Dos and Don’ts in Liver Disease

DATE: September 22, 2022

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Case #1

- 45 YOM with history of alcohol-related cirrhosis with hepatic hydrothorax requiring weekly thoracentesis presents with shortness of breath
- Labs on hospitalization demonstrate total bilirubin 6.3, Cr 1.7, MELD-Na 25, albumin 2.8
- Albumin infusion ordered with goal target 3-3.5 g/dL

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A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis

Table 2. End Points.*

Variable	Albumin Group (N=380)	Standard-Care Group (N=397)	Adjusted Odds Ratio (95% CI)†	P Value
Composite primary end point — no. (%)	113 (29.7)	120 (30.2)	0.98 (0.71–1.33)	0.87
Components of composite primary end point — no. (%)‡				
Incidence of new infection	79 (20.8)	71 (17.9)	1.22 (0.85–1.75)	
Incidence of kidney dysfunction	40 (10.5)	57 (14.4)	0.68 (0.44–1.11)	
Incidence of death	30 (7.9)	33 (8.3)	0.95 (0.56–1.59)	
Death at 28 days	53 (14.0)	62 (15.6)	0.86 (0.57–1.30)	
Death at 3 mo	92 (24.2)	93 (23.4)	1.05 (0.74–1.48)	
Death at 6 mo	132 (34.7)	119 (30.0)	1.27 (0.93–1.73)	
Total median albumin infused per patient (IQR) — g	200 (140–280)	20 (0–120)	143 (127–158)§	

* Unless stated, the time of the end point is during the trial treatment period (15 days after randomization).
† Odds ratios are adjusted for stratification variables, with sites as random intercept terms.
‡ The end points are defined in the original trial protocol.[26]
§ This is the adjusted mean difference between the groups.

China et al, *NEJM*, 2021.

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Table 3. Serious Adverse Events.*

Event	Albumin Group (N=380)	Standard-Care Group (N=397)	All Patients (N=777)
		number of events	
Serious adverse event			
Grade 3: severe event	28	11	39
Grade 4: life-threatening event	17	13	30
Grade 5: death	42	48	90
All events	87	72	159
Individual serious adverse events occurring in >1 patient†			
Anemia	1	1	2
Esophageal varices hemorrhage	5	6	11
Gastric hemorrhage	5	4	9
Multiorgan failure	23	31	54
Other infections and infestations: spontaneous bacterial peritonitis	0	5	5
Lung infection	15	8	23
Sepsis	4	3	7
Encephalopathy	4	1	5
Acute kidney injury	2	0	2
Adult respiratory distress syndrome	0	2	2
Hypoxia	1	1	2
Pleural effusion	1	1	2
Pulmonary edema	15	4	19
All serious adverse events that included pulmonary edema or gastrointestinal bleeding‡			
Any pulmonary edema or fluid overload	23	8	31
Any gastrointestinal bleeding	11	13	24

* Patients may have had more than one clinical diagnosis per serious adverse event. A serious adverse event was any new adverse event that was a life-threatening event or resulted in prolongation of an existing hospitalization.
† Serious adverse events are categorized with a single primary event name (graded by two assessors) according to the Common Terminology Criteria for Adverse Events, version 5.0 (2017).
‡ Serious adverse events were labeled by the investigators as involving a primary event but could have involved other contributing events.

China et al, *NEJM*, 2021.

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Takeaways

- Albumin infusion with goal target of 3 g/dL is not associated with better outcomes
- Albumin indicated in setting of SBP (protective of kidneys)

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IR calls after thoracentesis and asks you to put in a referral for TIPS….

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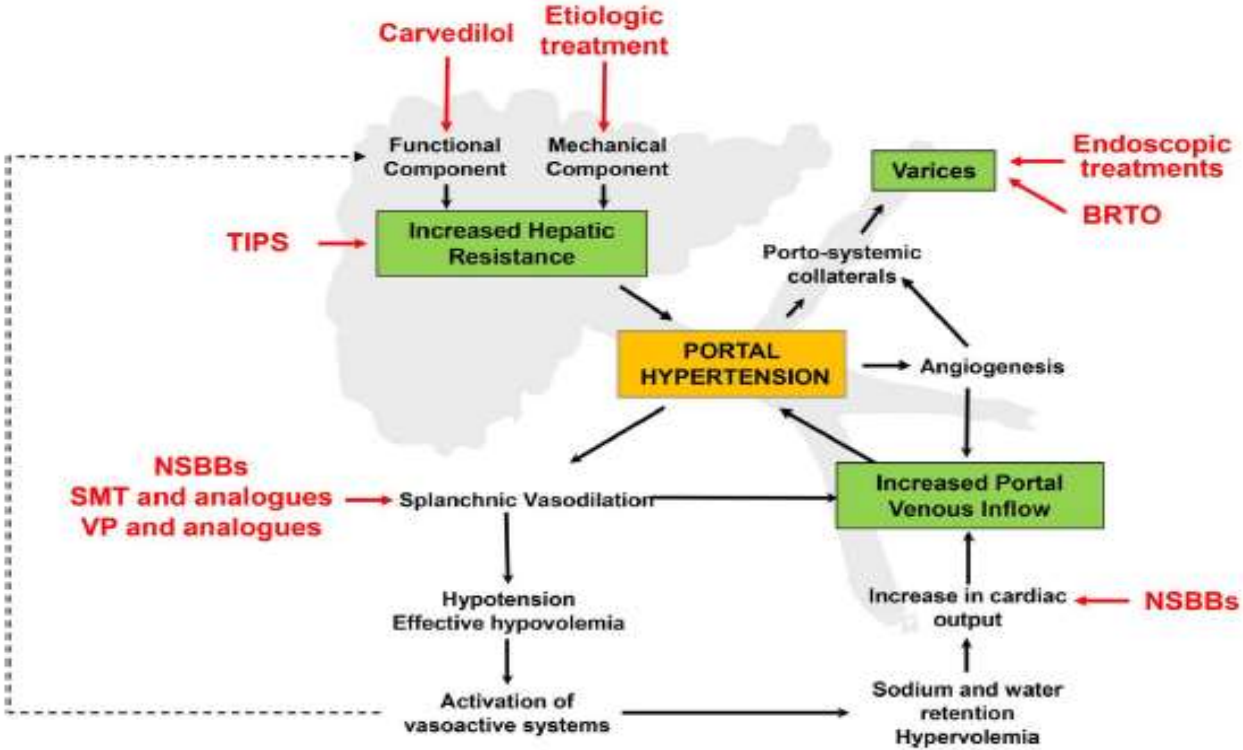
Development of Portal Hypertension



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

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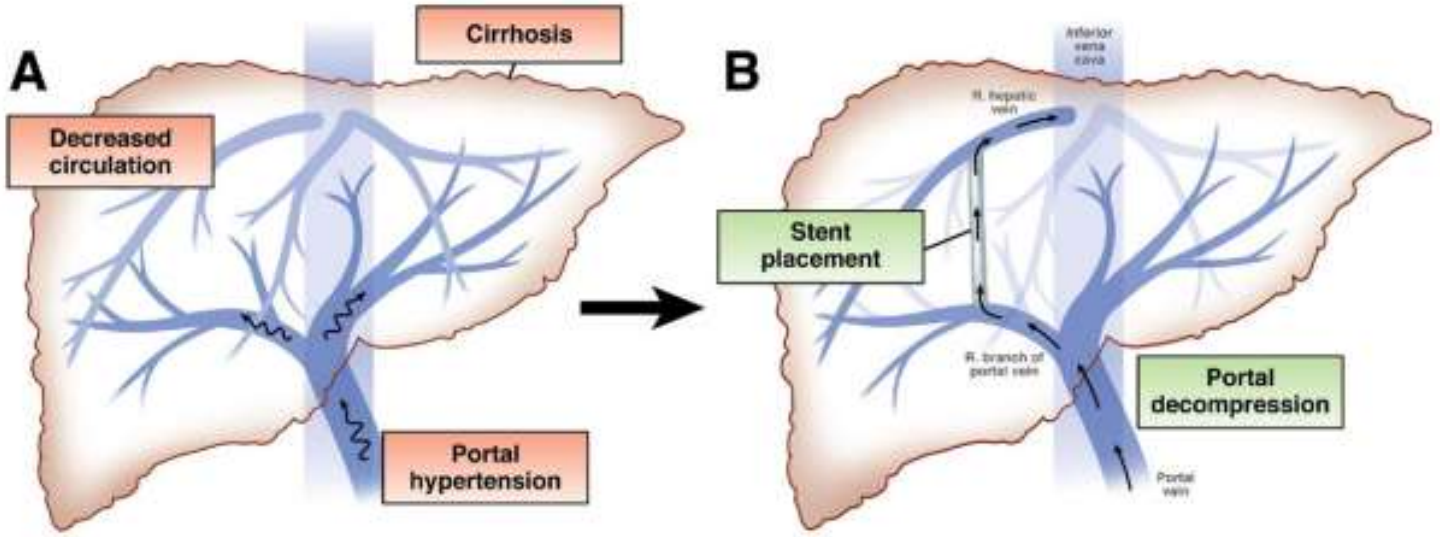
TIPS

Indications:

- Refractory ascites and/or hydrothorax
- Uncontrolled or recurrent variceal bleeding



Absolute Contraindications	Relative Contraindications
Congestive heart failure	International normalized ratio > 5
Severe pulmonary hypertension	Platelet count < 20,000/cm^3
Multiple hepatic cysts	Moderate pulmonary hypertension
Uncontrolled systemic infection; sepsis	Portal vein thrombosis
Unrelieved biliary obstruction	

Clinical Gastroenterolology and Hepatology, 2011.
Bhogal et al, *Clinical Liver Disease*, 2012.

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TIPS-associated risks

- Heart failure
  - Pre-procedure TTE needed
- Liver decompensation
  - Higher risk if bilirubin > 3 and/or MELD-Na > 18
- Hepatic encephalopathy
  - Incidence post TIPS can range from 20-40%, refractory disease around ~10%
  - Consideration for prophylactic lactulose
  - TIPS can be narrowed/constrained pending clinical course

Casadaban et al, *Dig Dis Sci*, 2015.
Fonio et al, *Radiol Med*, 2017.

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Takeaways

- TIPS should likely be avoided for this patient due to high MELD-Na and associated risk of liver-related decompensation (MELD-Na > 18)
- Very important to consider home environment of patient before TIPS given risk of HE, need for monitoring at home
- What else should we consider for this patient?

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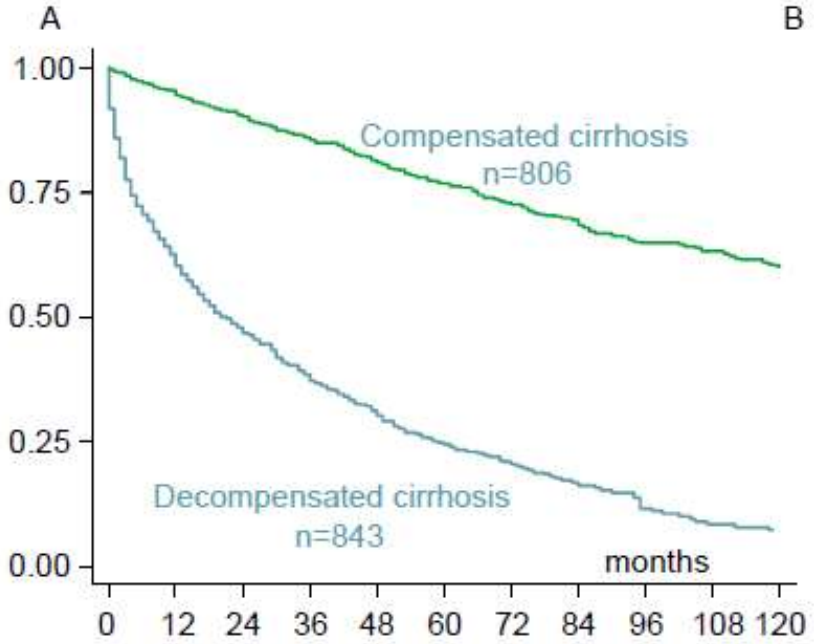
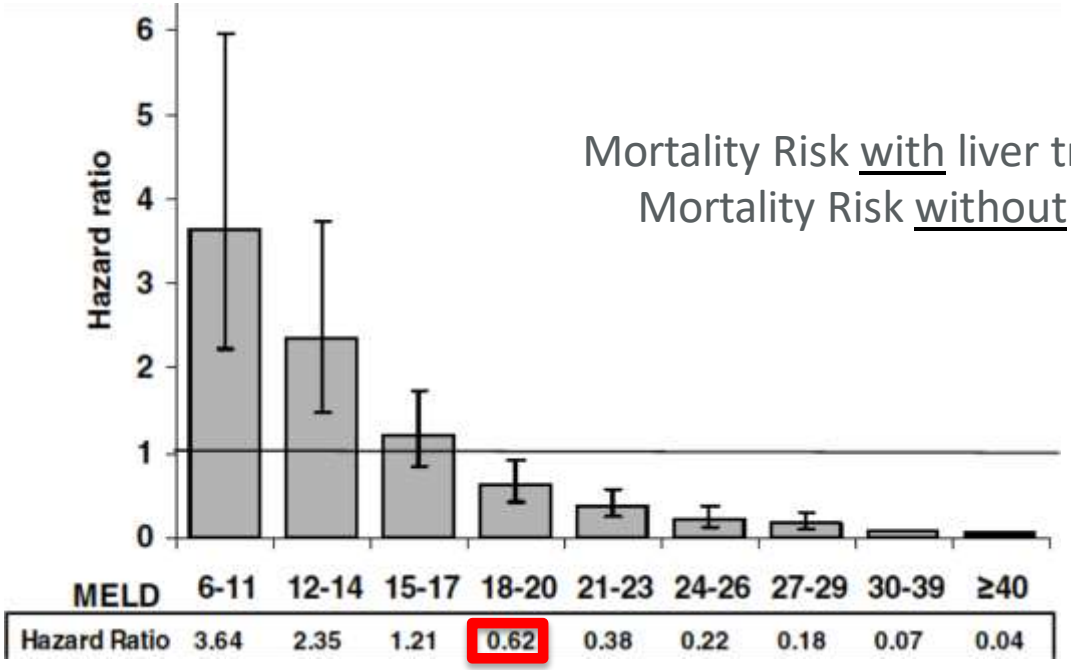
Liver Transplantation

- *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



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

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Liver Transplant Contraindications

Relative	Absolute
MELD <15	Severe pulmonary hypertension
Mod PHT (mean PAP >35)	Brain death
Poor social support	Sepsis
Severe psychiatric disease	Active/untreated alcohol/substance use disorders
Portal/mesenteric thrombosis	AIDS
HIV	Extrahepatic malignancy
Age >70-75 years	Advanced cardiopulmonary disease
Morbid obesity (BMI >40-45)	
Malnutrition (BMI <19)	
Poor functional status	
Prior abdominal surgery	

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Complications of Liver Transplant

- Bleeding
- Bile duct issues
  - Anastomotic stricture
  - Bile leak
  - Ischemic cholangiopathy (high risk with DCD donor)
- Hepatic artery thrombosis
- Primary non-function (transplanted graft does not work)
- Rejection
  - Acute cellular
  - Chronic
- Long-term
  - Malignancy (skin cancer is highest risk)
  - Metabolic complications from immune suppressives (DM, HTN, kidney disease, HLD
  - Osteoporosis

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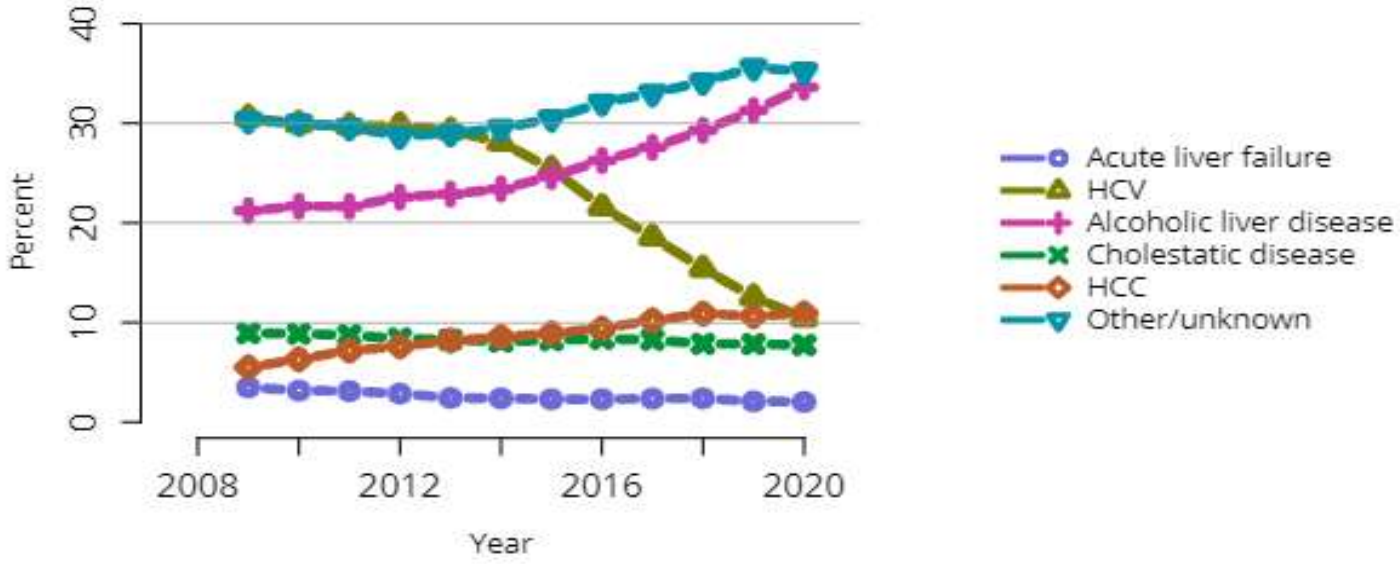
Trends in Liver Transplant



Source: OPTN/SRTR, 2020.

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Case #2

- 67 YOF with NASH cirrhosis complicated by ascites who presents with confusion; this is her 3rd hospitalization this month
- Diagnosed with SBP and treated with antibiotics and albumin
- 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 – she feels she is ready to go home now after completing antibiotics

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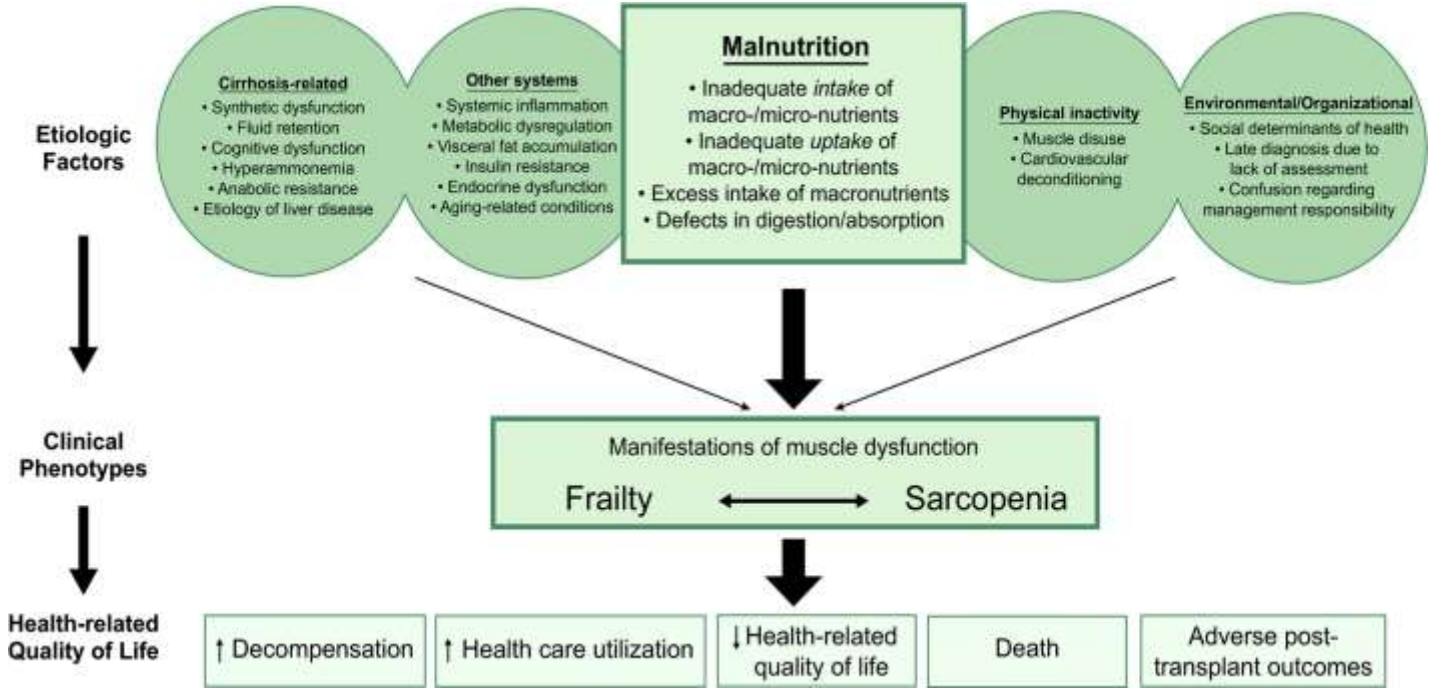
Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases



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

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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.

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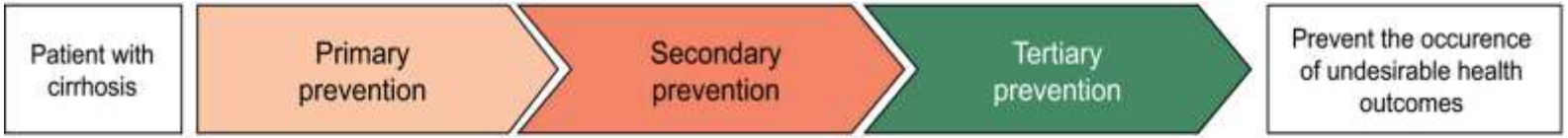
Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases



Aim	- Prevent development - Delay onset	- Early diagnosis - Prompt initiation of treatment - Slow progression	- Rehabilitate - Reverse
Assessment	- Malnutrition screening - Assessment of muscle dysfunction	- Evaluate for etiologic risk factors - Explore dietary preferences and barriers to exercise	- Reassess for progression of malnutrition, frailty, and/or sarcopenia despite primary and secondary preventative efforts
	Diagnostic toolbox		
Action	- Educate patients and caregivers - Encourage positive health behaviors - Empower patients with specific skills	- Apply management toolbox - Co-management with a registered dietician and certified exercise physiologist/physical therapist, if available	- Refer to a registered dietician, certified exercise physiologist/physical therapist, and/or health behavior specialist for co-management - Consider center-based rehabilitation, intensive nutritional supplementation
	Management toolbox		

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

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Takeaways

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

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Case #3

- 69 YOM with HCV-related cirrhosis complicated by ascites, hepatic encephalopathy, bleeding from esophageal varices with MELD-Na 25 hospitalized with HE
- He is wondering about overall prognosis
- What to discuss next?

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The Reality of Organ Transplant

Supply-Demand Mismatch

The Demand **>>>>>>** **The Supply**

Annual U.S. Deaths

- Cirrhosis: 44,358 (2019)
- HCC: 30,230 (2021)

Annual U.S. Liver Transplants

- 8,906 (2020)
- Deceased-donor: 8,415
- Living-donor: 491

From: CDC WONDER, American Cancer Society, Organ Procurement and Transplantation Network

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Survival in Compensated and Decompensated Cirrhosis

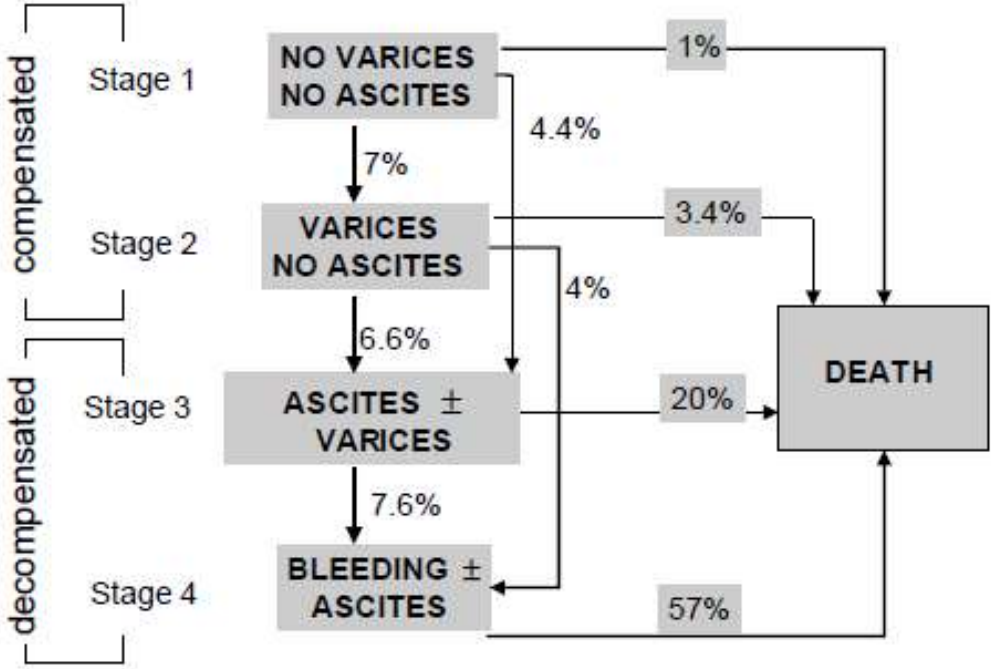

Fig. 4. Clinical course of cirrhosis: 1-year outcome probabilities according to clinical stages.

D'Amico, Journal of Hepatology 2006

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
or			
International normalized ratio	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points	100% 1 year survival		
Class B = 7 to 9 points	80%		
Class C = 10 to 15 points	45%		

https://cdn.hepatitisc.uw.edu/doc/125-3/child-turcotte-pugh-classification-severity-liver-disease.jpg

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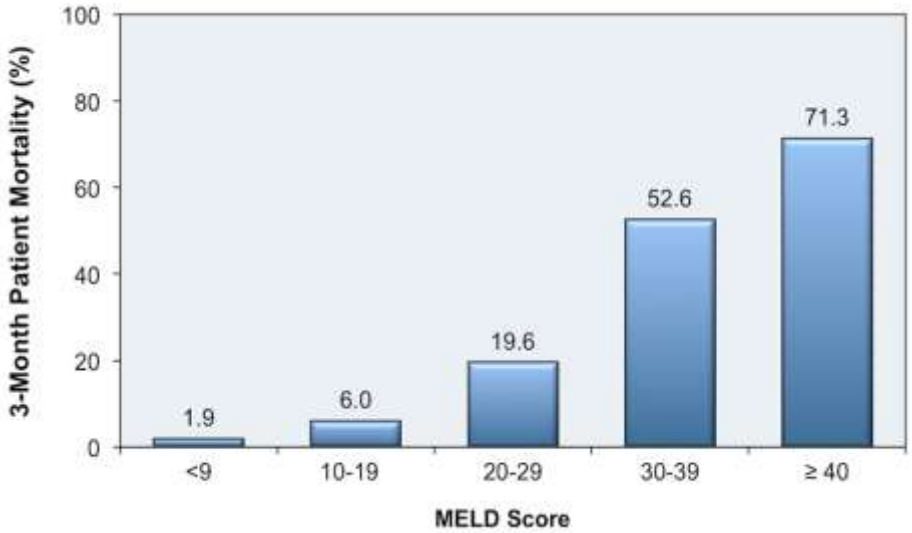
MELD

- Originally designed to predict mortality after TIPS
- Predicts 3 month mortality
- **M**odel of **E**nd-Stage **L**iver **D**isease-Na (Na-MELD)
- Components:
  - Total bilirubin
  - INR
  - Creatinine
  - Na
- Currently used to prioritize patients waiting on the liver transplant list



https://cdn.hepatitisc.uw.edu/

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] coagulopathy,[c] circulatory failure,[d] respiratory failure,[e] serum creatinine 1.5–1.9 mg/dL and/or mild to moderate hepatic encephalopathy OR brain failure[f] with creatinine 1.5–1.9 mg/dL	
A			5%
B			20%
C			55%
MELD Score	Grade 2	Two organ failures	
10-19	Grade 3	Three or more organ failures	n/a
20-29			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.

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Palliative Care in Liver Disease

- Referrals are often quite late in clinical course or non-existent
  - **Kathpalia et al**
    - 17% of patients who died awaiting liver transplant received referral to palliative care
    - Majority of evaluations happened in the inpatient setting
    - Half of evaluations occurred at late stage, within 72 hours of patient's death
  - **Poonja et al**
    - Of those removed from transplant waiting list, only 11% received a referral to palliative care despite > 50% of patients having severe symptoms
    - Goals of care and code status are rarely discussed with patients

Kathpalia et al, *World J Transplant*, 2016.
Poonja et al, *Clin Gastroenterol Hepatol*, 2014.

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Underutilization of palliative care in those denied for transplant

- ~35% of patients received inpatient palliative care consultation with similar percentage referred directly to hospice
- ~28% of patients transitioned to comfort measures without palliative care consultation
- Median time interval between denial for liver transplant and palliative care consultation was 28 days

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Kelly et al, *Ann Hepatol*, 2017.

Takeaways

- Decompensated cirrhosis is associated with increased mortality with varying predictive tools
- Palliative care is under-utilized especially at an early stage in advanced liver disease

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Thank You