Improving Frailty in Patients Listed for Liver Transplantation

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Let's start with a case…

- Ms. B is a 61-year-old with HCV-related cirrhosis (on SVR)
  - CTP 9 (Albumin 2.2, prior HE, ascites – diuretic resistant/AKI) & MELD-Na 16
  - BMI 40, depression, hypertension
  - No medical contraindication for LT

Physical performance assessment

	5/09/19	11/21/19
LFI	4.67	5.19
- Hand grip	16 kg	18 kg
6MWT	180 m	N/A
UGST	0.6 ms	N/A
Daily step count	N/A	540

Some questions arising from case…

Can this patient be transplanted?

Yes → What are the risks?

No → Is **frailty** enough reason to deny LT?

Is **frailty** enough reason to deny LT? → How should we define frailty?

Is **frailty** enough reason to deny LT? → What to do about **frailty**?

Frailty and its associated clinical outcomes

Infections

Hospital admission

LT complications

Prolonged hospital stay

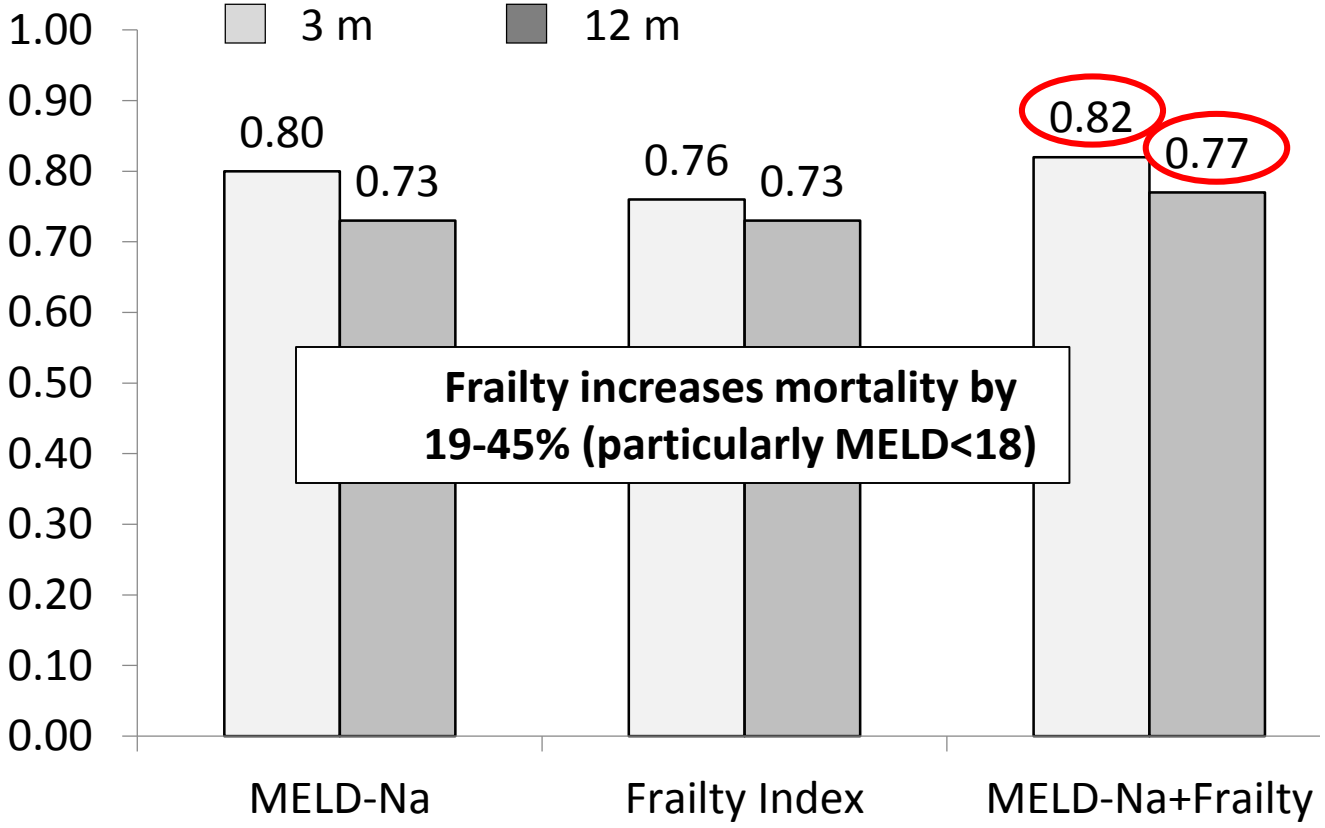
Falls

Increased healthcare costs

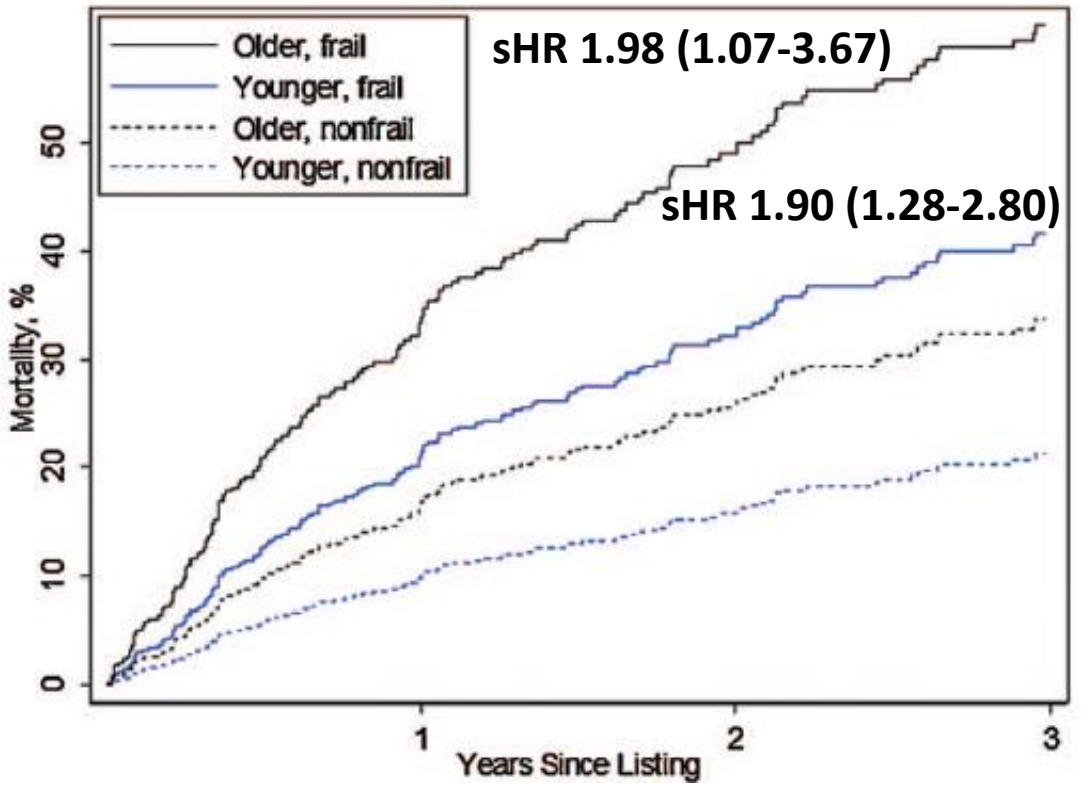
Mortality

Frailty and its associated clinical outcomes

- Frailty predicts pre-LT mortality
  - 536 LT-waitlisted patients



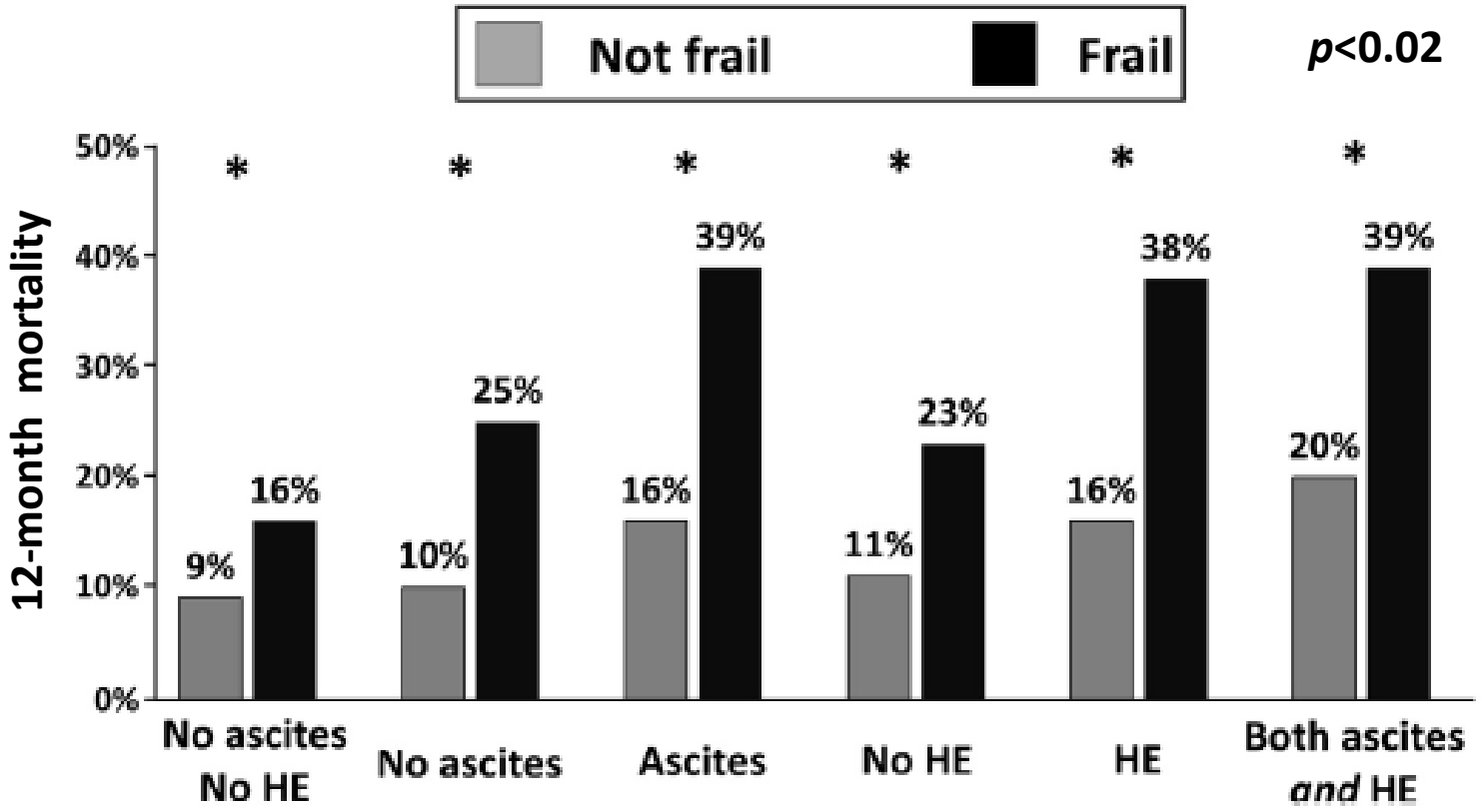
- Frailty effect is independent of age
  - 882 LT-waitlisted patients



Lai. Hepatology 2017;66:564. / Lai. Am J Transplant 2014;14:1870 / Haugen. Ann Surg 2019;in press

Frailty and its associated clinical outcomes

- Frailty predicts pre-LT mortality independently of HE and ascites
  - 1099 LT-waitlisted patients (FrAILT consortium)



Ascites: sHR 1.52 (1.14-2.05)

HE: sHR 1.84 (1.38-2.45)

Frailty: sHR 2.38 (1.77-3.20)

Frailty: sHR 1.82 (1.31-2.52)

Lai. Gastroenterology 2019;156:1675

Some questions arising from case…

Can this patient be transplanted?

Yes

What are the risks?

No

Is **frailty** enough reason to deny LT?

How should we define frailty?

What to do about **frailty**?

Decision making in frailty…

- Assess frailty within its clinical context

Is Frailty REVERSIBLE?	What is the patient's RESILIENCE?
Acute vs. Chronic	Age
Inpatient vs. Outpatient	Cognitive status
Hepatic vs. Non-Hepatic	Severity / chronicity of comorbidities

Chen. In: Tandon & Montano-Loza. Frailty & Sarcopenia in Cirrhosis. Springer 2019

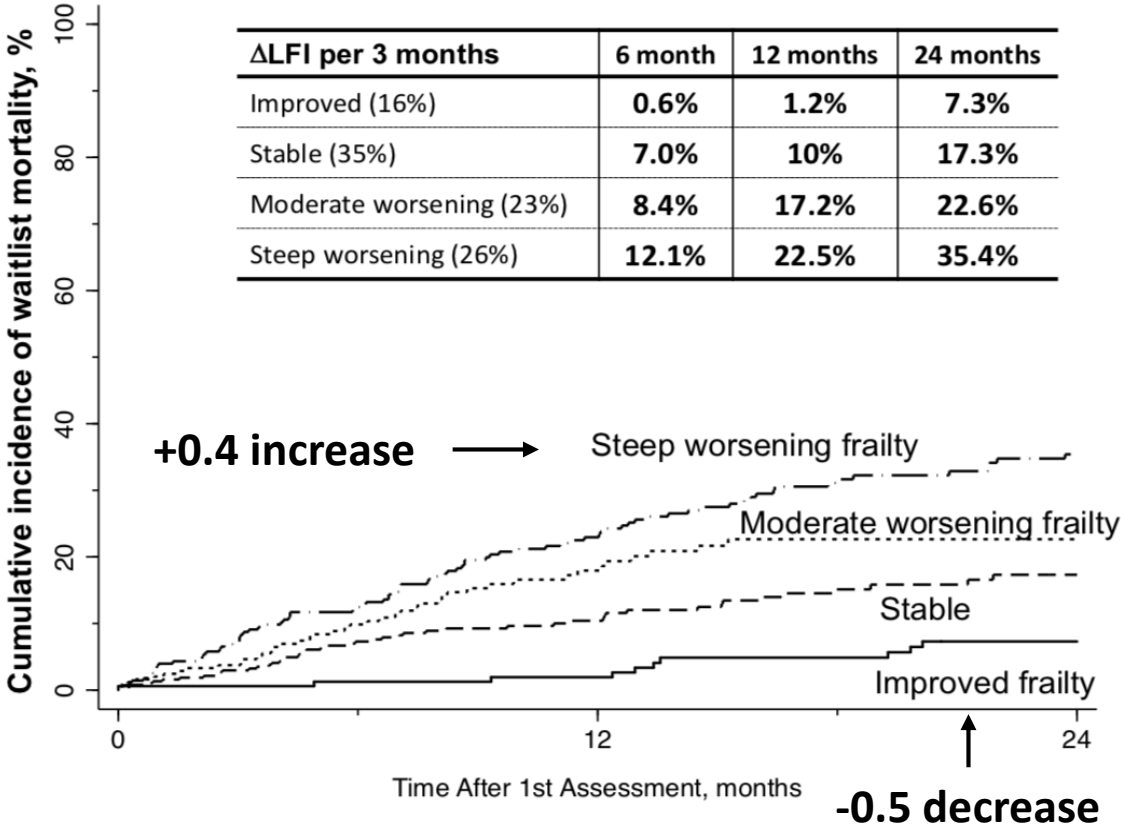
Decision making in frailty…

Frailty is a dynamic condition – its trajectory matters

Decision making in frailty…

- Worsening of frailty strongly predicts waitlist mortality
  - 1,093 outpatients with cirrhosis at 8 U.S. LT centers

ΔLFI per 3 months	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%**
Steep worsening (26%)	**12.1%**	**22.5%**	**35.4%**



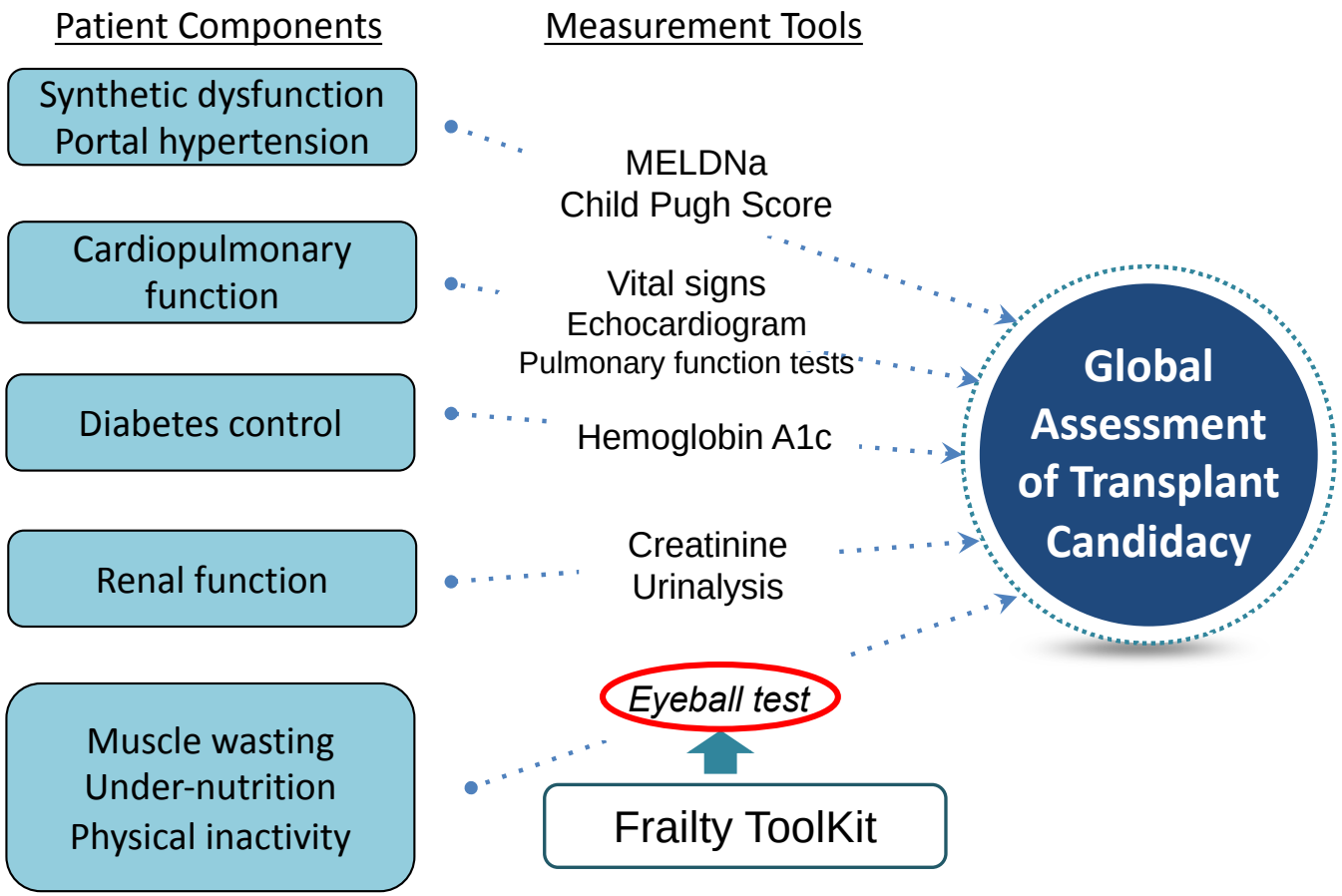
	Subhazard Ratios (95% CI)		
	Univariable	Stepwise multivariable	
ΔLFI 0.1-unit worsening	**3.9 (2.8-5.4) <0.001**	**1.8 (1.2-2.8) 0.004**	**2.0 (1.3-3.0) 0.001**
Base LFI 0.1-unit increase	1.0 (1.0-1.1) <0.001	1.0 (1.0-1.1) <0.001	1.0 (1.0-1.1) <0.001
MELDNa 5-unit increase	1.2 (1.1-1.4) <0.001		1.0 (1.0-1.0) 0.11

Delta LFI strongly predicts mortality

Lai. AASLD 2019

Decision making in frailty…

- **Frailty is not enough of a reason to deny LT to a patient**



Lai. Am J Transplant 2019

Some questions arising from case…

Can this patient be transplanted?

Yes

What are the risks?

No

Is **frailty** enough reason to deny LT?

How should we define frailty?

What to do about **frailty**?

How should we define frailty?

- American Society of Transplantation frailty toolkit

	Stages of Frailty		
	Severe (FRAIL)	Moderate	Mild / Absent
Activities of Daily Living	**≥2 ADLs impaired**	1 ADL impaired	Executes all ADLs
Clinical Frailty Scale	**≥7**	6	1-5
Fried Frailty Phenotype	**≥3**	1-2	0
Karnofsky	**0 to 40**	50 to 70	≥ 80
Liver Frailty Index	**≥4.5**	3.2 to 4.4	<3.2
6-minute walk test	**<250 m**	<350 to 250 m	>350 m
Usual gait speed test	***≤0.8 m/s***	*>0.8 m/s*	
Cardiopulm. exercise test	***<60%***	*>60%*	

Lai. Am J Transplant 2019
Chen. In: Tandon & Montano-Loza. Frailty & Sarcopenia in Cirrhosis. Springer 2019

How should we define frailty?

- Liver Frailty Index (LFI)

Hand grip

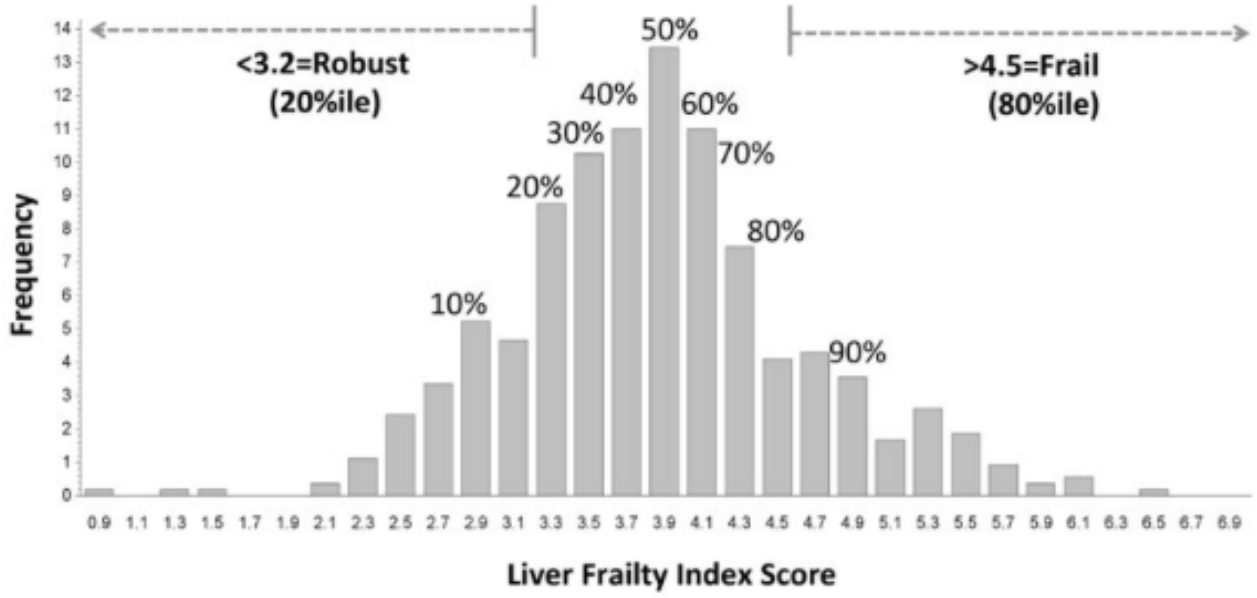
Five Chair stands (time)

Balance Test: seconds on each position

Lai. Hepatology 2017;66:564

How should we define frailty?

- Liver Frailty Index (LFI)



Liver Frailty Index

Inputs: For instructions, see below.

1. Gender: Male Female

2. Dominant hand grip strength (kg):

attempt 1:	attempt 2:	attempt 3:	Avg:	
18	19	18	18.33	kg

3. Time to do 5 chair stands: 40 sec

4. Seconds holding 3 position balance:

Side:	SemiTandem:	Tandem:	Total:	
10	8	4	22.00	sec

Results: refresh results

The Liver Frailty Index is **4.99**.

LFI:	<3.2	3.2-4.4	≥4.5 Frail

www.liverfrailtyindex.ucsf.edu

How should we define frailty?

- Other performance-based assessments

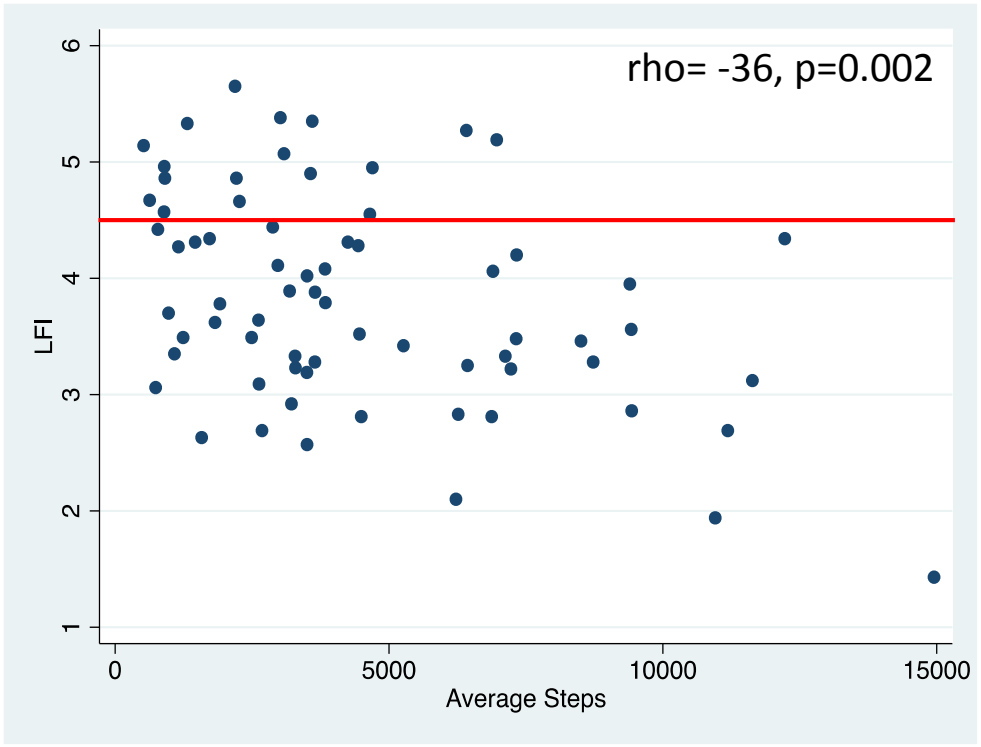
6MWT
Distance strolled in 6 minutes

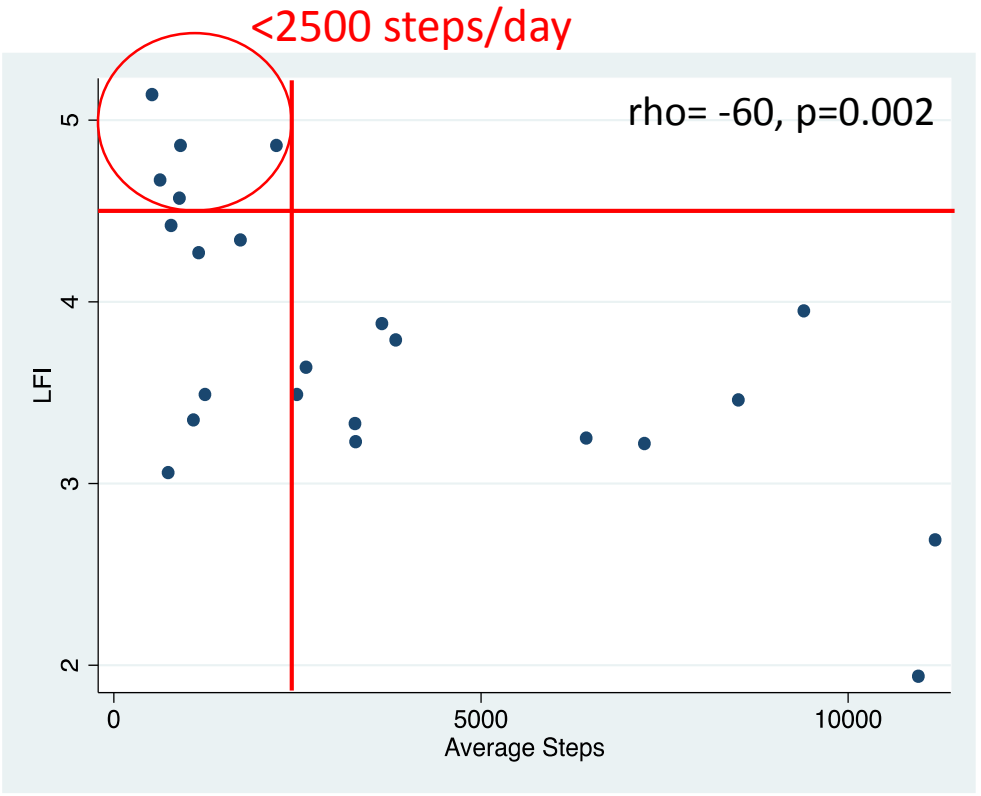
UGST
Usual pace gait speed over 5 m

Performed by Pulmonary

How should we define frailty?

- Other performance-based assessments





Some questions arising from case…

Can this patient be transplanted?

Yes

What are the risks?

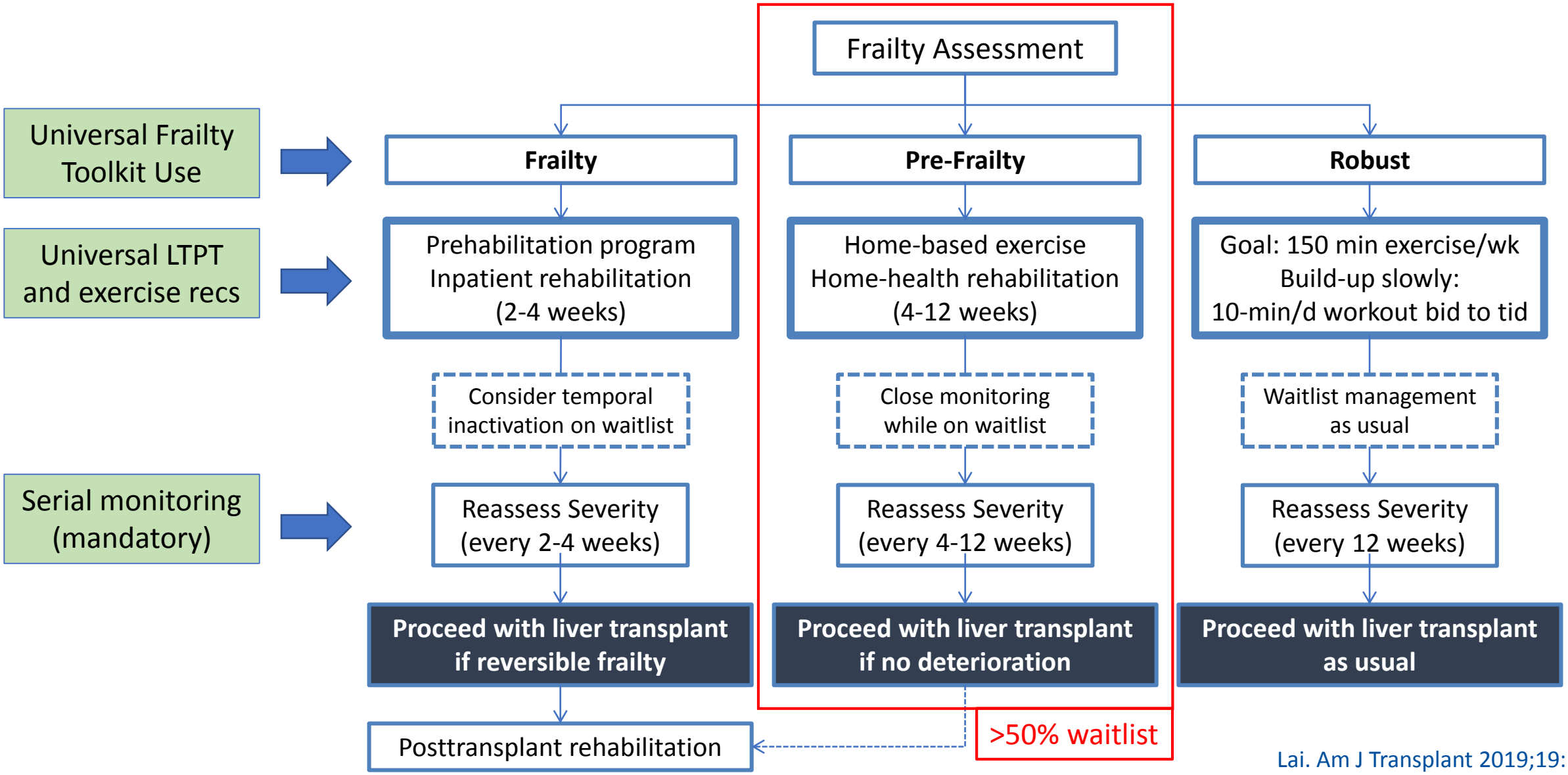
No

Is **frailty** enough reason to deny LT?

How should we define frailty?

What to do about **frailty**?

What do we do about frailty?



Lai. Am J Transplant 2019;19:1896

Exercise clinical trials in cirrhosis

Author	Design	Population	Intervention(s)	Outcome
Pattullo 2013	ONCT, 24-wk	n=16 (F4=6), CTP A 83%	Home-based + nutrition	HOMA-IR, adiposity, leptin, step, fatigue/mood improved
Roman 2014	RCT, 12-wk	Allocated=20, CTP A 82%	Supervised + L-Leu	CPE, muscle mass, Wt, HRQoL, and Alb. improved (exercise)
Zenith 2014			Supervised + nutrition	CPE, muscle mass, and HRQoL improved (exercise)
Debette-Gratien			Supervised	CPE and muscle strength improved
Macias-Rodrigue			Supervised + nutrition	HVPG, CPE, BIA, and hyper-NH3 improved (exercise)
Roman 2016			Supervised	CPE/muscle mass ⬆, fat mass/**risk of falls** ⬇ (exercise)
Berzigotti 2017			Superv./gym + nutrition	HVPG, CPE, HR, anthropometry, IR, adipokines, and HRQoL improved (exercise)
Nishida 2017		%	Home-based + BCAA	CPE improved
Hiraoka 2017			Home-based + BCAA	Daily steps, muscle mass and strength improved
Kruger 2018			Home-based + nutrition	CPE and muscle mass improved (exercise)
Williams 2019	ONCT, 12-wk	n=18, MELD 13 (12-26)	Home-based + nutrition	CPE, step count, and **SPPB** improved
Aamann 2019	RCT, 12-wk	n=39, MELD 11±3	Supervised/Resistance	CPE, muscle mass and strength improved
Chen (*submitted*)	RCT, 12-wk	N=20, CTP A 20%	Home-based + nutrition	CPE and step count improved

Supervised (CP rehab)

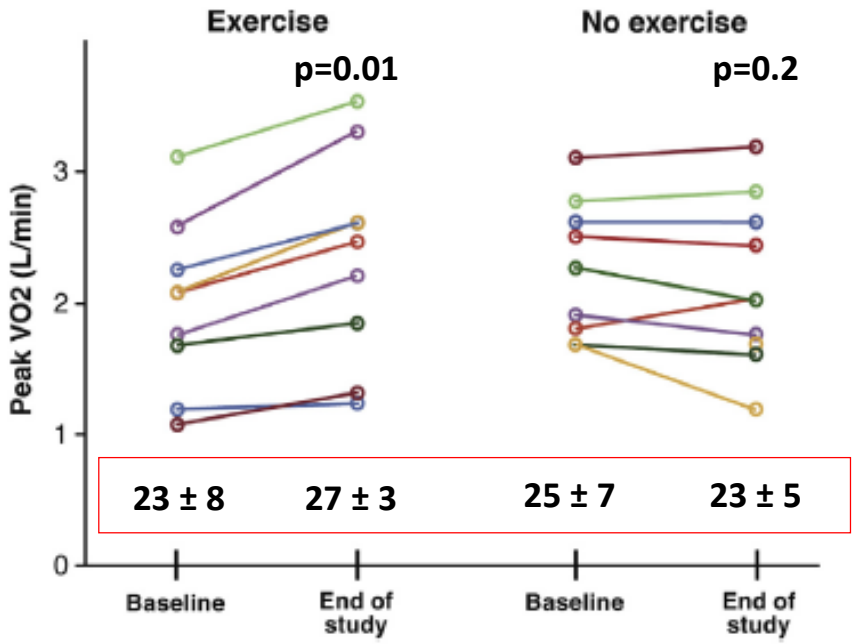
Home-based (structured)

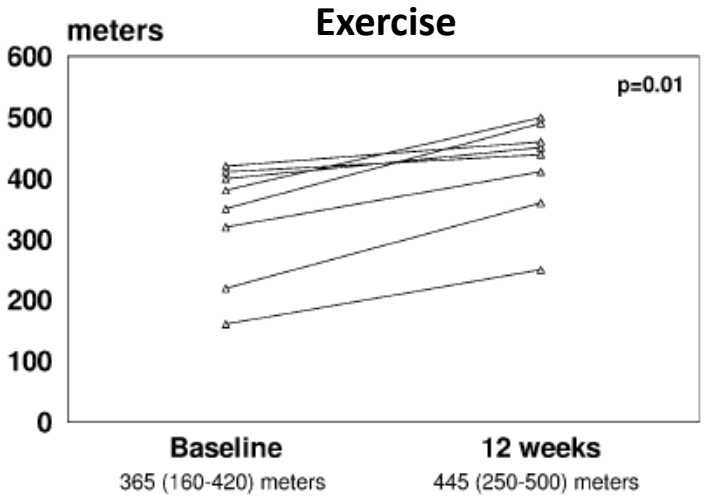
Home-based (*ad libitum*)

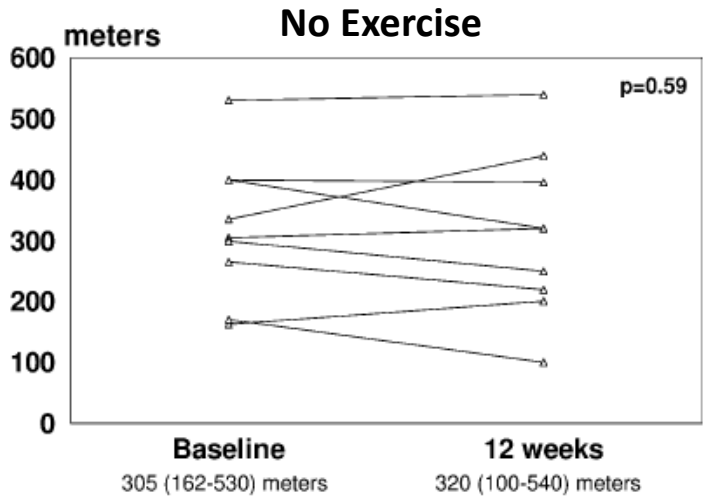
Hybrid

Impact on cardiopulmonary fitness

- Peak VO_2 from CPET and distance from 6-MWT





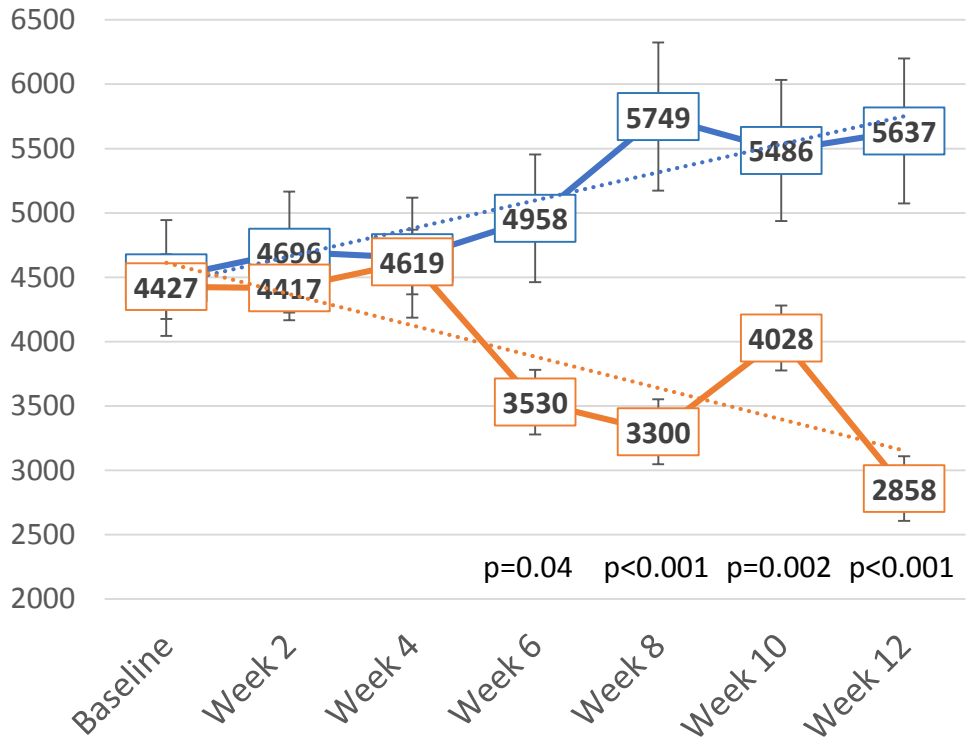


Supervised (CP rehab)

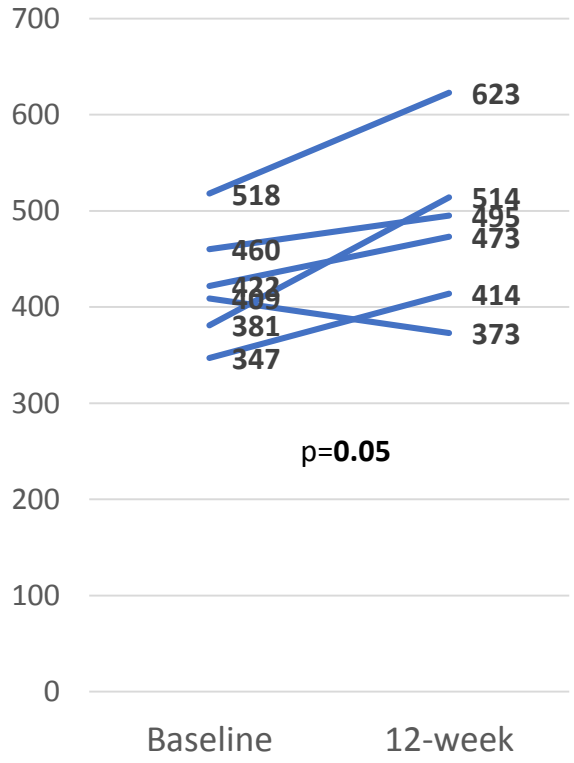
Zenith. Clin Gastroenterol Hepatol 2014:12:1920
Roman. Dig Dis Sci 2014:59:1966

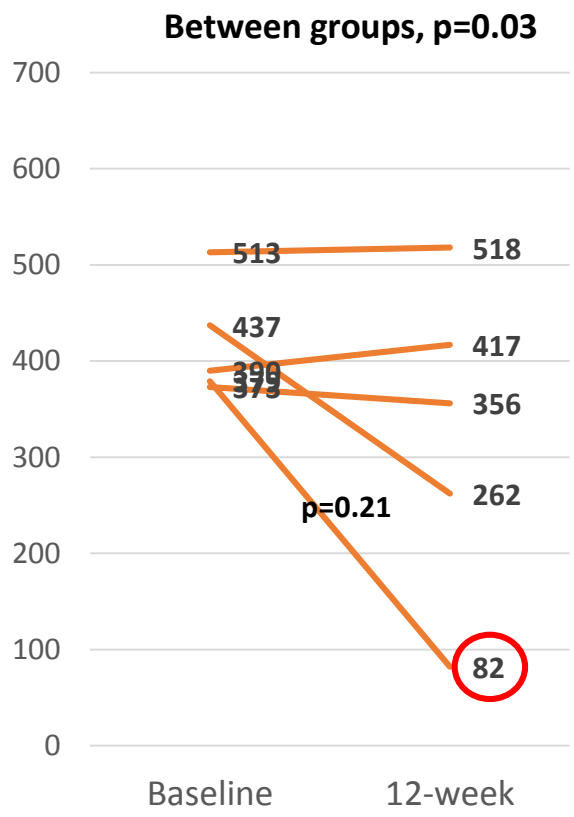
Impact on cardiopulmonary fitness

- Home-based exercise RCT in patients with MELD ≥10



Home-based (*ad libitum*)

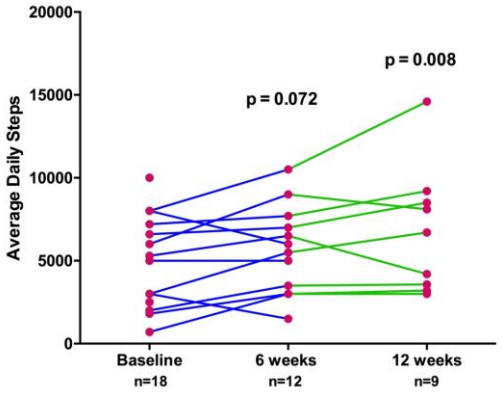


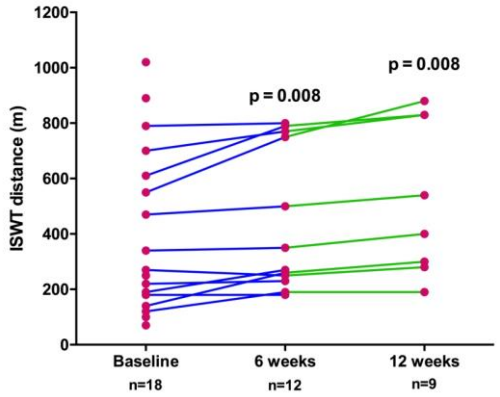


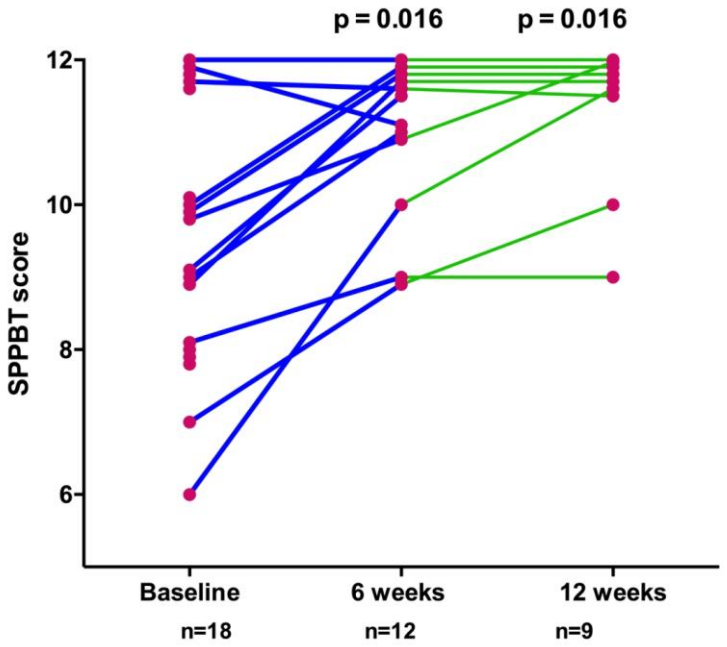
Chen. Submitted

Impact on frailty

- Home-based exercise in waitlisted candidates







Frailty reduced from 50% to 11%

a)

Lunges

b)

Rock press

c)

Frog squat

d)

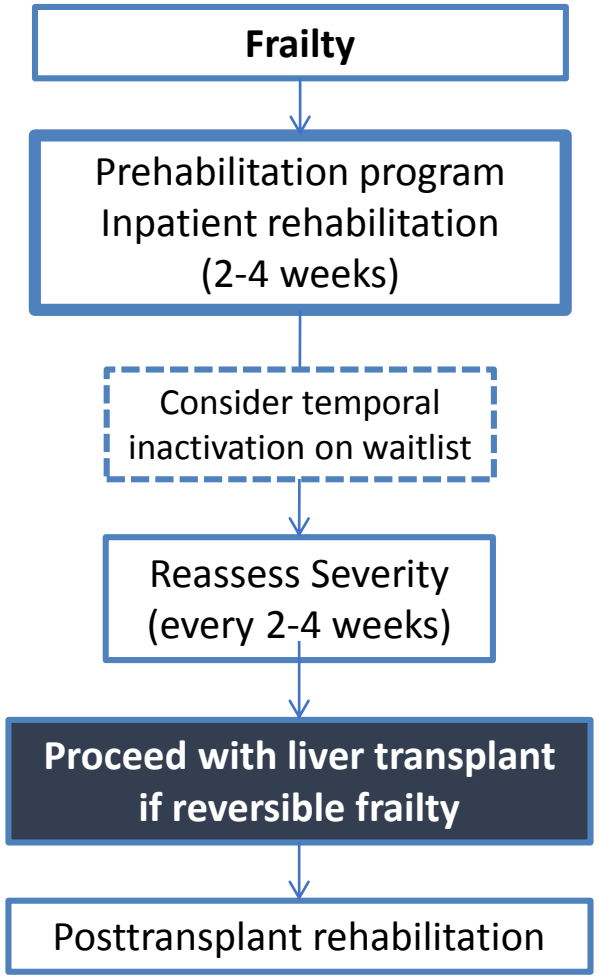
Bear crawl

Williams. Liver Transpl 2019;in press

What do we do about frailty?

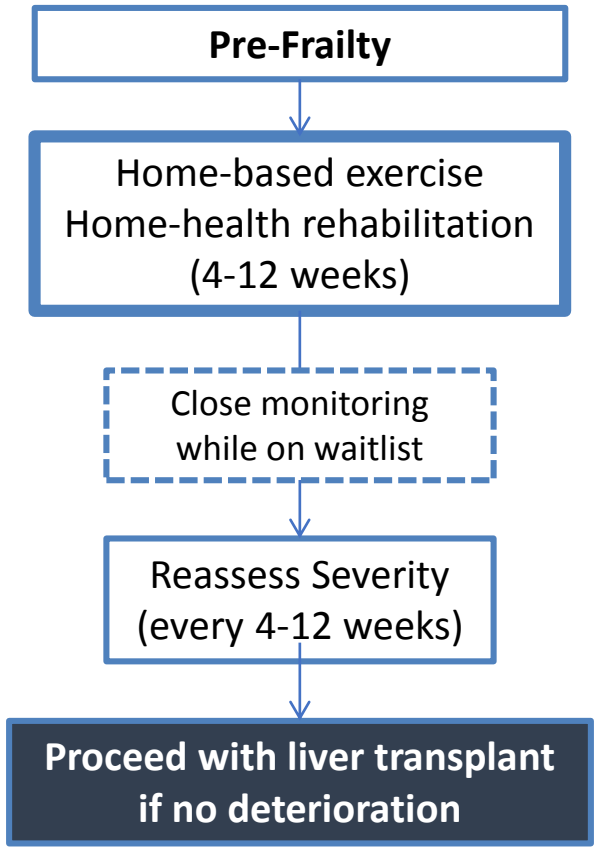
- UPMC LT prehabilitation protocol → baseline assessment
  - Exercise prescription
    - Falls in last 6 months
    - Balance problems
    - Ortho/Neuro lesions
    - Orthostatic hypotension
    - Beta-blockers
    - Large varices (no intervention)
    - EBL last 4 weeks
  - Safety
    - Overt HE (MO-log score)
    - Review:
      - H & P
      - TTE
      - ABG
      - CXR
      - Cardiac stress test

Intervention in frail patients



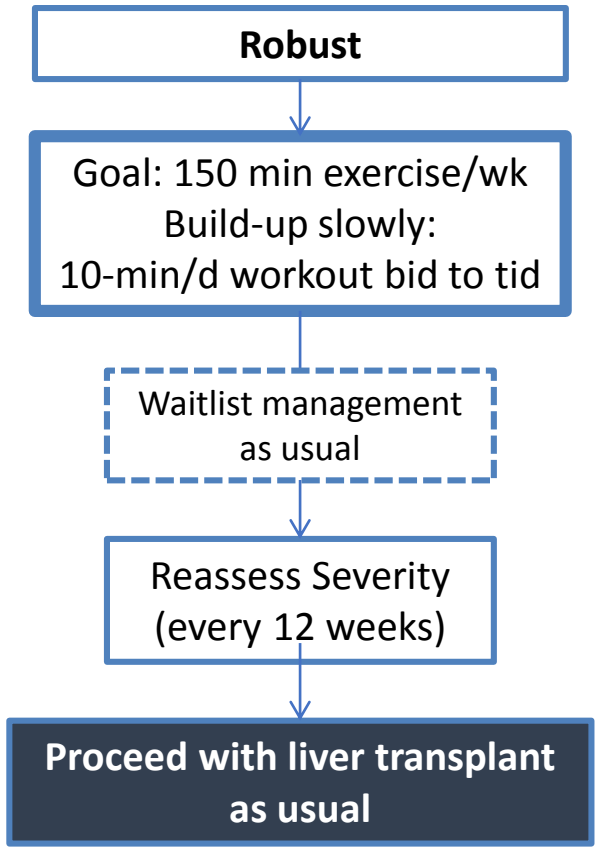
- **Outpatient PT Supervised Program (preferred)**
  - Try to avoid home-health PT
- **Exercise prescription per LT-PT**
  - Activities of daily living (non-exercise activity thermogenesis)
  - Professional-driven home-based exercise program
    - Equipment recommendations (weights, restorator, resistance bands)
- **1-week** telephone follow-up (enhance adherence)
  - Weekly to biweekly calls or clinic LT-PT visits as needed
- **4-week** follow-up to assess changes in 6MWT/LFI

Intervention in prefrail patients



- **Exercise prescription per LT-PT**
  - Activities of daily living (non-exercise activity thermogenesis)
  - Professional-driven home-based exercise program
    - Equipment recommendations (weights, restorator, resistance bands)
- **Attend local gym if possible**
- **Home-health PT when adherence becomes an issue**
- **1-week** telephone follow-up (enhance adherence)
  - Weekly to biweekly phone calls or clinic LTPT visits as needed
- **3-month** follow-up to assess changes in 6MWT/LFI

Intervention in robust patients



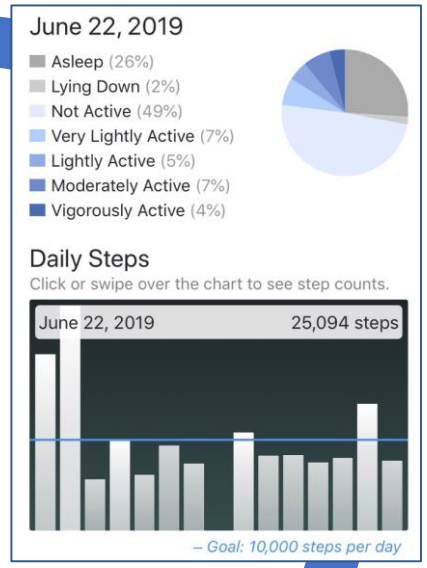
- Patient to do lifestyle intervention encouraging **30 min/day of aerobic/resistance activity**.
- **6-month** follow-up to assess changes in 6MWT/LFI

Use of personal activity trackers

- Available for ALL PATIENTS as part of clinical research:
  - Remote continuous monitoring with Fitbit or Apple Watch via EL-FIT
  - Remote continous monitoring with Fitbit via Fitabase.
  - Biweekly reports on step counts and intensity of activities

- When using a personal fitness tracker
  - Aim for moderate intensity: cadence ≥ 80 steps per minute
  - **2500 to 4999** steps/day if frail
  - **5000 to 7499** steps/day if pre-frail
  - **≥7500** if non-frail

EL-FIT: *E*xercise and *L*iver *FIT*ness

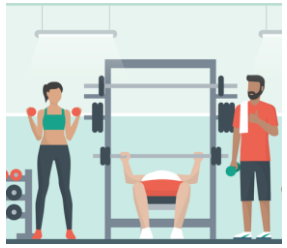


Cerner

Epic

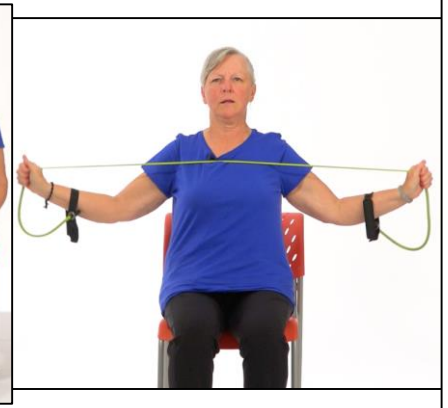
TRACKING

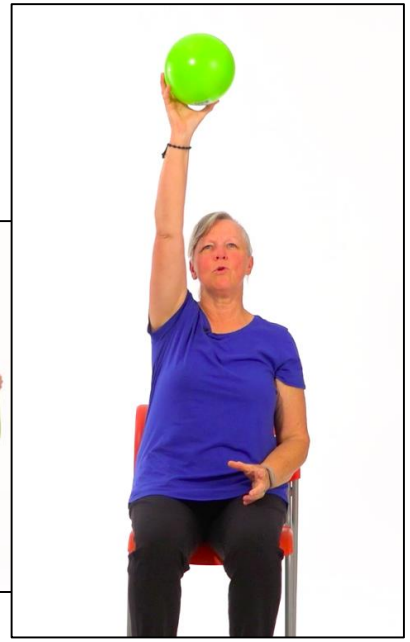
Fitness (databases/statistics)



ASSESSMENT

Algorithm stratifies training intensity

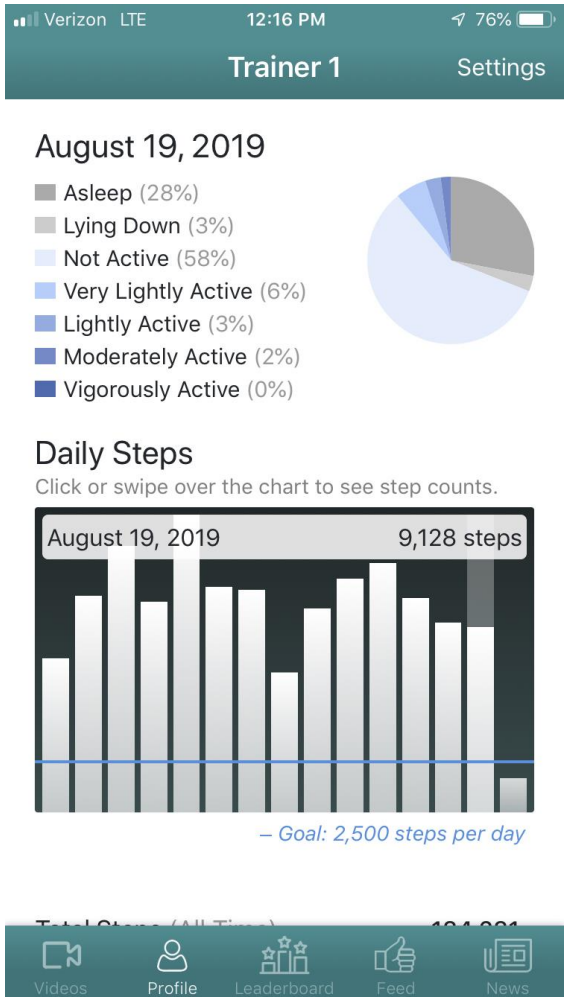


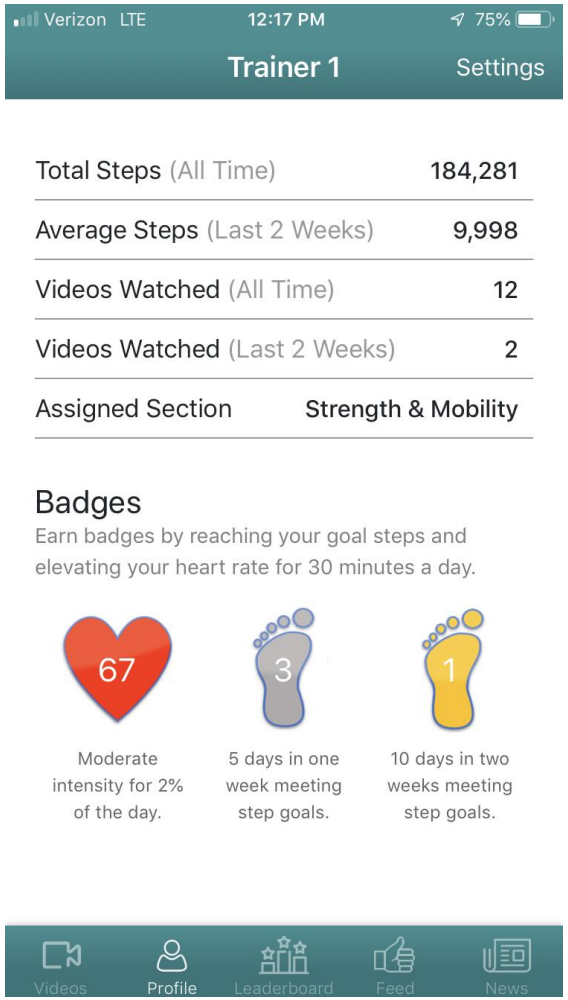


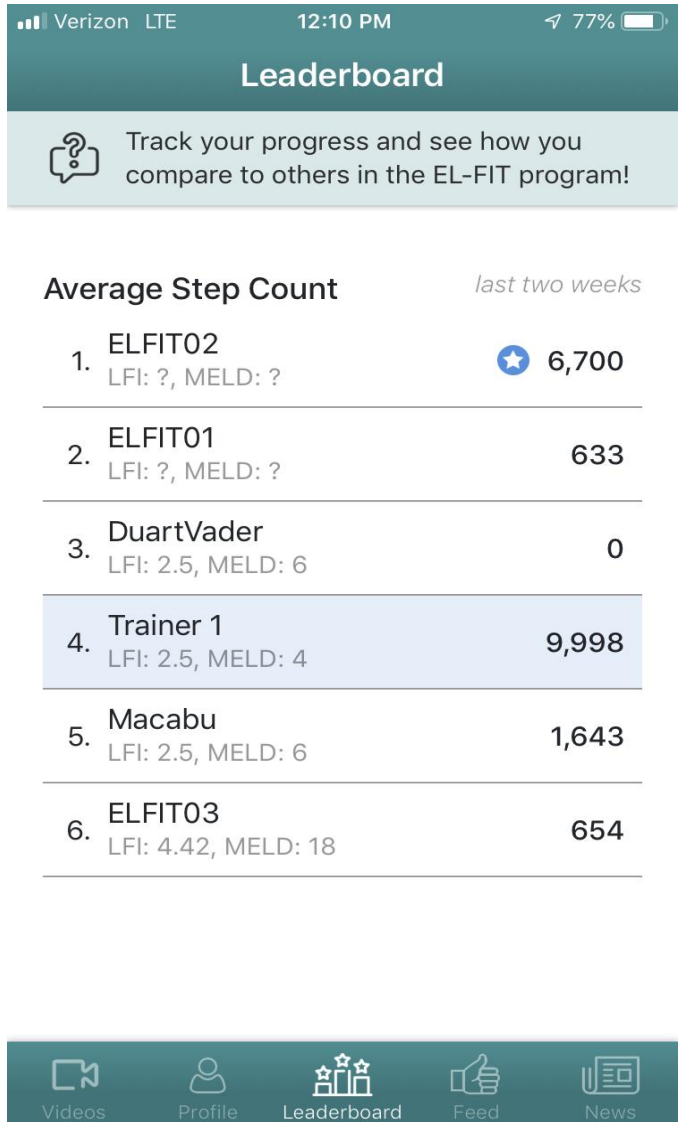
DEMONSTRATION

Education / Training videos

EL-FIT: *E*xercise and *L*iver *FIT*ness







A tool to create an exercise community and engage patients with cirrhosis

Safety issues for exercise in cirrhosis

- Monitor at each LT-PT visit:
  - Falls or other injuries, and muscle cramps
  - Barriers to exercise or becoming physically active
    - Discuss medical barriers with MD to improve adherence

Current Hepatology Reports
https://doi.org/10.1007/s11901-018-0404-z

PORTAL HYPERTENSION (J GONZALEZ-ABRALDES AND E TSOCHATZIS, SECTION EDITORS)

Is Exercise Beneficial and Safe in Patients with Cirrhosis and Portal Hypertension?

Elliot B. Tapper[1] & Roberto Martinez-Macias[2] & Andres Duarte-Rojo[2]

Exercise-induced increase in portal pressure

- Exercise increases portal hypertension
  - Effect was transient with return to normal after 5 min

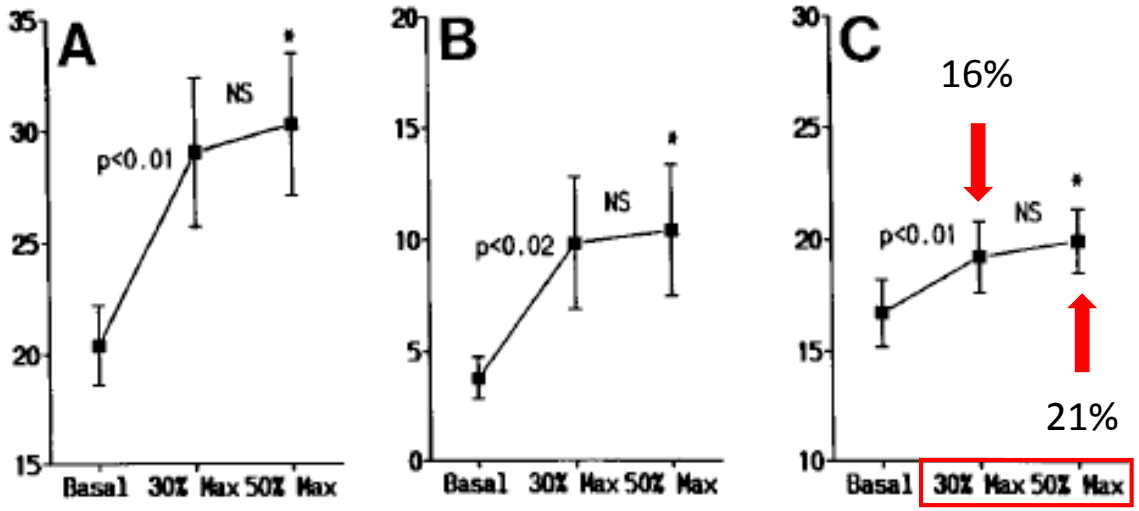


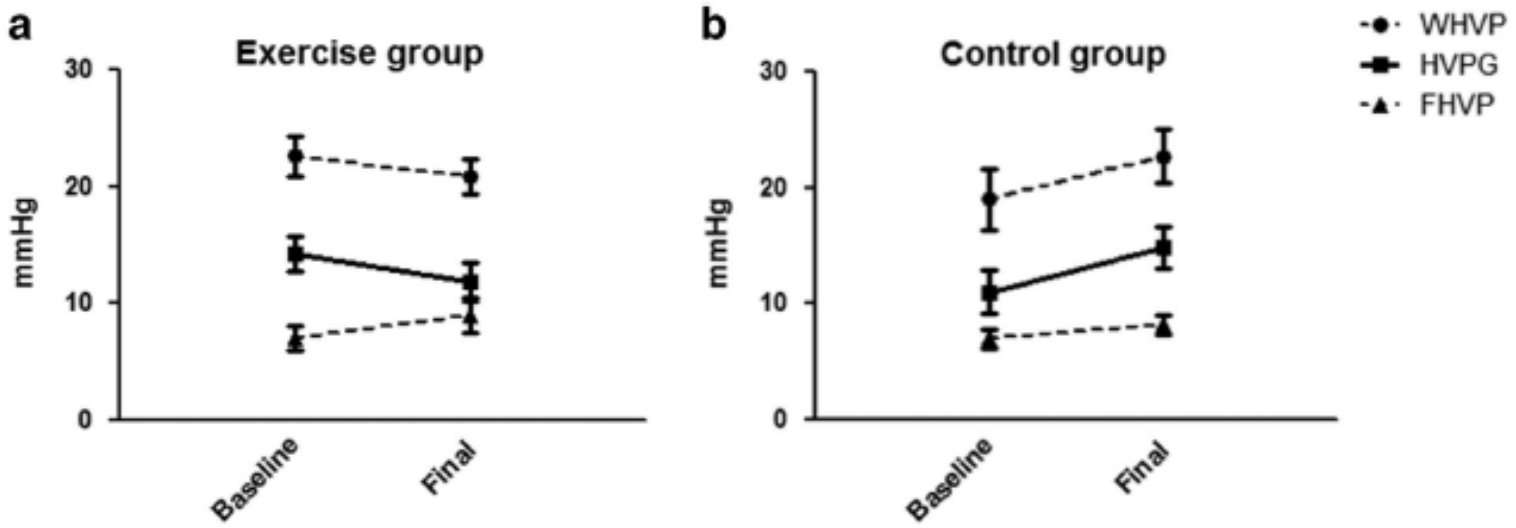
Figure 1. Effects of graded exercise (30% and 50% of target workload) on (*A*) WHVP, (*B*) FHVP, and (*C*) HVPG. *$P < 0.01$ vs. basal. Values are expressed in mm Hg.

No increase in GI bleeding associated to exercise

Garcia-Pagan. Gastroenterology 1996;111:1300
Bandi. Hepatology 1998;28:677

Physical training reduces in portal pressure

- RCT → 210-min moderate exercise/week vs. control for 14 weeks
  - 29 patients w/HVPG at baseline and end of study (14 exercise)



Appropriate exercise effort (Borg 12-14)

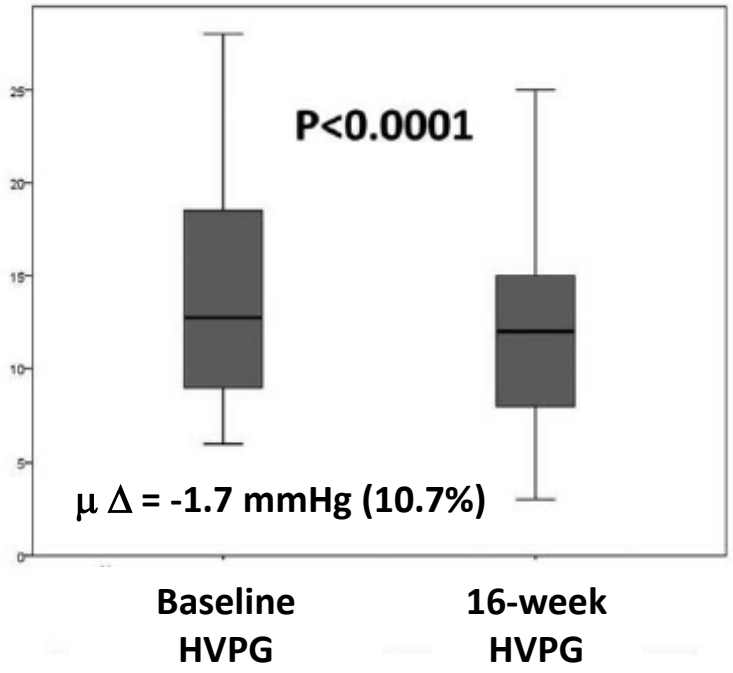
No weight changes in either group

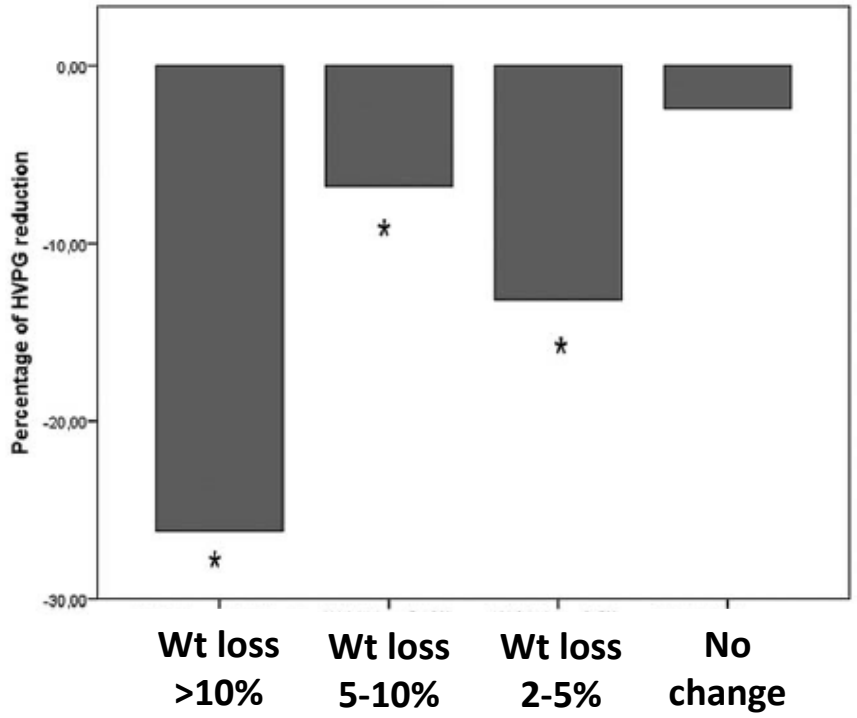
Supervised (CP rehab)

Macias-Rodriguez. Clin Transl Gastroenterol 2016;7:e180

Physical training reduces in portal pressure

- ONCT → 60-min exercise/week + (hypo)diet for 16 weeks
  - 60 patients w/HVPG at baseline and end of study (10 lost)

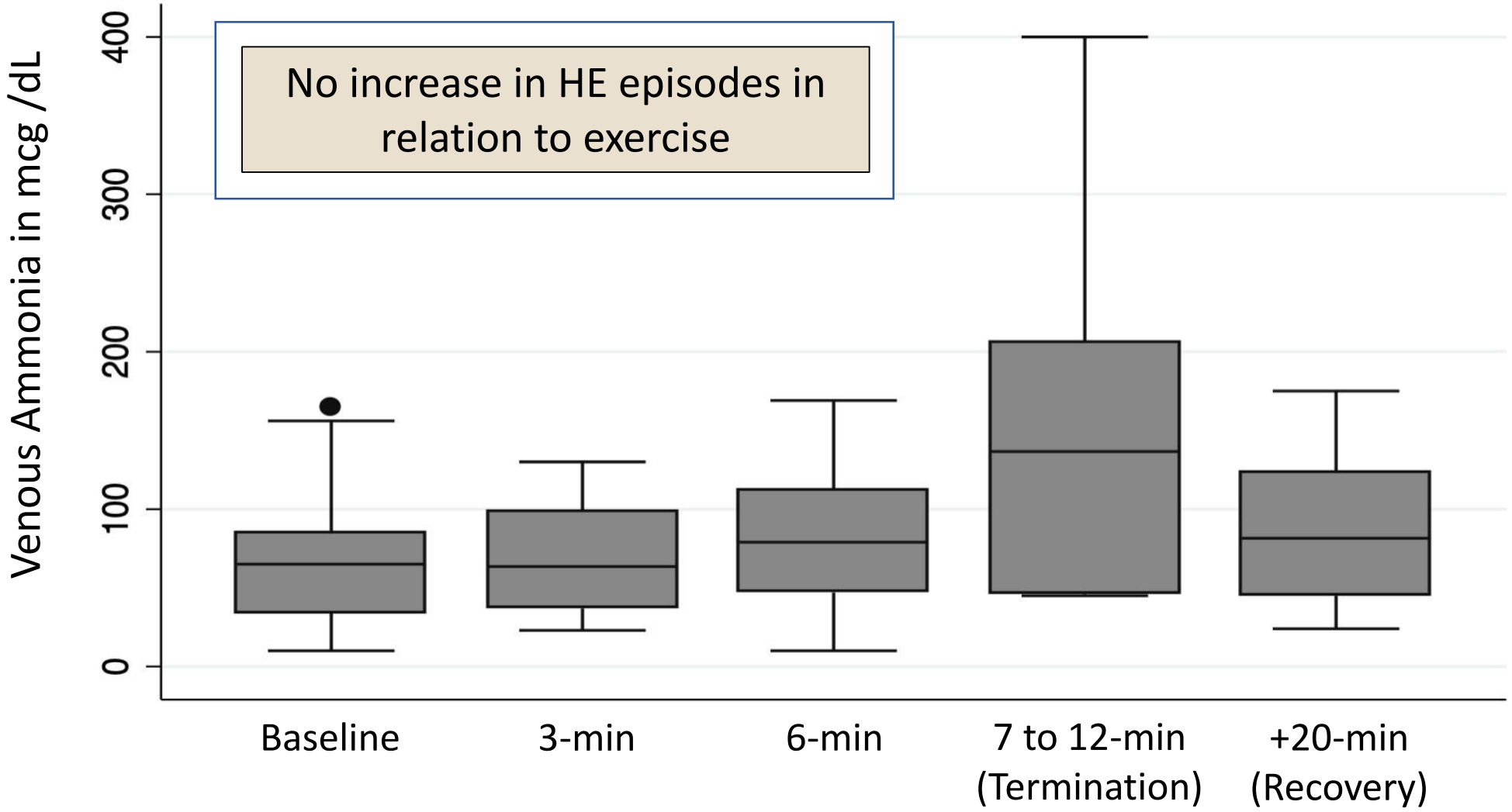




Weight loss linked to HVPG drop

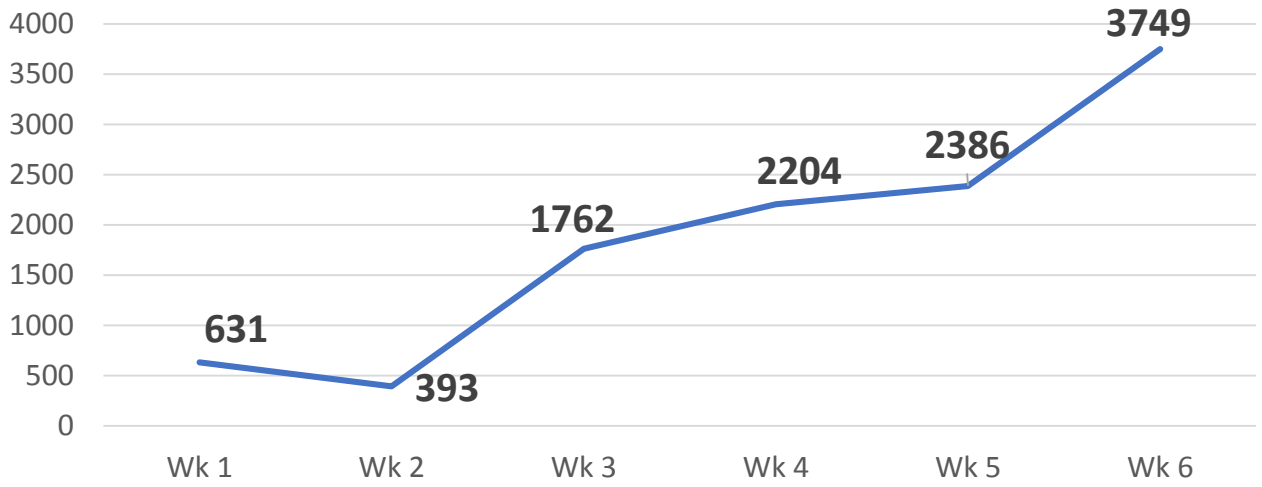
Berzigotti. Hepatology 2017;65:1293

Exercise-induced hyperammonemia



Let's close with a case…

- Mr. A is a 64-year-old with cryptogenic (NASH risk factors) cirrhosis
  - CTP 9 (Albumin 2.8, prior HE, ascites) & MELD-Na 19
  - BMI 33, no medical contraindication for LT



LFI 4.86

LFI 4.28

Take home messages

- Frailty is present in ≈25% of transplant candidates on the waitlist
- Frailty is associated with ↑ mortality and other poor outcomes
- Performance-based timely diagnosis (+ serial monitoring) is key
- Exercise is the only promising strategy to battle frailty and sarcopenia
  - Multiple benefits and safe in spite of ESLD and portal hypertension
- Prehabilitation strategies
  - **Home-based** vs. supervised at facility (only former can be generalizable)
- UPMC LT prehabilitation program
  - Fundamentally home-based taking advantage of novel technology

Acknowledgements

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  - Creative Services and trainers at UAMS
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    - E. Tapper (U. Michigan)
  - Arny Ferrando (UAMS)
  - W. Ray Kim (Stanford)

Sponsors:

Thanks!

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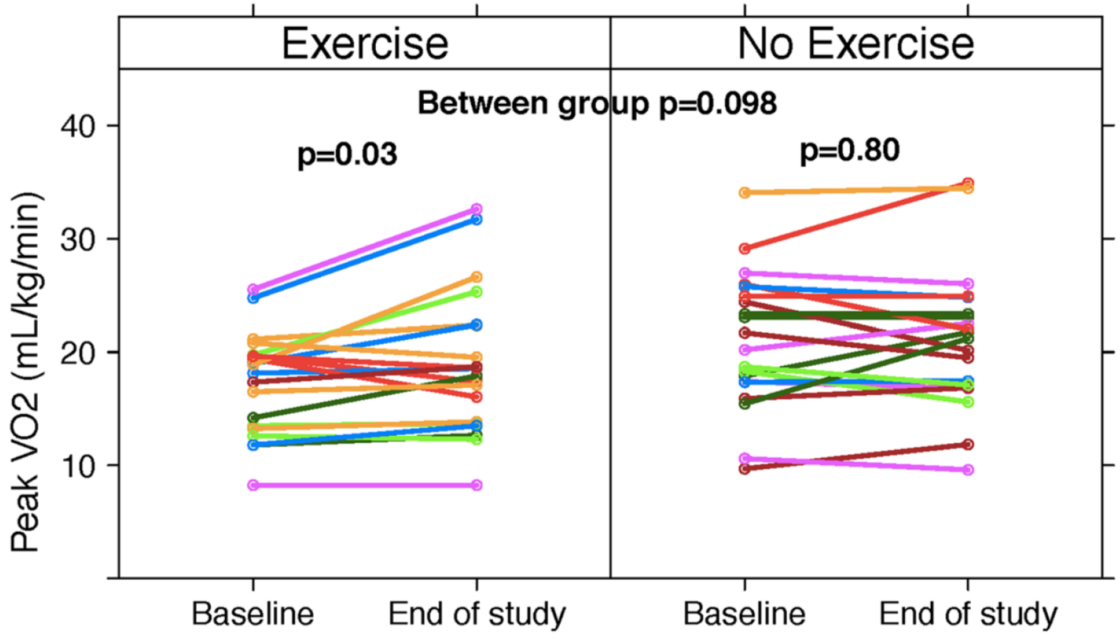
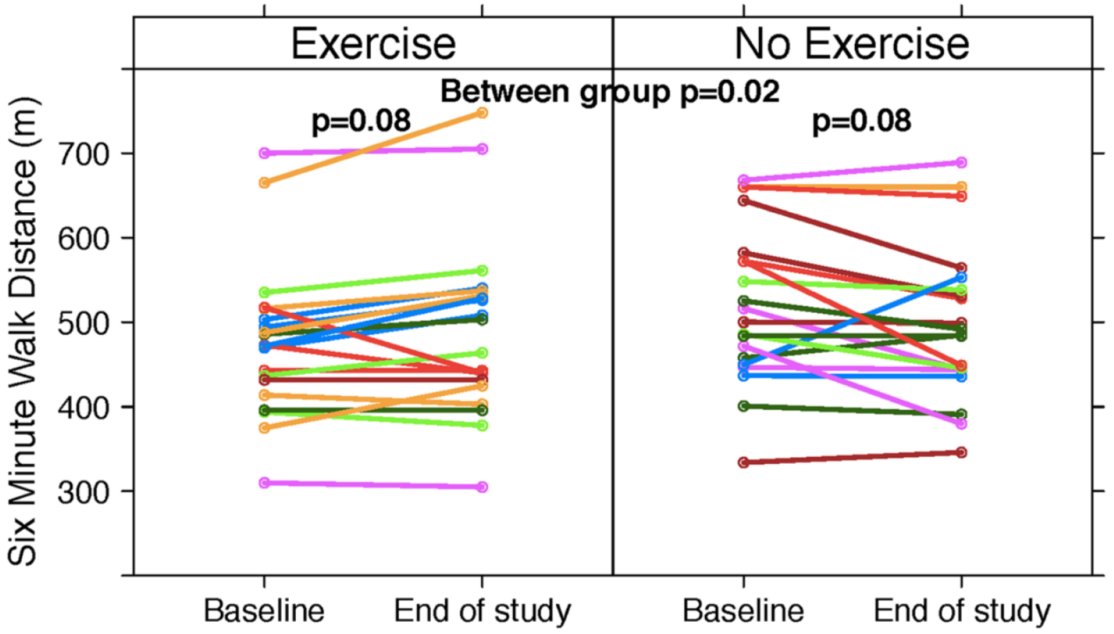
Impact on cardiopulmonary fitness

- Peak VO_2 from CPET and distance from 6-MWT





Home-based (structured)

Kruger. Sci Reports 2018:8:99

Exercise recommendations (general outline)

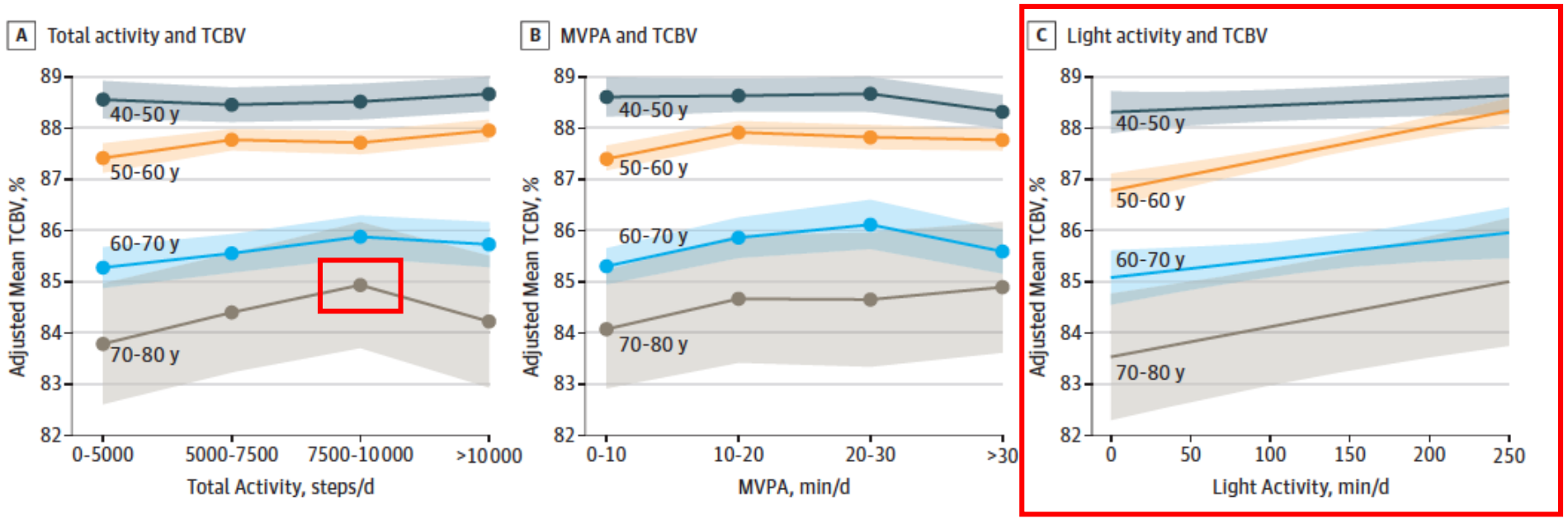
- Difference between exercising and being physically active
- Exercise 30 min per day on 5 days of week (walking is the easiest)
  - Bouts of exercise of at least 5-10 min
  - As many as needed (spaced out throughout the day) to add up 30 min
- Combine aerobic (3/5) and resistance (2/5) training
- Educate regarding rate of perceived exertion
  - Favor moderate intensity (Borg 12-13, or “talk test”)
- Follow exercise phases:
  - warm-up → conditioning → cool down/stretching

Exercise recommendations (safety issues)

- Exercise prescription safety checklist:
  - If LVP or thoracocentesis, have them properly scheduled not to limit mobility
  - Limit weights / machine lifting to 2-3 pounds (favor repetitions)
  - Have caregiver available when exercising, particularly if frail or HE
  - If stability issues or falls, exercise next to sturdy bars, countertops, sofa, etc.
  - Use appropriate shoes (rubber sole), exercise on an even floor free of clutter
  - Pace-out exercises to prevent exhaustion
  - Maintain hydration (consider need for fluid restriction for hyponatremia)

Should we focus on walking..?

- Framinham Heart Study
  - 2354 participants using an accelerometer and having MRI between 2009-2014

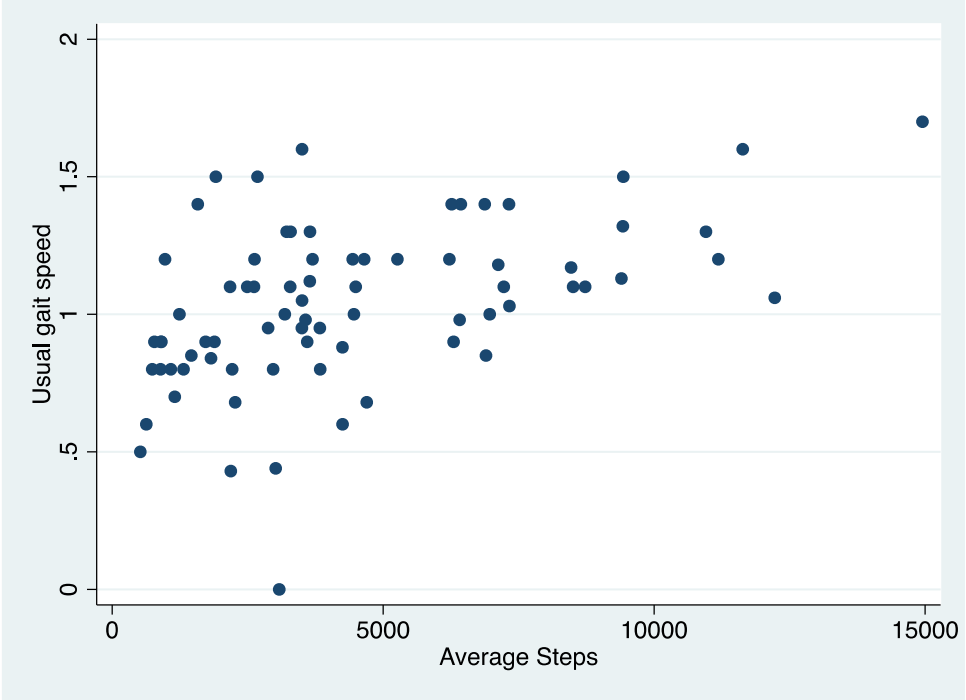


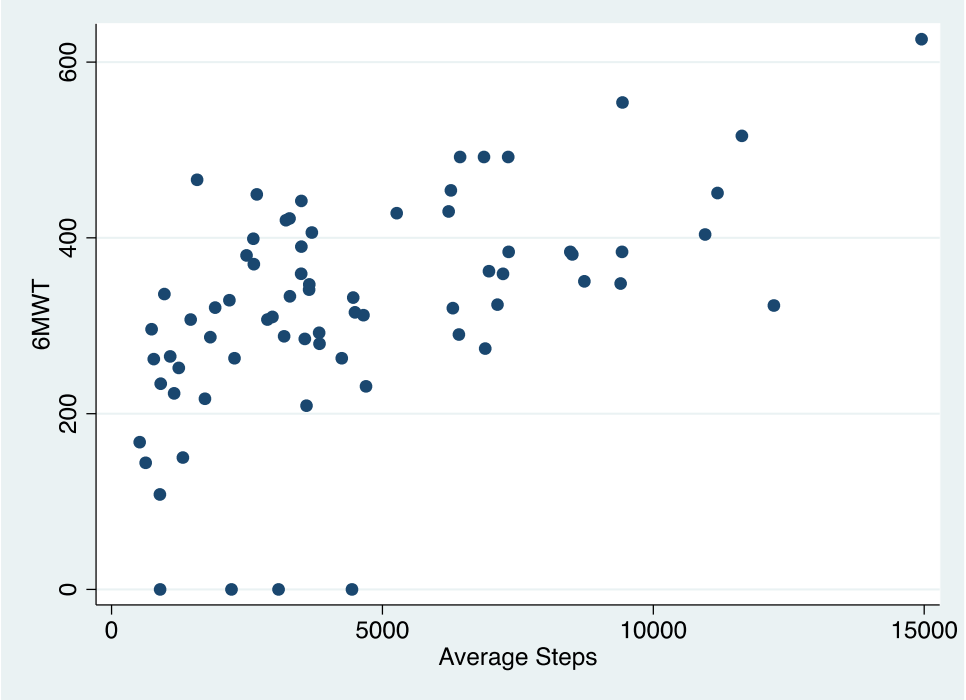
Each hour of light activity and/or walking >7500 steps/day decreased brain aging

Spartano. JAMA Network 2019;2:e192745

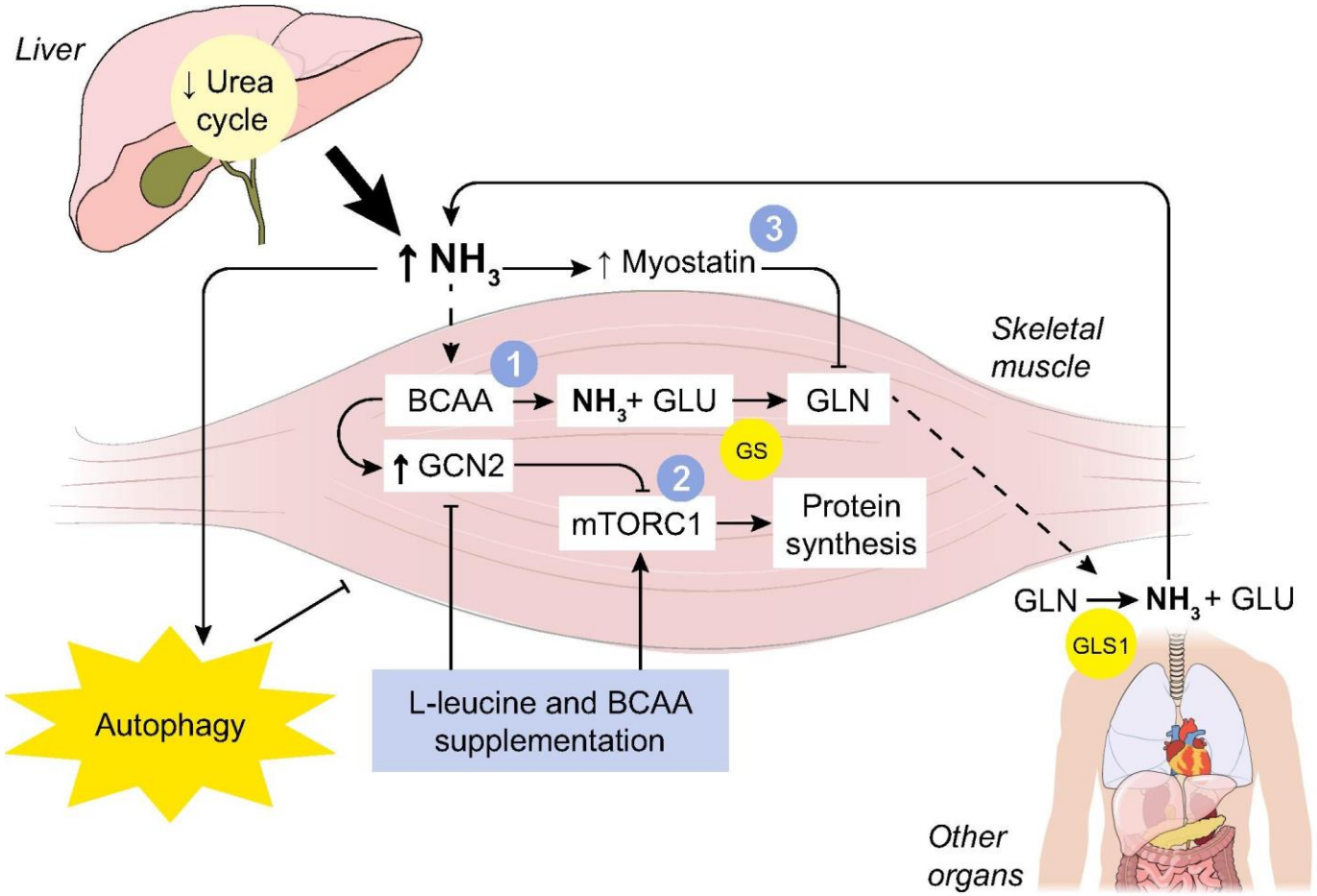
How should we define frailty?

- Other performance-based assessments





The muscle-NH_3 vicious cycle



Tandon. J Hepatol 2019;69:1164

Exercise safety concerns in cirrhosis

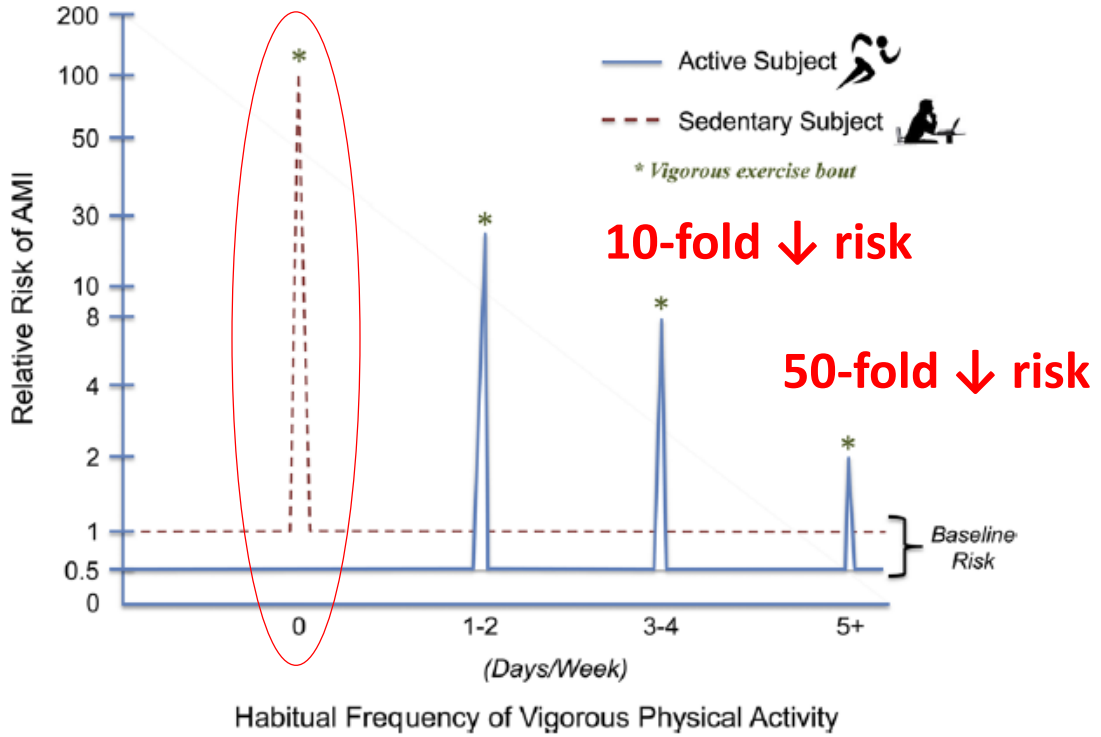
- From clinical trial's experience

Less / 'as expected' ASCVD risk

3 in 147 (2%) positive cardiac stress tests in cirrhosis (EKG)

129 in 1500 (9%) positive cardiac stress test in sportsmen

Exercise decreases AMI risk



Riebe. Med Sci Sports Med 2015;47:2473

Tapper. Curr Hepatology Rep 2018;17:175 / Hupin. Int J Cardiol 2018;257:16