Updates in Inpatient Cirrhosis Care

DATE: September 19, 2024

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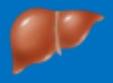
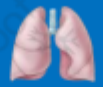
Disclosures

- None

ED Utilization and Outcomes among Adults with Cirrhosis

	Cirrhosis	No Cirrhosis	Congestive Heart Failure	Chronic Obstructive Pulmonary Disease
				
Adults at entry	198,439	38,221,211	1,817,628	2,394,037
ED visits per person-year	1.72 (1.71-1.74)	0.46 (0.46-0.46)	1.66 (1.66-1.66)	1.22 (1.22-1.22)
Post-ED 90-day mortality rate	12.2% (12.1-12.4)	4.8% (4.8-4.8)	6.9% (6.9-6.9)	6.3% (6.3-6.4)

Note: All parentheticals represent 95%CI

Key Findings

- ↑ ED visits per person-year in cirrhosis vs. CHF, COPD
- **~2x** post-ED 90-day mortality in cirrhosis vs CHF, COPD
- **~2x** post-ED 90-day mortality in cirrhosis patients without (vs with) outpatient follow-up within 30-days post-ED discharge

Elhence, et al. (2024) Clinical Gastroenterology and Hepatology

Journal Pre-proof

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Case #1

- 26 YOM with no significant PMH who presents with 2-3 weeks of feeling 'unwell.'
  - Started to notice dark urine a few days ago
  - Has also noticed some abdominal distention with weight gain
- PMH: No other known health issues
- SH: endorses increased alcohol consumption over the last few years due to work and social related changes
- Pertinent labs:
  - WBC 18,000 (normal hemoglobin and platelets)
  - AST 126, ALT 55, alk phos 156, total bilirubin 25, INR 1.7, albumin 3.1, creatinine 0.6
  - Viral hepatitis testing is pending
- Imaging (US):
  - Hepatomegaly
  - No bile duct dilation, normal gallbladder with no stones

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Next steps? Potential diagnosis?

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Alcohol-related hepatitis

- Syndrome defined:
  - Jaundice within the last 8 weeks
  - Heavy alcohol consumption for at least 6 months, < 60 days of abstinence
  - AST/ALT 1.5, AST > 50, both enzymes < 400
  - Total bilirubin > 3
- Significant clinical associations:
  - AKI/hepatorenal syndrome

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Scoring/Prognostic Assessments in AAH

SCORE	COMPONENTS	WHEN TO USE IN CLINICAL COURSE	INTERPRETATION	LIMITATIONS
MDF	• PT (measured and control) • Bilirubin (total)	Initial presentation	Score > 32: • High short-term mortality • Consider steroids	Static, unable to estimate long-term mortality, and low specificity
MELD	• INR • Bilirubin (total) • Creatinine • Sodium	Initial presentation	MELD or MELD-Na ≥ 21: • High-short-term mortality • Consider steroids	Over-estimation of mortality due to incorporation of renal function, and other external factors that can influence creatinine
LILLE	• Age • Bilirubin (initial and day 4 or 7) • Albumin • Creatinine • PT	Day 4 and/or Day 7 of steroid therapy	Score < 0.45: • Good response, continue steroids for 28 day course Score > 0.45: • Stop steroids	
MELD-LILLE MODEL	Components as above for both scores	Initial presentation	• Provides continuum of mortality risk, potentially more precise • Best combination model at assessing 2 and 6 month mortality risk	

Acute Management: AH

- Consider steroids for severe alcoholic hepatitis given potential short-term mortality benefit
  - MDF > 32 and/or MELD-Na > 20
  - Contraindications
    - Infection
    - GI bleeding
    - AKI
- Alcohol abstinence
- Nutritional support
- Liver transplant
  - Involves very tailored and specific criteria in assessing patient's candidacy
    - Failure to respond to medical therapy
    - 1st time presentation for any liver related complication
    - Stable psychosocial evaluation with good overall social support
    - Willingness to participate in AUD-related treatment

Ongoing alcohol consumption worsens 6 month mortality in AH

	Patients		Univariate		Multivariate†	
Predictors	At Risk	Death	HR (95% CI)	*P*	HR (95% CI)	*P*
Alcohol relapse						
No	7,860*	44	1.00 (reference)	—	1.00 (reference)	—
Yes (≥30 g/day)	2,554*	55	3.90 (2.61-5.82)	<0.0001	4.14 (2.76-6.20)	<0.0001
Lille model						
<0.45	183	78	1.00 (reference)	—	—	—
≥0.45	35	21	1.83 (1.12-2.98)	0.015	—	—
Per 0.1 increase	218	99	1.11 (1.02-1.21)	0.017	1.14 (1.05-1.23)	0.002
MELD score						
Per 5-point increase	209	97	0.94 (0.76-1.15)	0.55	—	—

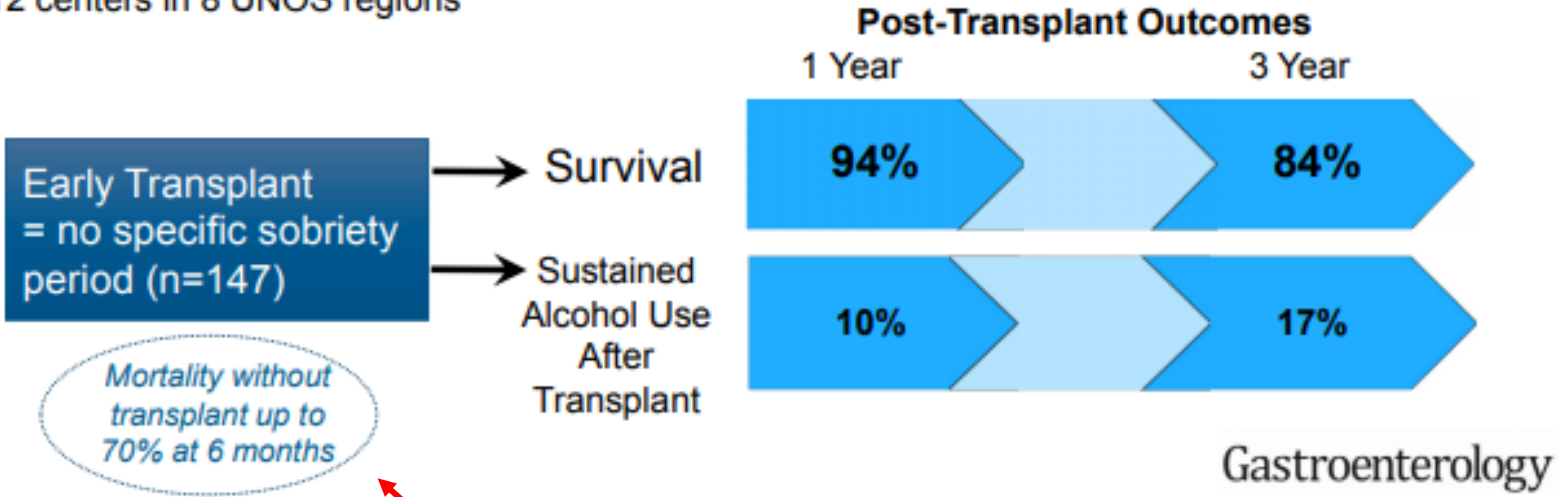
*Expressed as patient-months.
†Multivariable Cox's regression model including alcohol relapse and Lille model (treated as continuous variable).

Louvet et al, *Hepatology*, 2017.

Outcomes of LT in AAH patients

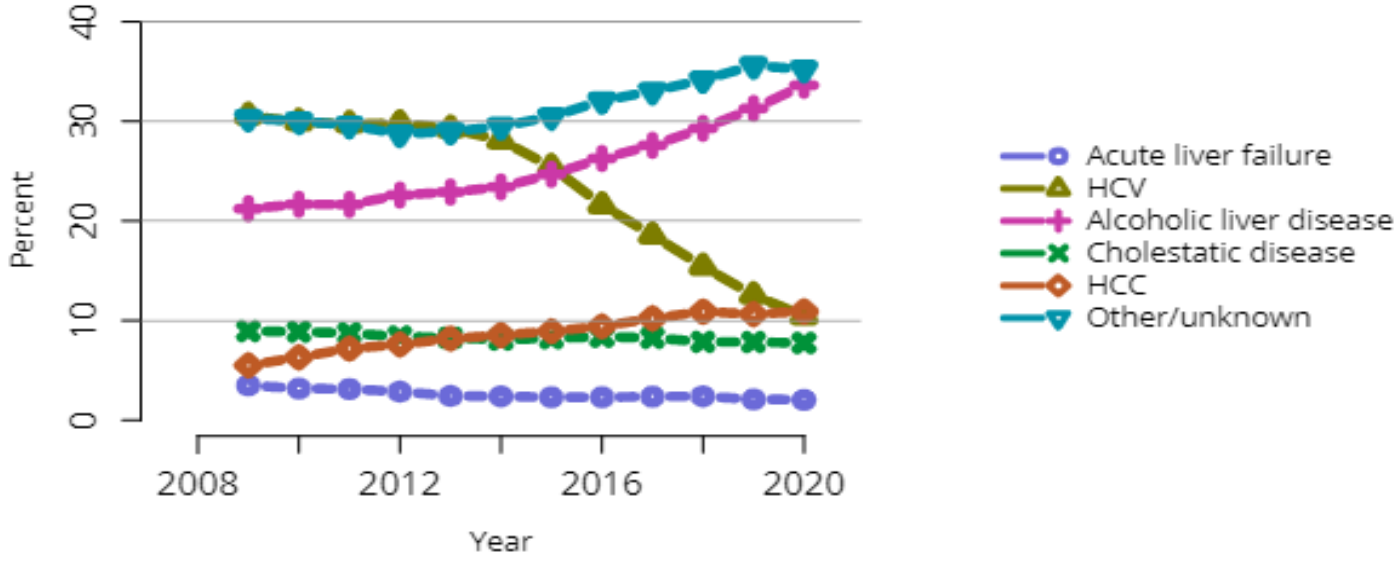
American Consortium of Early Liver Transplantation for Alcoholic Hepatitis: ACCELERATE-AH

12 centers in 8 UNOS regions



Lee et al, *Gastroenterology*, 2018.

Trends in Liver Transplant



Source: OPTN/SRTR, 2020.

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Importance of AUD (alcohol use disorder) treatment

A Kaplan-Meier analysis of association between treatment and decompensation

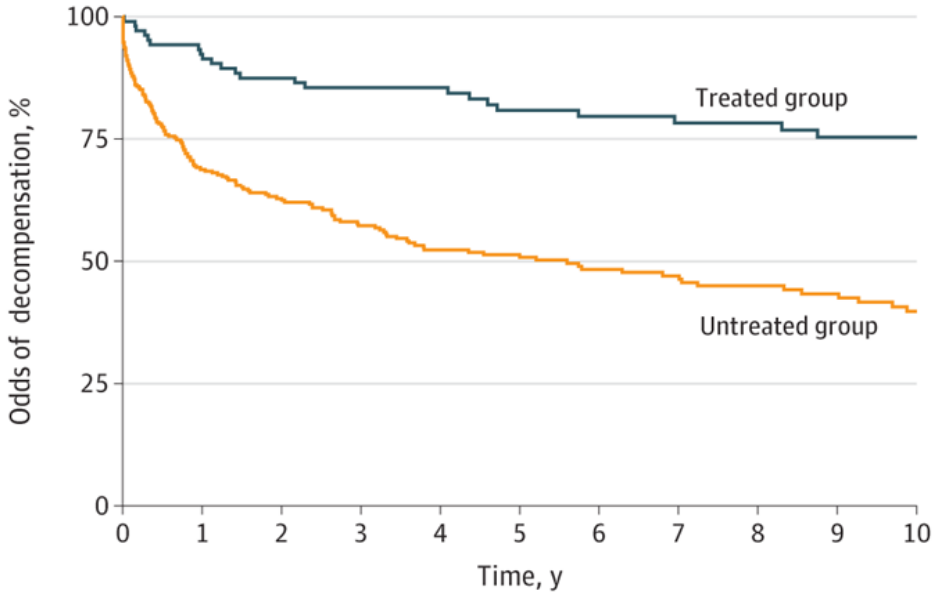

Table 2. Odds Ratios for the Development of Alcohol-Associated Liver Disease After Medical Addiction Therapy

Medical addiction therapy	Adjusted odds ratio (95% CI)	*P* value
Any pharmacotherapy	0.37 (0.31-0.43)	<.001
Gabapentin	0.36 (0.30-0.43)	<.001
Topiramate	0.47 (0.32-0.66)	<.001
Baclofen	0.57 (0.36-0.88)	.01
Naltrexone	0.67 (0.46-0.95)	.03
Disulfiram	0.86 (0.43-1.61)	.66
Acamprosate	2.59 (1.84-3.61)	<.001

- **Key Point**
  - Treatment of AUD reduces incidence and progression of alcohol-related liver disease

Vannier et al, *JAMA* 2022.

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Takeaways

- Severe alcohol-related hepatitis is associated with increased short-term mortality
- Steroids can be considered in some though there is only potential short-term benefit
- Alcohol abstinence is of utmost importance
- Liver transplant is now utilized for a select group of patients with severe alcohol-related hepatitis
- Linking patients to treatment for AUD has a significant impact on developing and reducing progression of liver disease

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Variation on Case #1

- Patient endorses 35 lb weight gain over the last few weeks
- He has significant abdominal distention, LE swelling – mobility is significantly reduced
- Labs: BUN 75, Cr 5.6

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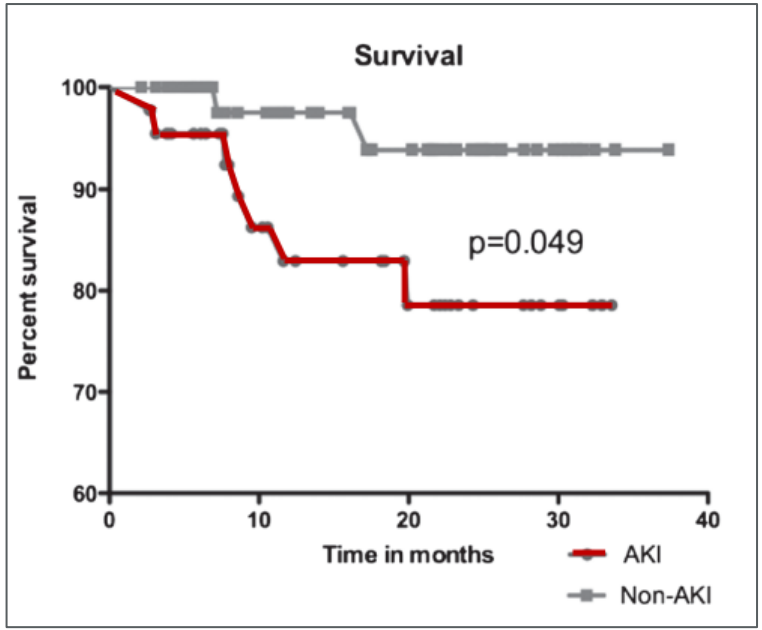
Why is identifying AKI in cirrhosis important?

Prospective cohort study of outpatients with cirrhosis and ascites



Tsien et al. Gut 2013

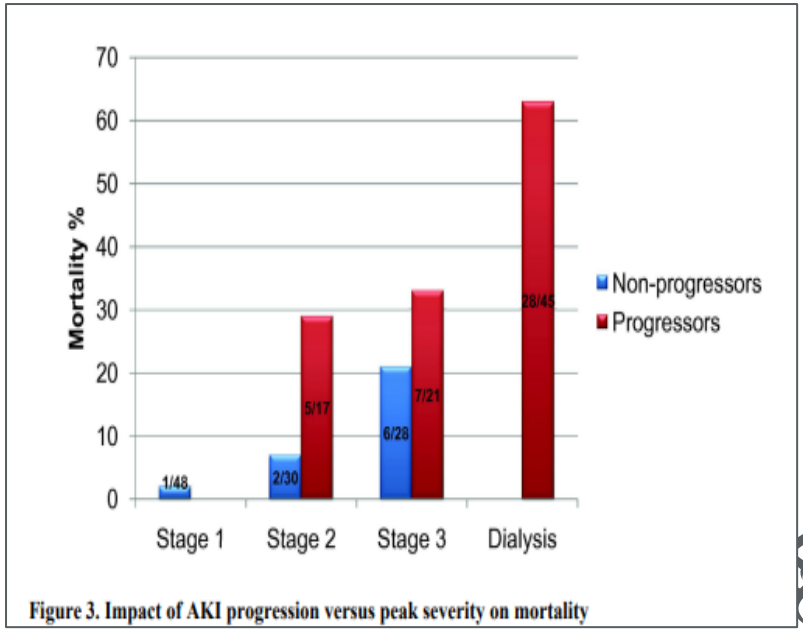


Figure 3. Impact of AKI progression versus peak severity on mortality

Belcher et al. Hepatology 2013

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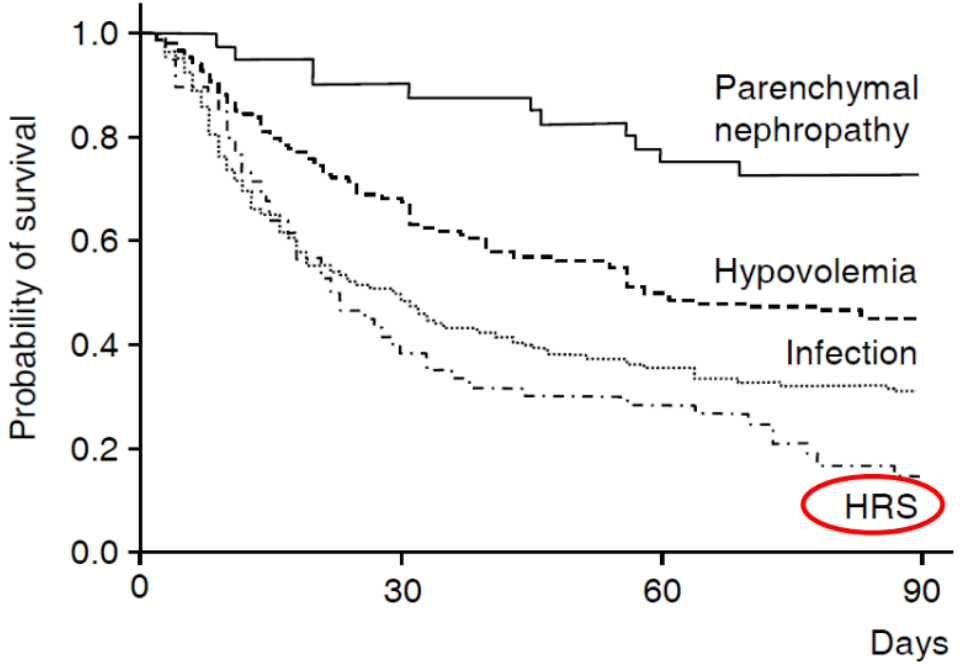
Why is it important to differentiate HRS-AKI from ATN-AKI?



Martin-Llahi et al. Gastroenterology 2011;140:488-496

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NEJM Confirm Study: Terlipressin for treatment of HRS

Primary endpoint: HRS reversal

Table 2. Primary and Four Secondary End Points Included in Multiplicity Adjustment.*

End Point	Terlipressin	Placebo	P Value
	number/total number of patients (percent)		
Primary end point of verified reversal of HRS†			0.006
Clinical success	63/199 (32)	17/101 (17)	
Clinical failure	121/199 (61)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	
Secondary end points included in multiplicity adjustment			
HRS reversal§			<0.001
Clinical success	78/199 (39)	18/101 (18)	
Clinical failure	105/199 (53)	79/101 (78)	
Competing event‡			
Liver transplantation	11/199 (6)	4/101 (4)	
Death	5/199 (3)	0/101	
HRS reversal with no renal-replacement therapy through 30 days			0.001
Clinical success	68/199 (34)	17/101 (17)	
Clinical failure	116/199 (58)	80/101 (79)	
Competing event‡			
Liver transplantation	10/199 (5)	3/101 (3)	
Death	5/199 (3)	0/101	

- Clinical success (HRS reversal)
  - Two consecutive measurements of Cr 1.5 or less
  - Up to day 14
  - No renal replacement therapy for at least additional 10 days
- Clinical Failure
  - Needing RRT
  - Use of vasopressors before day 14
  - If no improvement of creatinine by day 4
  - If creatinine did not improve to 1.5 or less by day 14

Key Points:

- Terlipressin led to significantly increased reversal of HRS
  - Increased rate of HRS reversal by day 14
  - Increased rate of HRS reversal without needing RRT by day 30

Wong et al Confirm Study NEJM 2021

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Adverse Side Effects:
Respiratory failure and death within 90 days more likely in the terlipressin group (11% vs placebo 2%)

TERLIVAZ (terlipressin) Packaging Insert

TERLIVAZ®
(terlipressin)

for injection, for intravenous use

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TERLIVAZ® safely and effectively. See full prescribing information for TERLIVAZ.

TERLIVAZ (terlipressin) for injection, for intravenous use
Initial U.S. Approval: 2022

WARNING: SERIOUS OR FATAL RESPIRATORY FAILURE

TERLIVAZ may cause serious or fatal respiratory failure. Patients with volume overload or with ACLF Grade 3 are at increased risk. Assess oxygenation saturation (e.g., SpO_2) before initiating TERLIVAZ.

Do not initiate TERLIVAZ in patients experiencing hypoxia (e.g., SpO_2 <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue TERLIVAZ if SpO_2 decreases below 90% (2.1, 4, 5.1).

INDICATIONS AND USAGE

TERLIVAZ is a vasopressin receptor agonist indicated to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function. (1)

Limitation of Use
Patients with a serum creatinine >5 mg/dL are unlikely to experience benefit. (1)

DOSAGE FORMS AND STRENGTHS

For injection: TERLIVAZ 0.85 mg (1 vial) as a lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

TERLIVAZ is contraindicated:
In patients experiencing hypoxia or worsening respiratory symptoms. (4)
In patients with ongoing coronary, peripheral, or mesenteric ischemia. (4)

WARNINGS AND PRECAUTIONS

- Serious or Fatal Respiratory Failure: Monitor patients for changes in respiratory status using pulse oximetry and regular clinical assessments. Actively manage intravascular volume overload and adjust TERLIVAZ therapy as appropriate. (5.1)
- Ineligibility for Liver Transplant: TERLIVAZ-related adverse reactions may make a patient ineligible for liver transplantation, if listed. (5.2)
- Ischemic Events: TERLIVAZ is a vasoconstrictor and can cause ischemic events (cardiac, peripheral, or mesenteric) that may require dose interruption or discontinuation. (5.3)
- Embryo-Fetal Toxicity: TERLIVAZ may cause fetal harm when used during pregnancy. Advise females of reproductive potential of the potential hazard to the fetus. (5.4, 8.1)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) include abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea. (6.1)

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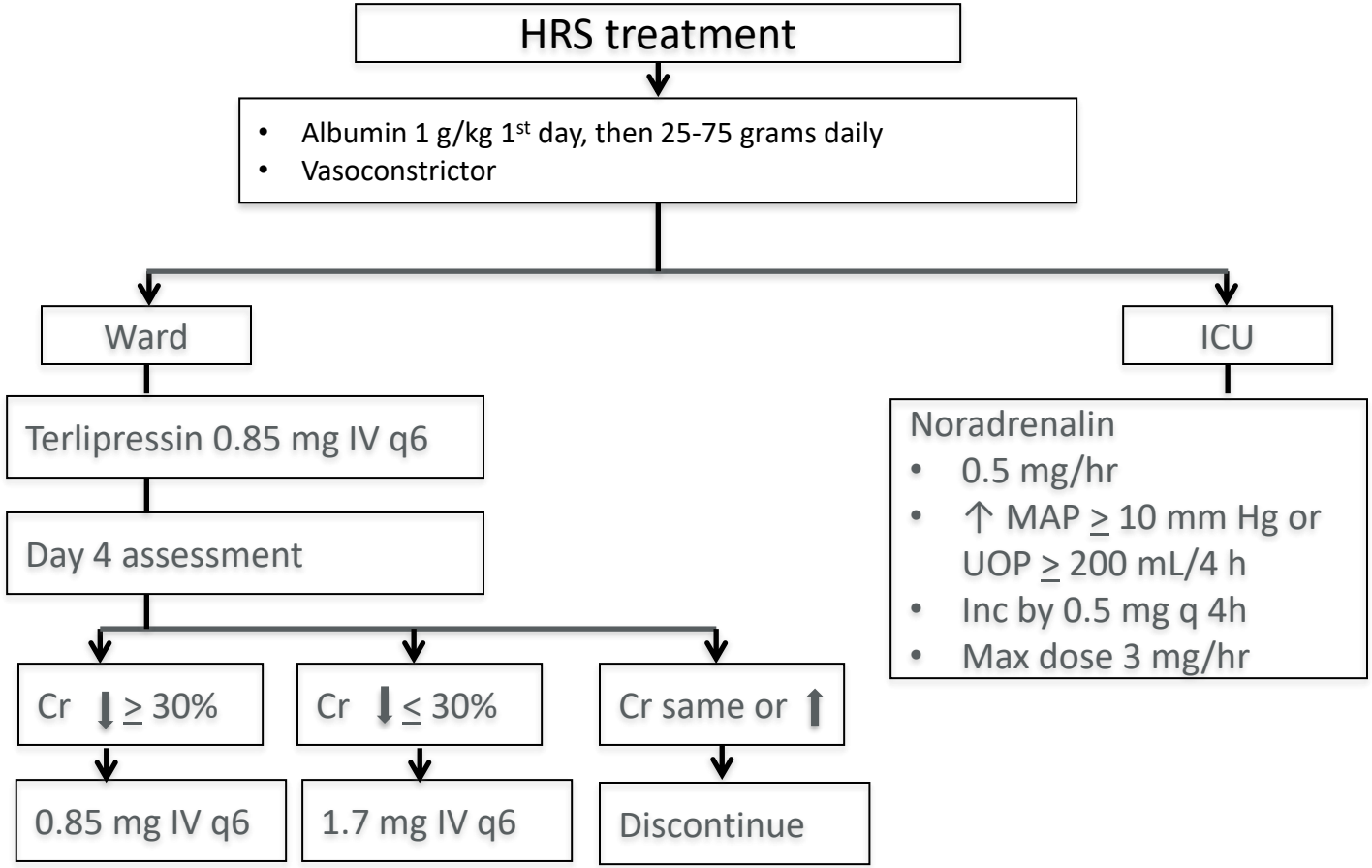

- Monitor for ischemic/respiratory complications
- Maximum treatment = 14 days
- Discontinue vasoconstrictor if creatinine < 1.5 mg/dL, or at/above baseline

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Takeaways

- AKI and specifically HRS is associated with worse outcome, survival
- Terlipressin with albumin has been shown to have better outcomes with regards to HRS reversal
- Important side effects include respiratory failure, ischemia
- Questions remain about its effectiveness as a bridge to more durable treatments (ie transplant)

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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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Frailty is associated with death and healthcare utilization after liver transplantation (LT)

FrAILT
Functional Assessment in Liver Transplantation

Study population

1,166 LT recipients
8 U.S. centers

Ambulatory frailty assessments:

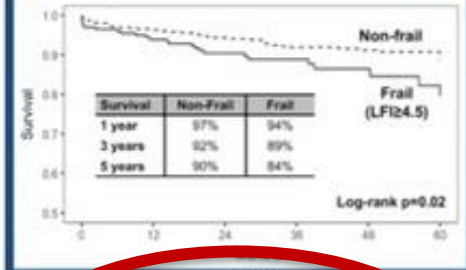
Liver Frailty Index®

Grip strength

Chair stands

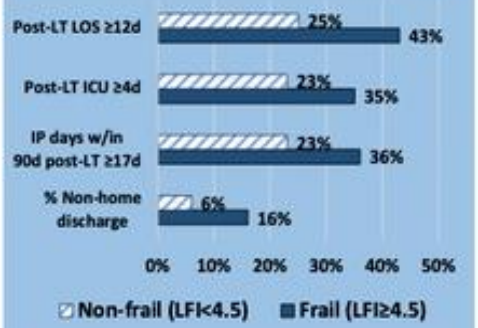
Balance

Post-LT mortality



Pre-LT frailty was associated with >2x risk of post-LT death
HR 2.13, 95% CI 1.39-3.26

Post-LT Healthcare utilization



Pre-LT frailty was associated with higher post-LT healthcare utilization.

Lai JC, et al. *Hepatology.*

HEPATOLOGY
JOURNAL OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

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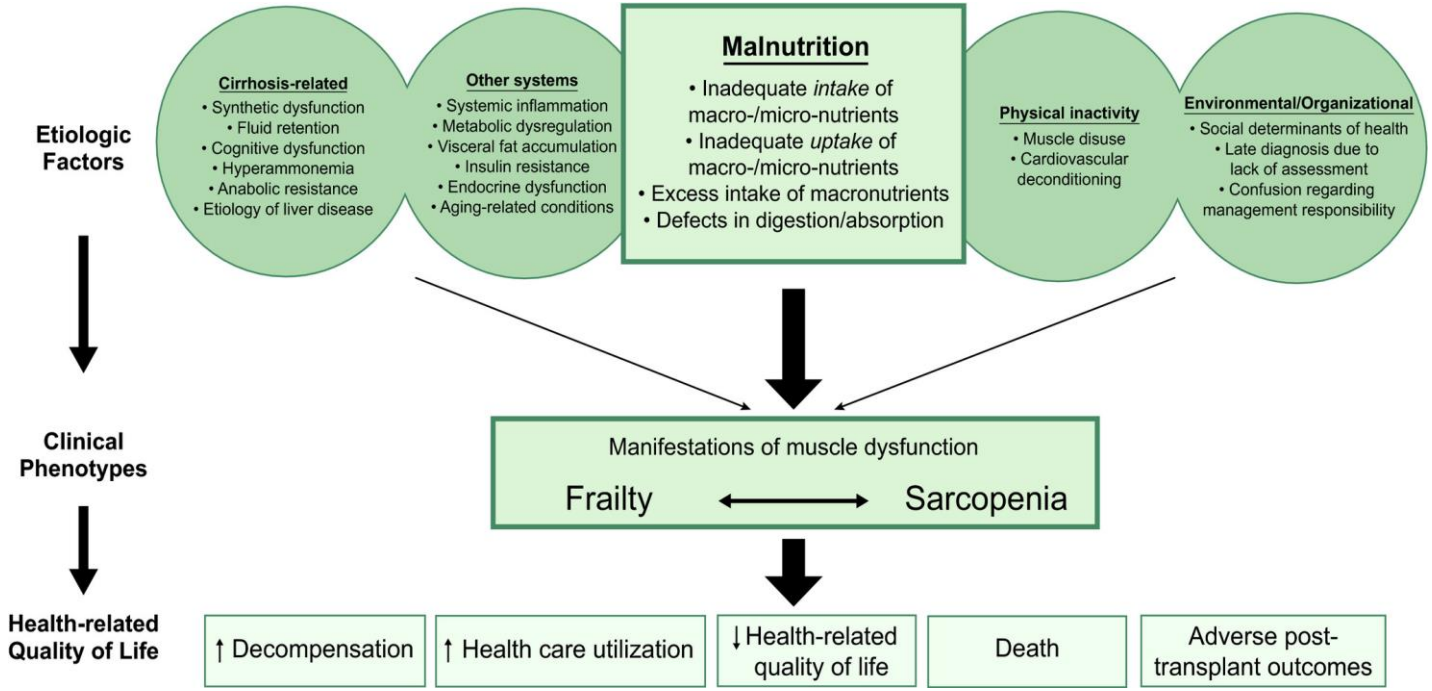
Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases



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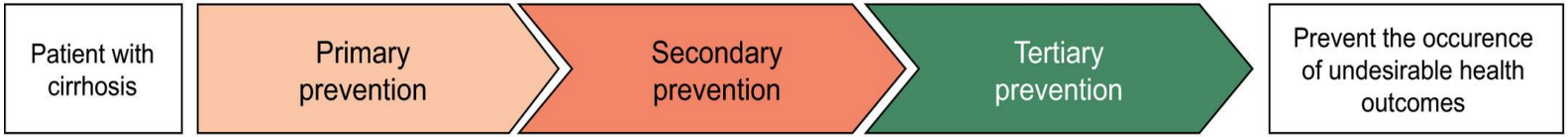
Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases



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.
  - Associated with worse outcomes, 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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Summary

- Alcohol-related hepatitis is now an indication for liver transplant evaluation, though with narrow/specific criteria
  - Linking patients to AUD treatment early is key
- Terlipressin can be considered for HRS-1, but does have serious respiratory/ischemia-related side effects and questions about medium/long-term effectiveness
- Frailty is major risk factor for poor outcome with regards to liver transplant
  - Early intervention with PT, OT, nutrition is key

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Thank You