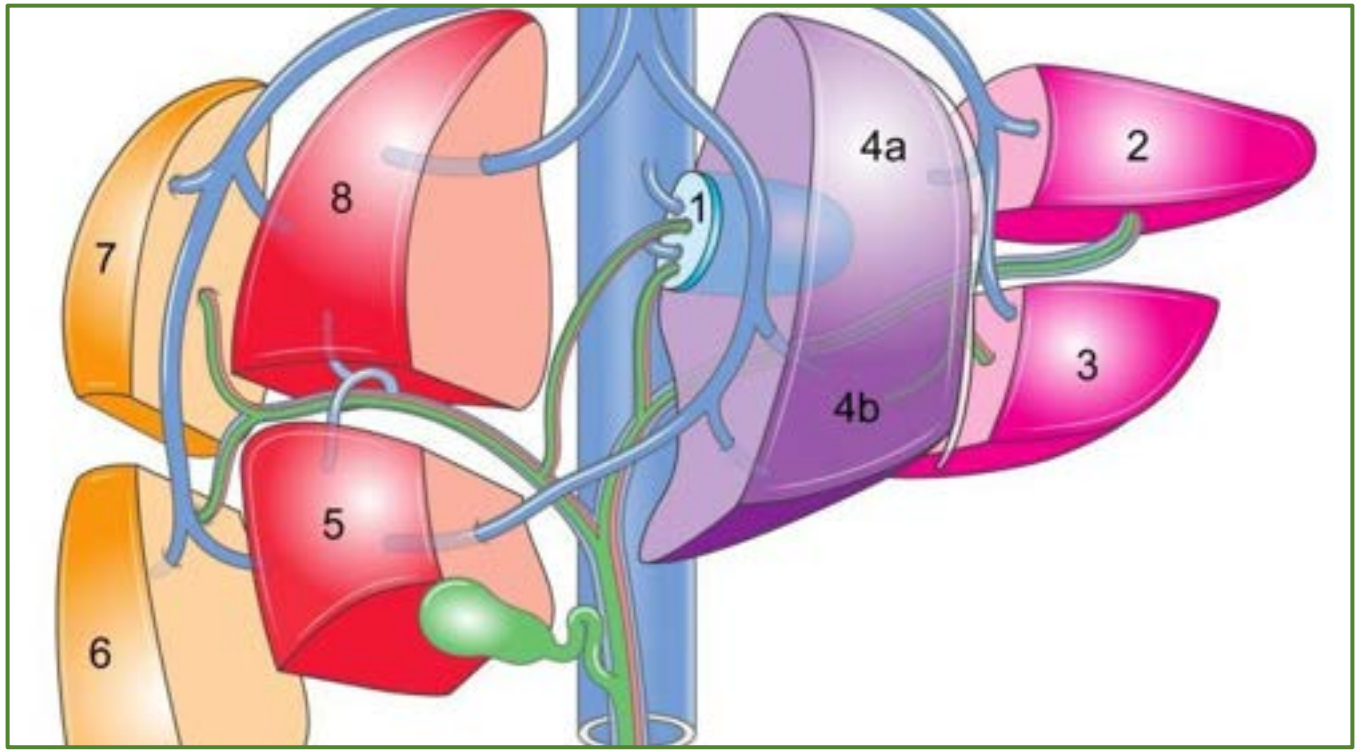
- **Physical Exam:**
  - Well-appearing with normal vital signs
  - BMI 34.9
  - Oriented to person, place and time
  - Anicteric sclera
  - Bronze skin, acanthosis nigricans
  - Mild tenderness to palpation
  - No dullness to percussion
  - No peripheral edema







Burden of Disease



- The mass was infiltrative and tumor involved segments 5,6,7 and 8 and partly into IVb. Largest diameter 13 cm.
- There is tumor thrombus extending into the right and main portal veins.
- There are minute lesions in the left hepatic lobe worrisome for metastatic HCC.

Diagnostic Criteria for MASLD

*Cardiometabolic criteria

Adult Criteria

At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

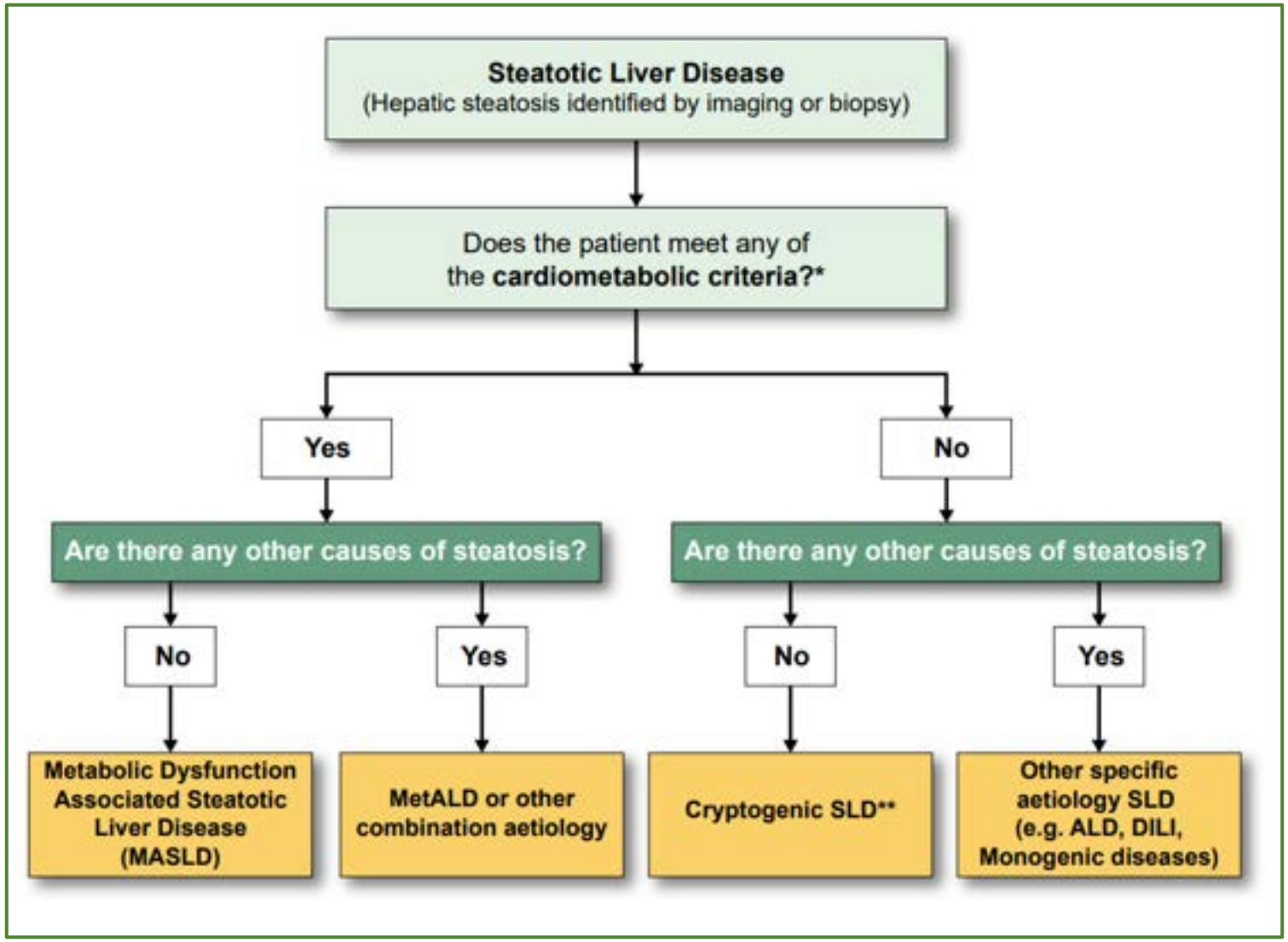
Pediatric Criteria

At least 1 out of 5:

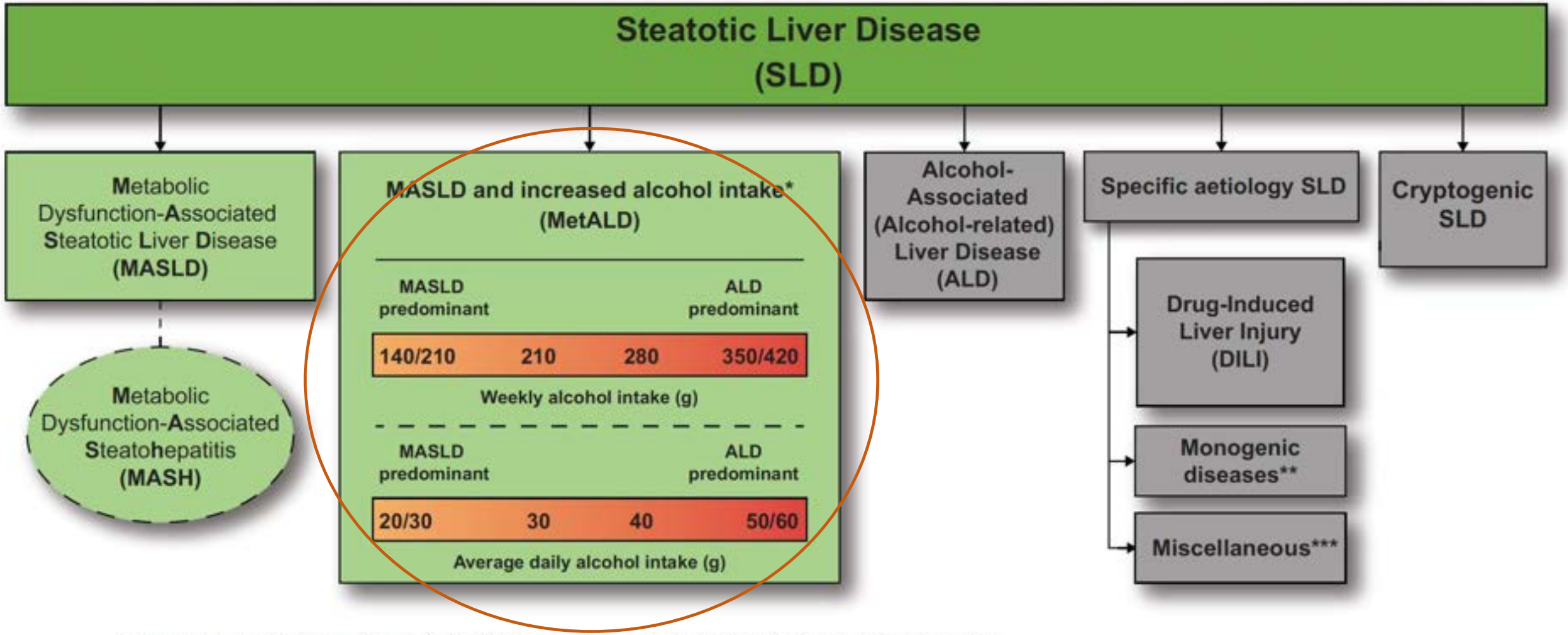
- ☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

https://www.aasld.org/new-masld-nomenclature

Decision Support Tool



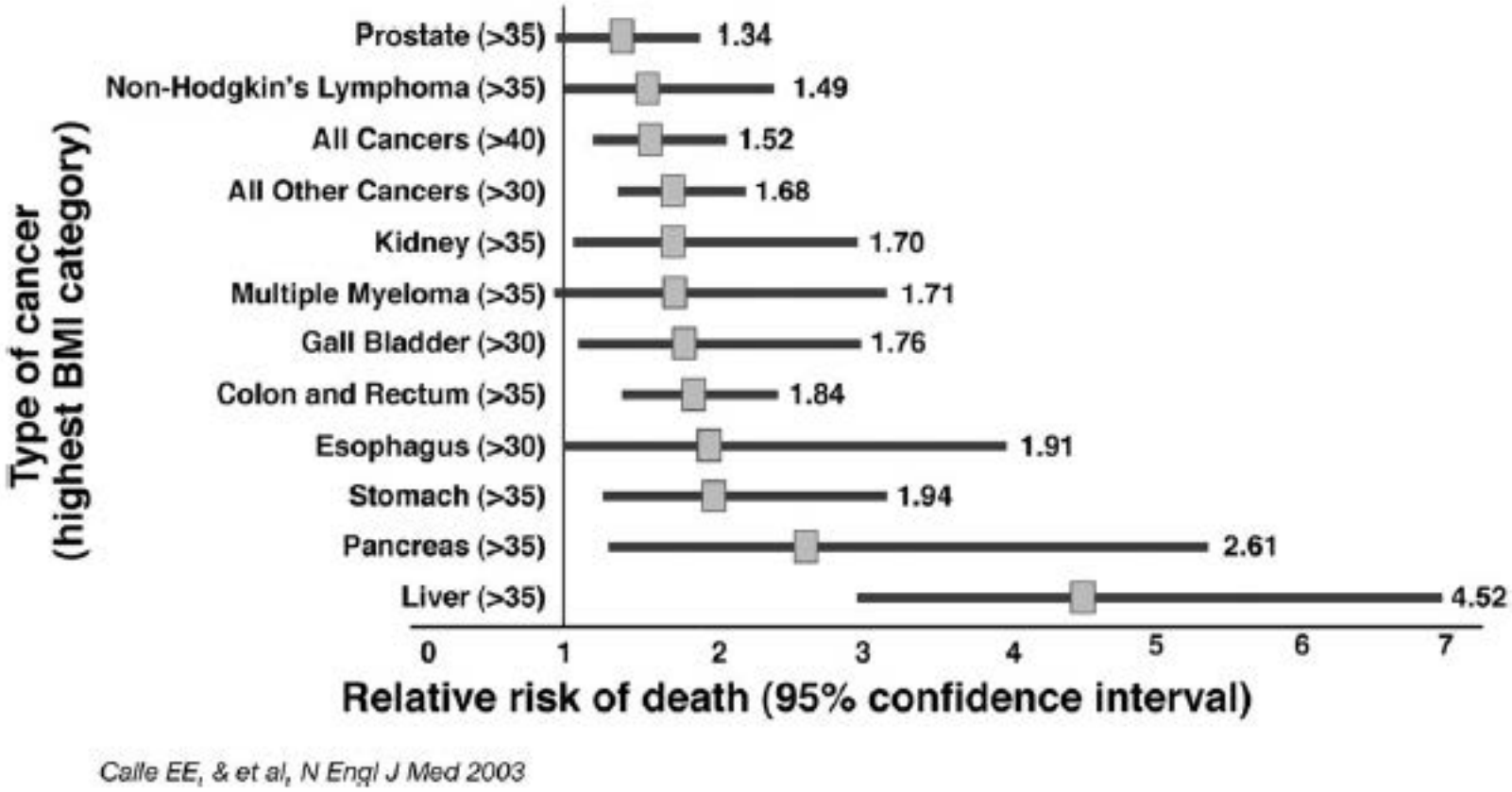
https://www.aasld.org/new-masld-nomenclature



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

https://www.aasld.org/new-masld-nomenclature

Obesity and Cancer Risk:



Calle EE, & et al, N Engl J Med 2003

El-Serag HB, Rudolph KL. *Gastroenterology*. 2007;132(7):2557-76

Diabetes and Hepatocellular Carcinoma:

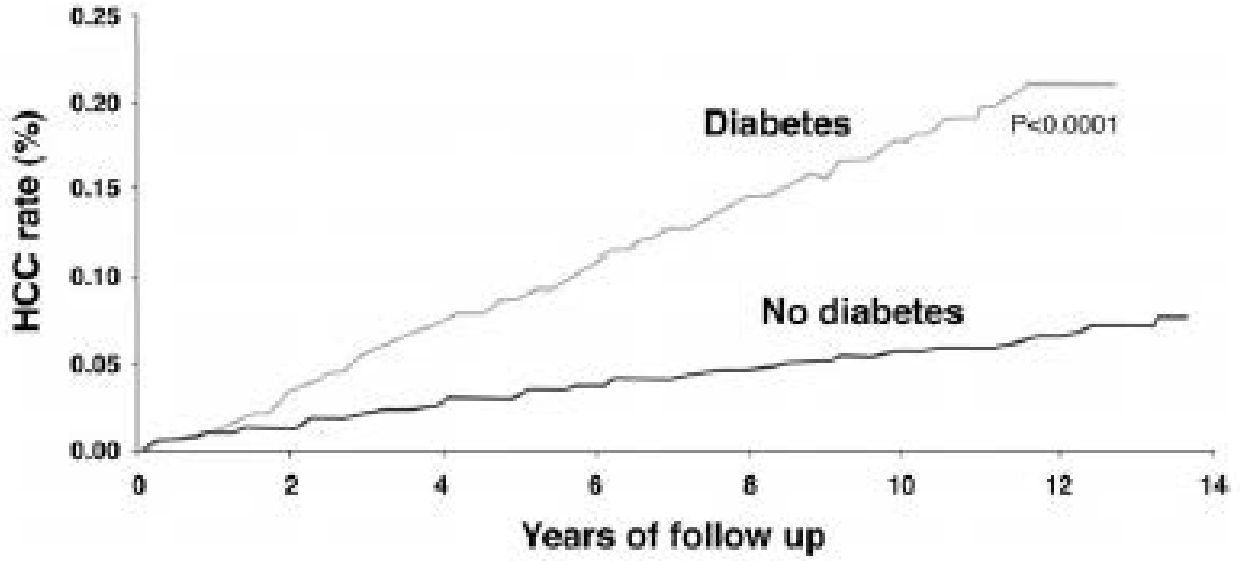


Figure 8. Diabetes and the risk of HCC. The study examined 173,463 patients with diabetes and 650,620 without diabetes. No patient had acute or chronic liver disease recorded before, during, or within 1 year of his or her index hospitalization. Reprinted with permission.[8]

El-Serag HB, Rudolph KL. *Gastroenterology*. 2007;132(7):2557-76

Global Burden of NAFLD-Related HCC

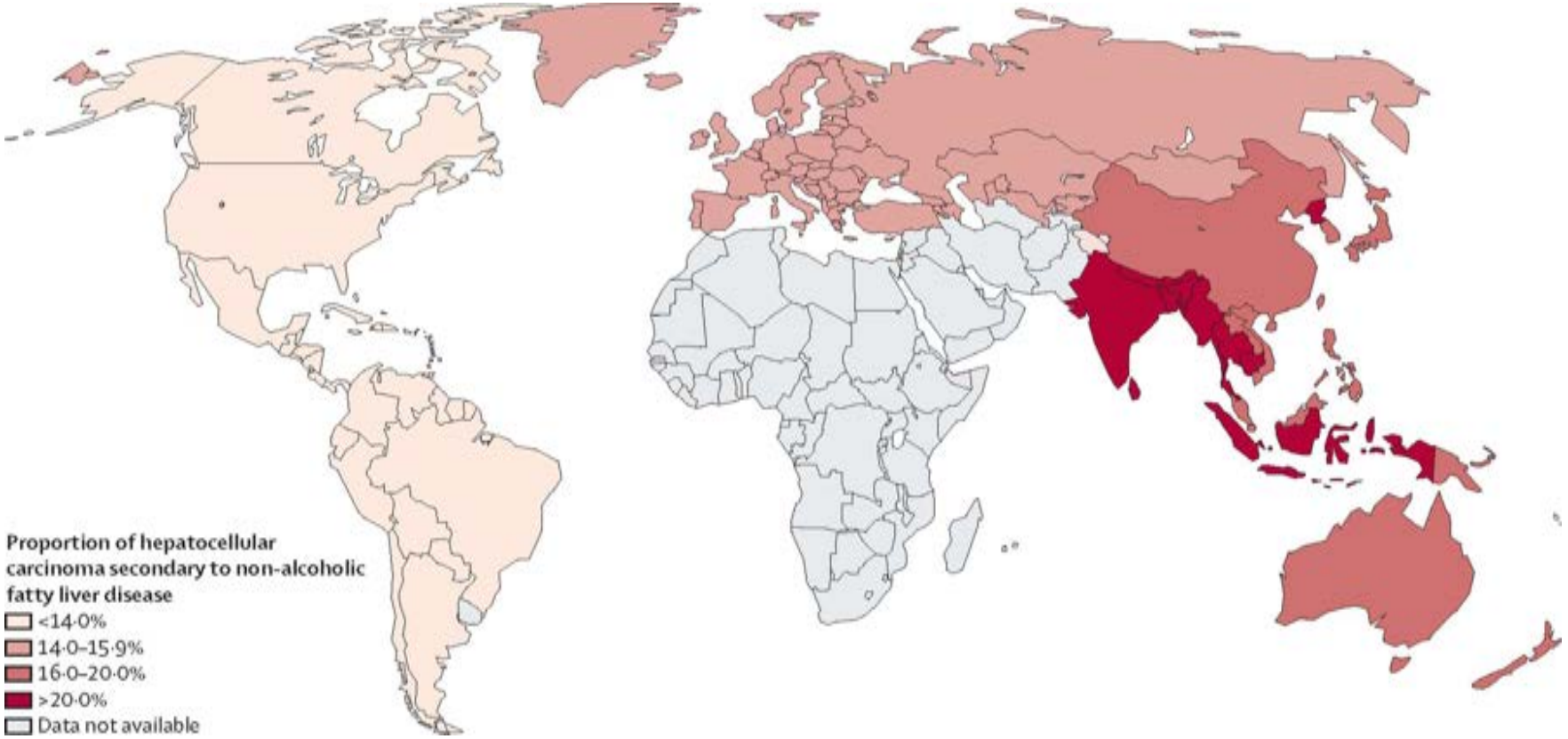


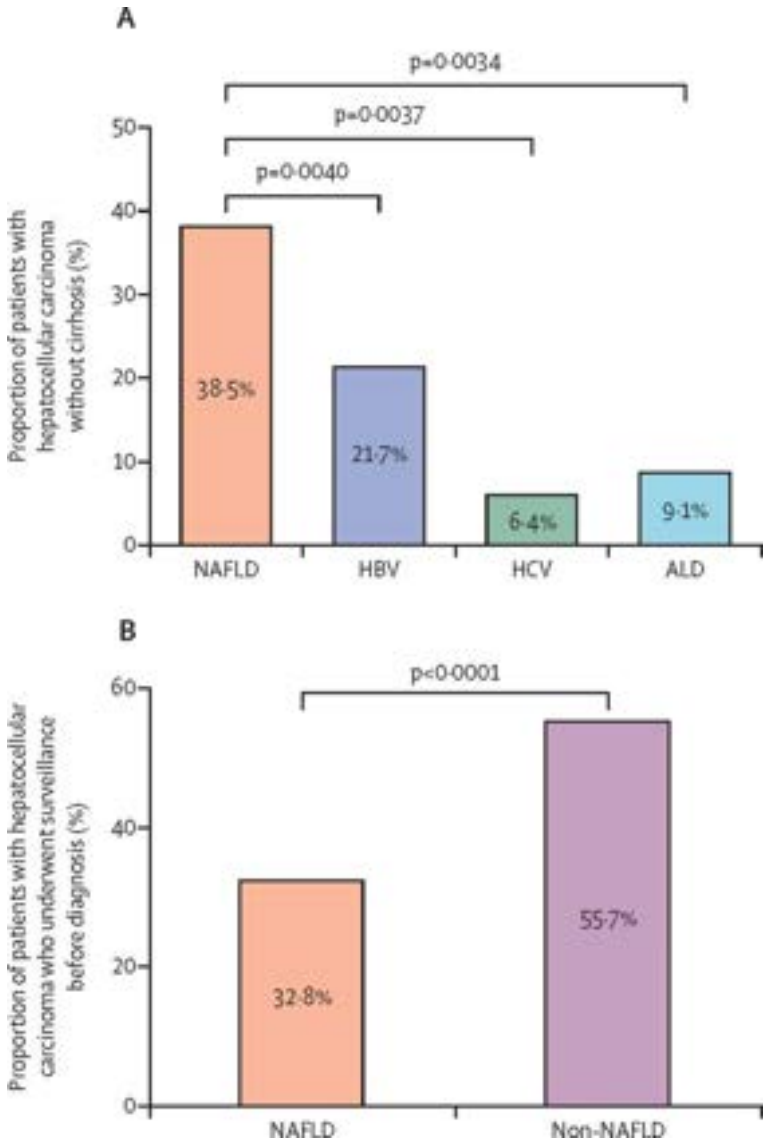
Figure 2
Proportion of hepatocellular carcinoma secondary to non-alcoholic fatty liver disease worldwide, by WHO region

Tan DJH et al. *Lancet Oncol*. 2022 Apr;23(4):521-530. doi: 10.1016/S1470-2045(22)00078-X.

How does NAFLD-related HCC differ from non-NAFLD HCC?

- In 61 studies (1980-2021) of 94,636 patients with HCC, NAFLD accounted for 15.1% of HCC.

- Compared to non-NAFLD HCC patients, NAFLD-HCC patients
  - were older, had higher BMI and more likely to have metabolic comorbidities, e.g. diabetes, HTN, HLD) or cardiovascular disease at presentation.
  - were more likely to be non-cirrhotic 38.5% (95% CI 27.9-50.2), compared to 14.6% in non-NAFLD HCC (95% CI 8.7-23.4)
  - were less likely to have received surveillance 32.8% (95%CI 12-63.7), compared to 55.7% (95% CI 24-83)
  - had larger tumors
  - had similar BCLC, ECOG, AFP, treatment allocation and survival.
  - less likely to undergo transplant in favor of resection.



Tan DJH et al. *Lancet Oncol*. 2022 Apr;23(4):521-530. doi: 10.1016/S1470-2045(22)00078-X.

Fibrosis Drives HCC Risk in NAFLD

Table 5. The Annual Risk of Hepatocellular Cancer in Groups of Patients With Non-Alcoholic Fatty Liver Disease Stratified by the Presence of Cirrhosis Diagnosis and/or Fibrosis-4 Score During Follow-Up

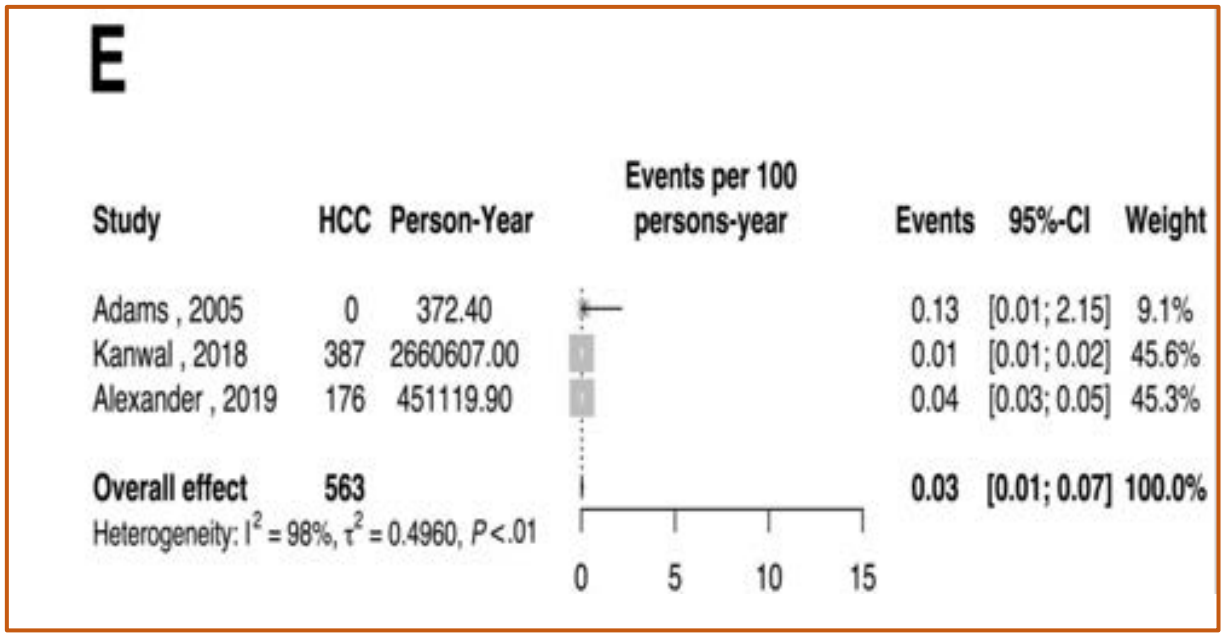
Group	Subjects	HCC cases	Total PYs of follow-up	IR (95% CI) (per 1000 PYs)
Cirrhosis diagnosis and high FIB-4 score	2,871	252	18,598	13.55 (11.93–15.33)
Cirrhosis without high FIB-4 score	1,364	45	9323	4.82 (3.52–6.46)
High FIB-4 score without cirrhosis diagnosis	34,392	101	259,942	0.39 (0.31–0.47)
Neither cirrhosis diagnosis nor high FIB-4 score	258,074	92	2,094,427	0.04 (0.04–0.05)

NOTE. FIB-4 scores were available for 95% of the cohort. Patients with no cirrhosis diagnosis and missing FIB-4 score are excluded from the table.
CI, confidence interval; HCC, hepatocellular carcinoma; IR, incidence rate; PY, person-years.

- The prevalence of NAFLD has doubled over the past two decades and is approximately 30%.
- **20% of patients with NAFLD-related HCC did not have cirrhosis**
  - Retrospective cohort study of 296,707 NAFLD patients in the VA.
  - The absolute risk of HCC in NAFLD is low 0.21/1000 person-years or 0.8% five-year and 1.7% ten-year cumulative HCC risk.
  - The absolute risk is too low in non-cirrhotic patients to recommend HCC surveillance.
- Risk was highest among oldest Hispanics.

Kanwal et al. Gastroenterology 2018; 155: 1828-1837

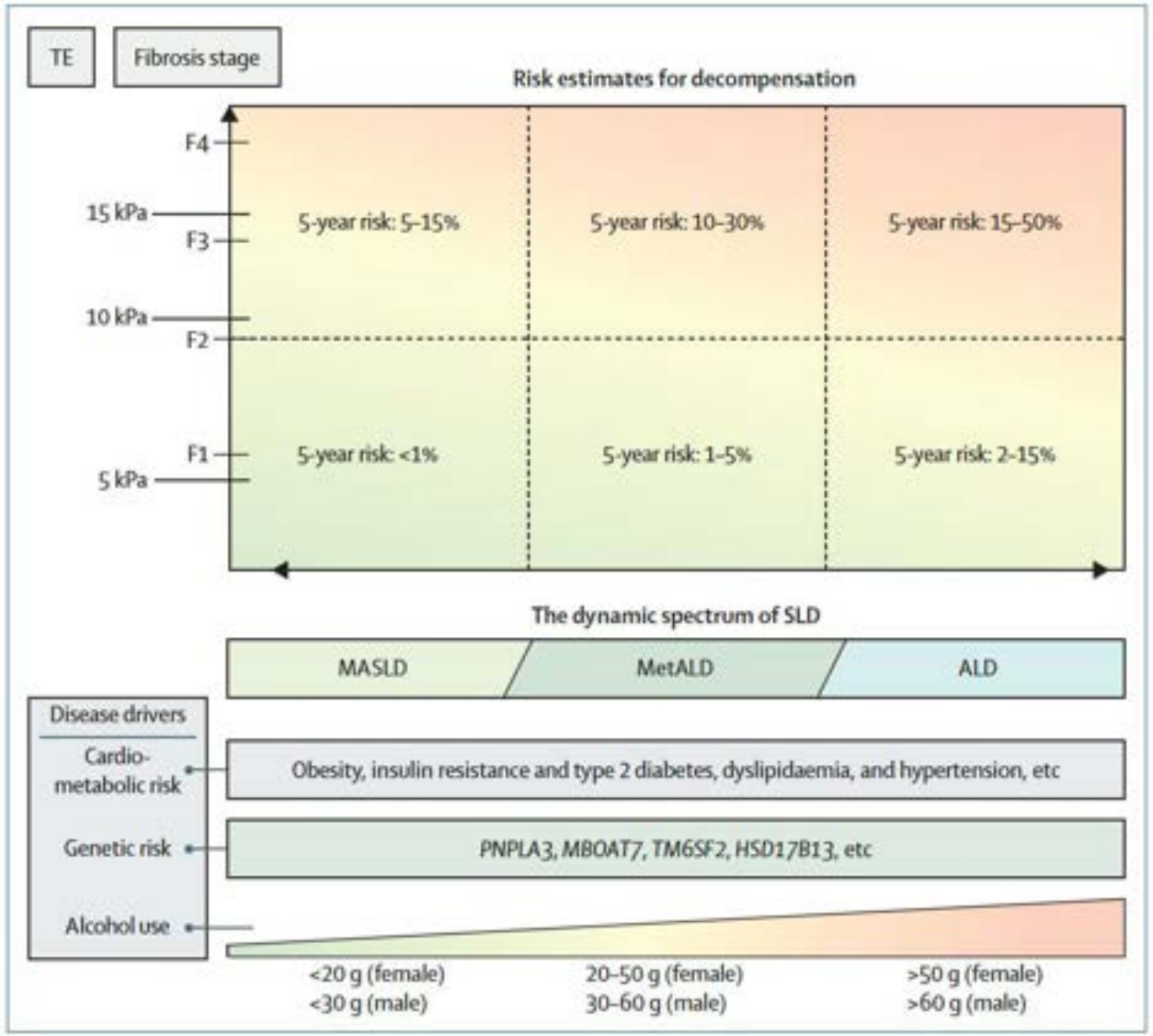
Pooled Incidence Rate in Non-cirrhotic NAFLD Patients



- In 18 studies of 470,404 patients with NAFLD.
  - Almost half from the VA study.
- Pooled incidence rate 2.39/100 person years (95% CI 1.4-4.08)
  - Cirrhosis: 3.78/100 person years
  - Cirrhosis enrolled in screening: 4.62/100 person years
  - Non-cirrhotic NAFLD: 0.03/100 person years

Orci LA et al. *Clin Gastroenterol Hepatol*. 2022 Feb;20(2):283-292.e10. doi: 10.1016/j.cgh.2021.05.002.

Dynamic Spectrum of MASLD-MetALD-ALD



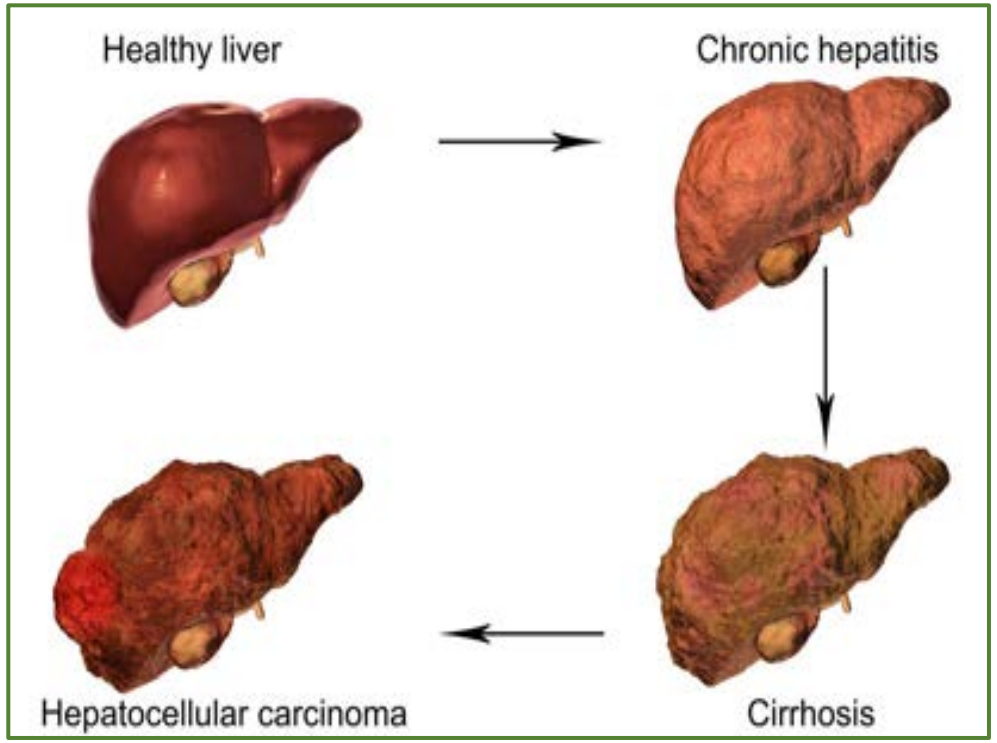
Alcohol use interacts with cardiometabolic risk factors and impacts risk of decompensation

Israelsen et al. MetALD: new opportunities to understand the role of alcohol in steatotic liver disease. *Lancet GI Hep* 2023

https://www.aasld.org/new-masld-nomenclature

Cirrhosis is the Strongest Risk Factor for HCC

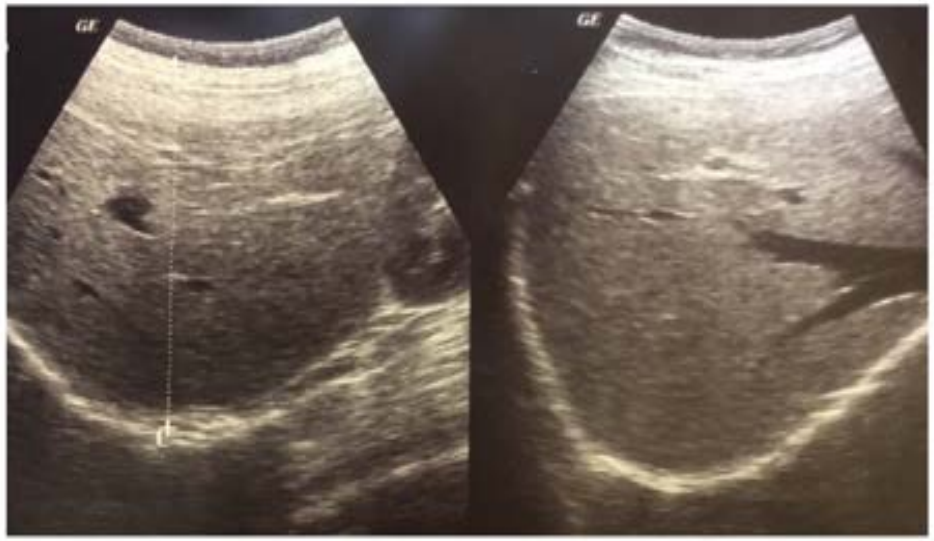
- 85-95% of patients with HCC have cirrhosis.[1]
- The risk of developing HCC ranges from 1-8% each year.[2]
- Rarely develops in patients under age 40
- Male predominance with 2:1 to 4:1 male:female ratio.
  - Men develop HCC 5 years earlier then women
- The 5-year cumulative risk for development of HCC in patients with cirrhosis ranges from 5-30% and depends on etiology of liver disease, region, ethnicity, and stage of cirrhosis. [3]
  - The highest risk of HCC is among patients with decompensated cirrhosis.



1. Heimbach J et al. *Hepatology*. 2018 Jan; 67 (1):358-380. doi: 10.1002/hep.29086
2. Journal of Hepatology 2018 vol. 69 j 182–236
3. El-Serag HB. *N Engl J Med.* 2011;365(12):1118-27.

Risk and Surveillance:

Only between **6%** and **25%** of HCC patients received HCC screening.
Consistent surveillance leads to earlier diagnosis and improved survival.



- **Recommended Screening Modality: Ultrasound ± ∝-fetoprotein (AFP)**
  - Ultrasound alone: Sensitivity 58-89%, Specificity 90%; operator-dependent and may be inadequate in up to 20%.
  - Neither CT nor MRI are *cost-effective* for surveillance and have increased risk of false-positives
  - Patient characteristics (e.g. ascites, obesity) limit sensitivity of ultrasound
- **Recommended Screening Interval : 6 months**

Marquardt P et al. *Hepatol Commun*. 2021 Sep;5(9):1481-1489. doi: 10.1002/hep4.1735. Epub 2021 May 4
Choi DT et al. *Clin Gastroenterol Hepatol*. 2019 Apr;17(5):976-987.e4. doi: 10.1016/j.cgh.2018.10.031. Epub 2018 Oct 26.

Performance of Imaging Studies

Table 1. Test Performance of Imaging Modalities for HCC

Imaging Modality	Unit of Analysis	Sensitivity (95% CI)	Studies, *n*	Specificity (95% CI)	Studies, *n*	Positive LR	Negative LR
Detection of HCC							
Surveillance settings							
US without contrast	Patient	0.78 (0.60–0.89)	4	0.89 (0.80–0.94)	3	6.8 (4.2–11)	0.25 (0.13–0.46)
CT	Patient	0.84 (0.59–0.95)	2	0.99 (0.86–0.999)	2	60 (5.9–622)	0.16 (0.06–0.47)
US without contrast	Lesion	0.60 (0.24–0.87)	1	No data	–	–	–
CT	Lesion	0.62 (0.46–0.76)	1	Insufficient data	–	–	–
Nonsurveillance settings							
US without contrast	Patient	0.73 (0.46–0.90)	8	0.93 (0.85–0.97)	6	11 (5.4–21)	0.29 (0.13–0.65)
CT	Patient	0.83 (0.76–0.88)	17	0.91 (0.84–0.95)	12	9.1 (5.1–16)	0.19 (0.13–0.27)
MRI	Patient	0.86 (0.79–0.91)	14	0.89 (0.82–0.93)	12	7.7 (4.6–13)	0.16 (0.10–0.24)
US without contrast	Lesion	0.59 (0.42–0.74)	11	0.83 (0.53–0.95)	2	3.4 (1.2–9.4)	0.50 (0.37–0.66)
US with contrast	Lesion	0.75 (0.57–0.88)	9	0.97 (0.84–0.999)	1	–	–
CT	Lesion	0.76 (0.72–0.80)	80	0.89 (0.84–0.93)	21	7.1 (4.7–11)	0.26 (0.22–0.32)
MRI	Lesion	0.83 (0.80–0.86)	82	0.87 (0.79–0.93)	20	6.5 (3.8–11)	0.20 (0.16–0.24)
Evaluation of focal liver lesions							
US without contrast	Patient	0.78 (0.69–0.86)	1	No data	–	–	–
US with contrast	Patient	0.87 (0.79–0.92)	12	0.91 (0.83–0.95)	8	9.6 (5.1–18)	0.14 (0.09–0.23)
CT	Patient	0.86 (0.75–0.92)	8	0.88 (0.76–0.95)	5	7.4 (3.3–17)	0.16 (0.09–0.30)
MRI	Patient	0.75 (0.66–0.83)	5	0.82 (0.60–0.93)	5	4.1 (1.8–9.2)	0.31 (0.23–0.40)
US without contrast	Lesion	0.62 (0.18–0.93)	4	0.92 (0.84–0.96)	3	8.1 (3.6–18)	0.41 (0.12–1.4)
US with contrast	Lesion	0.87 (0.80–0.92)	21	0.91 (0.85–0.95)	10	9.8 (5.7–17)	0.14 (0.09–0.23)
CT	Lesion	0.79 (0.67–0.87)	13	0.90 (0.37–0.99)	6	7.7 (0.71–84)	0.24 (0.15–0.38)
MRI	Lesion	0.82 (0.74–0.88)	15	0.92 (0.78–0.97)	12	10 (3.6–29)	0.20 (0.14–0.28)

CT = computed tomography; HCC = hepatocellular carcinoma; LR = likelihood ratio; MRI = magnetic resonance imaging; US = ultrasonography.

Screening, specifically CT and MRI may be associated with potential harm, caused by false positives

Chou R *et al. Ann Intern Med*. 2015;162(10):697-711

Blood-Based Biomarkers for HCC

TABLE 2 Status of surveillance tests for the early detection of hepatocellular carcinoma

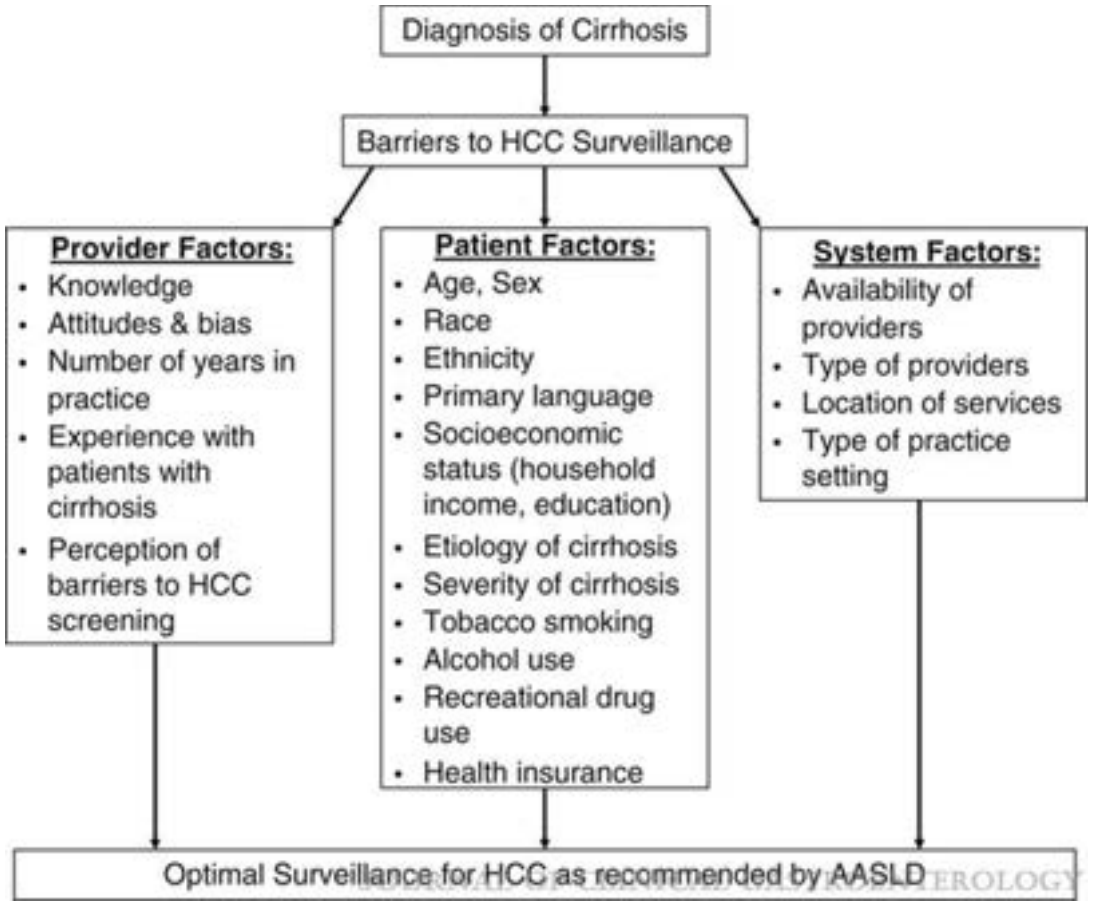
Test	Early detection research network (EDRN) phase of validation	Performance characteristics	
US plus AFP[55]	5	Sensitivity	61%
		Specificity	92%
AFP-L3%[69]	3	Sensitivity	62%
		Specificity	90%
DCP[69]	3	Sensitivity	40%
		Specificity	81%
Multitarget algorithm[70]	2	Sensitivity	82%
		Specificity	87%
GALAD[71]	2/3	Sensitivity	54–72%
		Specificity	90%
Doylestown plus[72]	2/3	Sensitivity	90%
		Specificity	95%

Abbreviations: AFP, alpha fetoprotein; AFP-L3%, *Lens culinaris* lectin binding subfraction of AFP; DCP, des-gamma carboxyprothrombin; GALAD, gender, age, AFP-L3%, AFP, and DCP model; US, ultrasound.

Singal AG et al. *Hepatology*. 2023 Dec 1;78(6):1922-1965. doi: 10.1097/HEP.0000000000000466. Epub 2023 May 22. Erratum in: Hepatology. 2023 Oct 16;: PMID: 37199193

Disparities in HCC Screening

Potential patient-, provider-, and health care system-specific barriers that contribute to disparities in HCC surveillance



HCC Screening rates are generally lower in Black individuals, those who are uninsured, those who live in neighborhoods with higher levels of poverty.

Ladhani S et al. *J Clin Gastroenterol*. 2020 Mar;54(3):218-226.

How To Screen:

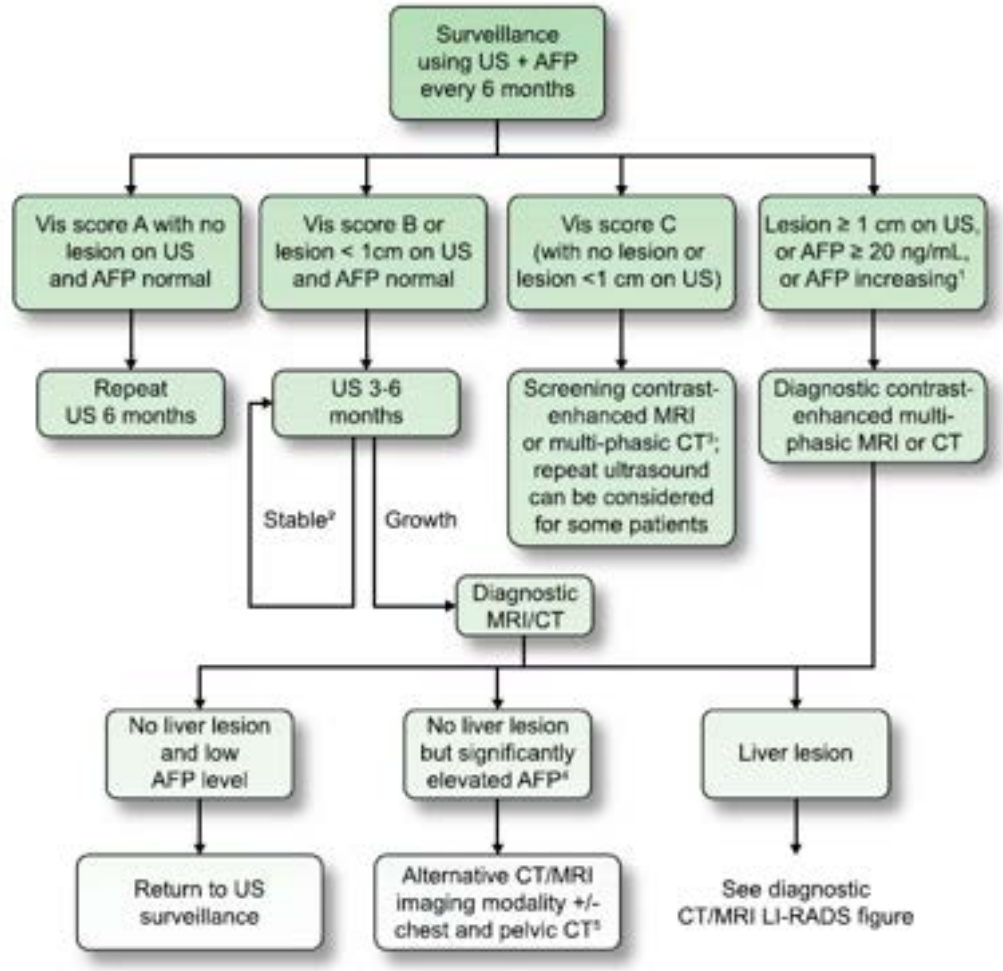


FIGURE 5 Recall algorithm for hepatocellular carcinoma (HCC) surveillance. Abbreviations: AFP, alpha fetoprotein; CT, computed tomography; LI-RADS, Liver Imaging Reporting and Data System; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound; Vis, visualization. [1]Increasing AFP represents doubling of AFP, increase on two consecutive tests, or ≥ 20 ng/ml. [2]Can return to US q6 months if lesion stable on two exams. [3]CT/MRI may be preferred particularly in patients with obesity, alcohol or NASH-related cirrhosis, or Child Pugh class B or C cirrhosis. [4]Significantly elevated AFP: although no clear threshold has been established, AFP ≥ 200 ng/ml or ≥ 400 ng/ml may be considered significant elevations depending on clinical context. [5]Can perform chest and pelvic imaging in addition to alternative modality. If these are negative, other workup, including PET, can be considered.

Another barrier to screening and early diagnosis is limited availability of high-quality ultrasound.

Ultrasound visualization score is rarely reported.

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LI-RADS 5 Lesions

- Enhance
- Washout
- Threshold growth
- Enhancing capsule

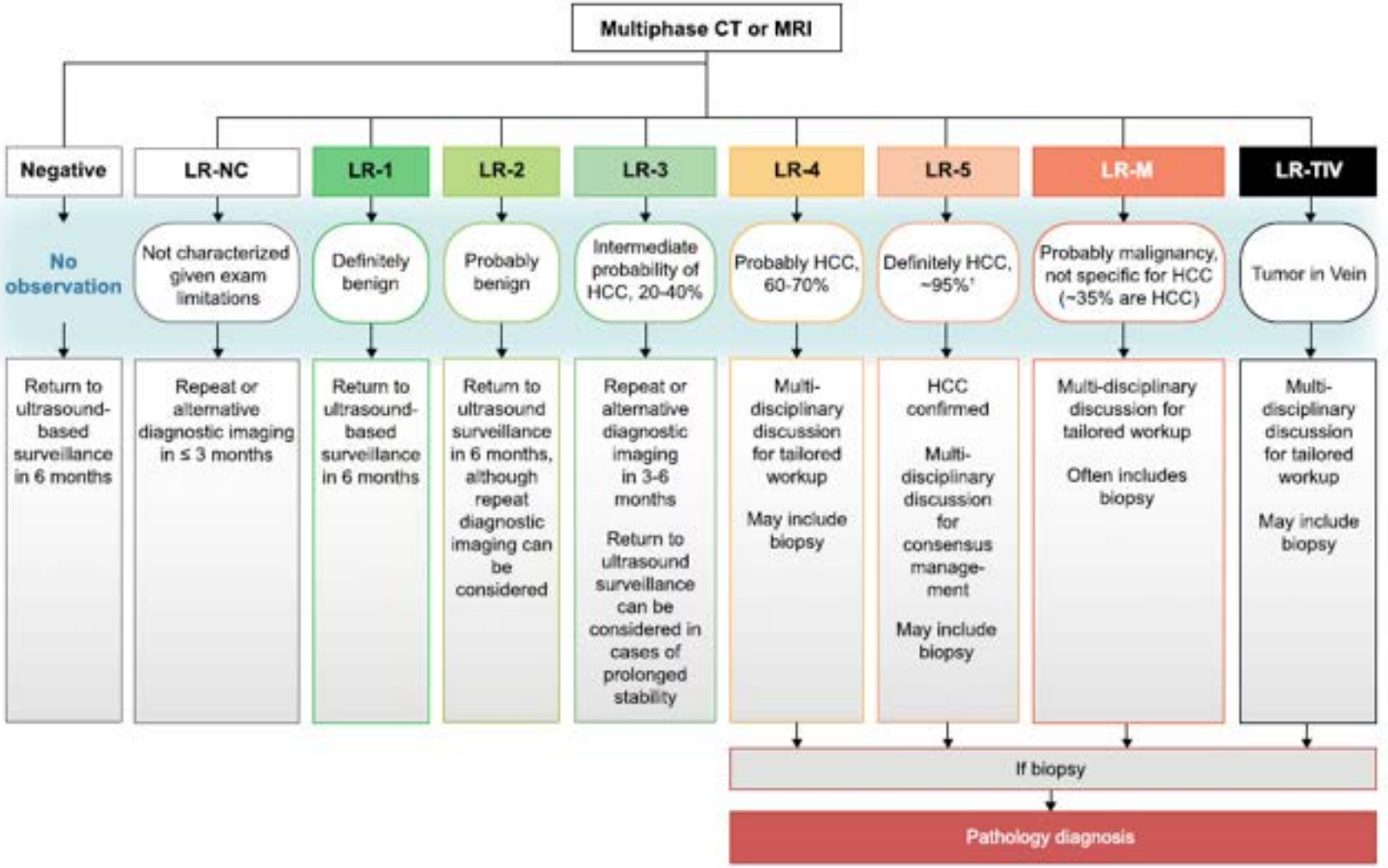

FIGURE 8 Risk of hepatocellular carcinoma (HCC) and recommended management strategy. Abbreviations: CT, computed tomography; LR, LI-RADS; MRI, magnetic resonance imaging.

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DIAGNOSIS
Name:
Doctor's name:
Age:
Liver cancer

Take Home Points

- The burden of steatotic liver disease-related HCC is increasing.
- All patients with cirrhosis should be screened for HCC every six months. There is limited data about other populations.
- Ultrasound ± AFP is the recommended screening modality.
  - Some patient characteristics may require cross-sectional imaging.
- A team-based multidisciplinary approach to HCC management is standard of care.
  - Treatment must be individualized based on tumor burden, performance status and liver function.
- The treatment landscape has changed dramatically since 2017 and there are new treatments on the horizon.

Thank You

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