Impact of Frailty on Transplant Outcomes

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Relevant Financial Relationship Disclosure Statement

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We *will not* discuss off label use and/or investigational use of drugs/devices.

The following relevant financial relationships exist related to our role in this session: None

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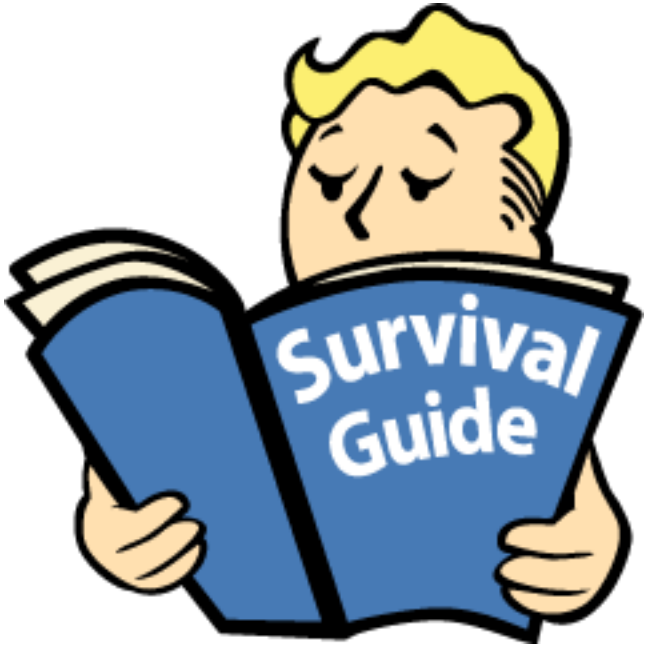
The Goals of Solid Organ Transplant

Increased quantity of life

Increased quality of life



Common Criteria for Transplant Candidacy

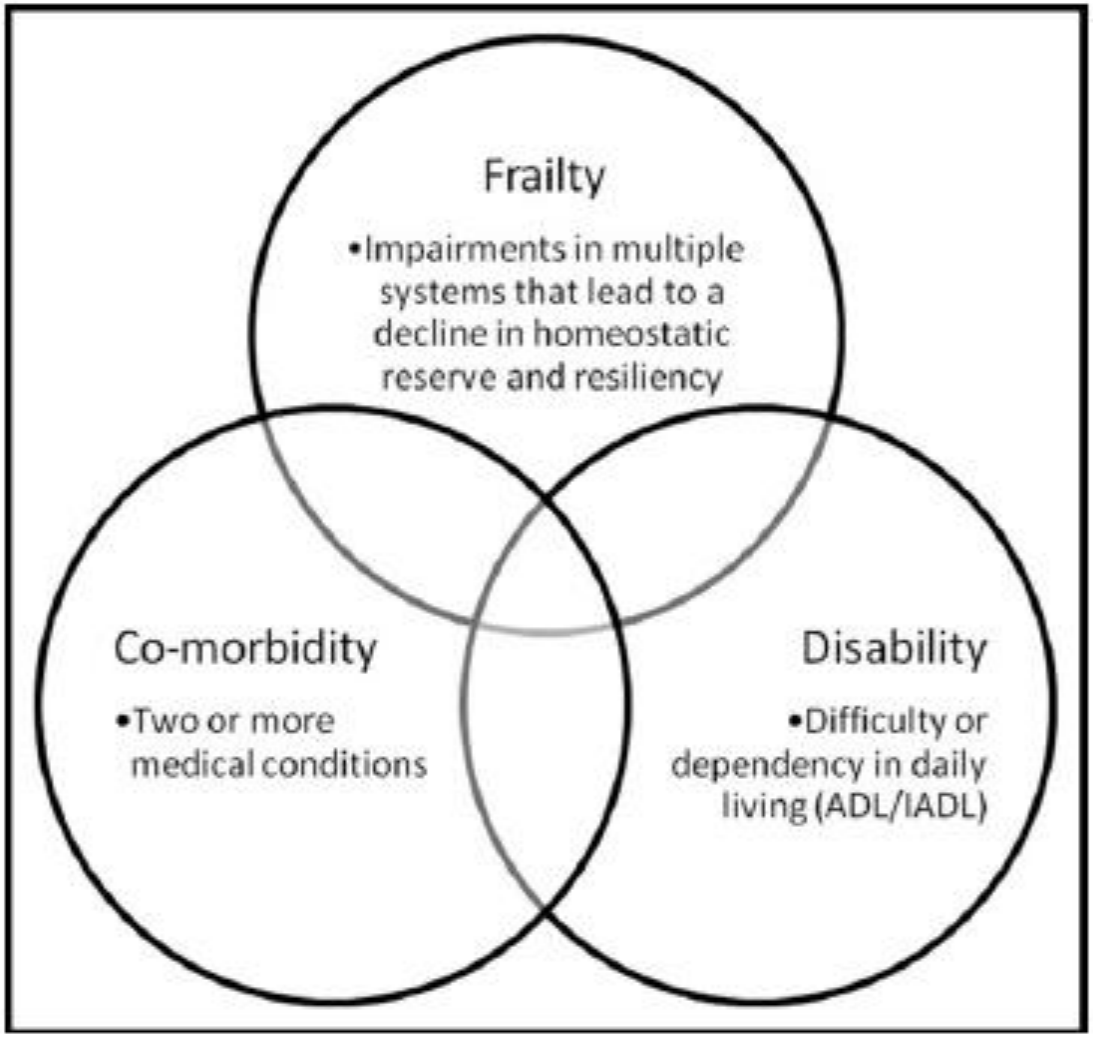
- Patient suffers from end-stage organ disease
- There are no other non-transplant therapies that could enhance quantity and quality of life
- The candidate's quantity and quality of life is most likely to be improved by a solid organ transplant
- The candidate is expected to be able to withstand the challenges of surgery and recovery
- The candidate is predicted to be able to care for the transplanted organ

Frailty

- Frailty is characterized as increased vulnerability to acute stressors due to a decline in overall function and reduction in physiologic reserves.
- Elements frequently described include sarcopenia, and reductions in physical activity, energy expenditure, nutritional intake, weakness, gait speed.
- Not a new concept – but in the most recent decade renewed attention has been focused on it.
- The “eyeball” test – subjective, insensitive to small changes, not amenable to research; when chronological age and biological age are less well correlated, frailty is ***one*** of the elements that may be contributing to the mismatch.
- Frailty is common in those with end-stage organ disease, and affects waitlist and post-transplant mortality.

Fried, 2001; Singh, 2008; Jha, 2016; Eisen, 2016; Kobashigawa, 2018

Frailty is Interrelated with Comorbidity and Disability



Afilalo, 2012

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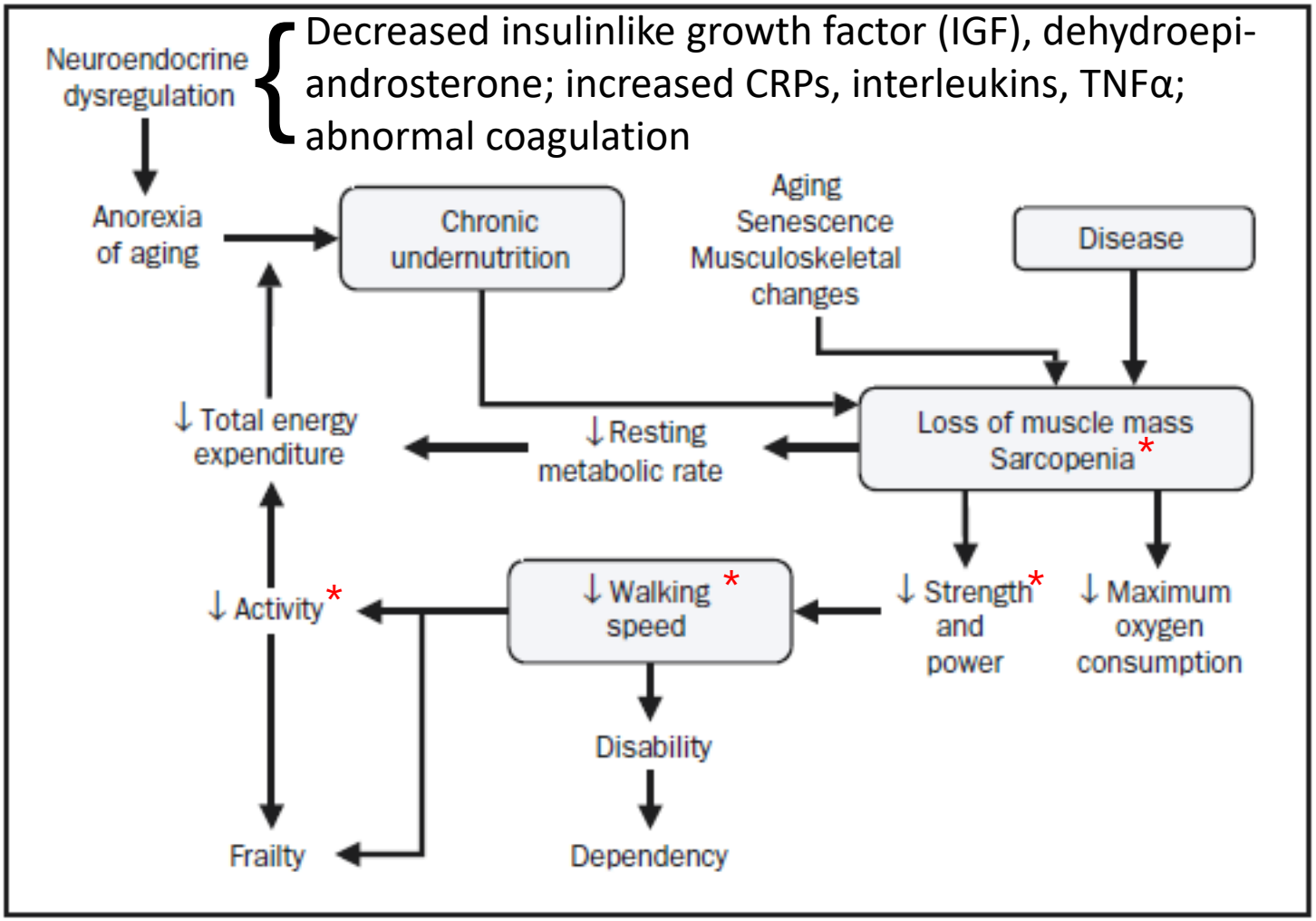
Physiology of Frailty



Singh, 2008; Singer, 2015

Common Assessments Tools in Transplant related to Frailty

- 6-minute walk test (6MWT)
- Karnofsky Scale
- Cardiopulmonary exercise test
- Short Physical Performance Battery
- Activities of Daily Living (ADLs), Instrumental Activities of Daily Living (IADLs)

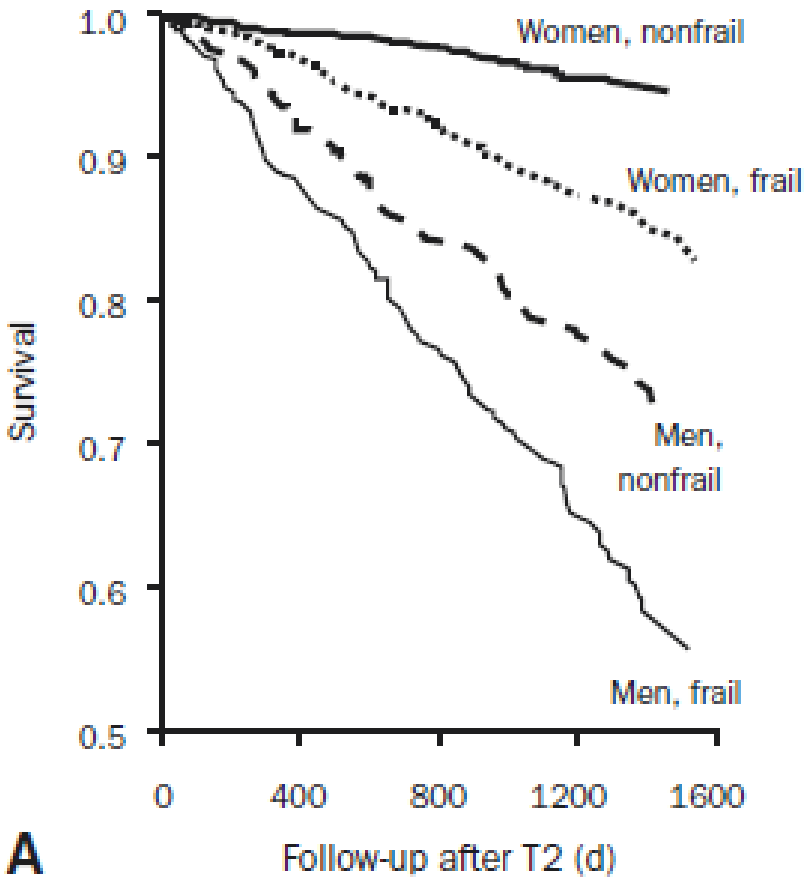
Research in Frailty Assessment

- Guralnik (1994)
  - Short Physical Performance Battery (SPPB) (in geriatrics)
  - Scores based on balance, 4-meter gait speed, timed sit-to-stand x5 test
  - Lower performance scores associated with disability, mortality, and nursing home admission
- Linda Fried (2001)
  - Fried Frailty Phenotype (FFP) is based on 5 metrics (grip strength, weight loss, slow walking speed, low physical activity, exhaustion)
  - Score yes in 1-2 categories = pre-frail; yes in 3-5 categories = frail

Research in Frailty Assessment

- Puts (2005)
  - Longitudinal Aging Study Amsterdam (LASA) included more than 2700 subjects
  - Considered 19 criteria, expanding on those outlined by Fried
- Kenneth Rockwood (2005)
  - Scores based on accumulation of deficits (clinical symptoms, laboratory abnormalities, functional impairments, comorbities and disabilities (more deficits = more frail)
  - Broader basis of assessment, considering some 70 potential indicators of frailty

LASA Survival Outcomes and Frailty



Longitudinal Aging Study Amsterdam (LASA) (n = 2,257)

Puts, 2005

Table 2. Associations Between Single Frailty Markers and Mortality

Frailty Marker	Men	Women
	Relative Risk (95% Confidence Interval)	
Static, T2		
Body mass index $<23\ kg/m^2$	1.5 (1.0–2.2)†	1.8 (1.1–2.9)†
Low peak flow	2.0 (1.4–2.9)§	1.8 (1.1–2.8)†
Mini-Mental State Examination score <24	1.8 (1.3–2.5)‡	2.4 (1.6–3.7)§
Poor vision	1.4 (0.8–2.7)	1.7 (1.0–2.7)†
Poor hearing	1.3 (0.9–1.9)	1.5 (0.9–2.4)
Incontinence	1.1 (0.8–1.6)	1.2 (0.8–1.8)
Low mastery	1.3 (0.9–1.8)	1.2 (0.8–1.8)
Depression	1.6 (1.1–2.3)†	1.7 (1.1–2.6)‡
Low physical activity	2.2 (1.6–2.9)§	3.7 (2.4–5.6)§
Dynamic, T1–T2†		
Weight loss	2.0 (1.3–2.9)‡	1.8 (1.1–3.0)‡
Decline peak flow	1.4 (1.0–1.9)	2.6 (1.6–4.1)§
Decline cognition	1.2 (0.8–1.6)	2.1 (1.4–3.2)§
Loss of vision	0.9 (0.6–1.4)	2.0 (1.3–3.1)‡
Loss of hearing	1.1 (0.8–1.5)	1.2 (0.8–1.9)
New incontinence	1.1 (0.7–1.7)	1.3 (0.8–2.2)
Decline in mastery	1.1 (0.7–1.6)	1.4 (0.9–2.3)
Increase depressive symptoms	2.4 (1.7–3.5)§	2.0 (1.3–3.0)§
Decline in physical activity	1.3 (0.8–2.0)	2.1 (1.3–3.6)§

Note: Covariates included age and education. Static frailty refers to low functioning at T2, and dynamic frailty refers to change in functioning between T1 and T2.

† All frailty markers with change between T1 and T2 are corrected for the baseline measurement.

†$P<.05$; ‡$P<.01$; §$P<.001$.

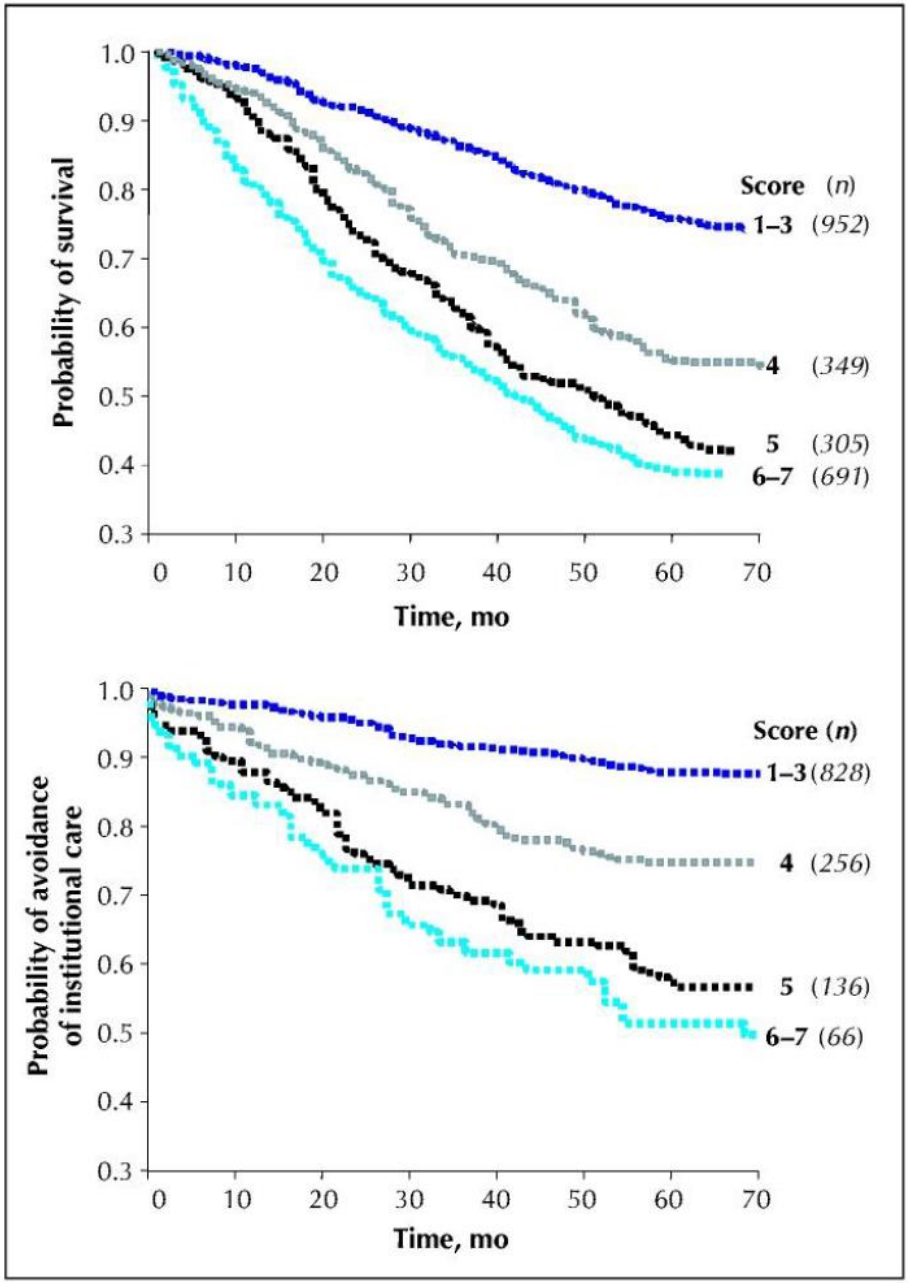


Fig. 1: Kaplan–Meier curves, adjusted for age and sex, for study participants (*n*) over the medium term (5–6 years), according to their scores on the CSHA Clinical Frailty Scale. Some scores were grouped. Top: Probability of survival. Bottom: Probability of avoidance of institutional care.

Rockwood, 2005

Frailty in the Abdominal Transplant Candidate or Recipient

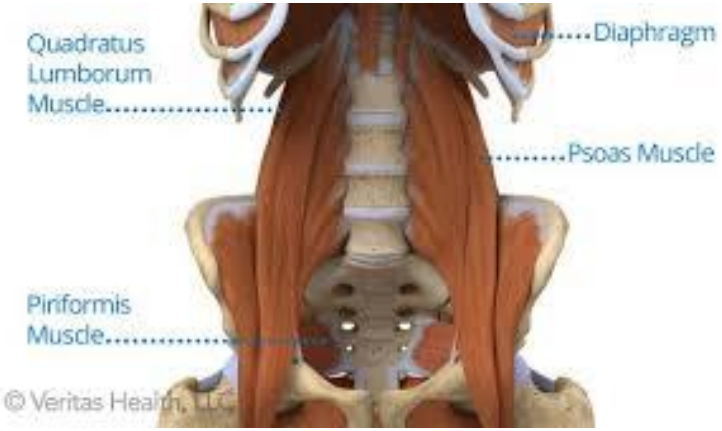
The Significance of Age and Frailty in Liver Transplant Candidates

- The mean age at time of liver transplantation is rising
  - Per UNOS data, recipients >65 yo comprised 7 % of total liver transplants in 2000 , but by 2010 were 11.3%, and were 19% of the total liver transplants in 2016
- Candidates $\geq$ 65 yo compared with $\leq$ 65 yo have a 35% increased risk of delisting for being too sick for transplant or death on the waitlist and 9% decreased odds of transplant
- In candidates >65 yo, poor physical function is associated with a nearly 3-fold increased odds of wait-list mortality compared with physically robust candidates less than 65 years

Kniepeiss et al 2011
Lai JC 2016
UNOS Data reports

Pathophysiology of Liver Disease Contributions to Frailty: Pre-transplant

- Sarcopenia, substantial loss of muscle mass and strength, occurs in 38-66% of people with cirrhosis
  - Thought to be caused by malnutrition, metabolic, hormonal, and inflammatory changes in ESLD, and hepatic encephalopathy
  - Presence of sarcopenia is associated with decompensation, increased complications, and a two-fold increase in waitlist mortality when adjusted for both MELD score and age



Lai JC 2016
Kachaamy T, 2012
Bhanji RA et al, 2017

Pathophysiology of Liver Disease Contributions to Frailty: Pre-transplant

- In assessing Frailty via Gait speed, a 0.1 m/s decrease in gait speed was associated with a significant increase in hospitalization for cirrhosis-related complications (Bhanji RA et al, 2017)
  - Patients with a gait speed of 1 meter/s (normal), averaged 6 hospital days/year versus 21 hospital days/year in those with a gait speed of 0.5 m/s and 40 days/year in those with gait speeds of and 0.25 m/s
- Higher MELD score, higher rates of ascites, and incidence of Hepatic Encephalopathy are also more common in frail individuals (Bhanji RA et al, 2017; Lai JC 2016)
- U of MI study found both high MELD and frail ESLD patients had low QoL scores, but the difference between frail & non-frail patients was much greater than in patients with low vs high MELD scores (Derck JE 2015)

Frailty Predicts Waitlist Mortality in Liver Transplant Candidates

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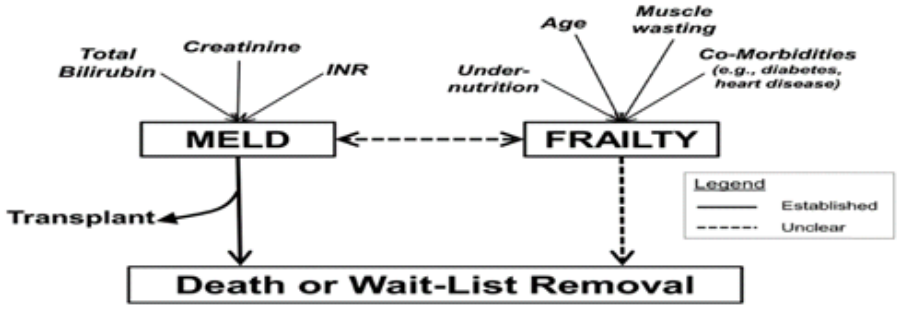

Figure 2: Conceptual model of the relationship between Model for End-Stage Liver Disease (MELD), frailty and waitlist outcomes.

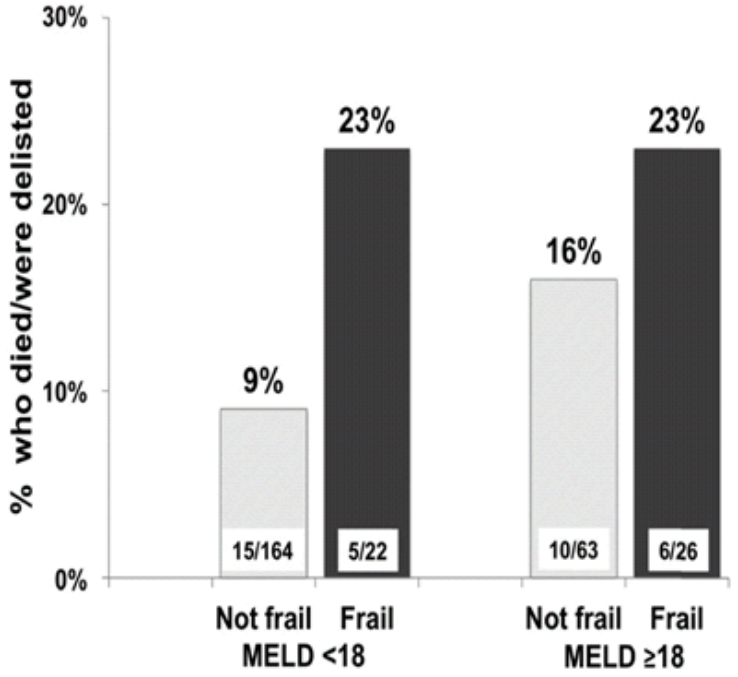

Figure 1: Proportion of candidates who died or were delisted, by frail status (Fried Frailty score ≥3) and Model for End-Stage Liver Disease (MELD) score category (<18 or ≥18).

- MELD Score underestimates risk of mortality in frail liver transplant candidates, even with adjustment for severity of liver disease

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FrAILT Pre-Liver Transplant Assessment

- FrAILT was originally a study that has now resulted in a clinical protocol for assessing and predicting Frailty in Liver Transplant
- Frailty adds 9 points to MELDNa score
- MELDNa+frailty index more accurately predicted 16% of deaths/delistings ($P = 0.005$) and 3% of nondeaths/delistings ($P = 0.17$), which are statistically significant ($P < 0.001$) when combined in comparison to MELDNa alone
- Compared to those with frailty index scores <20th percentile (good), patients with cirrhosis and frailty index scores >80th percentile (poor) were more impaired by gait speed, difficulty with ADLs, exhaustion, and low physical activity ($P < 0.001$ for each).

Lai JC 2017

FrAILT Assessment

FrAILT™
Functional Assessment in Liver Transplantation

Liverfrailtyindex.ucsf.edu

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:	
				kg

3. ⓘ Time to do 5 chair stands: sec

4. ⓘ Seconds holding 3 position balance:

Side:	SemiTandem:	Tandem:	Total:	
				sec

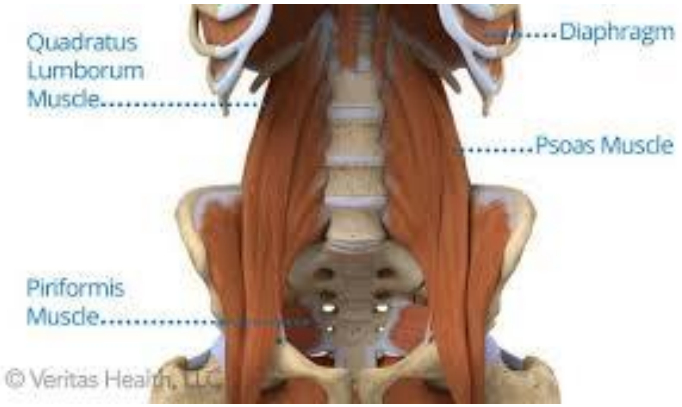
Results: refresh results

The Liver Frailty Index™ is ____

Decimal precision:
2

Pathophysiology of Liver Disease Contributions to Frailty: Post-Transplant

- 'Every 1000mm^2 in skeletal muscle mass areas of the psoas muscle at the 4th lumbar vertebra was associated with a 73% decreased risk in mortality' post-transplant



- Transplant recipients with BMI < 18.5 kg/m^2 experienced higher risk of death and graft loss compared with recipients with a BMI of 18.5–24.9 kg/m^2

Lai JC 2016

Frailty in Kidney Transplant

- Frailty is an independent predictor of longer LOS post kidney transplant
- Frailty independently predicts a 61% higher risk of early (< 30 days post-transplant) re-hospitalization, even adjusting for DGF
  - Frail younger recipients had the highest early readmission rate
  - Review of early re-hospitalization of Medicare claims kidney transplant recipients showed significant increases in death censored graft loss (83 vs 75% at 5 yrs), late hospital readmissions (30-365 days after transplant) and mortality (>1.43x higher)
- Frail recipients were have a 2x greater independent risk of DGF (Garonzik-Wang JM et al 2012)
- Frailty poses a 2x higher independent risk factor for mortality at 1, 3, and 5 years post transplant recipients

McAdams-DeMarco MA et al 2013; 2014; 2015; 2016

Frailty in Kidney Transplant

- Most frail Kidney Transplant candidates increase in frailty at 1 month post-transplant, return to pre-transplant frailty status at 2 months post, and are less frail than pre-transplant status at 3 months post-transplant
  - Hypothesized to be due to discontinuation of dialysis, improved appetite, increased QoL & physical activity
  - Pre-transplant, only frailty status at that time and DM were significant for change in pre-post Frailty scores
  - DGF was the only post-transplant score impacting frailty status

McAdams-DeMarco MA et al 2015

The Significance of Age and Frailty in Pancreas Transplant Candidate

- In pancreas transplantation, age is known to be the most significant risk factor for adverse outcomes post-transplant
  - Outcomes are worse in older vs younger transplant recipients (Foley et al., 2005).
- Diabetes may further increase the risk of negative outcomes

Kniepeiss et al 2011

Frailty: Inevitable?

Should we consider:

- Facilitating referral to exercise programs to improve gait speed, improve balance?
- Monitoring weight loss and consider dietary interventions to improve weight?
- Providing services/encourage for home support (from family caregivers or others) to address exhaustion, preserve energy?

Interventions to Improve Frailty in Transplant Candidates or Recipients

- Liver Transplant
  - Sarcopenia
    - Studies have shown increased oral intake, especially frequent snacks/supplements leads to increased muscle mass, and in 1 study, better survival
  - Wellnesstoolbox.ca
    - Evidence based exercise program to prevent Frailty for Liver Transplant candidates

Hanai T, 2015
Lai JC, 2017

Interventions to Improve Frailty in Transplant Candidates or Recipients

- Kidney Transplant 'Pre-habilitation'
  - 8.5 outpatient clinic weekly sessions
  - Diverse population, 23% frail pre Transplant
  - 100% of patients very satisfied with the experience
  - 61 % improvement in physical activity at 2 months post pre-habilitation program
  - LOS was shorter for KT recipients who participated in pre habilitation (5 vs 10 days)

McAdams-DeMarco MA, 2019

Frailty in the Thoracic Transplant Candidate or Recipient

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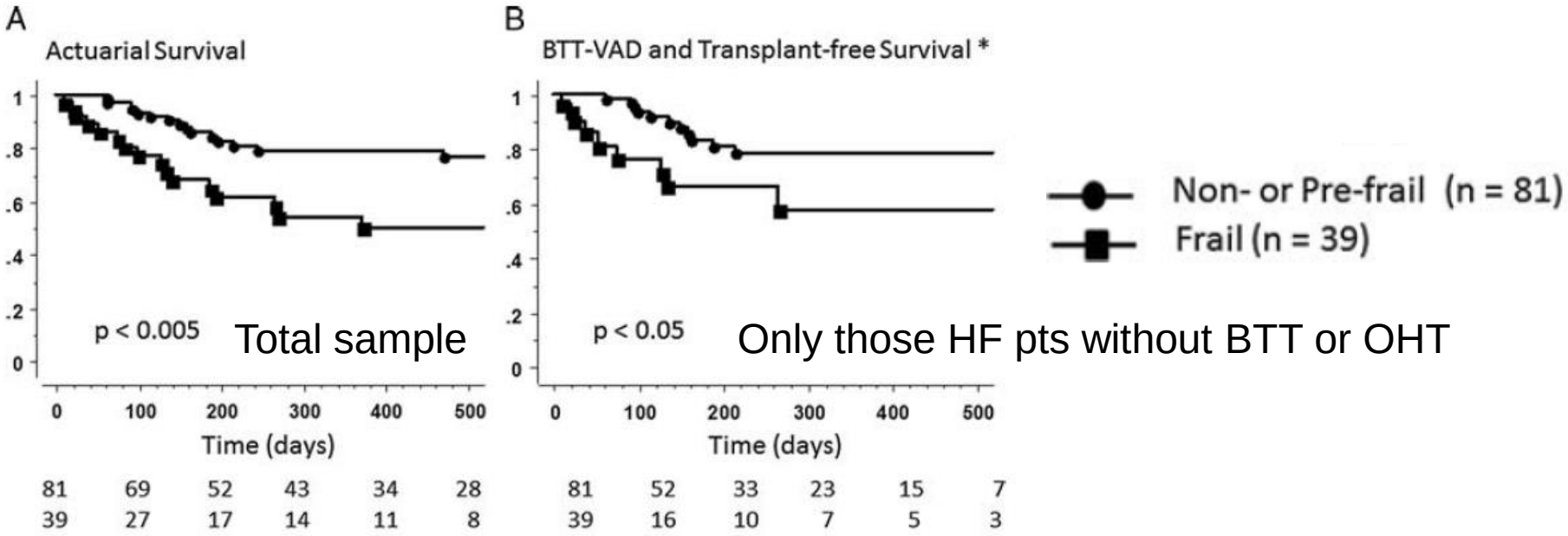
Frailty Predicts Mortality in Heart Transplant

- Jha and colleagues assessed 120 NYHA III-IV patients referred for or listed for heart transplant at their center beginning in 3/2013.
- Analysis included patients with on the list without intervention, with LVAD, with BiVAD, and after OHT.
- Frailty independently predicted all-cause mortality in the entire population (1-year actuarial survival for non-frail 79 ± 5%, for frail 54 ± 9%, $p<0.005$)
- It also predicted mortality within the group with no intervention (1-year actuarial survival 78 ± 6% for non-frail, 58 ± 12% for frail)
- Frailty was significantly associated with prolonged intubation, ICU LOS, hospital LOS and early mortality in those who underwent OHT (non-frail or pre-frail 100% survival at 12 months, frail 52 ± 23% at 12 months)

Sunita Jha, 2016



Total sample

Only those HF pts without BTT or OHT

TABLE 4.

Outcomes after heart transplantation stratified by frailty

	Total (n =34)	Nonfrail or prefrail (n = 25)	Frail (n = 9)
Age, y	49 ± 15	50 + 14	46 ± 18
Sex (male:female)	18:16	16:9	2:7
Intubation, h	28 (103)	27 (98)	110 (116)
ICU after HTx, d	7 (5)	6 (4)	8 (10)
LOS after HTx, d	25 (17)	24 (14)	27 (36)
Survival at 6 mo	93 ± 5%	100%	79 ± 14%
Survival at 12 mo	86 ± 8%	100%	52 ± 23%

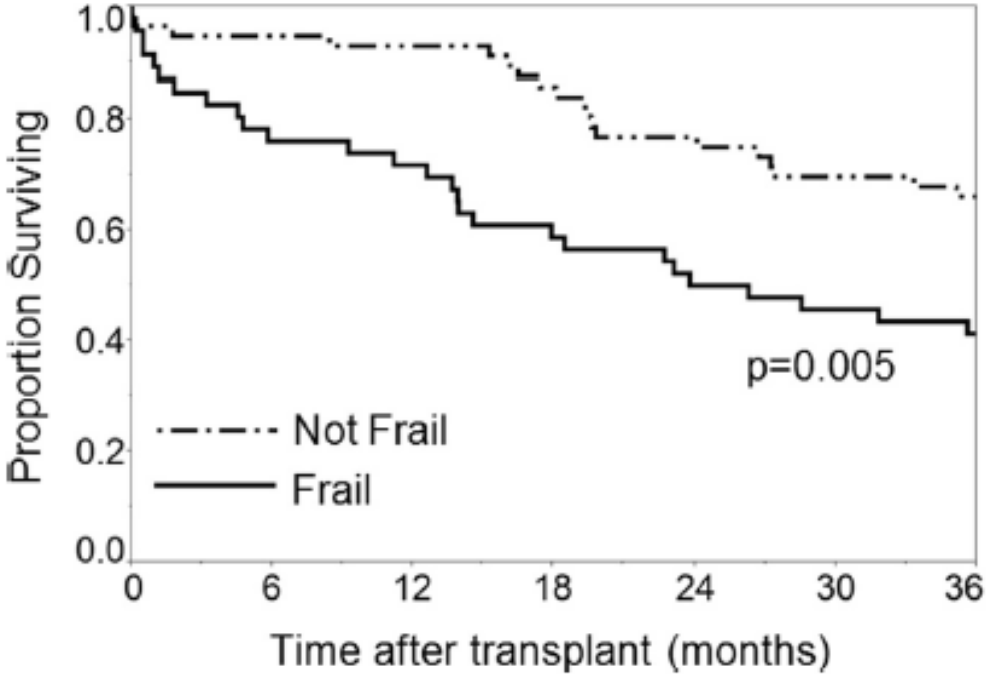
Values are mean ± SD for normally distributed continuous data, median (interquartile range) for non-normally distributed continuous data, and number for categorical data.
HTx indicates heart transplantation; LOS, length of stay.

Jha, 2016
McDonald, 2021

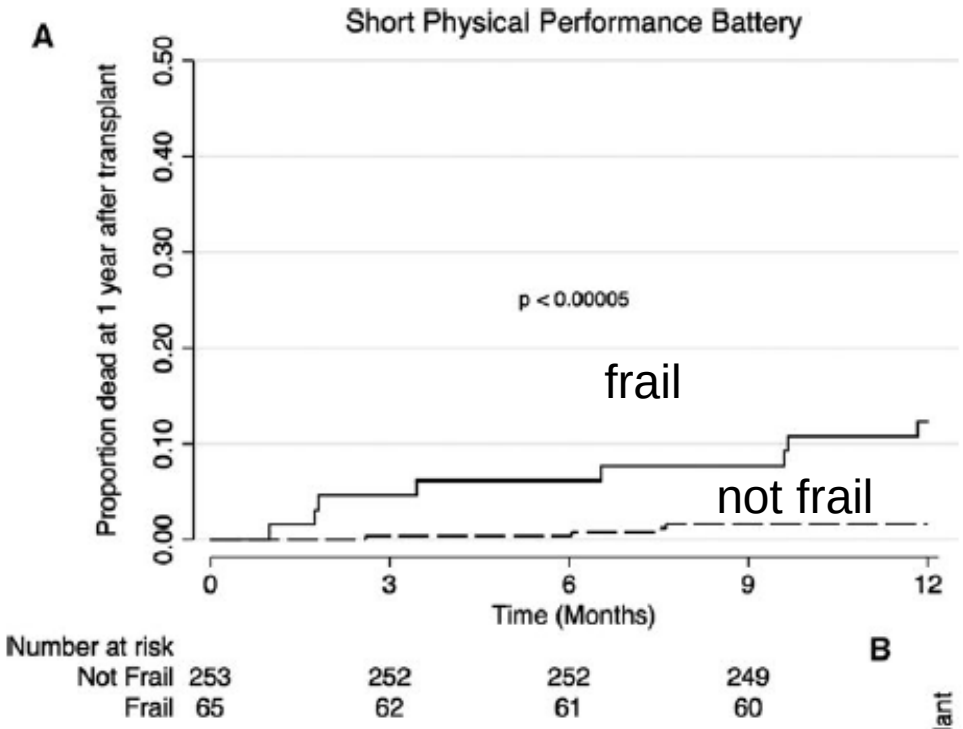
Frailty and Lung Transplantation

Wilson et al evaluated 102 patients who received a lung transplant (2002-2013) using the frailty deficit index 45% met frailty criteria (deficit index > 0.25)

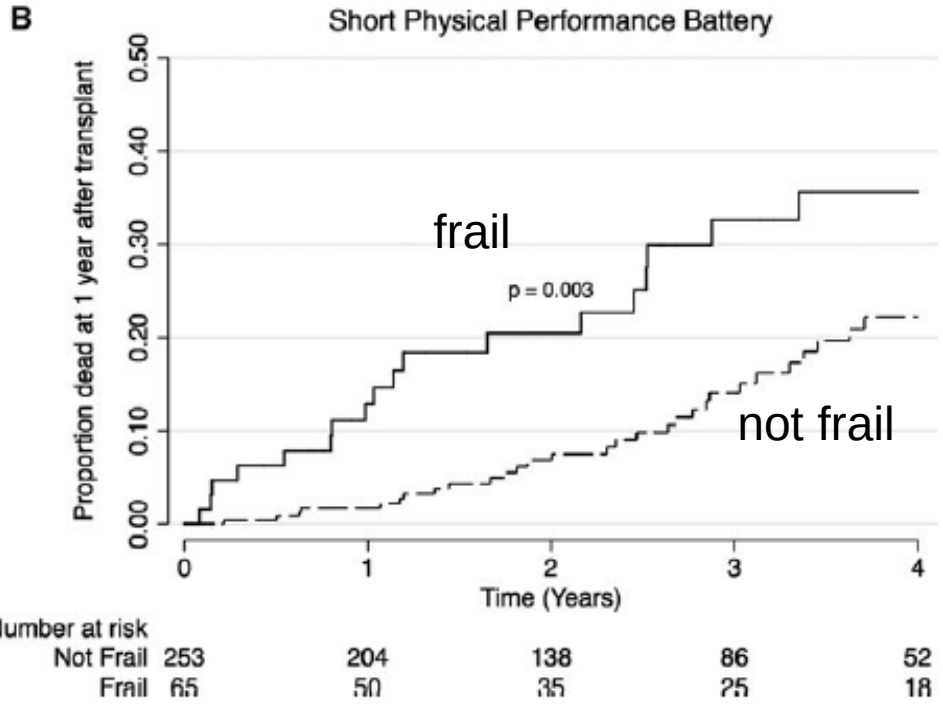
Pre-transplant frailty was significantly associated with early mortality (unadjusted HR 2.28, p=0.006)



Wilson, 2016



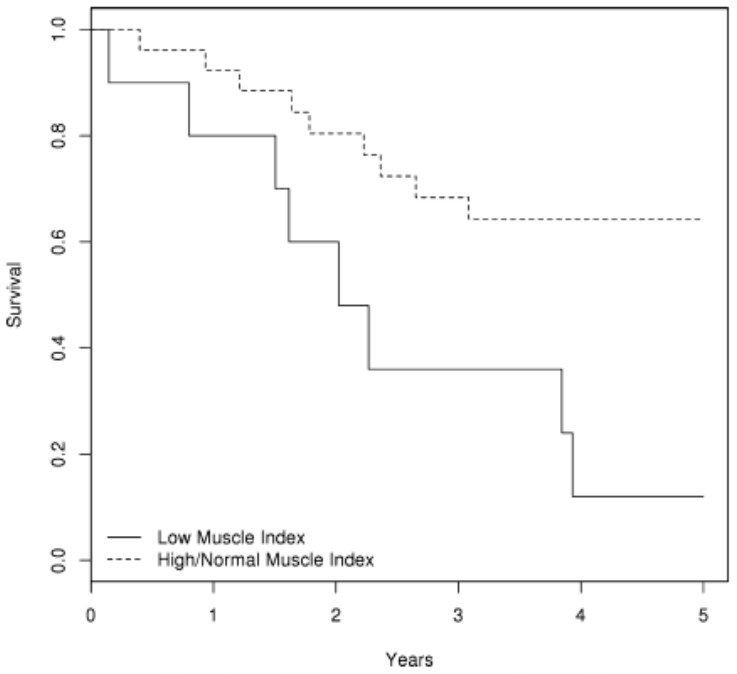
Singer and colleagues analyzed death in the first 1 year and in the first 4 years post Lung Tx in frail vs. not frail patients as assessed by the SPPB and FFP; frailty associated with increased risk at both time points



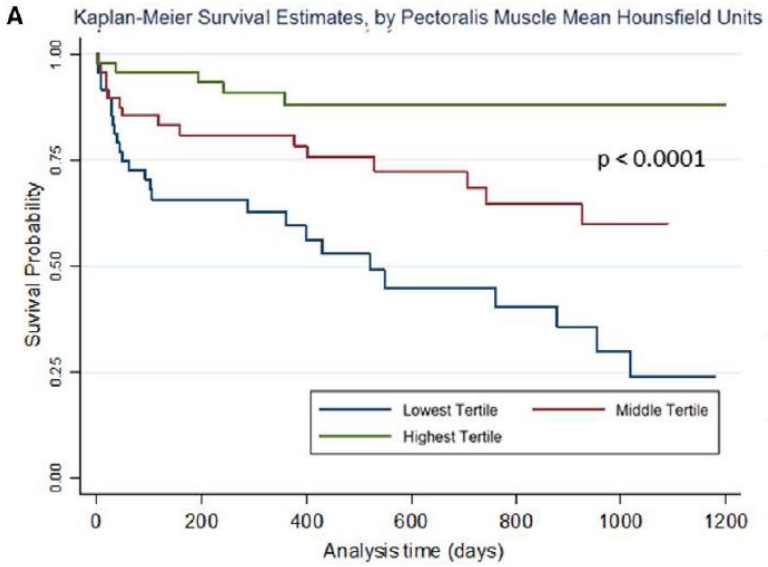
Singer JP et al, 2018

Alternate Measures of Frailty

Kelm and colleagues reviewed pre-op CT scans of 36 patients who had undergone lung transplantation, rating muscle mass at the L2-L3 vertebral interspace as low (lowest 25th percentile), normal (25th-75th percentile) or high (top 25th percentile); found Odds Ratio of 3.89 risk for death at 1 year in frail vs. non-frail group.



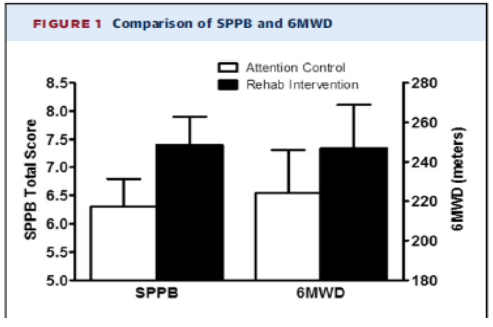
Cogswell et al analyzed pectoralis muscle density as a marker of frailty and its relationship to survival following heart transplant.



Kelm, 2016; Tiegen, 2017; Shah, 2020

Interventions to Improve Frailty (HF)

- Interventions have centered on exercise programs; meta-analysis found:
  - Improved gait speed, balance and performance of ADLs for the intervention group vs. control
  - No statistically significant impact on QOL (SF-36, PCS)
- HF-ACTION tested impact of aerobic exercise training on all-cause mortality or hospitalization (primary end-points) (n=2331)
  - Exercise training resulted in modest, non-significant reductions in all-cause mortality or hospitalization and cardiovascular mortality or heart failure hospitalization
- More recently REHAB-HF showed significant improvement in SPPB and 6MWT at 3 months compared with controls; reduction in all-cause hospitalizations at 6 months



Chou, *Archives of Physical Medicine and Rehabilitation,* 2012; O'Connor, *JAMA*, 2009; Reeves, *JACC: HF, 2017*

Lung Prehabilitation to Improve Outcomes in Lung Transplant

- Pulmonary rehabilitation for patients with end-stage lung disease is a standard practice prior to lung transplantation
- Goals include:
  - Prevent of deconditioning
  - Improve symptoms
  - Enhance quality of life
  - Improve endurance and activity tolerance
- Prehab has been shown to help a majority of pre-transplant patients maintain or improve 6MWT distance.

Adamkin, 2014; Massierer, 2020

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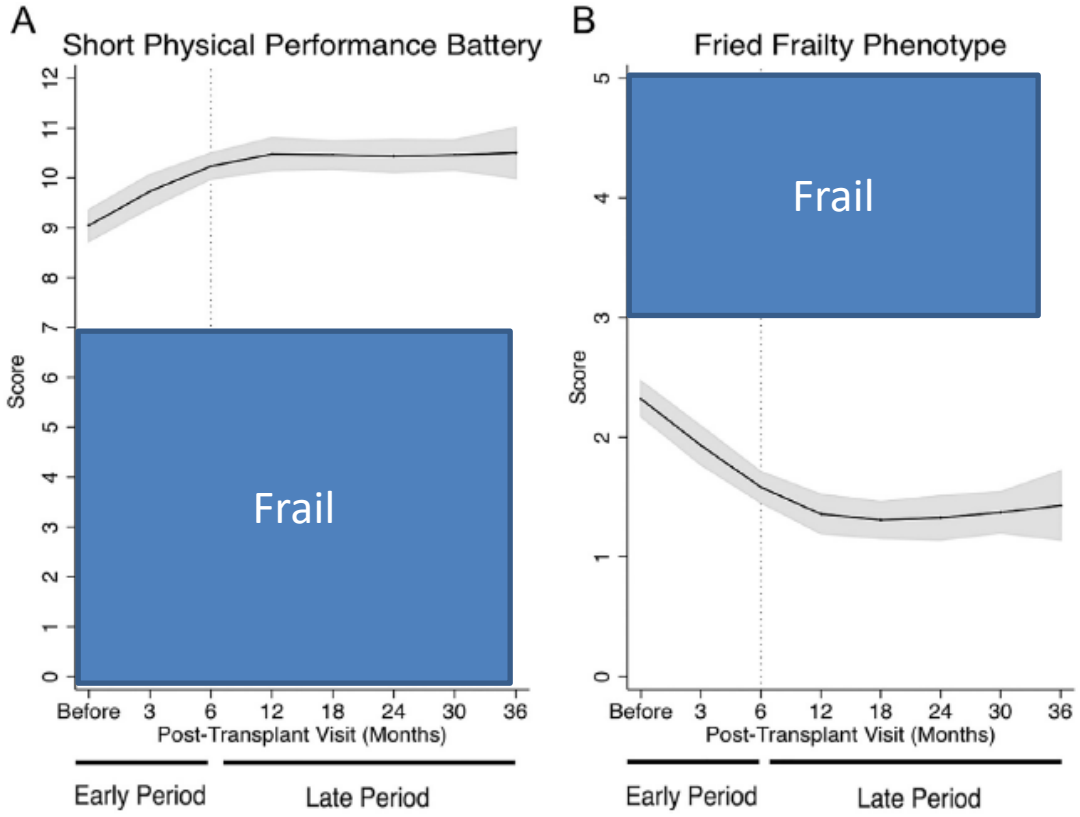
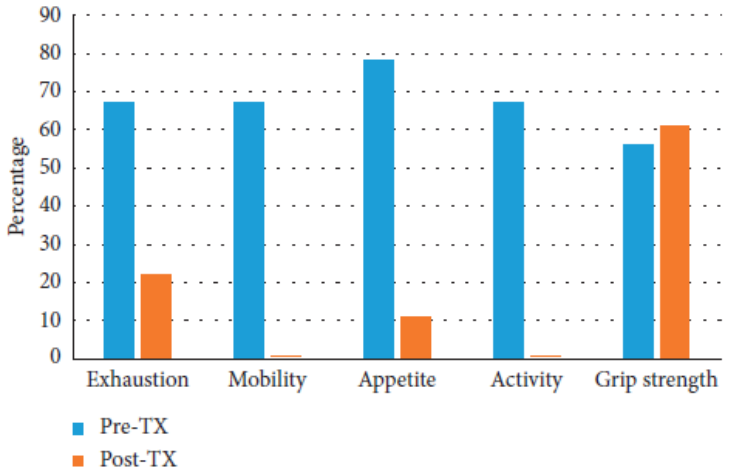
Lung Transplant Itself Reduces Frailty



Venado, 2019; Courtwright, 2019; Bottiger, 2019

Montgomery, 2020



Conclusions

- Frailty impacts pre-transplant and post-transplant mortality in all organ groups.
- Regularly evaluating patients for evidence of frailty can be a trigger to initiate interventions to reverse its progression.
- Developing, testing and implementing interventions to reverse frailty:
  - Will improve survival before and after transplant
  - Will enhance quality of life in transplant recipients.

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