Natural History of Cirrhosis and Management

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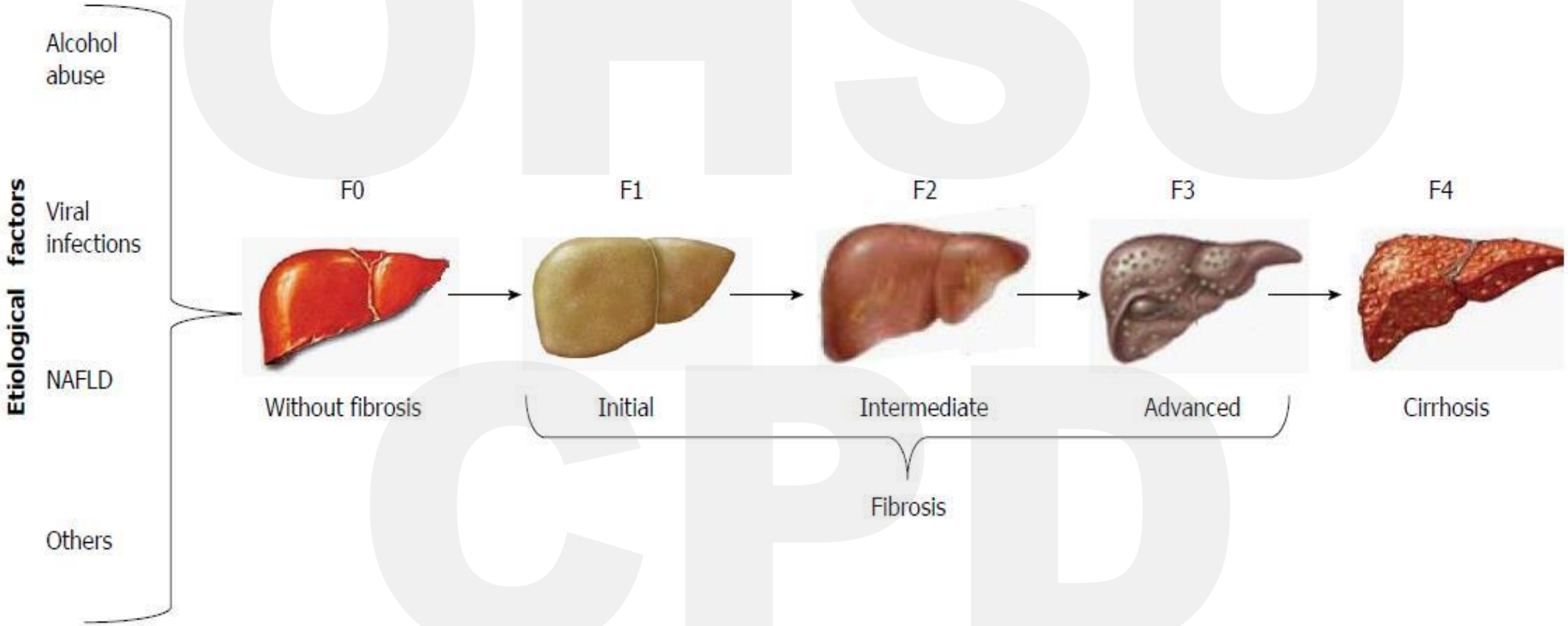
Spectrum of Liver Disease



Serum biomarker tests for fibrosis assessment

AST to Platelet Ratio Index (APRI)

$$\text{APRI} = \frac{\dfrac{\text{AST Level } (IU/L)}{\text{AST (Upper Limit of Normal) } (IU/L)}}{\text{Platelet Count } (10^9/L)} \times 100 =$$

- APRI ≥0.7 77% sensitivity and 72% specificity for those with significant fibrosis (F2 or greater).
- **APRI ≥1** 76% sensitivity and 72% specificity for those with F4 fibrosis/cirrhosis
- APRI < 0.5 – high NPV which can help to rule out cirrhosis

AST to Platelet Ratio Index (APRI) Calculator - Clinical Calculators - Hepatitis C Online

Lin et al, *Hepatology*, 2011.
HepatitisC.uw.edu

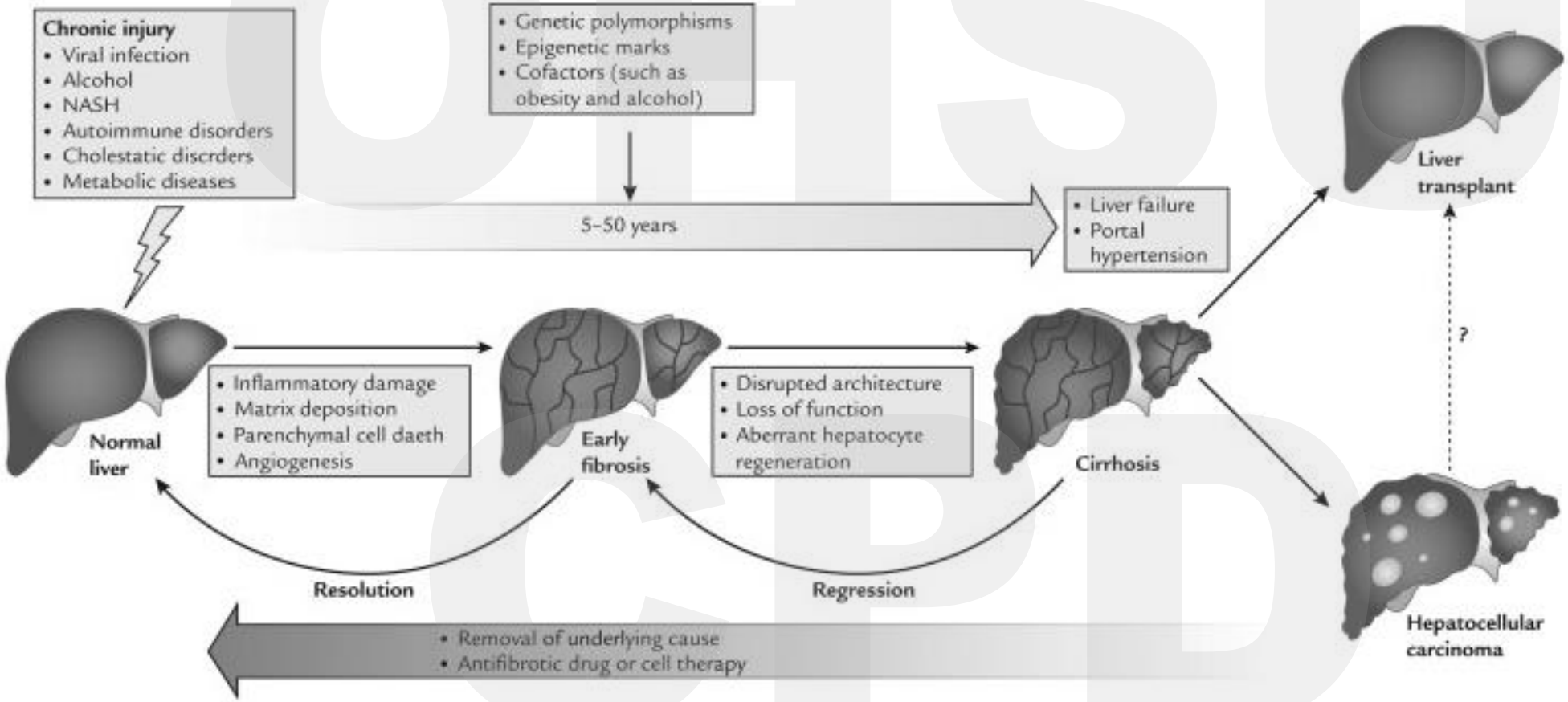
FIB-4

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}} =$$

- Score ≤1.45 with 90% NPV for advanced fibrosis
- Scores **≥3.25** have 97% specificity, 65% PPV for advanced fibrosis
- What do we do with those patients with score between 1.45 and 3.25?
  - Consider further fibrosis work-up with elastography or biopsy
- Limitations
  - Young or older age (> 65 has specificity less than 30%)
  - Other conditions that could affect AST, ALT, platelet count (hematologic conditions)

Sterling et al, *Hepatology* 2006.
HepatitisC.uw.edu

Natural History of Cirrhosis



Muir et al, *Clin Therapeutics*, 2015.

Mortality of Cirrhosis

- Compensated
  - Absence of ascites, variceal hemorrhage, jaundice, or hepatic encephalopathy
  - **1-3% annual risk of death**
  - Median survival in some studies of greater than 12 years
  - 1 year survival is 95%, 10% probability of death in 20 years

- Decompensated
  - One or more of the following: ascites, variceal hemorrhage, jaundice, hepatic encephalopathy, HCC
  - **1 year survival of ~61%**
  - Average survival without transplant is ~2 years

Dolan et al, 2007.

Garcia-Tsao, *Complications of Cirrhosis*, 2015.

Mortality With Decompensation

Decompensated Cirrhosis	5 year mortality
Bleeding with no other complication	20%
First non-bleeding complication	30%
Any second decompensation	88%

Goldberg et al, *Transplantation*, 2013.

Lai et al, *Curr Opin Organ Transplant*, 2016.

D'Amico et al, *Aliment Pharmacol Ther*, 2014.

Mazzarelli et al, *Liver Transplantation*, 2018.

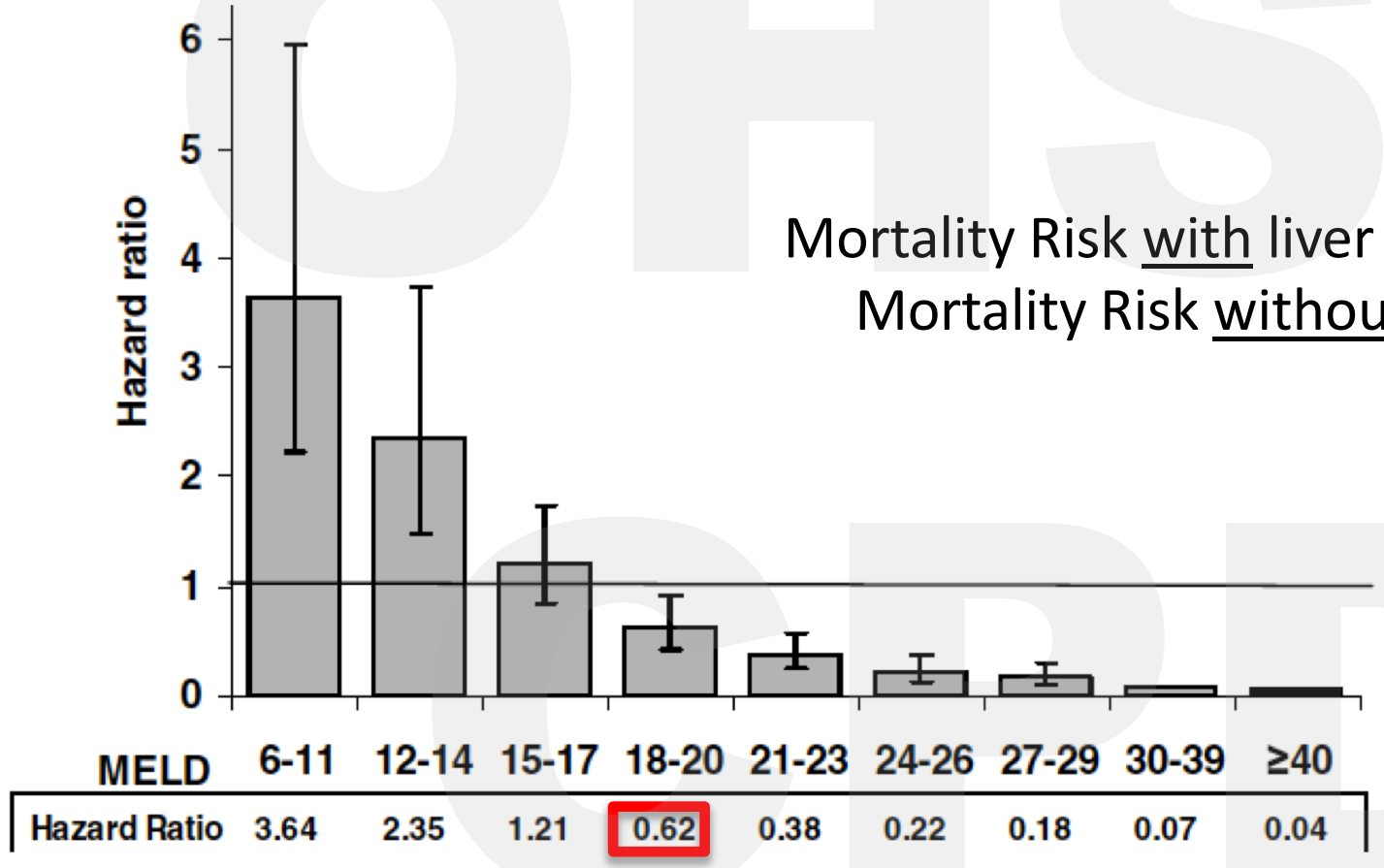
TABLE 1. Mortality of Patients With Cirrhosis Based on Child-Pugh, MELD Score, and ACLF Grade

	ACLF grade	Characteristics	65-day
		Acute liver damage associated with	
Child-Pugh	Grade 1	Single kidney failure[a] OR liver failure,[b]	
A		coagulopathy,[c] circulatory failure,[d] respiratory	5%
B		failure,[e] serum creatinine 1.5–1.9 mg/dL and/or	20%
C		mild to moderate hepatic encephalopathy OR	55%
MELD Score		brain failure[f] with creatinine 1.5–1.9 mg/dL	
10-19	Grade 2	Two organ failures	n/a
20-29	Grade 3	Three or more organ failures	n/a
30-39	n/a	53%	n/a
ACLF Grade			
ACLF 1	22%	41%	n/a
ACLF 2	32%	52%	n/a
ACLF 3	77%	79%	n/a

Mazzarelli et al, *Liver Transplantation*, 2018.

The ‘Survival Benefit’ of Liver Transplant

- LT survival benefit: MELD score ≥ 15

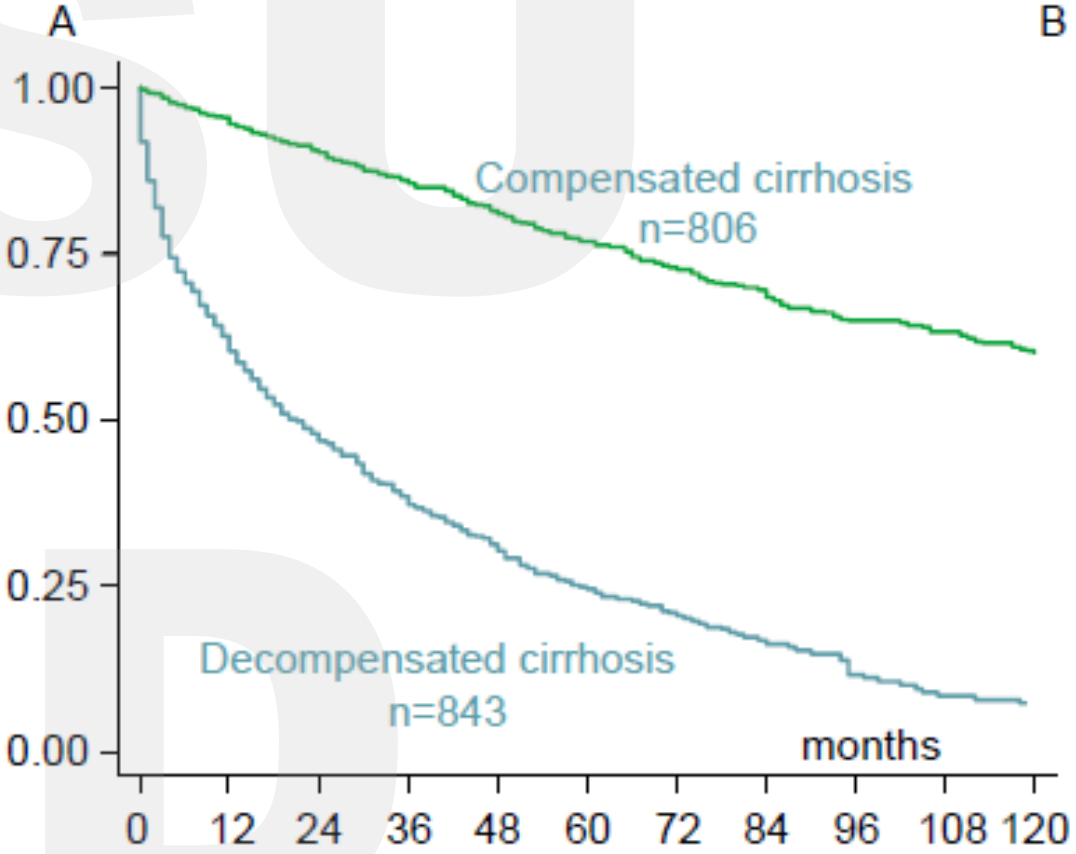


Mortality Risk with liver transplant –
Mortality Risk without liver transplant

Merion et al, Am J Transpl, 2005

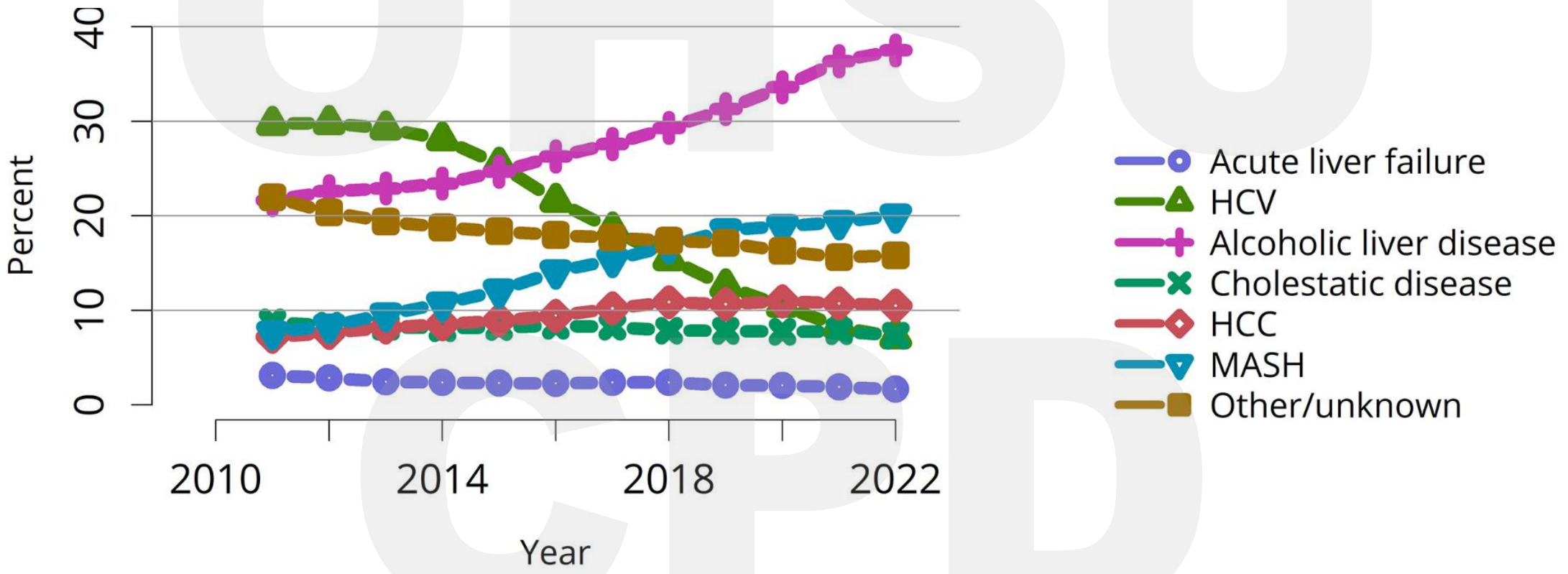
Liver Transplantation

- *Any decompensation* of liver disease is a reason to consider if patient would be a liver transplant candidate
  - In some situations – removing the offending agent (HCV, alcohol) can lead to significant improvement and reduce need for transplant
- Consider other factors: age, comorbidities, substance use disorder, social support
- MELD-Na>15 – threshold at which benefit > risk
- HCC within Milan criteria



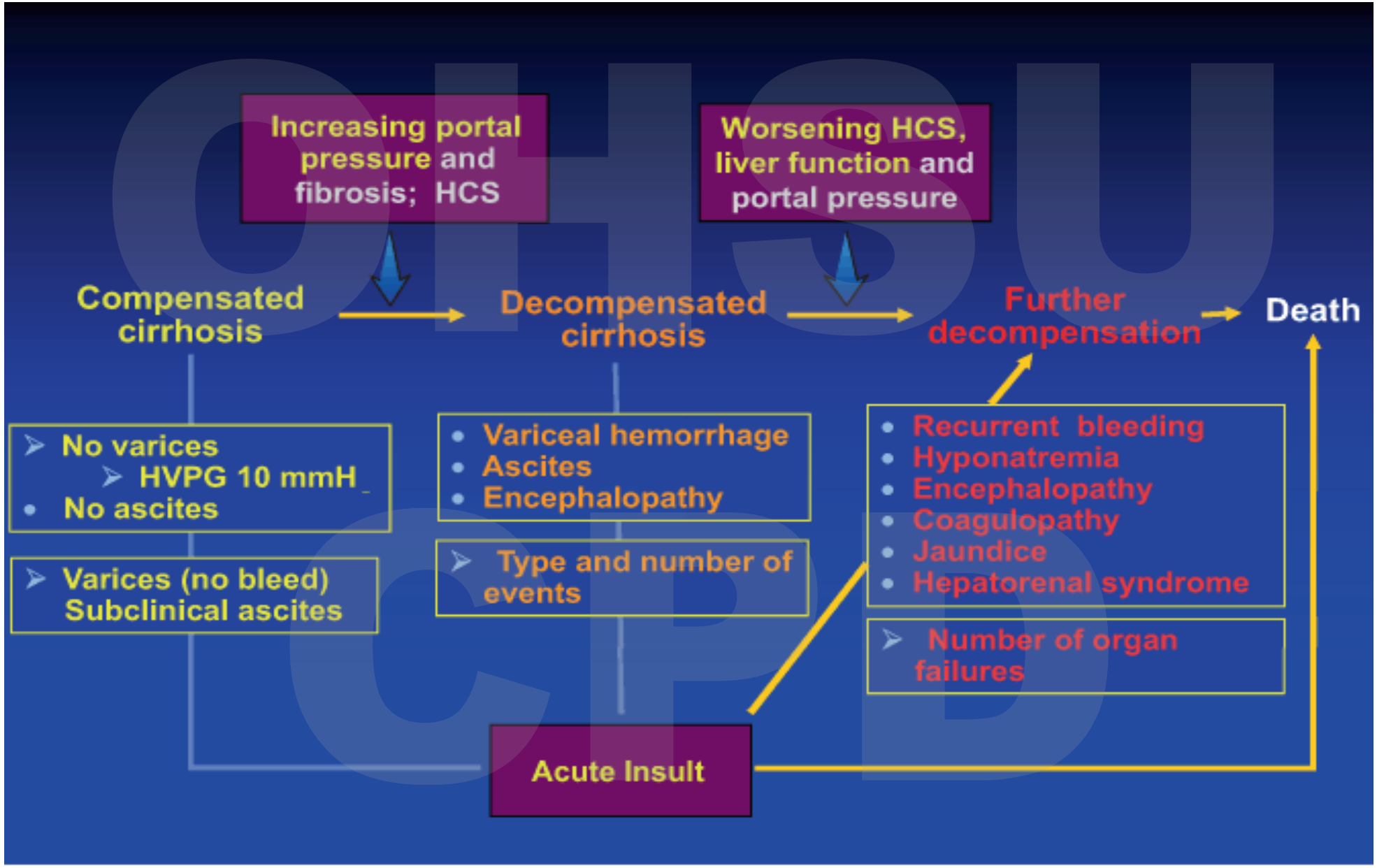
Trends in Liver Transplant

Source: OPTN/SRTR, 2022.



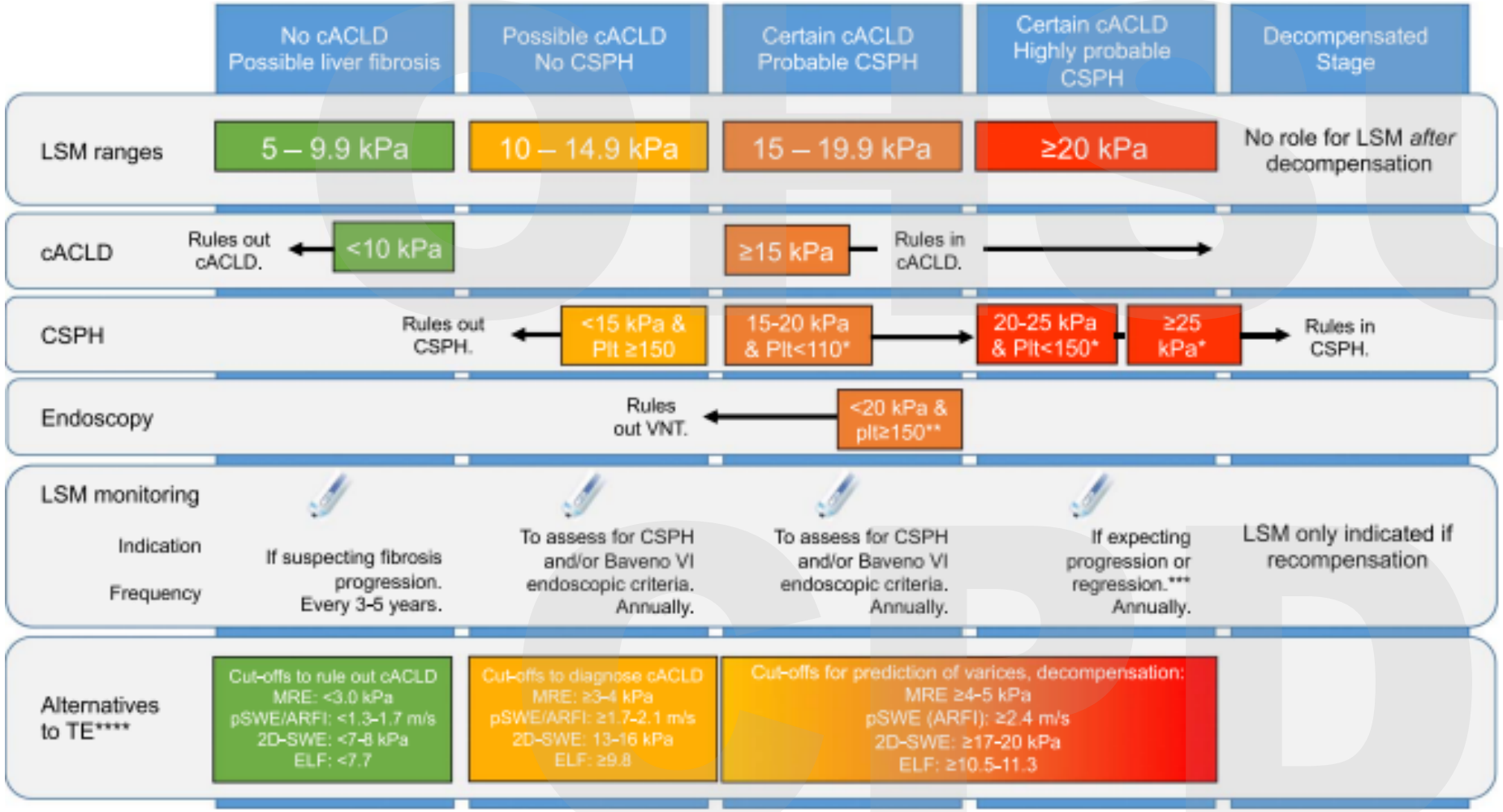
OPTN/SRTR 2022 Annual Data Report

Spectrum of Cirrhosis



Garcia-Tsao, *Complications of Cirrhosis*, 2015.

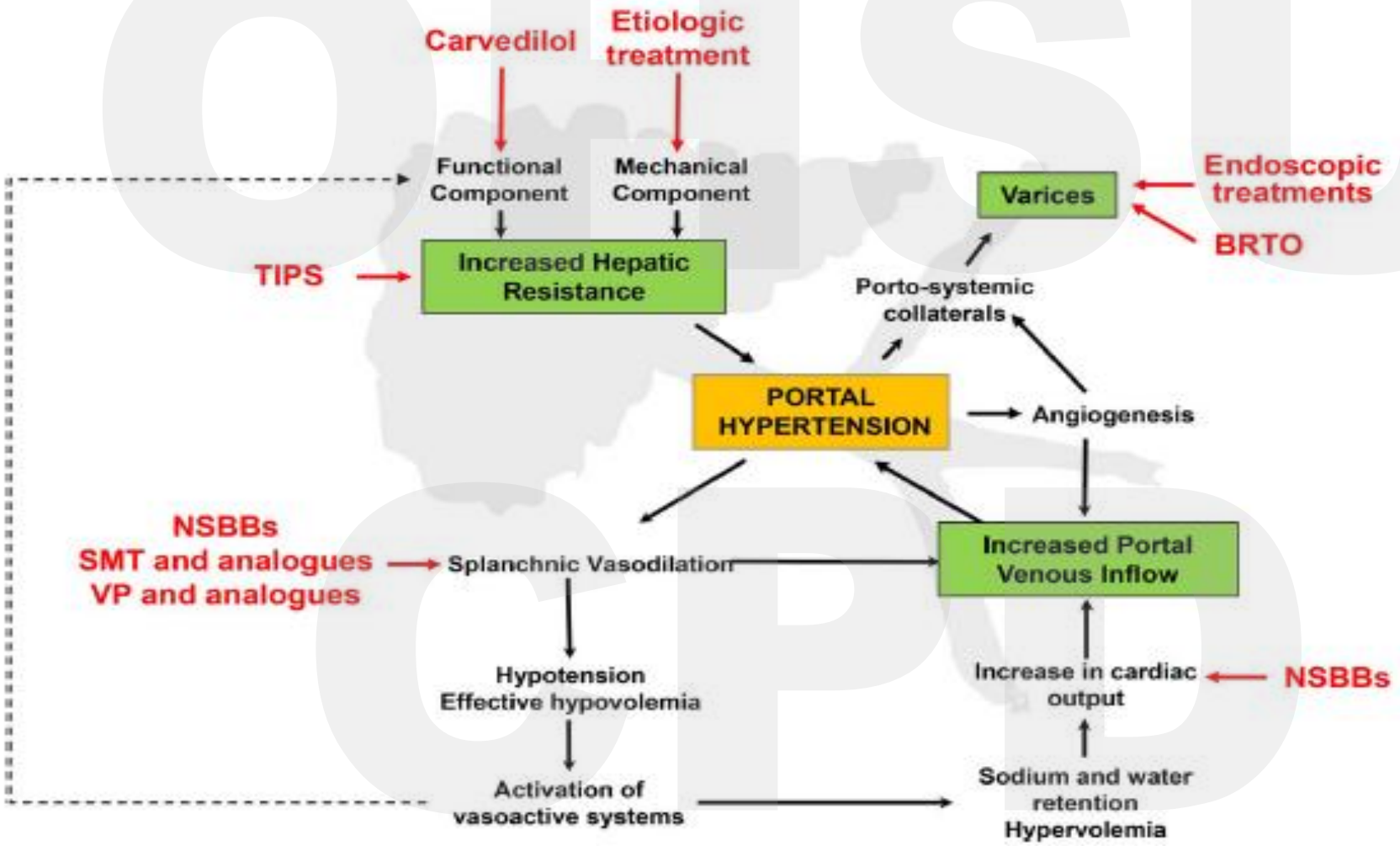
Portal hypertension risk stratification (non-invasive)



- LSM: liver stiffness measurement
- CSPH: clinically significant portal hypertension
- cACLD: compensated advanced chronic liver disease
- TE: transient elastography
- MRE: MR elastography

Kaplan et al, *Hepatology* 2024.

Development/Treatment of Portal Hypertension



NSBB:

- Beta 1 blockage (reduces cardiac output)
- Beta 2 blockage (splanchnic vasoconstriction)
- In addition to above, **carvedilol** has alpha 1 blockage leading to intrahepatic vasodilation

Garcia-Tsao et al, *AASLD Guideline on Portal Hypertensive Bleeding,* 2017.

Beta blocker usage

- Carvedilol preferred
  - Achieve total dose of 6.25 mg daily or ideally **12.5 mg daily**
  - Contraindications
    - Systolic blood pressure < 90 mm Hg
    - Asthma
    - History advanced heart block, bradyarrhythmias
- Benefits
  - Improved survival in patients with high-risk varices and ascites
  - Reduced risk of re-bleeding if used in conjunction with endoscopic variceal ligation (banding)

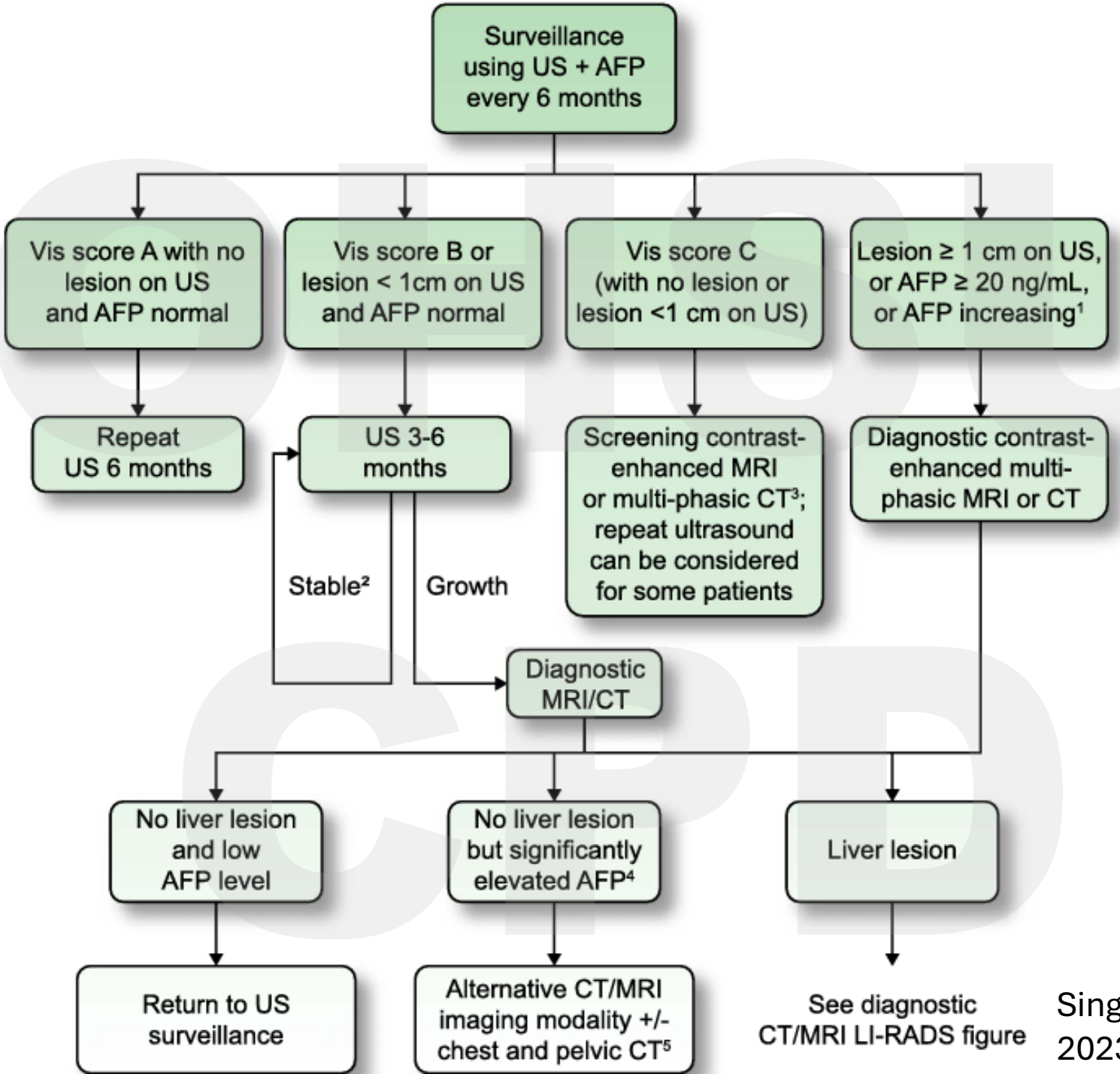
HCC Risk/Surveillance

10. HCC surveillance should be performed using ultrasound and AFP at semiannual (approximately every 6 months) intervals (**Level 2, Strong Recommendation**).
    a. AASLD recommends use of interventions such as best practice alerts or outreach programs to increase HCC surveillance adherence given the underuse of surveillance in clinical practice (**Level 2, Strong Recommendation**).

TABLE 1 At-risk population for surveillance

Population group	Incidence of HCC
Sufficient risk to warrant surveillance	
Child-Pugh A–B cirrhosis, any etiology	≥ 1.0% per year
Hepatitis B	
Hepatitis C (viremic or post-SVR)	
Alcohol associated cirrhosis	
Nonalcoholic steatohepatitis	
Other etiologies	
Child-Pugh C cirrhosis, transplant candidate	
Non-cirrhotic chronic hepatitis B	≥ 0.2% per year
Man from endemic country[a] age > 40 y	
Woman from endemic country[a] age > 50 y	
Person from Africa at earlier age[b]	
Family history of HCC	
PAGE-B score ≥ 10[c]	
Insufficient risk and in need of risk stratification models/biomarkers	
Hepatitis C and stage 3 fibrosis	< 0.2% per year
Noncirrhotic NAFLD	

Singal AG et al. Hepatology, 2023



Singal AG et al. Hepatology, 2023

LI-RADS:
Liver Imaging Reporting and Data System

CT/MRI Diagnostic Table

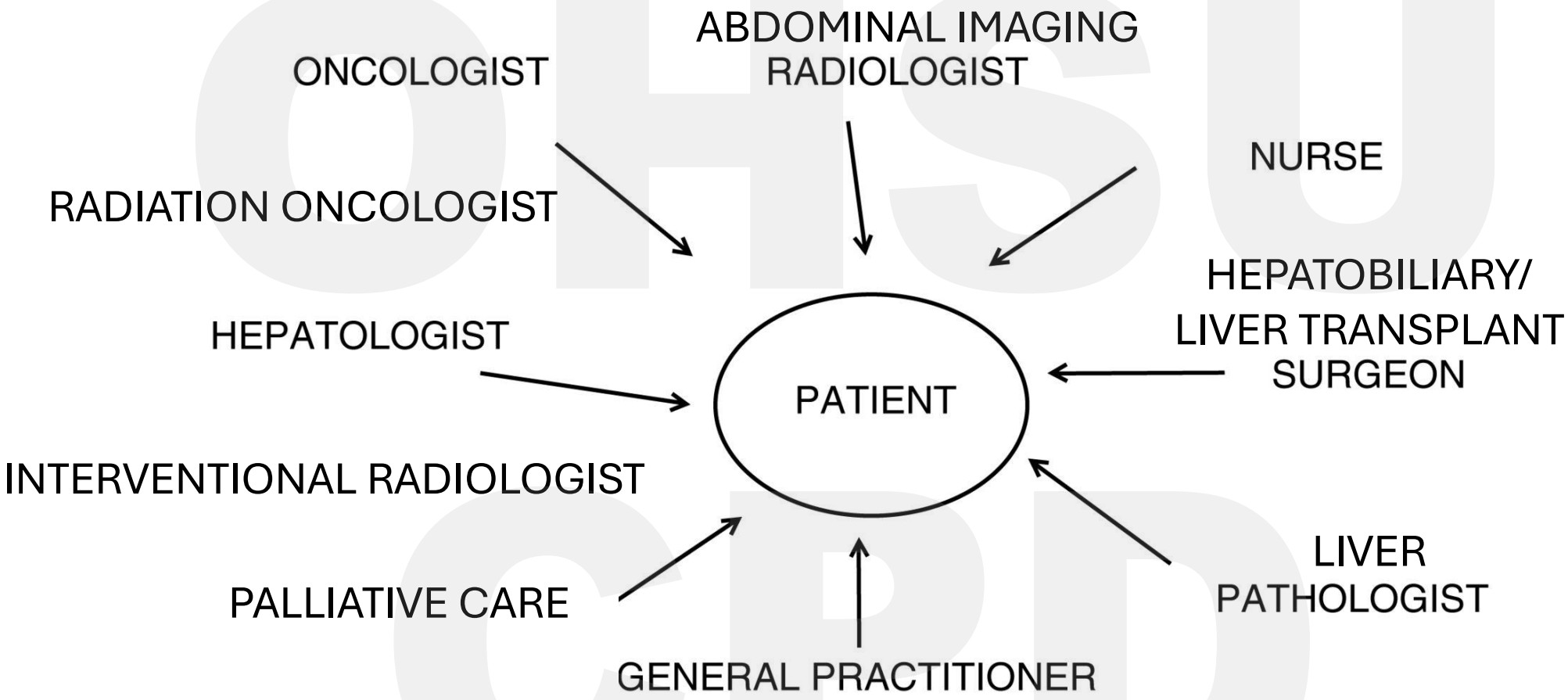
Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5

Observations in this cell are categorized based on one additional major feature:

- LR-4 – if enhancing "capsule"
- LR-5 – if nonperipheral "washout" **OR** threshold growth

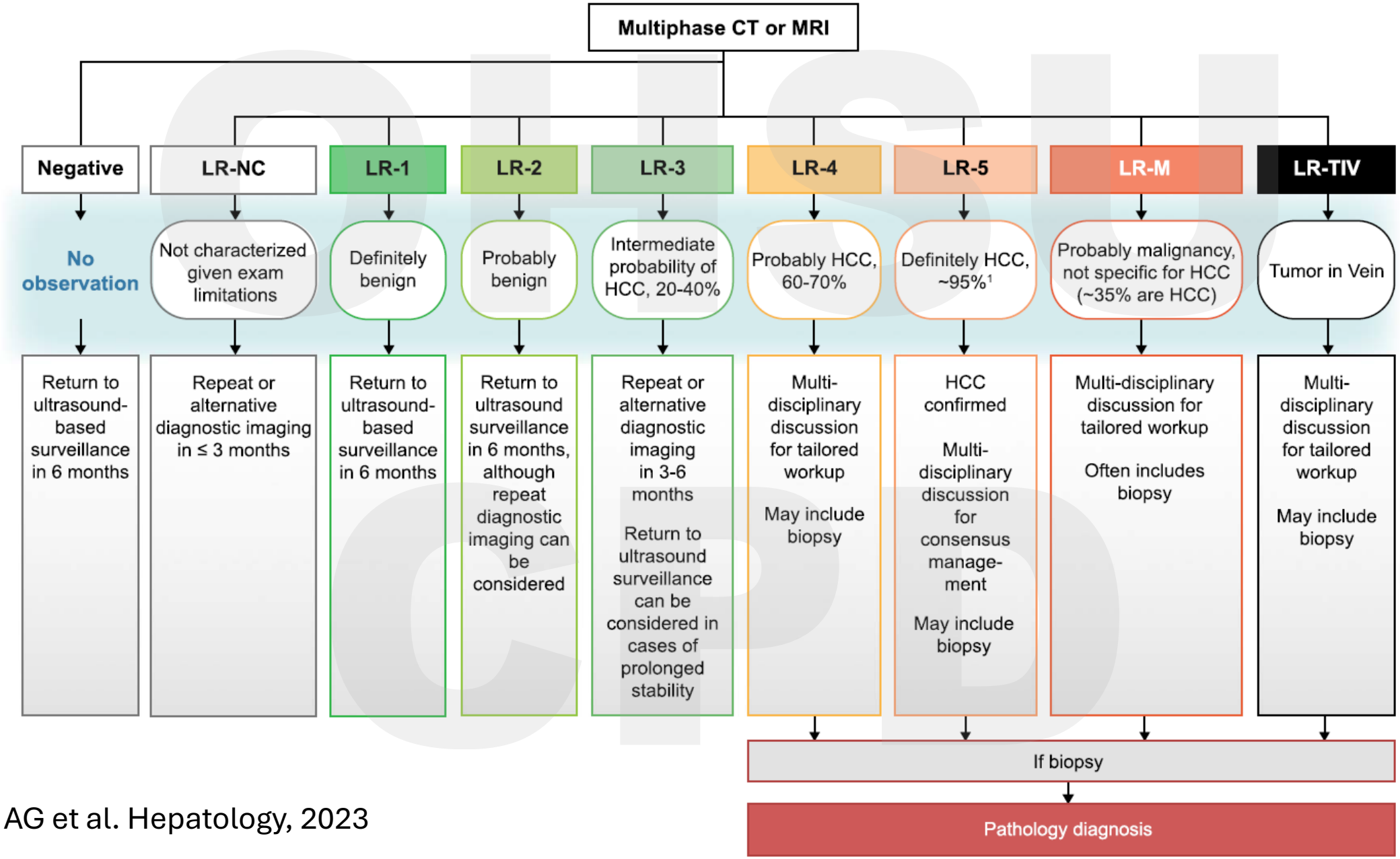
Multidisciplinary Liver Tumor Boards



Barone C et al. Ann Oncol 2013;24:ii15-ii23

Annals of Oncology

LI-RADS classification



Singal AG et al. Hepatology, 2023

When to stop HCC surveillance?

Table 1. Suggested scenarios for discontinuing HCC surveillance

HCC surveillance should be discontinued	HCC surveillance can be considered for discontinuation
Poor performance status and frailty—ECOG 3 or greater	Age >80 years
Child C cirrhosis, if not a liver transplant candidate	Impaired performance status, ECOG 2
Non-liver comorbid medical conditions limiting life expectancy to less than 2 yr	Comorbidities precluding adequate imaging and management of HCC (renal failure not on dialysis)

ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma.

Taddei T. AJG 2023

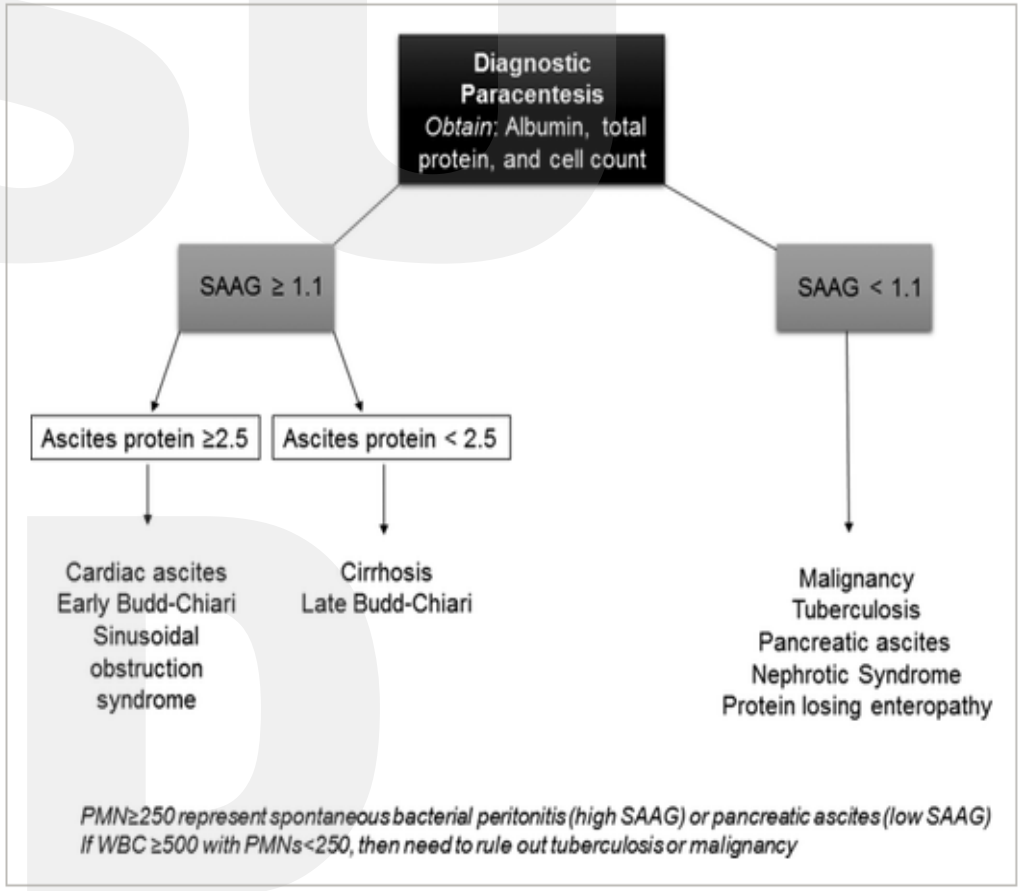
Case #1

- 41yo male with history of significant EtOH use (8-12 beers daily); presents to clinic with increased abdominal girth and jaundice
- Exam: scleral icterus, +fluid wave and bulging flanks, 2+LE edema

- Labs: Tbili 4.1, Alk phos 192, AST 210, ALT 37, albumin 2.9
  - INR 1.9
  - Cr 0.5
  - Na 130
  - WBC 12.2, PLT 191
  - MELD 3.0 of 23
- Next steps?

Diagnostic Work-up

- Imaging
  - U/S with Doppler vs. multiphase CT
- Paracentesis
  - SBP rule out
  - Fluid analysis
    - SAAG
      - > 1.1 likely indicator of portal hypertension
  - DDX of ascites >90% is related to cirrhosis
  - Important exceptions
    - Cardiac disease
    - Malnutrition
- Other work-up to consider
  - TTE
  - Fluid Cytology



Hernaez, *Clinical Liver Disease*, 2016.

Treatment

- Na restricted diet- 2g daily
- No free water restriction if Na >130
- Diuretics:
  - Starting dose Furosemide 40mg : Spironolactone 100mg
  - Max- Furosemide 160mg : Spironolactone 400mg, or limited by metabolic or renal effects of diuresis
- Serial large volume paracentesis as needed (provides faster relief compared to diuretics)
  - 6-8g albumin repletion per L removed
- Alcohol abstinence
- Discuss long-term management (?transplant)

Runyon BA. Hepatology 2013

Case #2

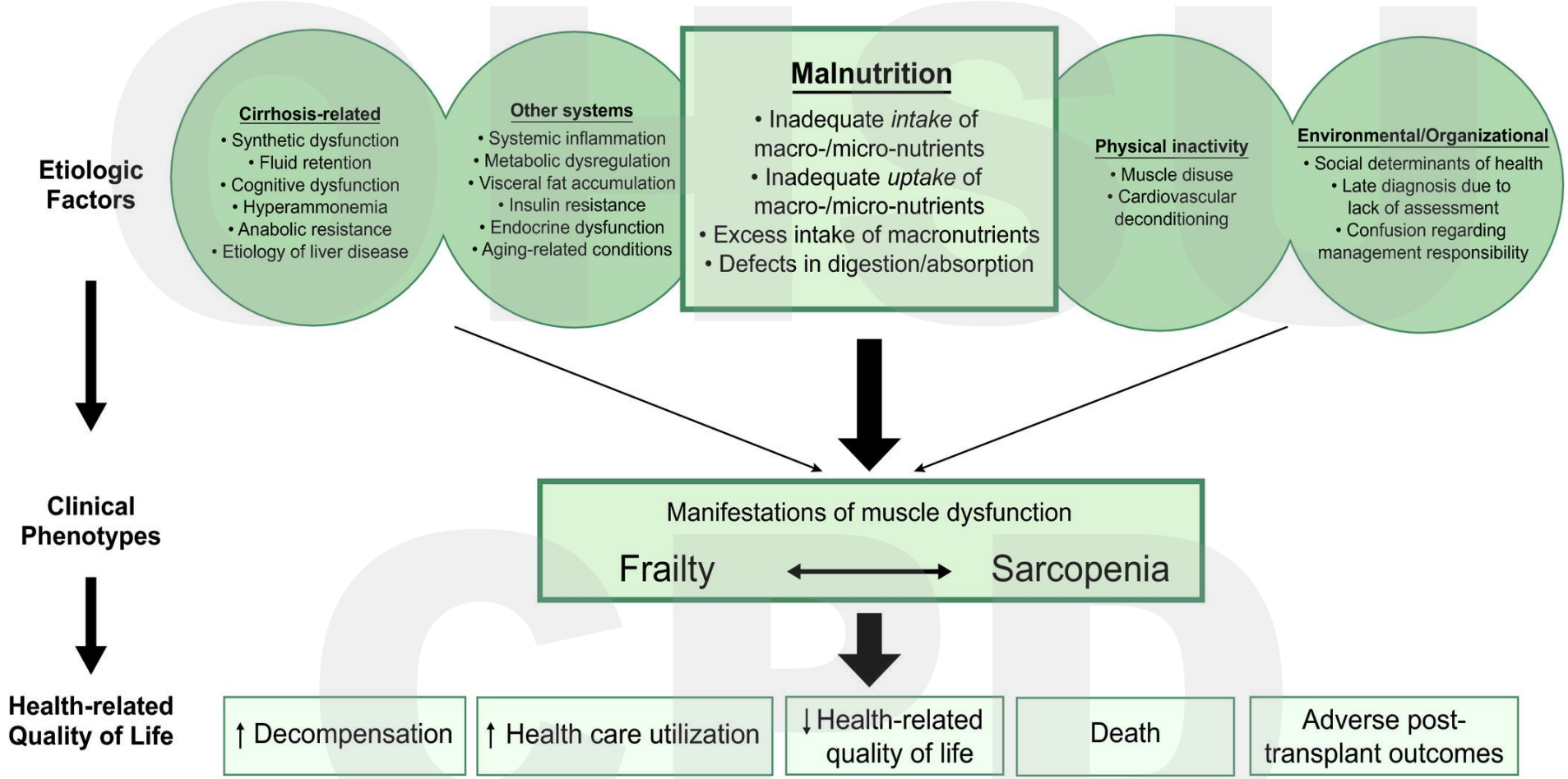
- 67 YOF with MASH cirrhosis complicated by ascites, SBP, and hepatic encephalopathy who presents in clinic for hospital follow up; has had 3 hospitalizations this month
- She feels she is eating well though she has lost significant weight and muscle over the last few weeks/months
- Previously could perform IADL's now requiring significant assistance – unable to walk medium/long distances
- Patient has outpatient referral for liver transplant pending

Table 1. Definitions for the Theoretical Constructs of Malnutrition, Frailty, and Sarcopenia and Consensus-Derived Operational Definitions Applied to Patients with Cirrhosis

Construct	Theoretical Definitions	Operational Definitions
Malnutrition	A clinical syndrome that results from deficiencies or excesses of nutrient intake, imbalance of essential nutrients, or impaired nutrient use[4]	An imbalance (deficiency or excess) of nutrients that causes measurable adverse effects on tissue/body form (body shape, size, composition) or function and/or clinical outcome[1]
Frailty	A clinical state of decreased physiologic reserve and increased vulnerability to health stressors[2]	The phenotypic representation of impaired muscle contractile function
Sarcopenia	A progressive and generalized skeletal muscle disorder associated with an increased likelihood of adverse outcomes including falls, fractures, disability, and mortality[3]	The phenotypic representation of loss of muscle mass

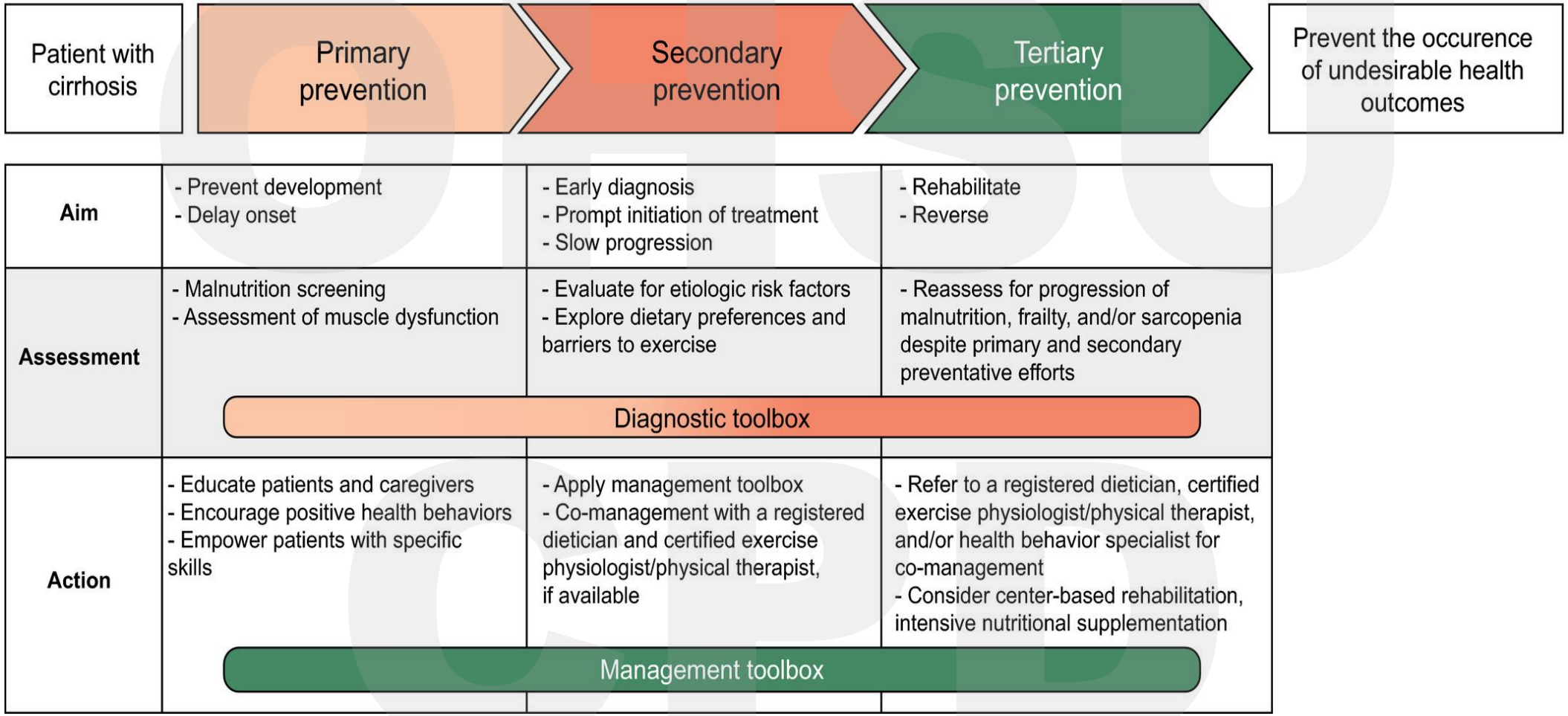
Lai et al, AASLD Practice Guidelines, 2021.

Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases



Hepatology, Volume: 74, Issue: 3, Pages: 1611-1644, First published: 07 July 2021, DOI: (10.1002/hep.32049)

Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases



Hepatology, Volume: 74, Issue: 3, Pages: 1611-1644, First published: 07 July 2021, DOI: (10.1002/hep.32049

Takeaways

- Frailty is a serious concern in those with decompensated cirrhosis and could potentially preclude liver transplant
  - Consider PT/OT, nutrition consults for *most* patients with decompensated cirrhosis
- There is not one superior tool for assessment of frailty
  - Liver frailty index is most commonly utilized tool
- Early intervention is key

Summary

- Chronic liver disease causes inflammation and fibrosis over many years that can sometimes lead to cirrhosis
- Mortality in liver disease is significantly increased in those with impaired synthetic function (higher MELD) and in particular those with decompensations
- Liver transplant can and should be considered in those patients with decompensated cirrhosis with prognostic impact from liver disease (ie MELD > 15)
- Patients with cirrhosis at risk for HCC and portal hypertension and should be screened regularly for this
  - HCC screening is with imaging + AFP every 6 months; HCC is diagnosed primarily with multi-phase cross-sectional imaging
  - Elastography has been validated and can be used for portal hypertension risk stratification
- Non-selective beta blockers have been validated in reducing risk of bleeding (or re-bleeding) in those with varices
- Frailty/sarcopenia is a major concern for those with decompensated cirrhosis and requires early diagnosis and intervention