Sarcopenia/Frailty in Cirrhosis and its Impact on Transplant

Puneet Puri, MD
Virginia Commonwealth University
Central Virginia Veterans Affairs Systems
Richmond, VA

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Malnutrition, Frailty, and Sarcopenia - Definitions for the Theoretical Constructs 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	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	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

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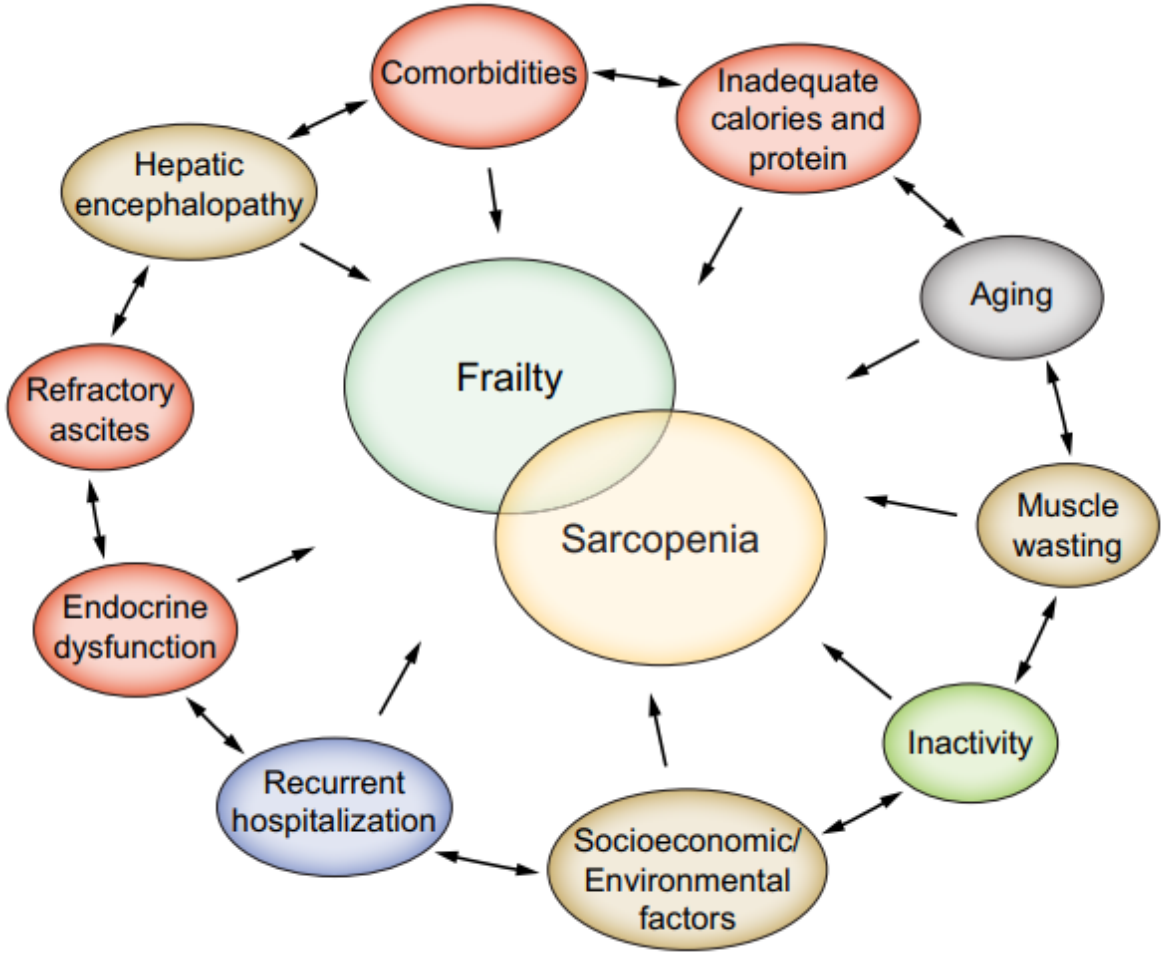
The conceptual overlap between frailty, sarcopenia, and their contributing factors



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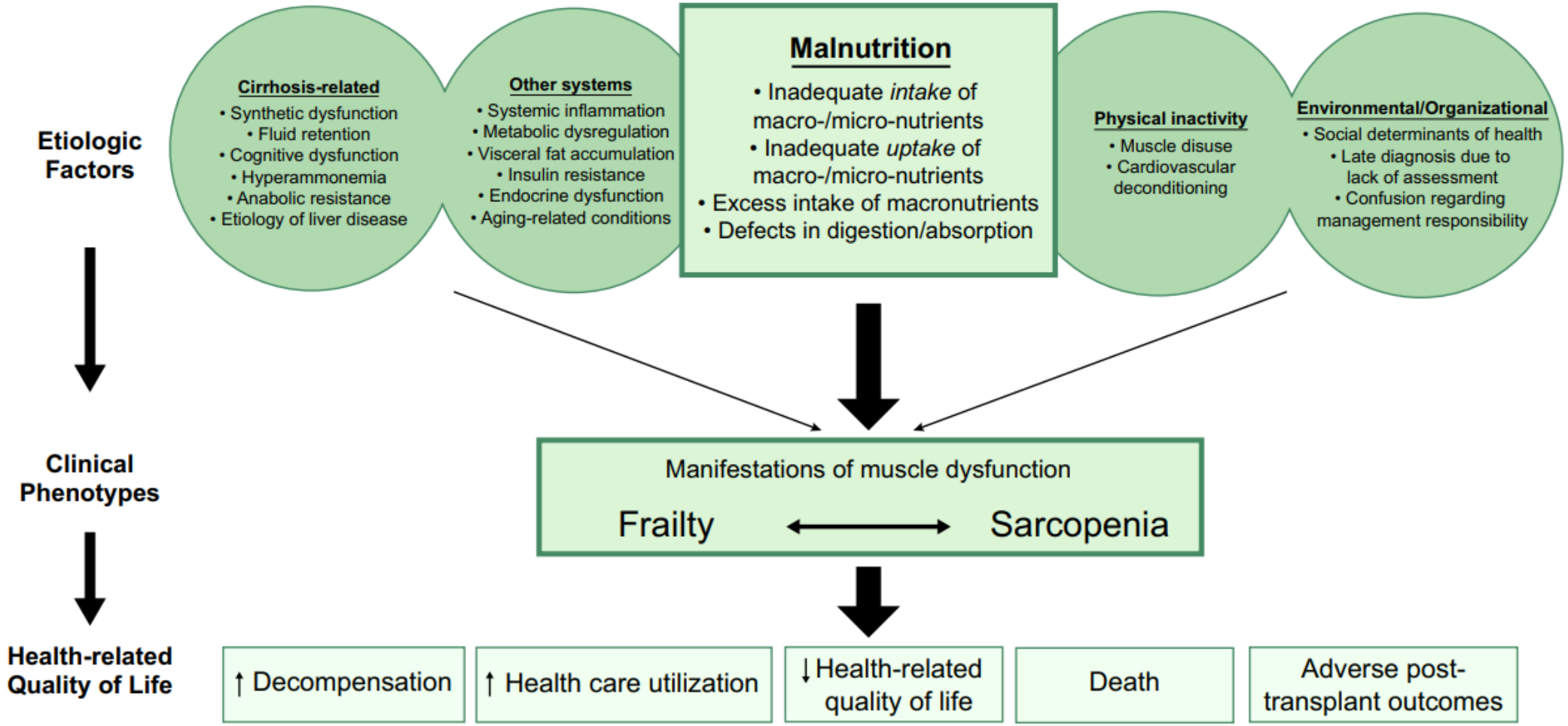
Factors contributing to malnutrition, frailty, and sarcopenia and the relationship between these three constructs



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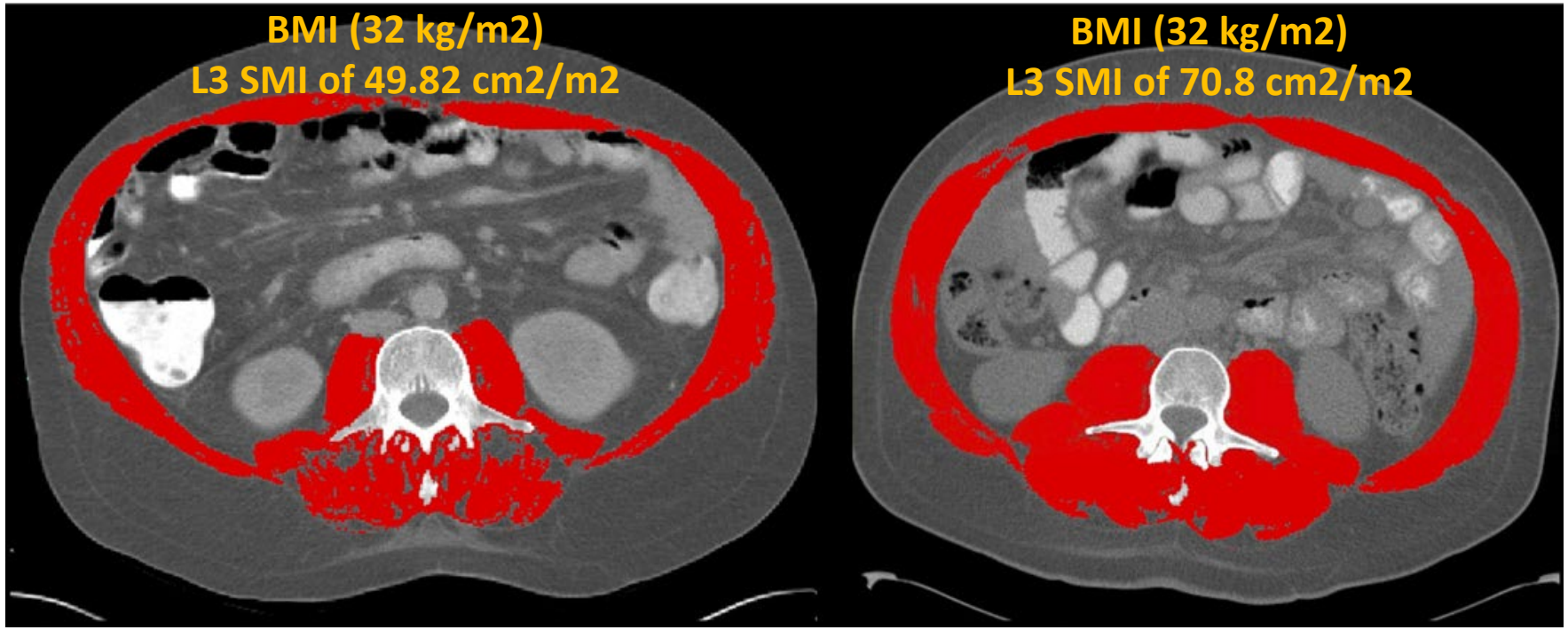
Sarcopenia in Cirrhosis

- Sarcopenia is the most common complication associated with cirrhosis
- Loss of muscle mass and strength
- Adversely affects
  - Survival
  - Quality of life
  - Development of other complications of cirrhosis
  - Outcome after liver transplantation

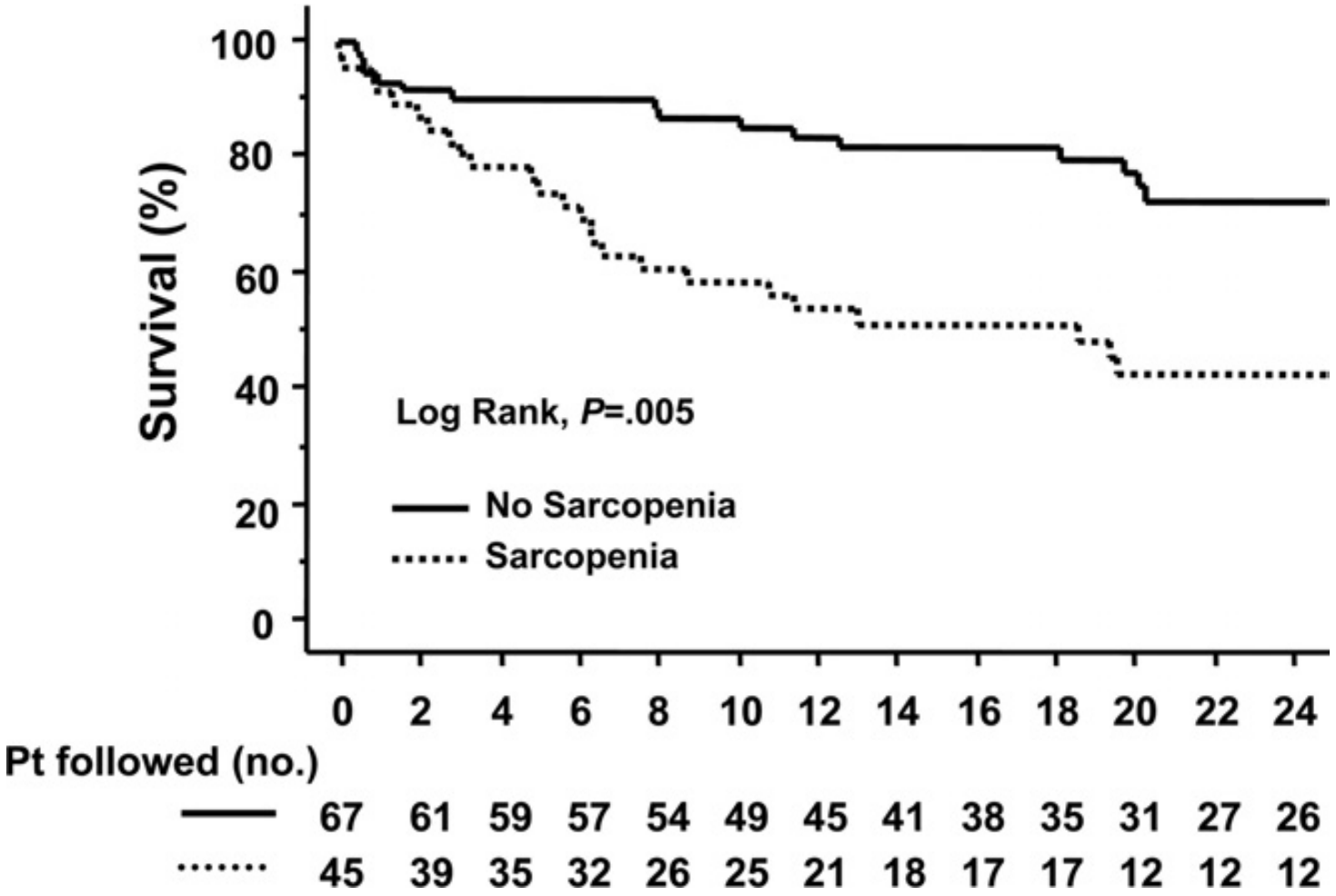
Muscle Wasting (Sarcopenia) is Associated with Increased Mortality in Cirrhosis



Red color indicates skeletal muscles:
Rectus abdominis, oblique and lateral abdominal muscles, psoas, and paraspinal muscles

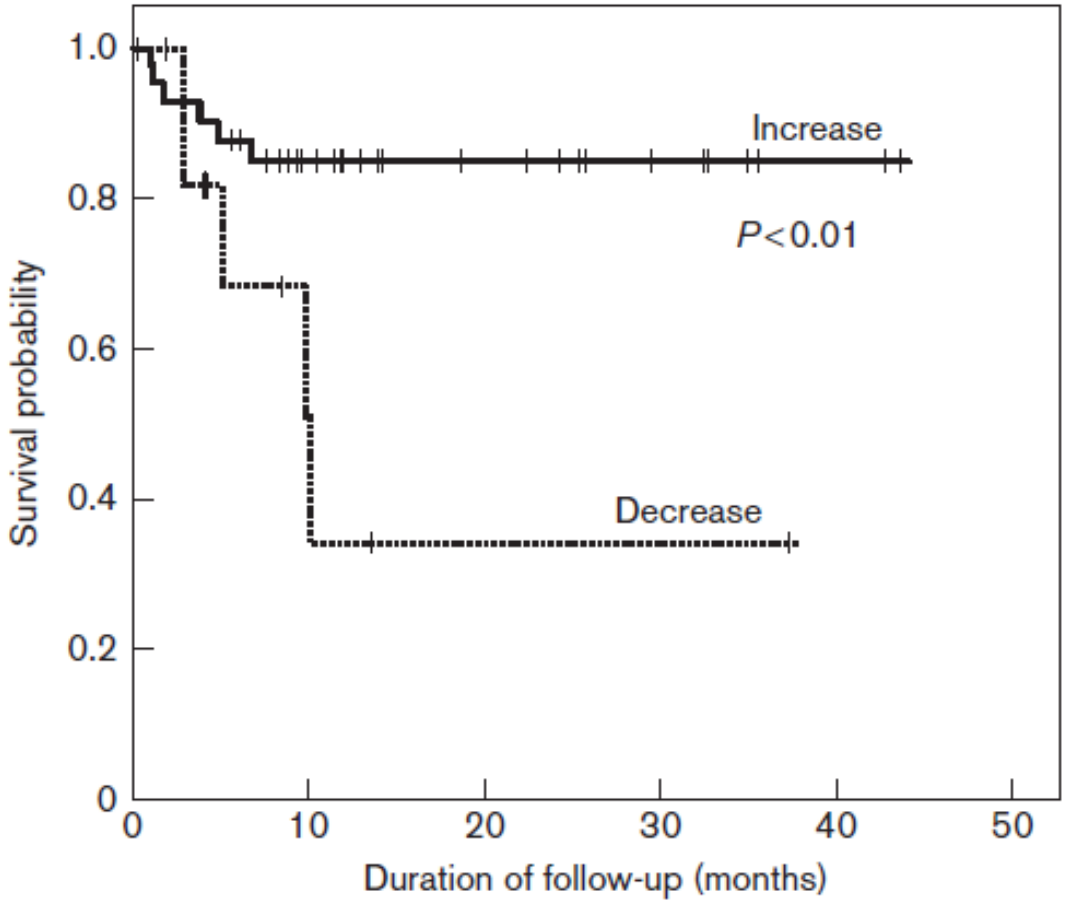
CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2011

Sarcopenia Adversely Affects Probability of Survival in Cirrhosis



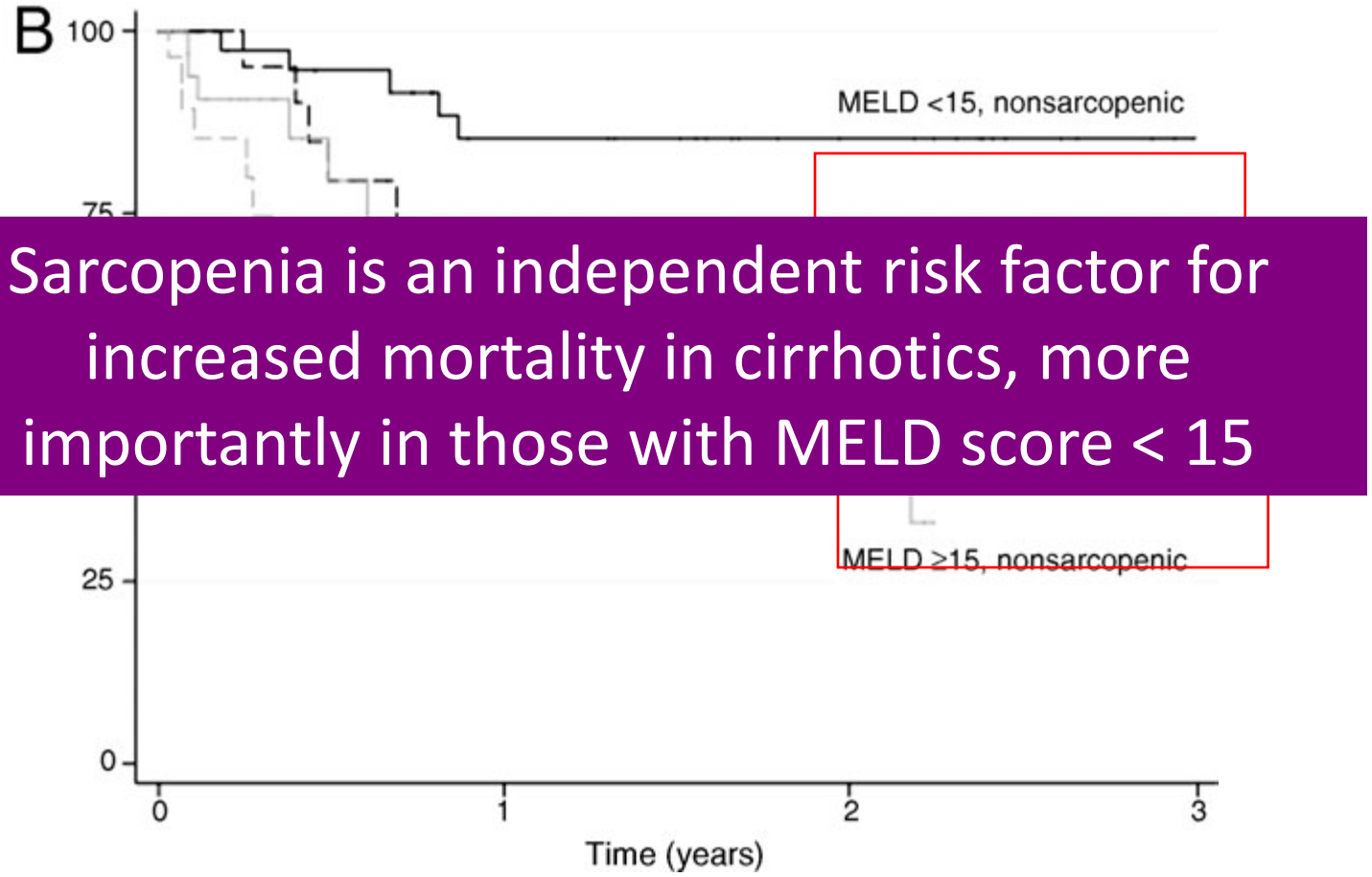
CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2011

Increased Muscle Mass Improves Survival Probability After TIPS



European Journal of Gastroenterology & Hepatology 2012

Sarcopenia Predicts Poor Survival in Cirrhotics with Low MELD Score on OLT Waiting List

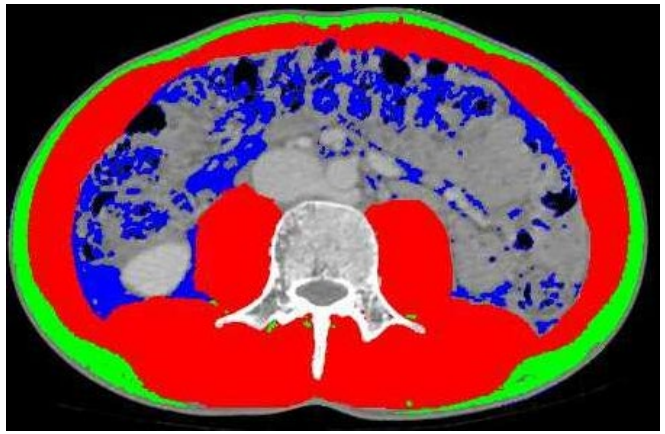


Sarcopenia is an independent risk factor for increased mortality in cirrhotics, more importantly in those with MELD score < 15

LIVER TRANSPLANTATION
18:1209-1216, 2012

Increased Muscle Loss with Worsening Child Class of Alcoholic Cirrhosis

a



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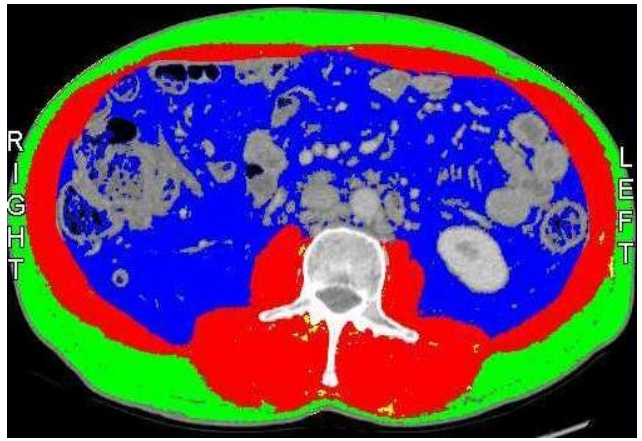

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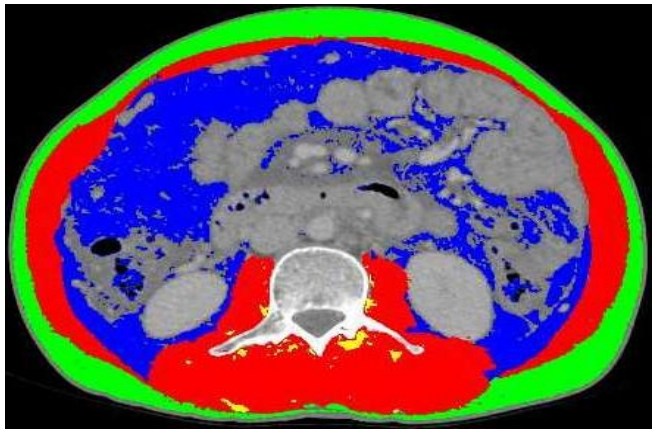

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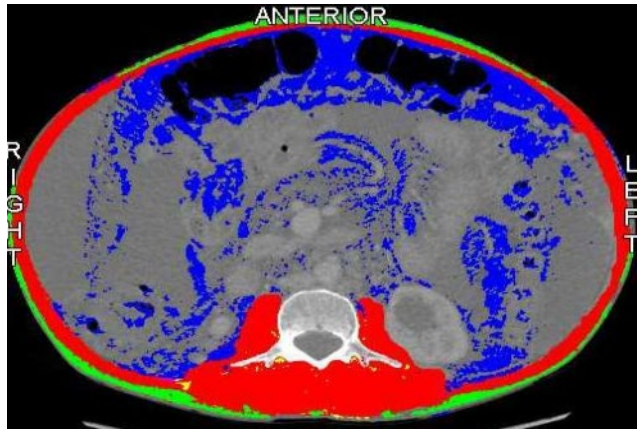


ILBS data – Liver International 2016

Impact of Sarcopenia in Cirrhosis

- Sarcopenia as a robust predictor of a wide spectrum of outcomes in adults with cirrhosis both with and without HCC

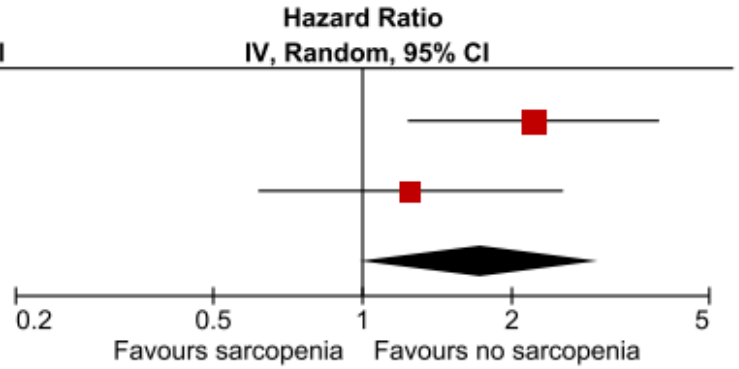
- These *outcomes* include
  - mortality both before and after liver transplantation
  - hepatic decompensation
  - reduced quality of life
  - increased risk of infection
  - prolonged hospitalization

Impact of Sarcopenia in Cirrhosis both Pre- and Post-Transplant Outcomes

A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Meza-Junco 2013	0.78845736	0.30629121	0.0%	2.20 [1.21, 4.01]
Montano-Loza 2012	0.79299252	0.29762791	56.4%	2.21 [1.23, 3.96]
Tandon 2012	0.85866162	0.33257851	0.0%	2.36 [1.23, 4.53]
Yadav 2015	0.22314355	0.36074724	43.6%	1.25 [0.62, 2.54]
Total (95% CI)			**100.0%**	**1.72 [0.99, 3.00]**

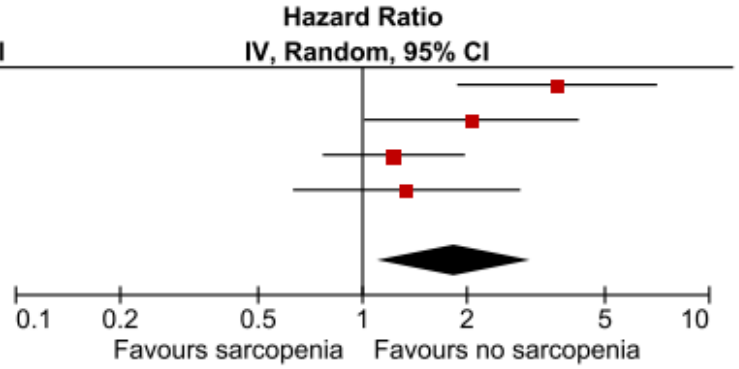
Heterogeneity: Tau² = 0.05; Chi² = 1.48, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 1.93 (P = 0.05)



B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Hamaguchi 2014	1.29198368	0.33878872	24.4%	3.64 [1.87, 7.07]
Masuda 2014	0.72270598	0.36355464	23.0%	2.06 [1.01, 4.20]
Montano-Loza 2014	0.20701417	0.24093408	30.8%	1.23 [0.77, 1.97]
Valero 2015	0.29266961	0.38508342	21.8%	1.34 [0.63, 2.85]
Total (95% CI)			**100.0%**	**1.84 [1.11, 3.05]**

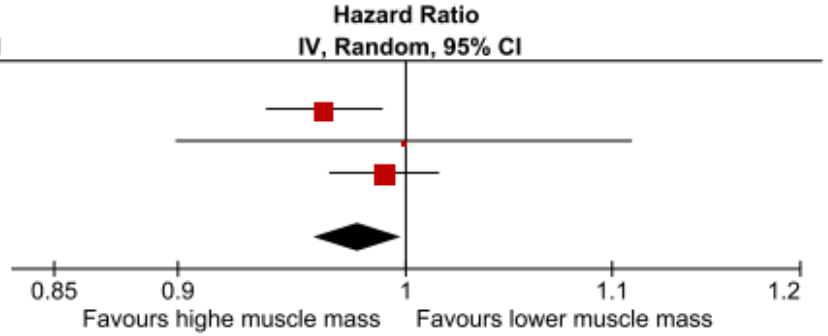
Heterogeneity: Tau² = 0.16; Chi² = 7.49, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 2.36 (P = 0.02)



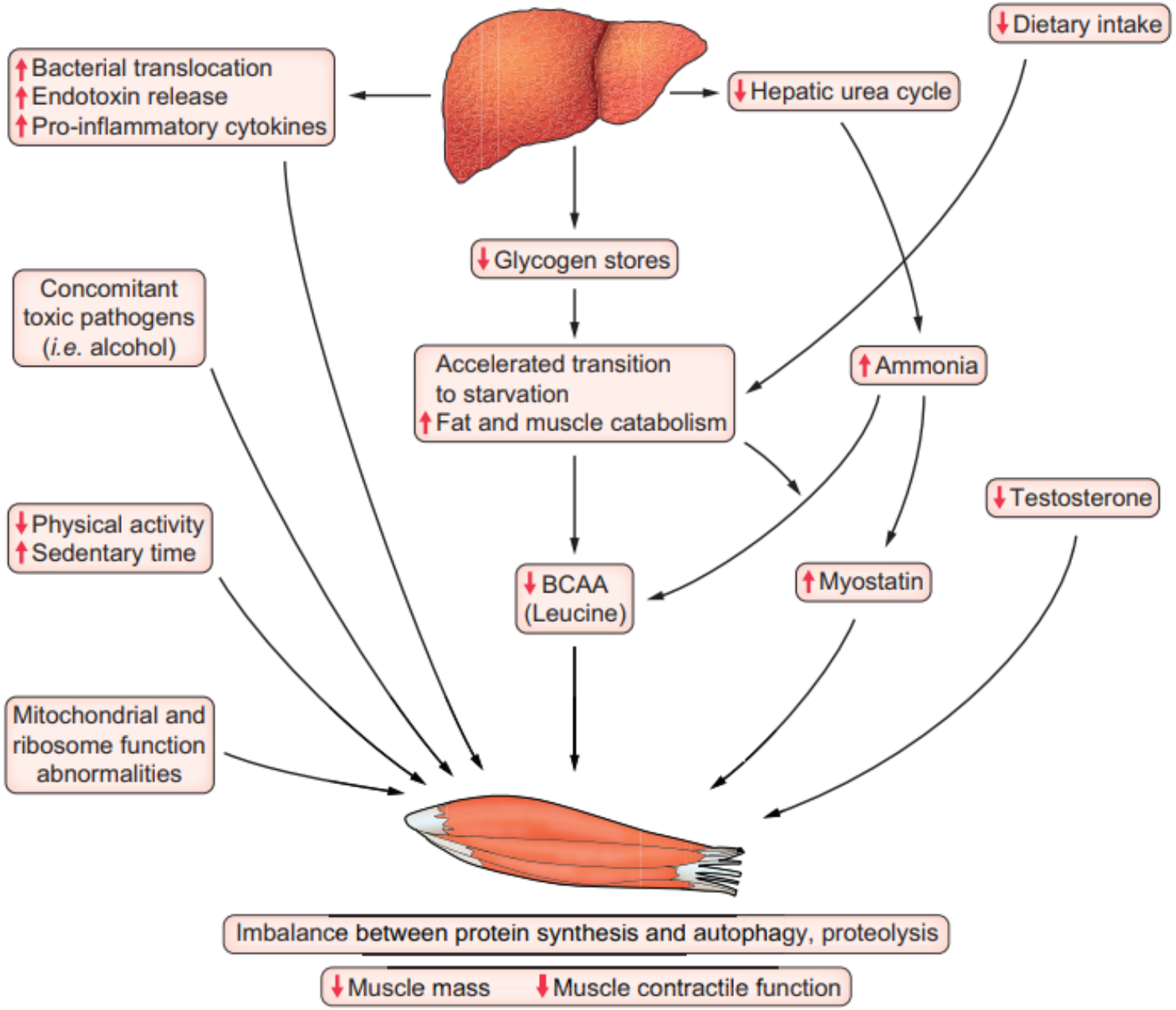
C

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Cruz 2013	-0.03045921	0.01322068	0.0%	0.97 [0.95, 1.00]
DiMartini 2013	-0.03770187	0.01376403	45.9%	0.96 [0.94, 0.99]
Giusto 2015	-0.0010005	0.05381212	3.7%	1.00 [0.90, 1.11]
Montano-Loza 2014	-0.01005034	0.01295212	50.4%	0.99 [0.97, 1.02]
Total (95% CI)			**100.0%**	**0.98 [0.96, 1.00]**

Heterogeneity: Tau² = 0.00; Chi² = 2.30, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 2.14 (P = 0.03)



van Vugt et al American Journal of Transplantation 2016



Some Key Proposed Mechanisms of Sarcopenia in Cirrhosis

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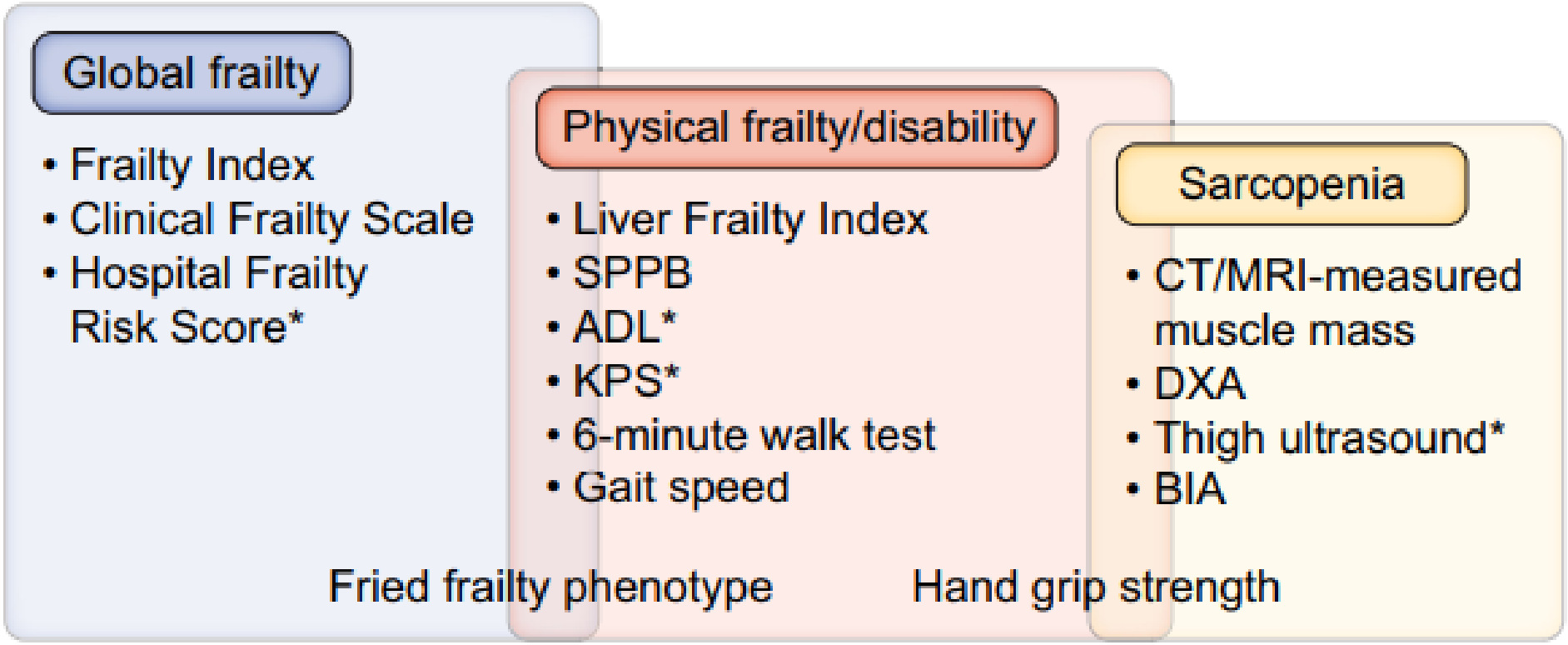
Tools to quantify multi-dimensional (global) frailty, physical frailty, and sarcopenia in patients with cirrhosis



* Instrument has been studied in the inpatient setting

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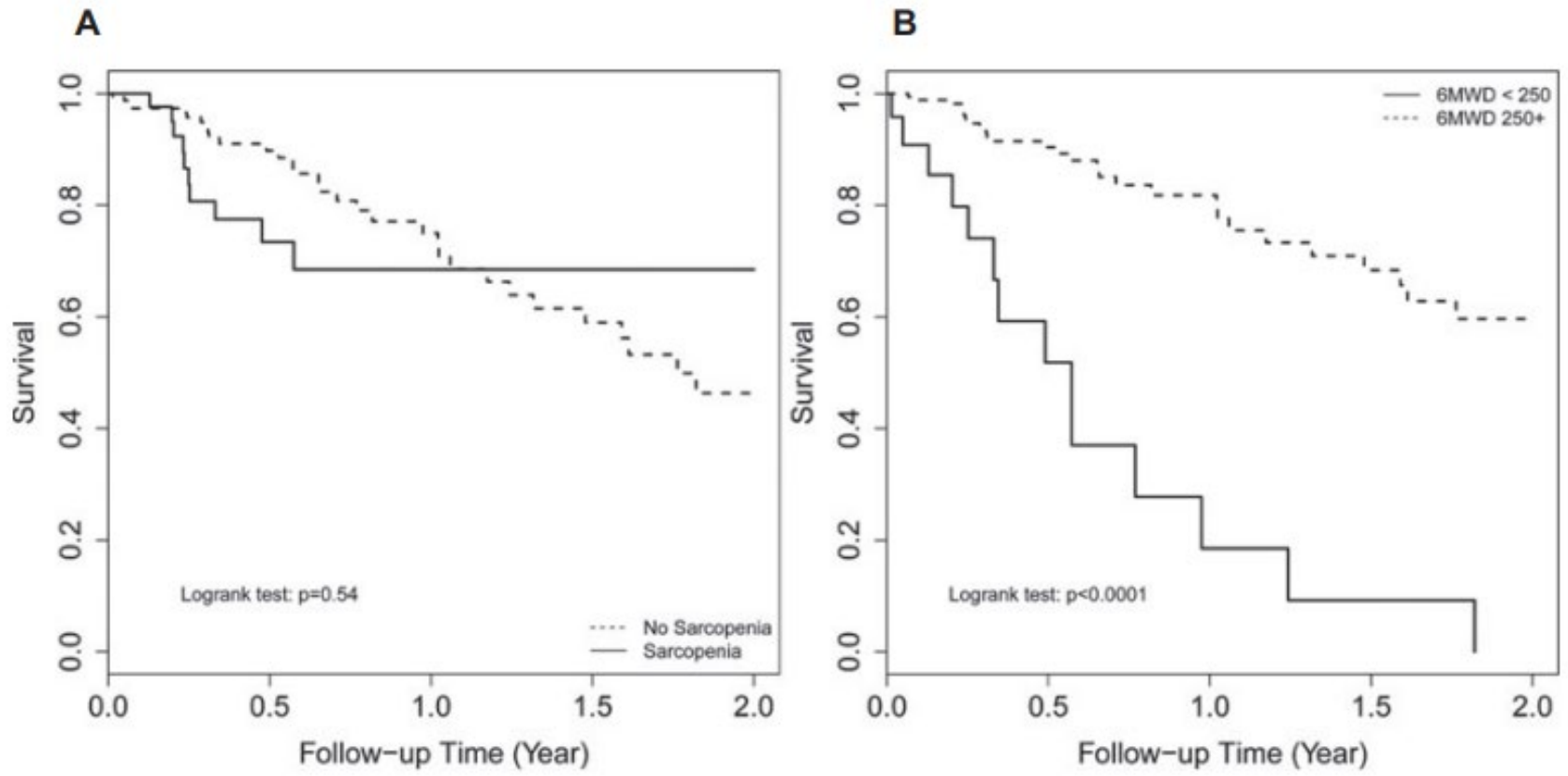
Studies Evaluating the Association Between Sarcopenia and Frailty in Patients with Cirrhosis

Study	Patient population	Sarcopenia assessment	Frailty assessment	Sarcopenia and frailty association	Main finding
Yadav *et al.*[97]	213 patients listed for liver transplant	CT	6MWD	A poor correlation between sarcopenia (SMI) and 6MWD existed (r = 0.19, p = 0.007) A poor correlation between sarcopenia (SMI) and 6MWD existed (r = 0.19, p = 0.007) Poor correlation between SMI and 6MWD (r = 0.19, p = 0.007)	6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. 6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. 6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. 6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia.
Wang *et al.*[98]	292 liver transplant candidates	CT	6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. SPPB	6MWD appears to be a more useful prognostic indicator than the presence of sarcopenia. No correlation between SPPB and SMI in men (ρ = 0.09; p = 0.24) or women (ρ = 0.07; p = 0.50)	6MWD was the main predictor of waitlist mortality SPPB was associated with waitlist mortality.
Sinclair *et al.*[99]	145 men referred for liver transplant	CT DEXA	Handgrip strength	The correlation between CT muscle mass and handgrip strength was present but weak (tau, 0.24; p <0.001). Handgrip strength was modestly correlated with DEXA-measured APLM (tau, 0.34; p <0.001) and DEXA-measured LM of arms (tau, 0.39; p <0.001). Correlation between CT muscle mass and handgrip strength was weak (tau, 0.24; p <0.001). Correlation between DEXA total LM and handgrip strength was modest (tau, 0.38; p <0.001) and DEXA-measured APLM (tau, 0.34; p <0.001).	Handgrip strength combined with MELD score was superior for the prediction of waitlist mortality
Dang *et al.*[123]	180 patients with cirrhosis evaluated for liver transplant	CT	6MWT	Weak correlation between SMI and 6MWT (r=0.022; p = 0.003).	Sarcopenia and low 6MWT (<489 m) were independently associated with mortality. Patients who had both sarcopenia and low 6MWT had the worst prognosis

6MWT, 6-minute walk test; DEXA, dual-energy X-ray absorptiometry; DEXA total LM, DEXA total lean mass; DEXA-measured APLM, DEXA-measured appendicular lean mass; SMI, skeletal muscle index; SPPB, short physical performance battery.

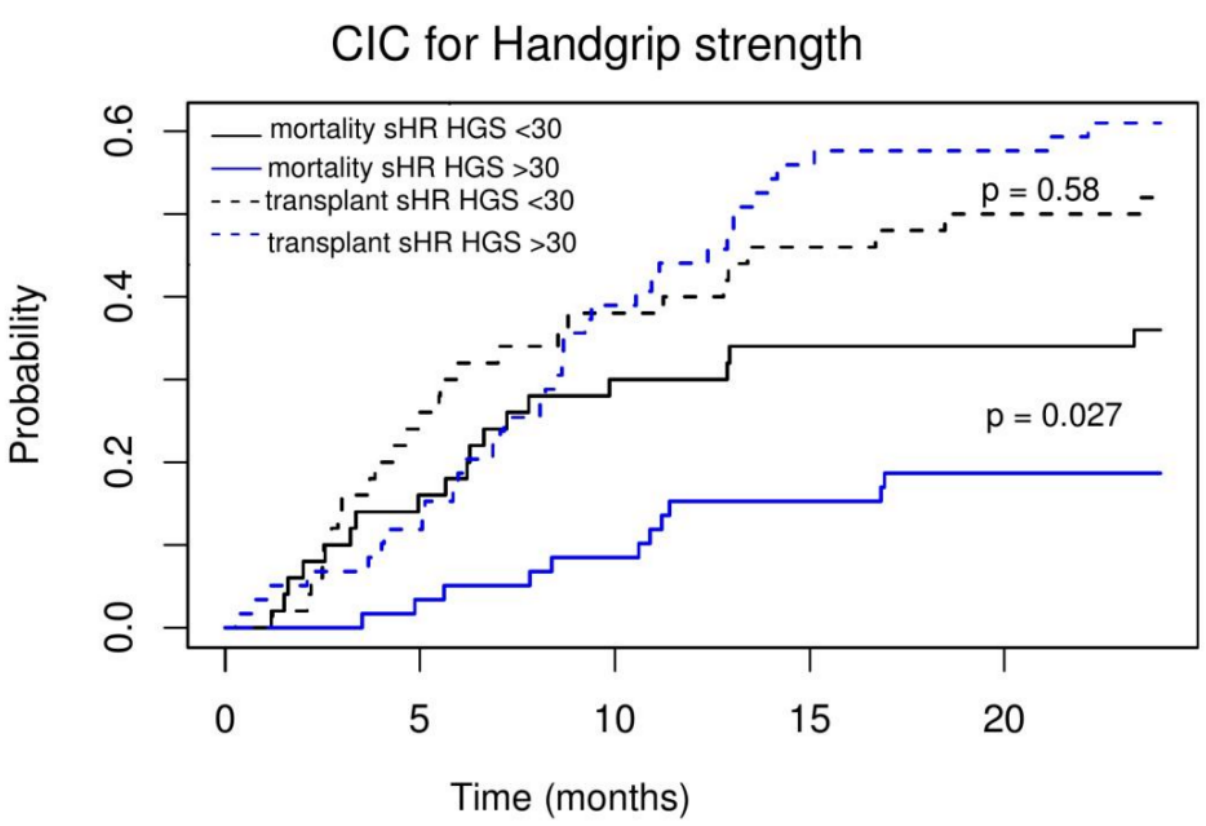
The 6MWD, but ***not*** Sarcopenia, Independently Predicted Waitlist Mortality

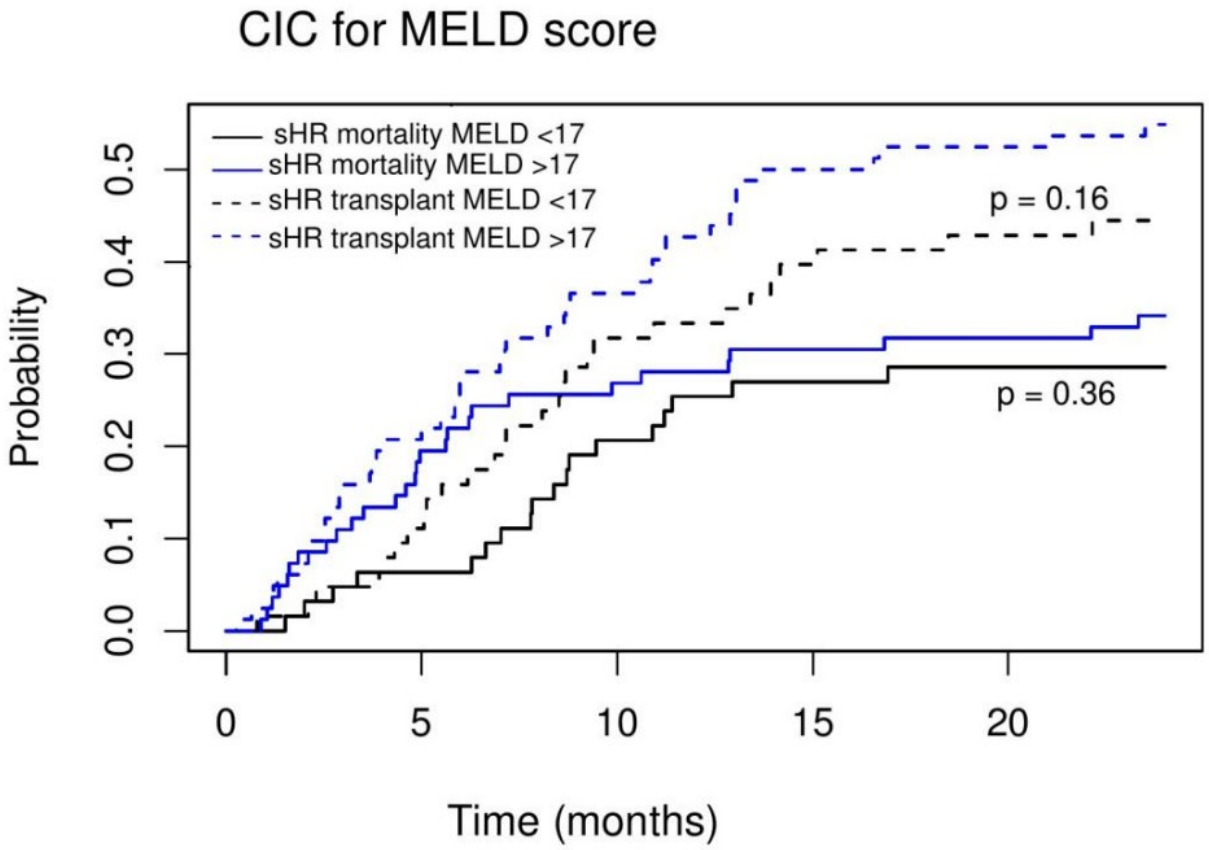


6MWD (≤250 vs. >250 m)
Adjusted HR 2.1 (0.9-4.7)

Yadav A, et al. Clin Transpl 2015;29:134–141

Handgrip Strength Adds More Prognostic Value to the Model for End-Stage Liver Disease Score Than Imaging-Based Measures of Muscle Mass in Men With Cirrhosis





Sinclair M, et al. Liver Transpl 2019;25:1480–1487

Liver Frailty Index (LFI)

1. Grip strength:

   The average of 3 trials, measured in the subject's dominant hand using a hand dynamometer

2. Timed chair stands:

   Measured as the number of seconds it takes to perform 5 chair stands with the subject's arms folded across the chest

3. Balance testing:

   Measured as the number of seconds that the subject can balance in 3 positions (feet placed side to side, semi-tandem, and tandem) for a maximum of 10 seconds each

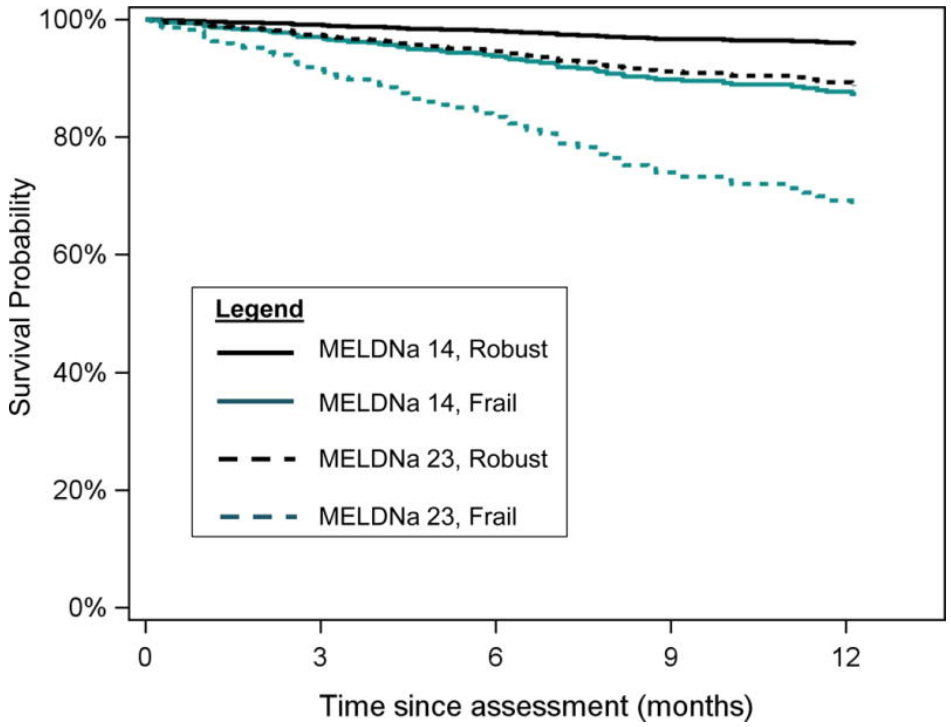
Fried LP, . J Gerontol A Biol Sci Med Sci 2001;56:146–156 *Guralnik JM J Gerontol 1994;49:85–94*

Liver Frailty Index (LFI)

- 0.330 x gender-adjusted grip strength
+ (-2.529 x number of chair stands per second)
+ (-0.040 x balance time) + 6

The Liver Frailty Index has established cut-points to define

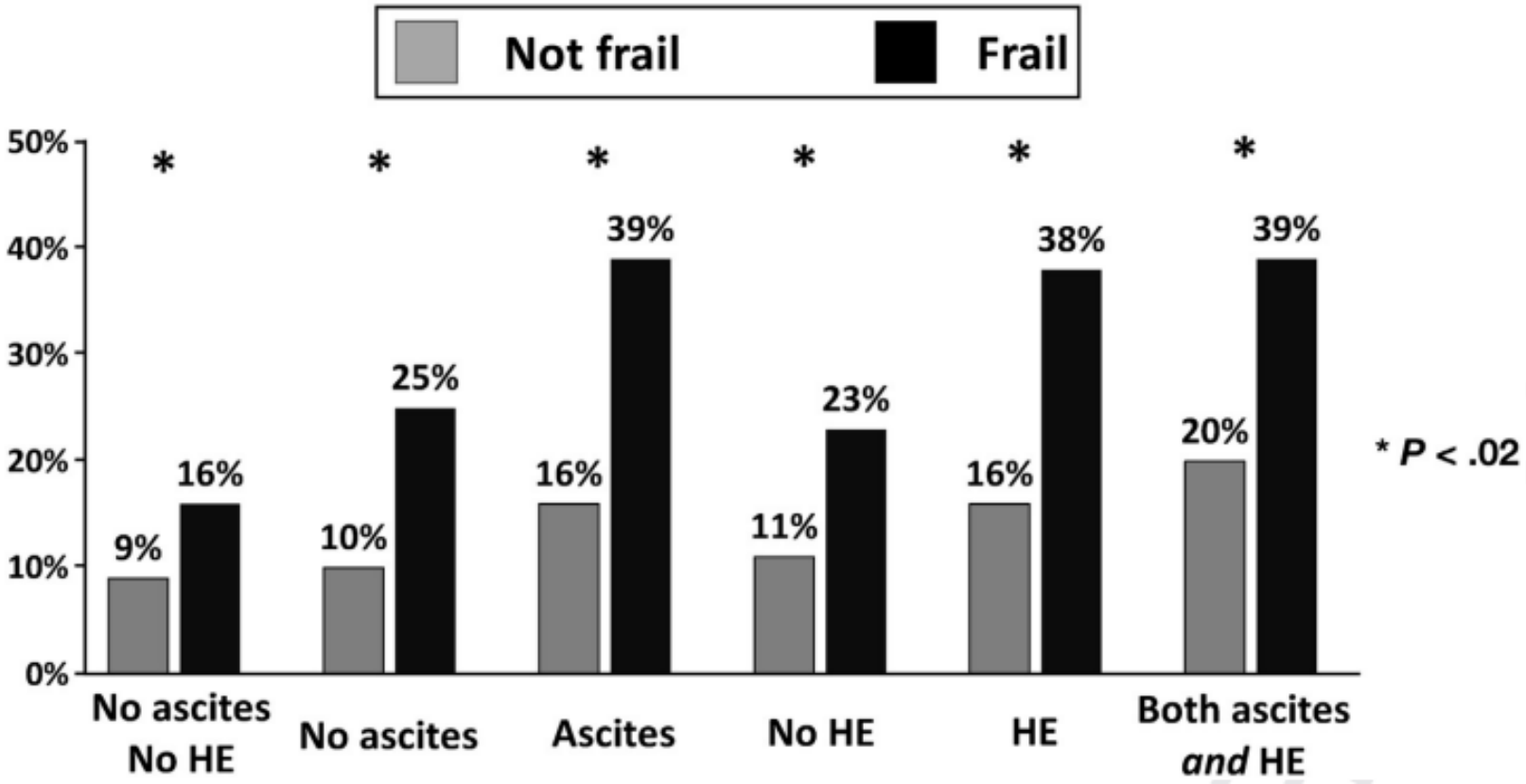
Robust (Liver Frailty Index < 3.2)
Prefrail (Liver Frailty Index 3.2-4.3)
Frail (Liver Frailty Index ≥ 4.4).(90,91)



https://liverfrailtyindex.ucsf.edu/

Lai, JC, et al Hepatology 2017 Aug;66(2):564-574
Kardashian A, Hepatology 2020;73:1132-1139

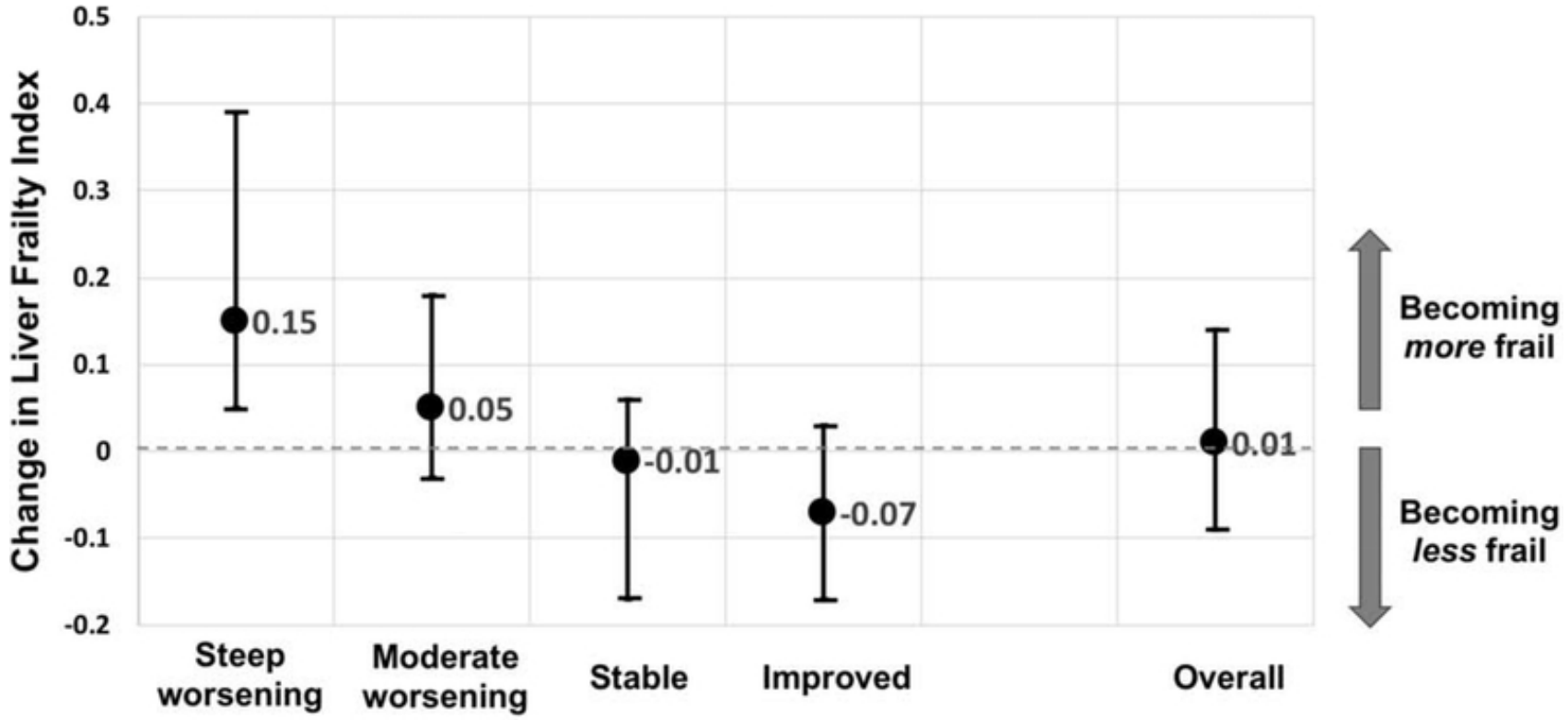
Frailty Significantly Increases 12-months Waitlist Mortality in Patients Listed for Liver Transplant



https://liverfrailtyindex.ucsf.edu/

Lai C et al Gastroenterology 2019

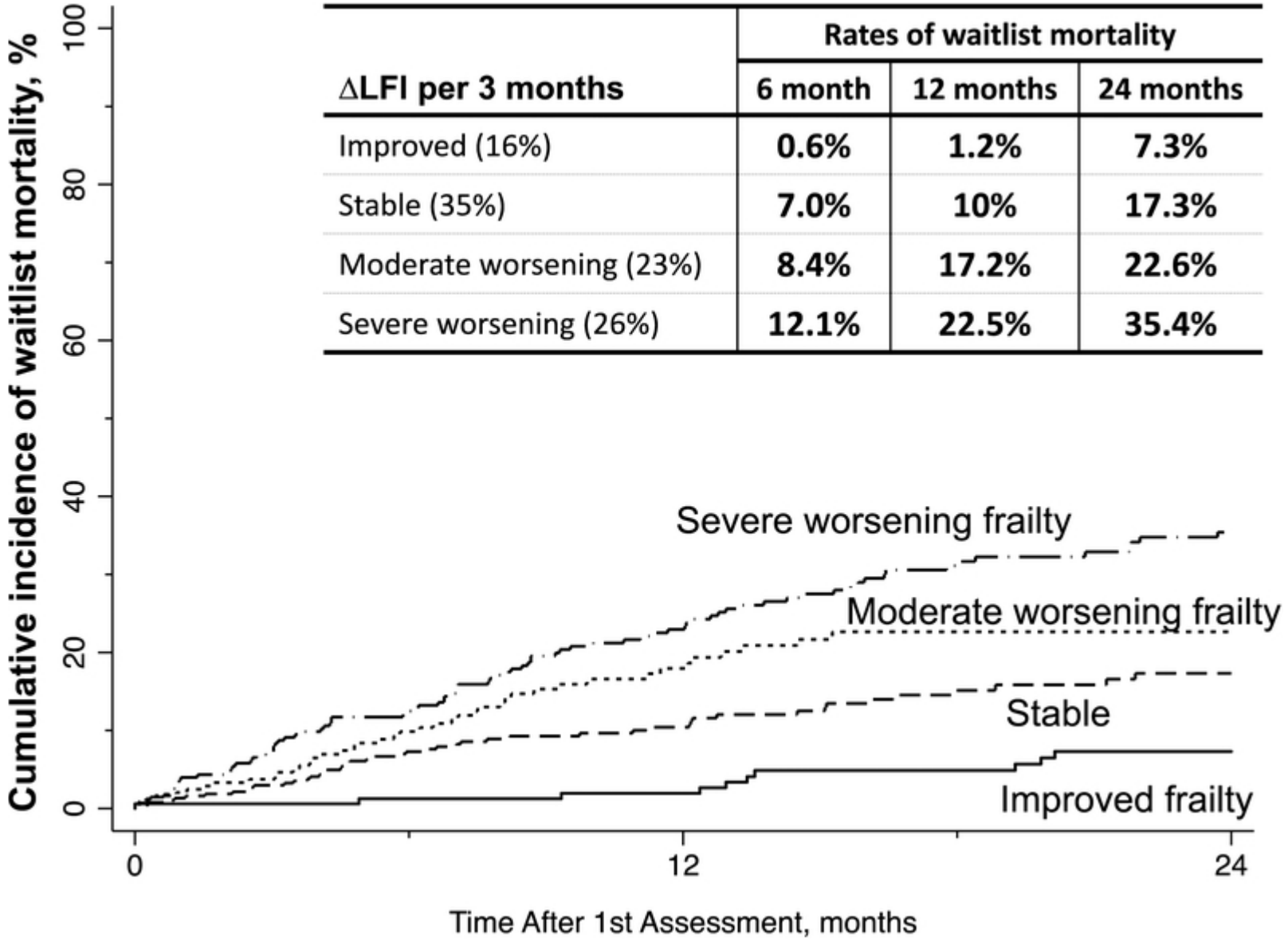
Change in the Liver Frailty Index scores per 3 months by ΔLFI trajectory group



Lai JC, et al J Hepatol. 2020 Sep; 73(3): 575–581.

Observed cumulative incidence of waitlist mortality by categories of ΔLFI per 3 months

ΔLFI per 3 months	Rates of waitlist mortality		
	6 month	12 months	24 months
Improved (16%)	**0.6%**	**1.2%**	**7.3%**
Stable (35%)	**7.0%**	**10%**	**17.3%**
Moderate worsening (23%)	**8.4%**	**17.2%**	**22.6%**
Severe worsening (26%)	**12.1%**	**22.5%**	**35.4%**



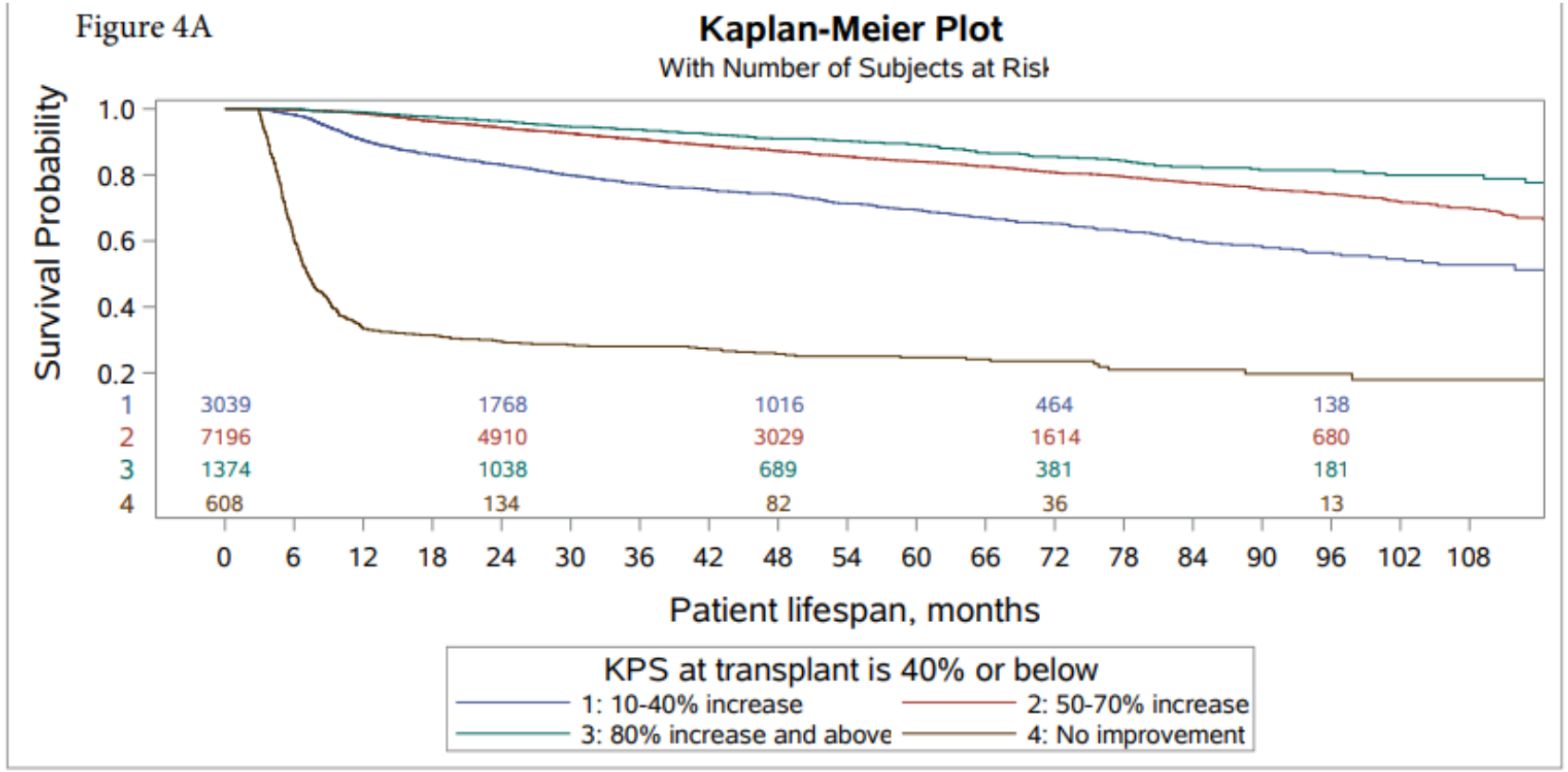
Lai JC, et al J Hepatol. 2020 Sep; 73(3): 575–581.

Changes in Baseline Risks Predict Waitlist Mortality

	Subhazard Ratios (95% CI) p-value		
	Univariable analysis	Stepwise multivariable analyses	
ΔLFI, per 0.1 unit worsening every 3 months	3.91 (2.80–5.46) <0.001	1.85 (1.22–2.82) 0.004	2.04 (1.35–3.09) 0.001
Baseline LFI, per each 0.1 unit worsening	1.07 (1.06–1.09) <0.001	1.08 (1.06–1.11) <0.001	1.07 (1.05–1.10) <0.001
MELDNa, per each 5 unit increase	1.26 (1.12–1.42) <0.001		1.11 (0.98–1.27) 0.11

Lai JC, et al J Hepatol. 2020 Sep; 73(3): 575–581.

Karnofsky performance status pre and post-liver transplantation predicts graft and patient survival



Thuluvath PJ, et al J Hepatol 2018;69:818-825.

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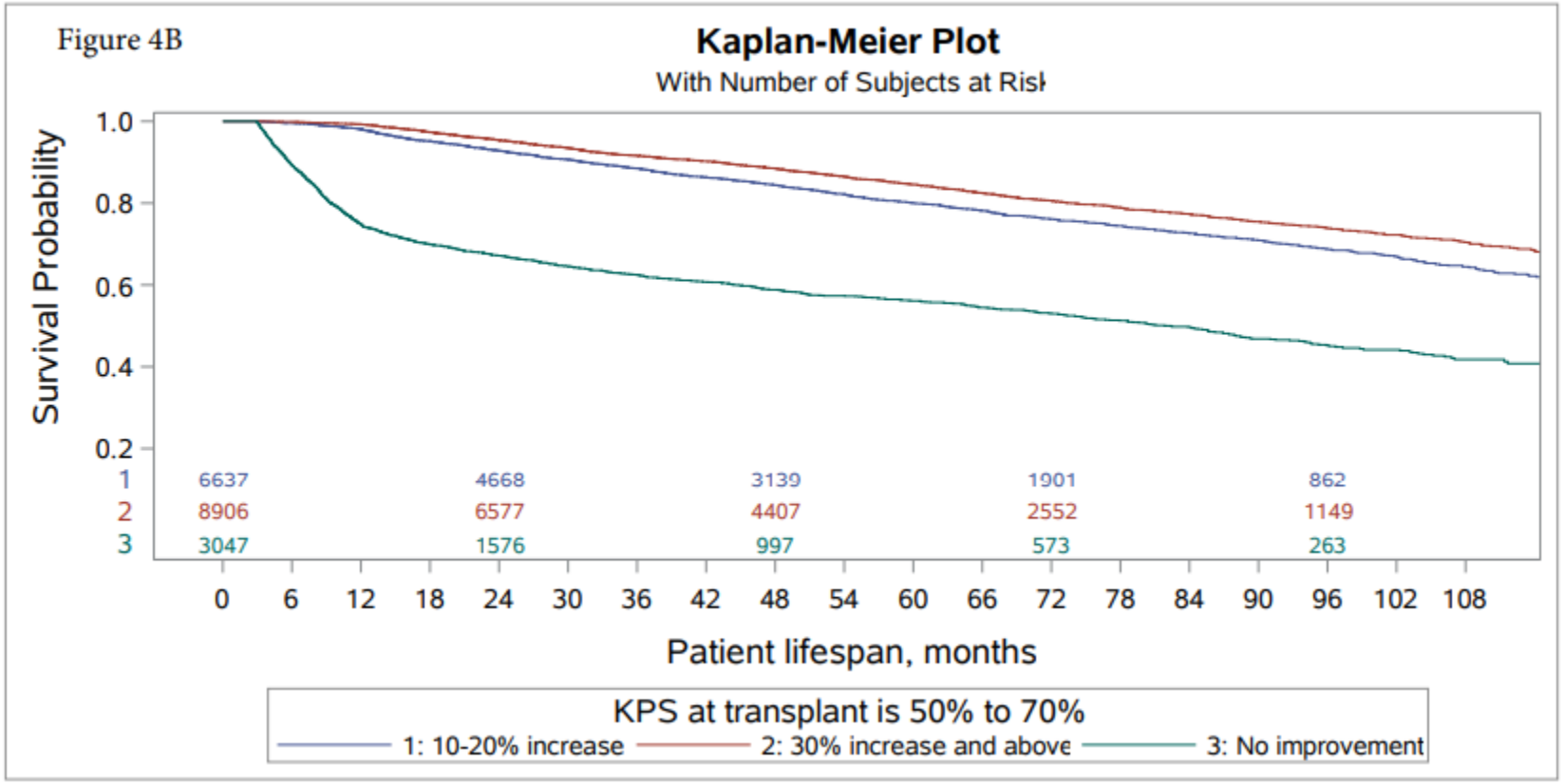

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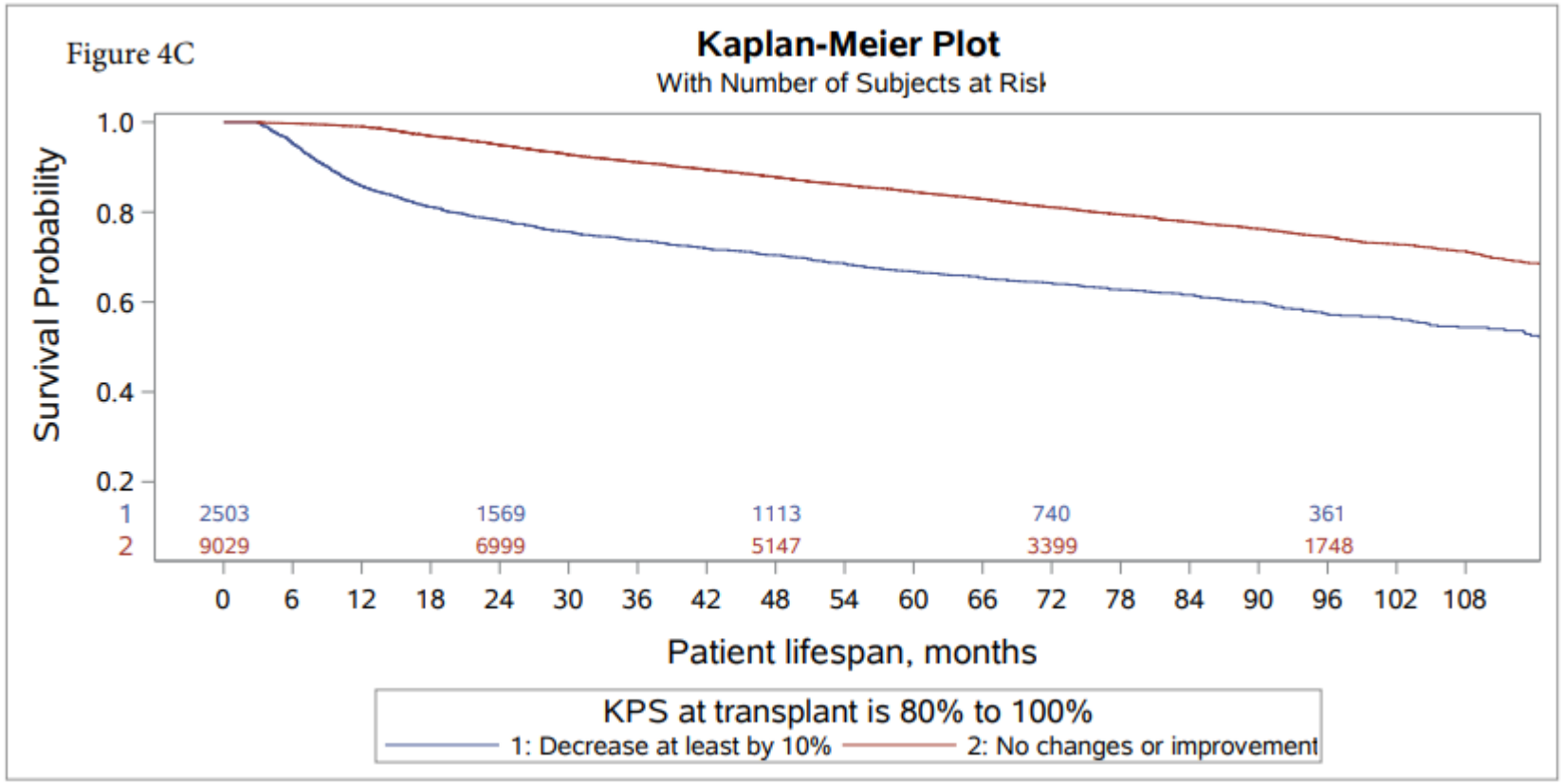

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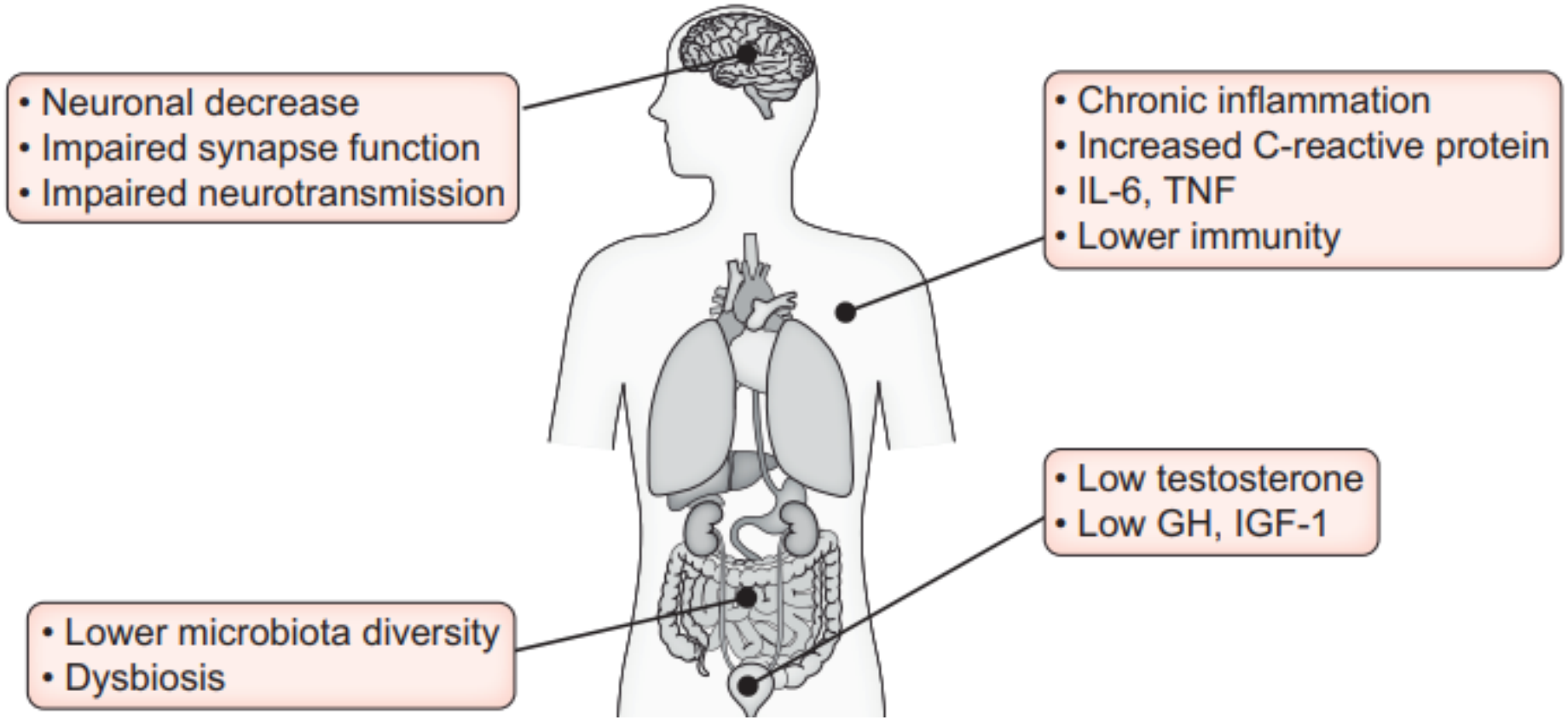
Some Key Proposed Mechanisms of Frailty in Cirrhosis



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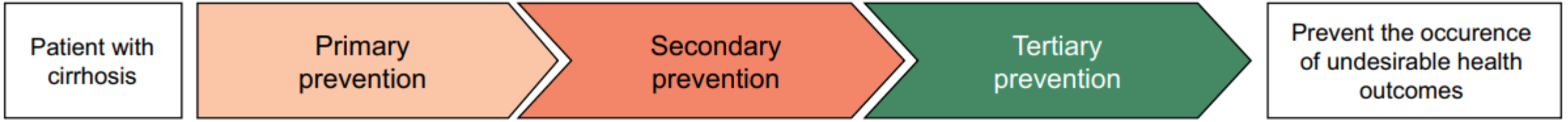
The three levels of disease prevention and health promotion as applied to management of malnutrition, frailty, and sarcopenia in patients with cirrhosis



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		

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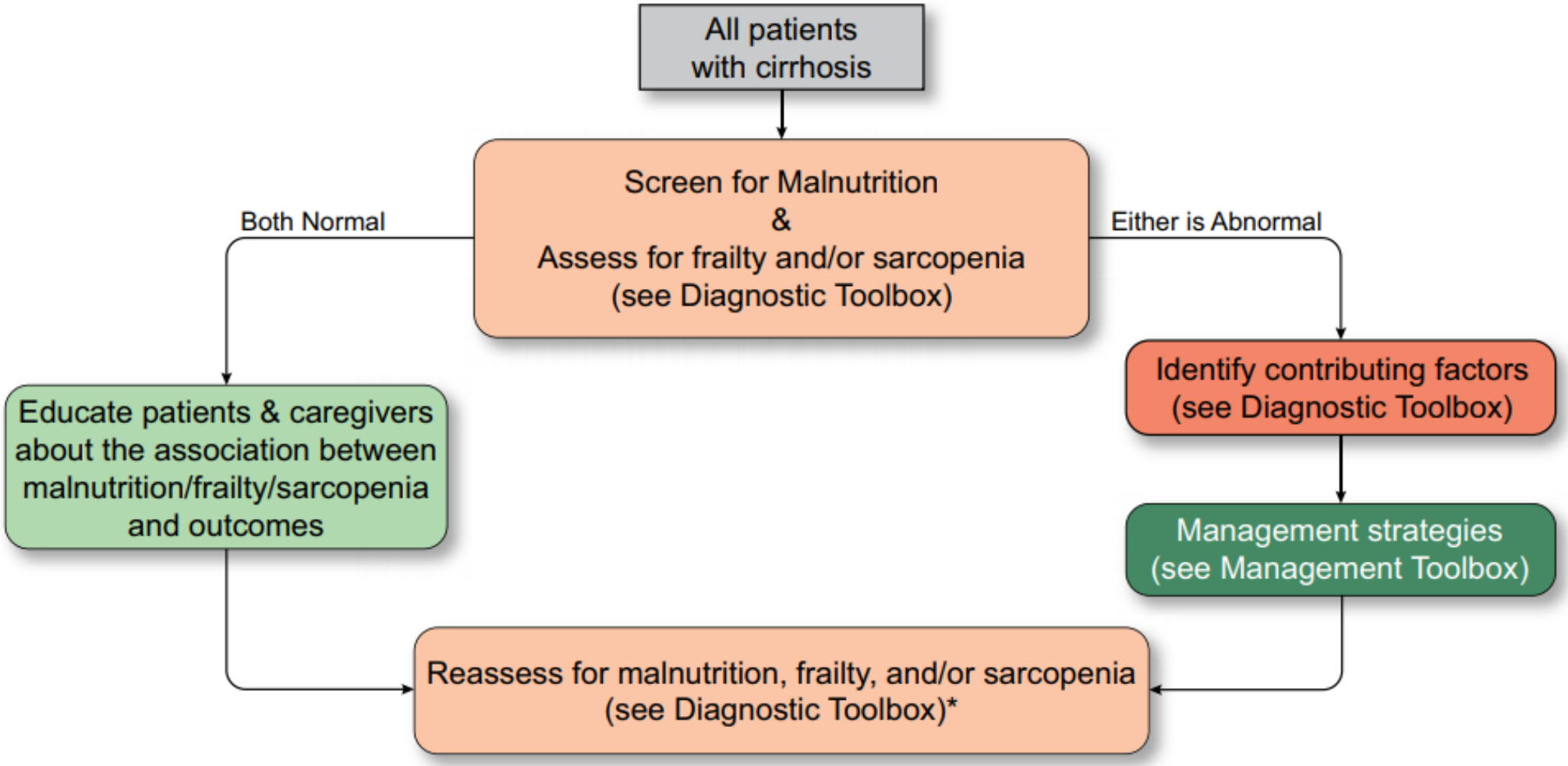

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Diagnostic Toolbox

Select tools based on the clinical scenario

	 Clinician questions	 Physical exam findings	 Objective measures

Screen for Malnutrition & Assess for frailty and/or sarcopenia	• **Karnofsky Performance Scale**
	• **Clinical Frailty Scale**
	• **Activities of Daily Living**
	• **Pediatric populations**
	  • **Royal Free Hospital-Nutrition Prioritizing Tool**
	  • **Lansky play performance scale**
	  • **Fried-exhaustion, shrinkage, Pediatric Quality of Life Inventory**
		• **Muscle wasting** – wasting at the temples, clavicle, shoulder, scapula/ribs, quadriceps, interosseous muscle between the thumb and forefinger
		• **Use of a walking aid**
		• **Inability to stand up from the chair independently or getting off the exam table independently, slowness**
			• **CT scan L3 skeletal muscle index**
			• **Liver frailty index**
			• **Handgrip strength**
			• **6 minute walk test**
			• **4 meter gait speed**
			• **Triceps skin-fold thickness (pediatrics)**

Identify factors contributing to malnutrition, frailty, and sarcopenia	• **Hunger Vital Sign** *(abnormal if either or both are true)*
	  • Within the past 12 months, we worried whether our food would run out before we got money to buy more.
	  • Within the past 12 months, the food we bought just didn't last and we didn't have money to get more.
	• **Physical inactivity**
	  • In the past week, on how many days have you done a total of 30 min or more of physical activity, which was enough to raise your breathing rate?
		• **Ascites**
		• **Hepatic encephalopathy**
		• **Poor dentition**
		• **Dysgeusia**
			• **MELD-Na**
			• **Child Pugh score**
			• **Testosterone level** (men)
			• **Data from patient's fitness tracker (e.g., daily steps, average heart rate)**

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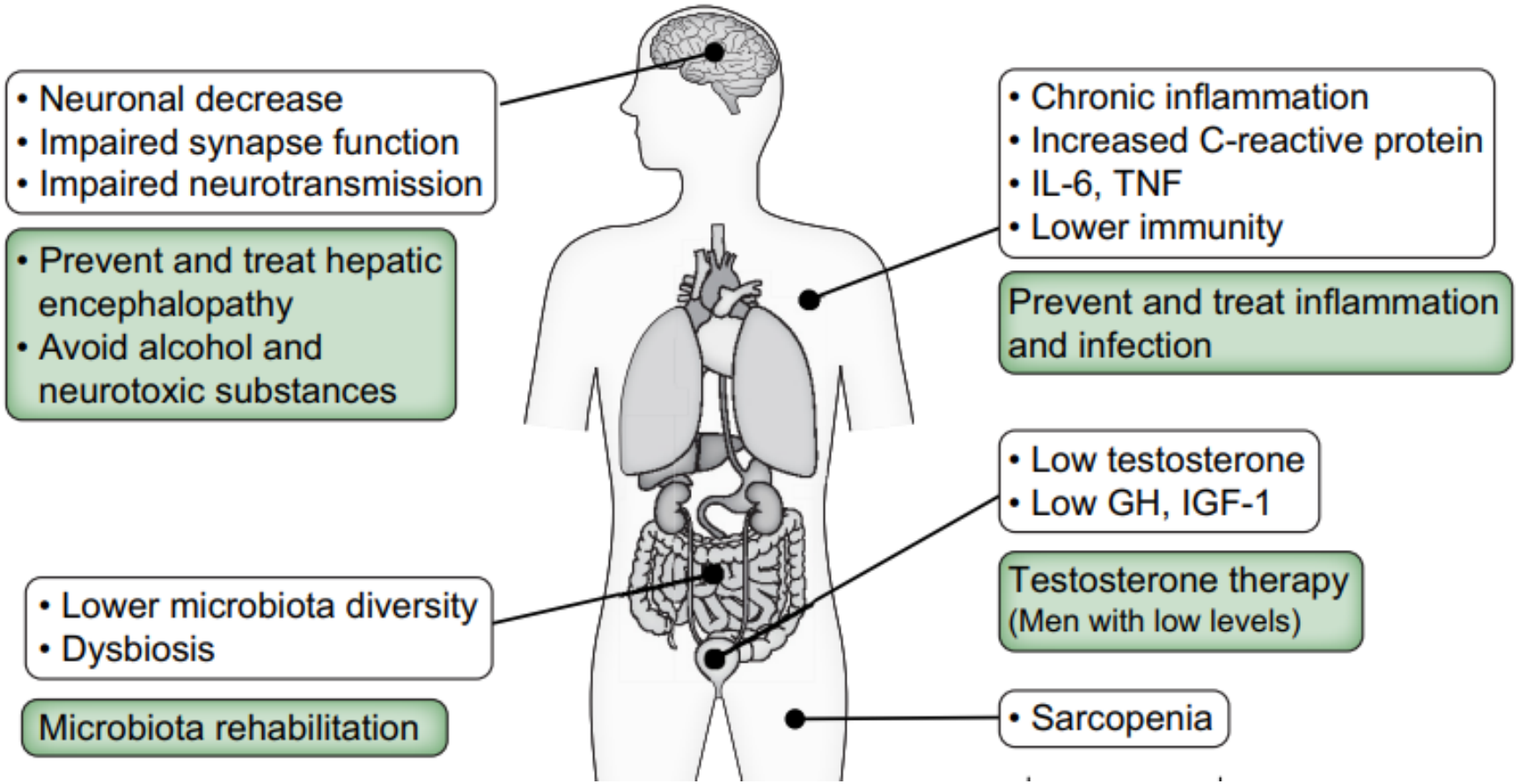
Some Key Proposed Targets to Treat Frailty in Cirrhosis



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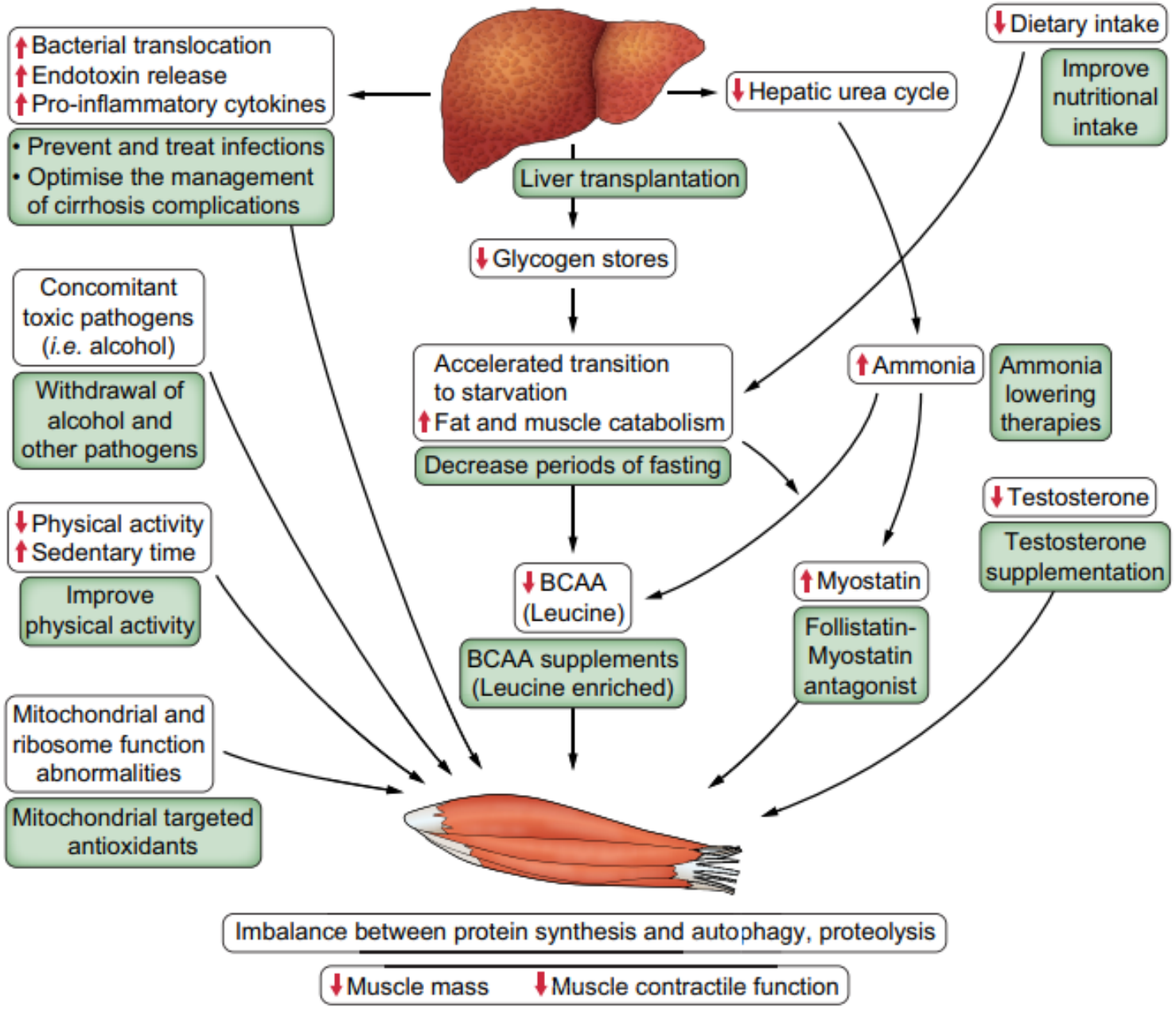

Some Key Proposed Targets to Treat Sarcopenia in Cirrhosis

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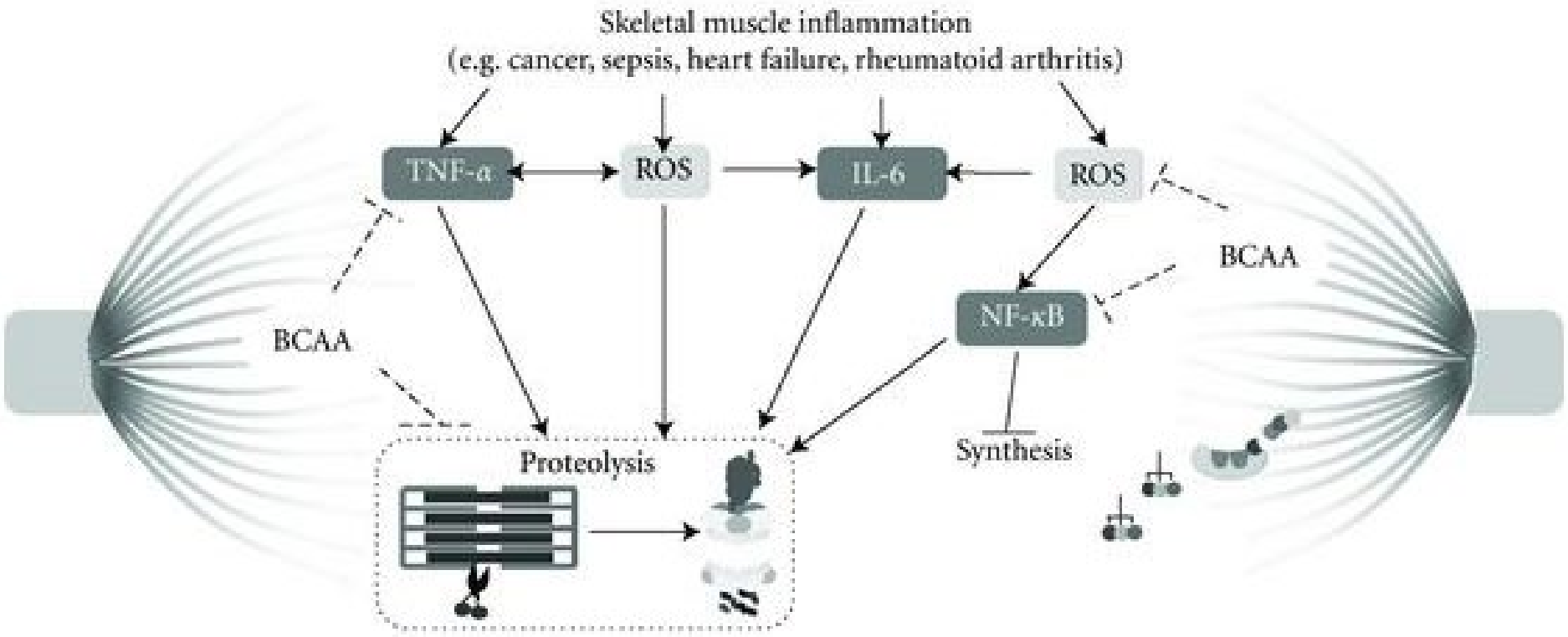
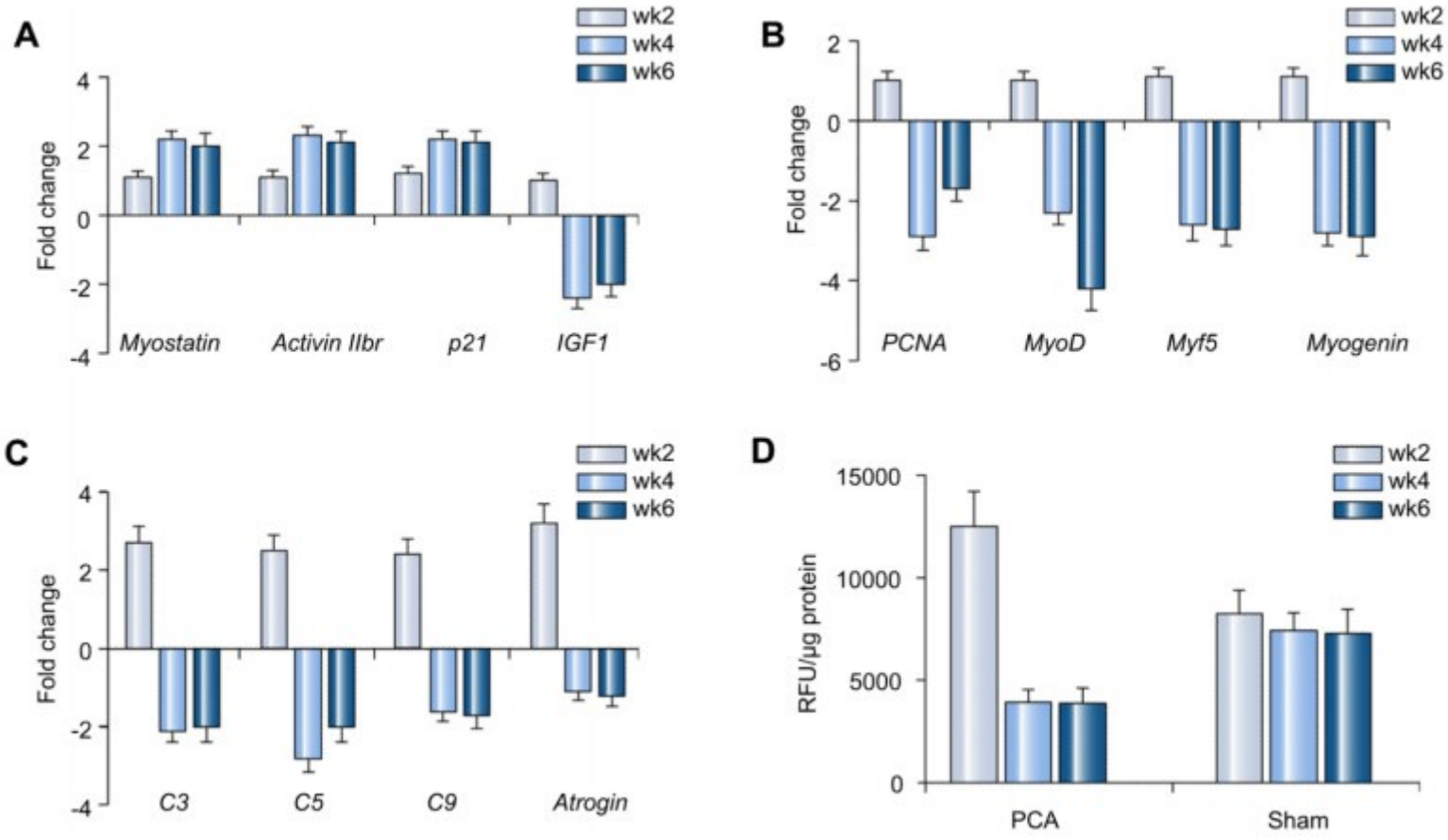
Branched-Chain Amino Acids Supplementation Modulate Skeletal Muscle Remodeling through Inflammation Modulation



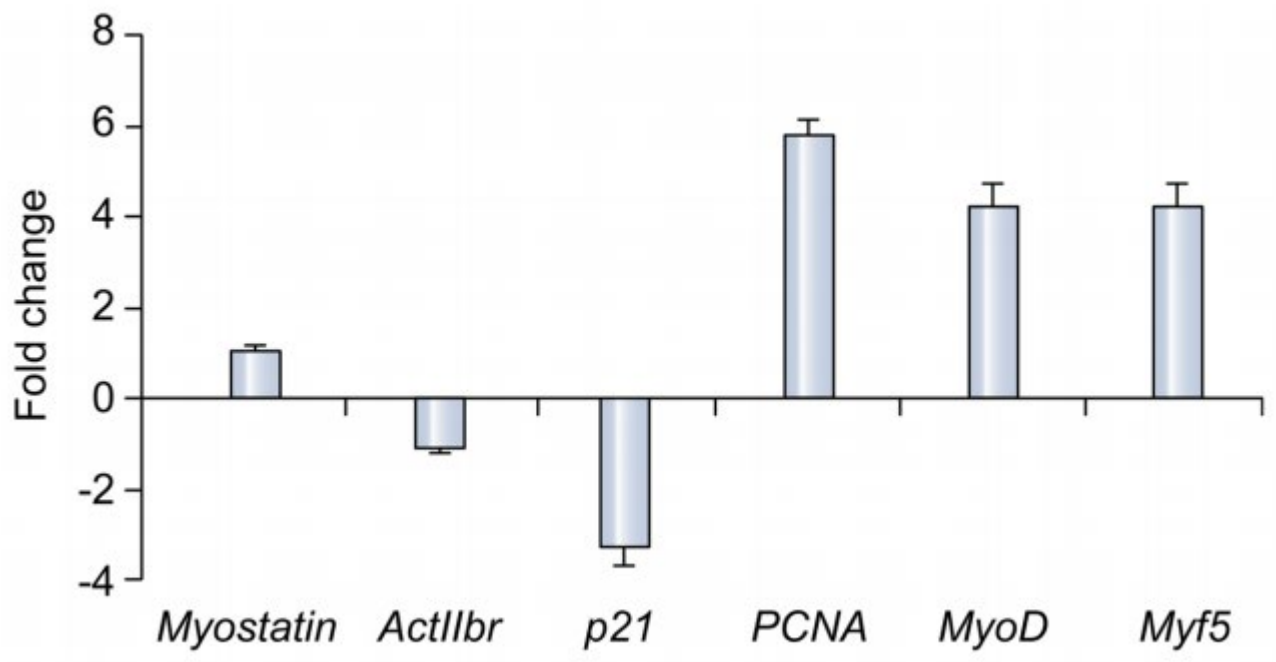
Nicastro H et al Journal of Nutrition and Metabolism, vol. 2012

Sarcopenia associated with portosystemic shunting is reversed by follistatin



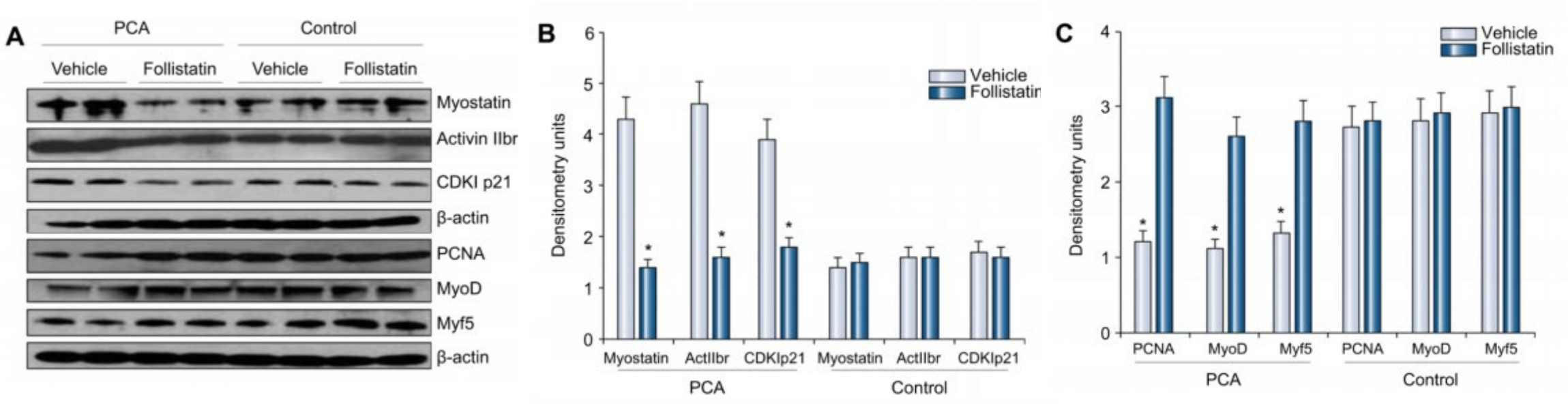
J Hepatol. 2011 May ; 54(5): 915–921

Gene Expression of Muscle Protein and Satellite Cell Function After Follistatin



J Hepatol. 2011 May ; 54(5): 915–921

Portacaval anastamosis (PCA) rat model of sarcopenia of portosystemic shunting (PSS)



J Hepatol. 2011 May ; 54(5): 915–921

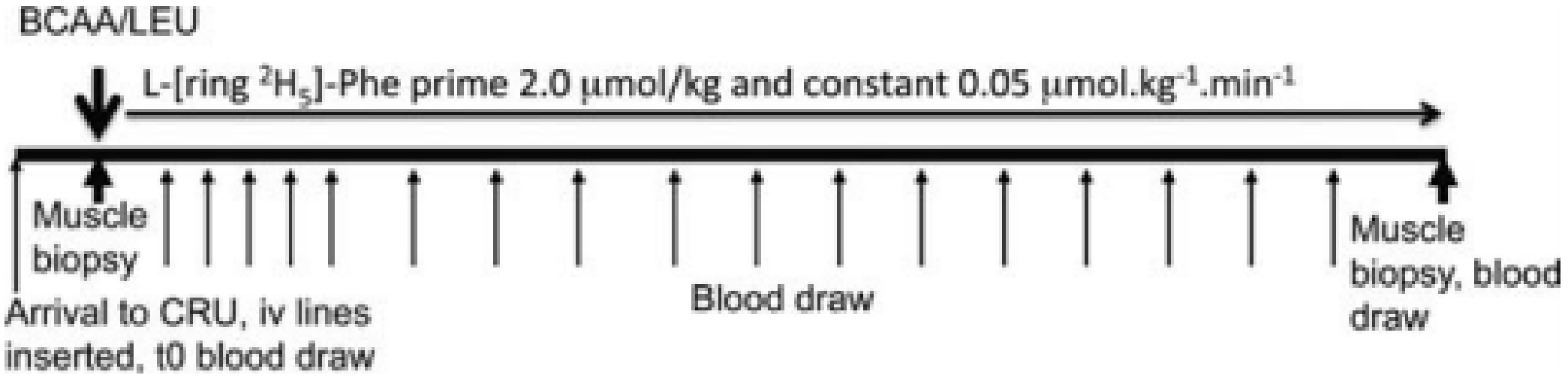
Anabolic Resistance Can Impact Treatment Response

- Anabolic resistance likely due to impaired mTOR signaling response,
- It can potentially be overcome by leucine-enriched supplementation with amino acids.
- Leucine is likely to result in increased utilization of other essential amino acids.

The role of glutamine supplementation in addition to leucine may reverse the molecular abnormalities of increased myostatin and mTOR resistance in cirrhosis to maximize the beneficial effects

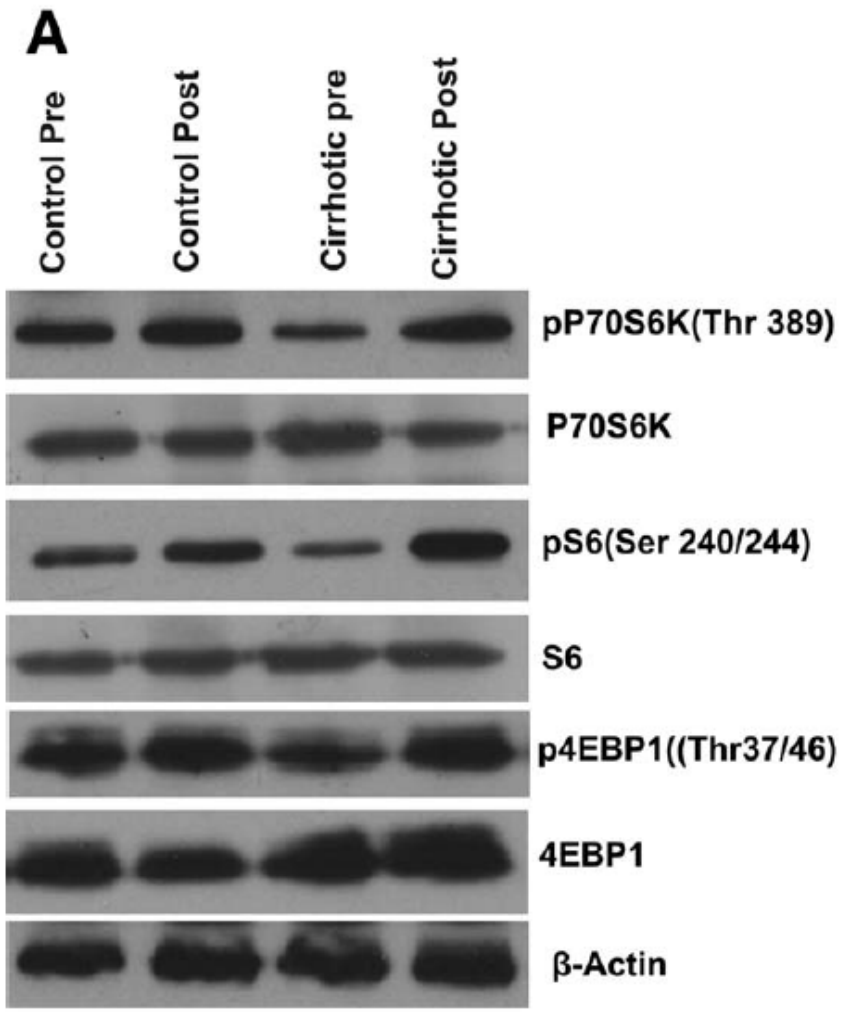
J Cachexia Sarcopenia Muscle 2012

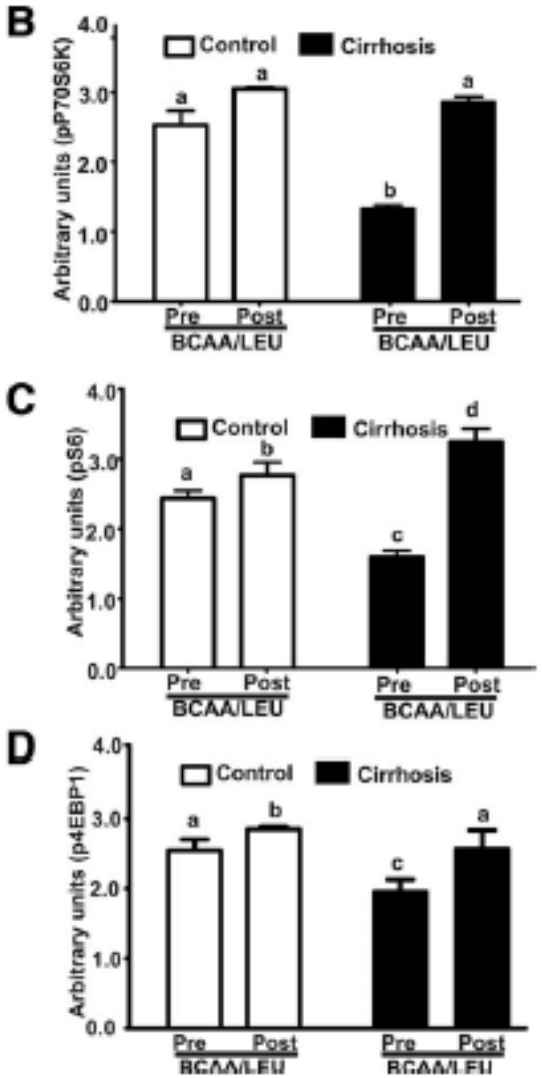
Metabolic and Molecular Responses to Leucine-Enriched Branched Chain Amino Acid Supplementation in the Skeletal Muscle of Alcoholic Cirrhosis



- Subjects ingested 15 g of leucine-enriched branched chain amino acid mixture (BCAA/LEU) containing 7.5 g L-leucine and 3.75 g each of L-isoleucine and L-valine at 0 minutes
- The mixed muscle protein fractional synthesis rate was determined from muscle biopsy samples collected before and after BCAA/LEU ingestion.
- Whole-body protein breakdown was calculated from the dilution of L-[ring 2 H5]- phenylalanine in plasma

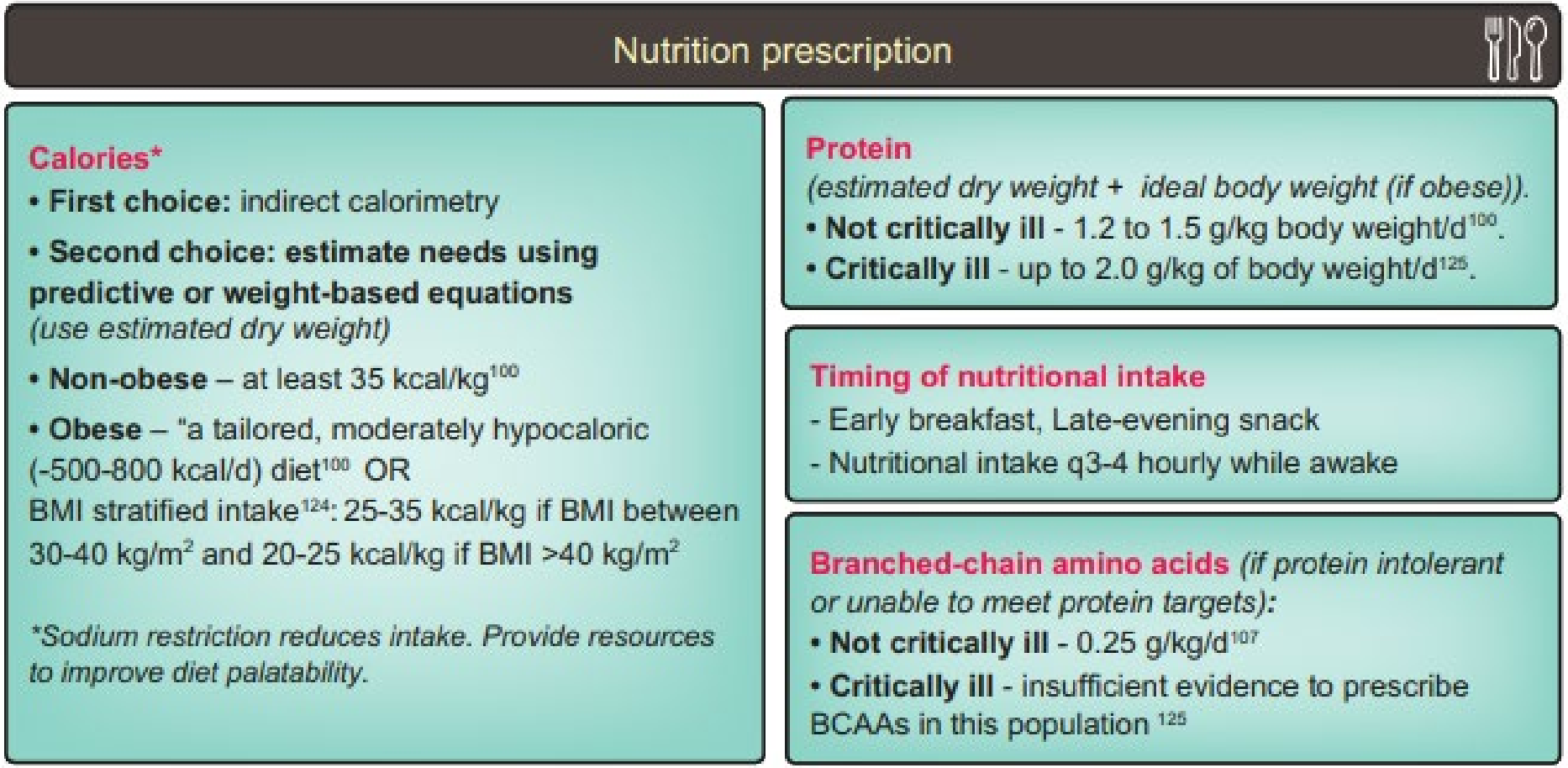
Impaired mTOR1 signaling and increased autophagy in skeletal muscle of patients with alcoholic cirrhosis is acutely reversed by BCAA/LEU.





HEPATOLOGY 2015;61:2018-2029)

Nutrition Prescription For Sarcopenia and Frailty in Patients with Cirrhosis



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Exercise Prescription For Sarcopenia and Frailty in Patients with Cirrhosis

Exercise prescription

Pre-exercise safety assessment

- **Cirrhosis related safety screening**
  - High risk varices: prophylaxis needed
  - Hepatic encephalopathy, ascites: optimise, supervision by caregivers
- **Cardiopulmonary safety screening**
- **Assess physiological competence**

Assess for fall risk, musculoskeletal limitations

FITT (Frequency, Intensity, Type, Time) recommendations

- **Frequency**

Aerobic: 4-7 d/week; **Resistance** 2-3 d/week; **Flexibility and balance**: 2-3 d/week

- **Intensity**

Borg scale: moderate intensity 3-5/10

Talk test: able to speak in full sentences but still notices laboured breath

- **Time**

Aerobic: build to 150 minutes per week. The very deconditioned may need to start with 1-min of walking followed by 1-min of rest.

Resistance: 3 sets of 10-15 repetitions.

Flexibility and balance: 1 set of 3 repetitions

- **Type**

Aerobic: walking is the most universal aerobic intervention

Resistance: functional (*e.g.* stairs) or progressive weight/band training

Flexibility and balance: stretching and balance exercises

Hormonal therapy (men)

Testosterone

A single RCT demonstrated benefit (higher muscle and bone mass and lower fat mass).

- Avoid if HCC, venous thrombosis or additional exclusion criteria detailed in the trial.
- Dose used in the Sinclair *et al.* trial: intramuscular testosterone undecanoate 1,000 mg IM, at 0, 6, 18, 30 and 42 weeks.

Across all interventions, encourage adherence using behaviour change principles/motivational interviewing

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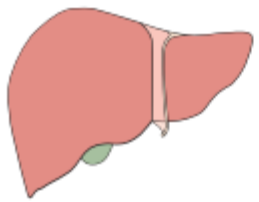
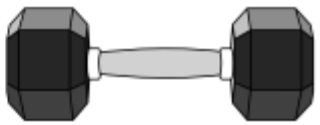
Management Toolbox



Liver specific

- **Management of disease etiology**
- **Management of ascites**
- **Management of hepatic encephalopathy**

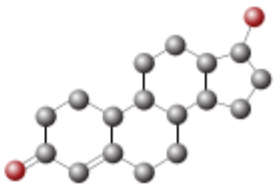


Physical activity

- **Personalized activity prescription (guided by FITT):**
  - **Frequency** – Aerobic (4-7 d/week); Resistance (2-3 d/week)
  - **Intensity** – Use the talk test (be short of breath but can still speak a full sentence); 3 sets of 10-15 repetitions at a time
  - **Time** – Start slow and build up
    - Aerobic: 150 min per week
    - Resistance: ≥ 1 days per week
  - **Type** – aerobic, resistance, flexibility and balance
- **Consult a certified exercise physiologist or physical therapist**

Intake/Uptake

- **Calorie intake of at least 35 kcal/kg (non-obese)**
- **Protein intake of 1.2 to 1.5 g/kg body weight/d**
- **Micronutrient repletion**
- **Frequent, small meals and minimize fasting (e.g. late evening snack)**
- **Address barriers to intake (e.g. liberalize sodium restrictions as needed)**
- **Consult a registered dietitian**



Other systems

- **Testosterone replacement** (men)
- **Refer to health behavior specialist**
- **Diabetes control**

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Future Directions

- Standardized, feasible assessment of frailty and sarcopenia in diverse populations of patients with cirrhosis with respect to sex/gender, race/ethnicity, and clinical acuity.
- Longitudinal assessment of frailty and sarcopenia.
- Development of therapeutics and multimodal strategies targeting frailty and sarcopenia.