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

<table>
<thead>
<tr>
<th></th>
<th>5/09/19</th>
<th>11/21/19</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFI</td>
<td>4.67</td>
<td>5.19</td>
</tr>
<tr>
<td>- Hand grip</td>
<td>16 kg</td>
<td>18 kg</td>
</tr>
<tr>
<td>6MWT</td>
<td>180 m</td>
<td>N/A</td>
</tr>
<tr>
<td>UGST</td>
<td>0.6 ms</td>
<td>N/A</td>
</tr>
<tr>
<td>Daily step count</td>
<td>N/A</td>
<td>540</td>
</tr>
</tbody>
</table>
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**?
Frailty and its associated clinical outcomes

- Infections
- LT complications
- Hospital admission
- Prolonged hospital stay
- Falls
- Increased healthcare costs
- Mortality
Frailty and its associated clinical outcomes

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

Frailty increases mortality by 19-45% (particularly MELD<18)

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

sHR 1.98 (1.07-3.67)
sHR 1.90 (1.28-2.80)

Frailty and its associated clinical outcomes

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

\[ \text{Ascites: } \text{sHR} \ 1.52 \ (1.14-2.05) \]
\[ \text{HE: } \text{sHR} \ 1.84 \ (1.38-2.45) \]
\[ \text{Frailty: } \text{sHR} \ 2.38 \ (1.77-3.20) \]
\[ \text{Frailty: } \text{sHR} \ 1.82 \ (1.31-2.52) \]

\[ p<0.02 \]
Some questions arising from case...

- Can this patient be transplanted?
  - Yes → What are the risks?
  - No
    - Is frailty enough reason to deny LT?
    - No → What to do about frailty?
    - Yes → How should we define frailty?
Decision making in frailty...

- Assess frailty within its clinical context

<table>
<thead>
<tr>
<th>Is Frailty REVERSIBLE?</th>
<th>What is the patient’s RESILIENCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute vs. Chronic</td>
<td>Age</td>
</tr>
<tr>
<td>Inpatient vs. Outpatient</td>
<td>Cognitive status</td>
</tr>
<tr>
<td>Hepatic vs. Non-Hepatic</td>
<td>Severity / chronicity of comorbidities</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>ΔLFI per 3 months</th>
<th>6 month</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved (16%)</td>
<td>0.6%</td>
<td>1.2%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Stable (35%)</td>
<td>7.0%</td>
<td>10%</td>
<td>17.3%</td>
</tr>
<tr>
<td>Moderate worsening (23%)</td>
<td>8.4%</td>
<td>17.2%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Steep worsening (26%)</td>
<td>12.1%</td>
<td>22.5%</td>
<td>35.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subhazard Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariable</td>
</tr>
</tbody>
</table>

- ΔLFI 0.1-unit worsening:
  - Univariable: 3.9 (2.8-5.4) \(<0.001\)
  - Stepwise multivariable: 2.0 (1.3-3.0) \(<0.001\)

- Base LFI 0.1-unit increase:
  - Univariable: 1.0 (1.0-1.1) \(<0.001\)
  - Stepwise multivariable: 1.0 (1.0-1.1) \(<0.001\)

- MELDNa 5-unit increase:
  - Univariable: 1.2 (1.1-1.4) \(<0.001\)
  - Stepwise multivariable: 1.0 (1.0-1.0) \(<0.001\)

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
Some questions arising from case...

Can this patient be transplanted?  
Yes  
What are the risks? 

No  
Is frailty enough reason to deny LT? 

What to do about frailty? 

How should we define frailty?
How should we define frailty?

- American Society of Transplantation frailty toolkit

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

Lai. Am J Transplant 2019
How should we define frailty?

• Liver Frailty Index (LFI)

- Hand grip
- Five Chair stands (time)
- Balance Test: seconds on each position
How should we define frailty?

- Liver Frailty Index (LFI)

Liver Frailty Index

Inputs: For instructions, see ① below.

1. Gender:  Male  Female

2. ① Dominant hand grip strength (kg):
   - attempt 1: 18
   - attempt 2: 19
   - attempt 3: 18
   - Avg: 18.33 kg

3. ① Time to do 5 chair stands:
   - 40 sec

4. ① Seconds holding 3 position balance:
   - Side: 10
   - SemiTandem: 8
   - Tandem: 4
   - Total: 22.00 sec

Results: refresh results

The Liver Frailty Index is 4.99.
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

\[ \rho = -36, \ p = 0.002 \]

\[ \rho = -60, \ p = 0.002 \]

<2500 steps/day
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?

Frailty Assessment

Pre-Frailty
- Home-based exercise
  - Home-health rehabilitation (4-12 weeks)
  - Close monitoring while on waitlist
- Reassess Severity (every 4-12 weeks)

Robust
- Goal: 150 min exercise/wk
- Build-up slowly: 10-min/d workout bid to tid
- Waitlist management as usual
- Reassess Severity (every 12 weeks)
- Proceed with liver transplant as usual

Pre-Frailty
- Home-based exercise
  - Home-health rehabilitation (4-12 weeks)
  - Close monitoring while on waitlist
- Reassess Severity (every 4-12 weeks)

Reassess Severity (every 12 weeks)
- Proceed with liver transplant if reversible frailty
- Posttransplant rehabilitation

Proceed with liver transplant if no deterioration

>50% waitlist

Universal Frailty Toolkit Use

Universal LTPT and exercise recs

Serial monitoring (mandatory)
## Exercise clinical trials in cirrhosis

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

- **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)**

Impact on cardiopulmonary fitness

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

Between groups, $p=0.03$

Home-based *(ad libitum)*
Impact on frailty

- Home-based exercise in waitlisted candidates

Frailty reduced from 50% to 11%
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 continuous 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 $\geq$ 80 steps per minute
    • **2500 to 4999** steps/day if frail
    • **5000 to 7499** steps/day if pre-frail
    • **$\geq$7500** if non-frail
EL-FIT: Exercise and Liver FITness

ASSESSMENT
Algorithm stratifies training intensity

Chair Exercises

DEMONSTRATION
Education / Training videos

TRACKING
Fitness (databases/statistics)

Cerner

Epic
EL-FIT: Exercise and Liver FITness

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

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

Eliot B. Tapper¹ & Roberto Martinez-Macias² & Andres Duarte-Rojo²
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
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)

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

- Weight loss >10%
- Weight loss 5-10%
- Weight loss 2-5%
- No change

μΔ = -1.7 mmHg (10.7%)
Exercise-induced hyperammonemia

Venous Ammonia in mcg/dL

No increase in HE episodes in relation to exercise
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
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

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

Thanks!

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Impact on cardiopulmonary fitness

- Peak VO₂ from CPET and distance from 6-MWT
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..?

- Framingham 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.
How should we define frailty?

• Other performance-based assessments
The muscle-NH$_3$ vicious cycle

Liver

↓ Urea cycle

↑ NH$_3$

↑ Myostatin

1. BCAA → NH$_3$ + GLU
2. mTORC1
3. GCN2

Protein synthesis

Skeletal muscle

GLN → NH$_3$ + GLU

GLN

L-leucine and BCAA supplementation

Autophagy

Other organs

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