Frailty and Sarcopenia in the Lung Transplant Candidate

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Disclosures

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Objectives

• Describe the evidence for frailty and sarcopenia in advanced lung disease.

• Recognize the clinical implications of frailty and sarcopenia in lung transplant patients.

• Identify various construct measures that might be helpful in assessing lung transplant candidates.
Construct of Frailty

• Conceptual Model:¹
  - Dynamic state
  - Several domains (physical, psychological, social).

• Operational Models:
  1) **Criteria Based Definition**: (Fried Frailty Index)²
  2) **Cumulative Deficits**: Multiple comorbidities (Rockwood)³
  3) **Clinical Frailty Scale**:⁴

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1. Gobbens RJ. J. American Medical Directors 2010
4. Rockwood K. CMAJ 2005
(1) Fried Frailty Index

- Most common operational model in elderly:
  - ≥ 3 of 5 dichotomous elements

1) Unintentional weight loss
2) Weakness
3) Self-reported exhaustion
4) Slowness
5) Reduced physical activity

Rockwood Frailty Indices

(2) Cumulative Frailty Index:¹
• Cumulative sum of impairments (70)
• Strong Predictive Validity
• Disadvantage: Time commitment

(3) Clinical Frailty Index:²
• Clinical Judgement
• Robust Health (1) ➔ Functional Dependence (7)

2. Rockwood K. CMAJ 2005
Prevalence of Frailty in Elderly

- **Community Studies**
  - Age > 65 years; n = 21 studies; 61,500
  - Large variation in prevalence (4 - 59%)

- **Operational model:**
  - Criteria Based Definition (9.9%)
  - Encompassing Frailty Model (13.6%)

- **Increases with Age**
  - Age 65-69 years (4 %)
  - Age > 85 years (26 %)

Prevalence of Frailty

• Vulnerable Social Status
  - Mortality increased at 5 years (32.5% vs. 11%)

• Comorbidities
  - 2/3 of Frail adults have ≥ 2 comorbidities

Importance of Frailty in the Elderly

Two Population Studies in the Elderly

1) Fried Frailty Index

2) Rockwood Clinical Frailty
Fried Frailty Index

- No Frailty
- Intermediate
- Frail

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Frailty</td>
<td>2469</td>
<td>260</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2480</td>
<td>474</td>
</tr>
<tr>
<td>Frail</td>
<td>368</td>
<td>130</td>
</tr>
</tbody>
</table>

Clinical Frailty Scale (CSHA) Risk for Institutionalization and Mortality

Institutionalization

(1) Very Fit (Robust)  (7) Severely Frail

Mortality

Why is Frailty Important?

• **Elderly Adults:**
  - Falls, disability, institutionalization and increased mortality
  - Sensitivity to air pollution

• **Post-operatively:**
  - Increased complications after general surgery
  - Delayed graft function in renal transplant recipients

• **Cardiac patients:**
  - ED visits, hospitalizations and mortality in CHF
  - LVAD implantation associated with mortality

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Frailty in Respiratory Disease

Soo Kyung Park, PhD, RN\textsuperscript{a,*}, Caroline R. Richardson, MD\textsuperscript{b,c}, Robert G. Holleman, MPH\textsuperscript{b,c}, Janet L. Larson, PhD, RN\textsuperscript{d}

- NHANES survey (n= 20,470); Final sample (n=211)
- Cumulative Frailty definition: Score 0-9; Frail \geq 2
• Prevalence of Frailty (58 %)

• Strongest predictor of frailty was dyspnea

• Co-morbidities (arthritis, DM2, liver disease, HTN)

• Frailty associated with disability of ADL/IADLs.

• Significant relationship between Frailty and inactive days secondary to health
Frailty in the Lung Transplant Candidate
Objectives:

1) Assess association of frailty with health related quality of life

2) Impact of frailty on transplant outcomes
Establishing Operational Frailty Index

- 194 patients (46%) HRQL & Rehab (Jan/04- June/09)

- Fried Frailty Phenotype (≥ 3 out of 5)
  - Shrinking (BMI < 18.5 kg/m²)
  - Quadriceps Training Volume
  - Exhaustion (SF-36 Vitality Score)
  - Slowness (6 Minute Walk Distance)
  - Low Activity (SF- 36 Physical Function)

- Reference Standard (SGRQ):
  “I have become frail or invalid because of my lung respiratory/problem”.

Rozenberg D. ISHLT Abstract Presentation 2014.
44 % Categorized as Frail

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frail (n=86)</th>
<th>Not Frail (n=108)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>57 IQR [50-62]</td>
<td>52 [36-62]</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>45 (52 %)</td>
<td>60 (56 %)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>37 (43 %)</td>
<td>29 (27 %)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>ILD</strong></td>
<td>32 (37 %)</td>
<td>36 (33 %)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>CF</strong></td>
<td>11 (13 %)</td>
<td>32 (30 %)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>6 (7 %)</td>
<td>11 (10 %)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Days on Transplant List</strong></td>
<td>157 [75-264]</td>
<td>131 [65-261]</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Rozenberg D. ISHLT Abstract Presentation 2014.
Frailty was the only significant predictor:

- SGRQ Total Score (+ 13.6 95% CI 10.1 to 17.2)
- EQ-5D (- 0.23 95% CI -0.30 to -0.15)

Rozenberg D. ISHLT Abstract Presentation 2014.
Frailty Associated with Increased Duration of Hospitalization and Lower 6MWD

<table>
<thead>
<tr>
<th>Post-transplant</th>
<th>Frail (n=86)</th>
<th>Not Frail (n=108)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Days</td>
<td>3 [2-10]</td>
<td>3 [2-6]</td>
<td>0.10</td>
</tr>
<tr>
<td>Length of Stay (Days)</td>
<td>22 [16-36]</td>
<td>17.5 [13-28]</td>
<td>0.02</td>
</tr>
<tr>
<td>Inpatient Rehab</td>
<td>15 (17%)</td>
<td>11 (10%)</td>
<td>0.20</td>
</tr>
<tr>
<td>6 MWD (m) 3 months</td>
<td>424 ± 88</td>
<td>475 ± 115</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Frailty and Diagnostic Category were significant:
• Median Length of Stay (2.1 days 95% CI 0.6 to 7.1)
• 6MWD Change from Pre-Tx (53 m 95% CI 23 to 84)

Rozenberg D. ISHLT Abstract Presentation 2014.
No Survival Difference Observed

Proportional Hazards Ratios:
- Unadjusted: 0.71 [95% CI 0.46 – 1.09]
- Adjusted: 0.94 [95% CI 0.61 – 1.47]

Hospital Mortality:
Frail 3 (4%) vs. Not Frail 8 (7%), p=0.35

Rozenberg D. ISHLT Abstract Presentation 2014.
Study Conclusion

• Frailty associated with decreased HRQL scores

• Increased length of stay and reduced 6MWD

• Frailty phenotype warrants additional study into its prognostic potential on survival

Rozenberg D. ISHLT Abstract Presentation 2014.
Frailty in Advanced Lung Disease

• High prevalence not surprising (~ 50%)

• Number of co-morbidities, psycho-social and physical limitations include many of the constructs of frailty

Figure Adapted from Fried LP. Journal of Gerontology 2001
Frailty in Lung Transplant Candidates

Physical:
• Older age\(^1\)
• Body Mass Index
• Low physical activity
• Reduced muscle mass & strength

Psycho-social:

Co-morbidities:
• Osteoporosis, Hypertension, Metabolic Syndrome

Older Lung Transplant Candidates

Recipient’s Age at the time of Lung Transplant in USA

BMI in Lung Transplant Candidates

Low Physical Activity Levels

Lung Transplant Candidates: Inactive compared to general Canadian population\textsuperscript{1}

- 6MWD was one of the main determinants of low physical activity\textsuperscript{2}

Lung Transplant Candidates: Psycho-social Domain

- Advanced Lung Disease associated with reduced HRQL and psychological impairment

- One study (n=243, Two centres)\(^1\)
  - Majority had mild somatic/depressive symptoms
  - 25% had significant anxiety/depression

Comorbidities: Lung Transplant Candidates

- High prevalence of osteoporosis (37%) and combined osteoporosis/osteopenia (86)\(^1\)
- Cohort of 67 lung transplant patients (48 ± 14 years)
- Prevalence of Metabolic Syndrome (3% to 24%)\(^2\)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>Year 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>19.4% (n = 13/67)</td>
<td>59.7% (n = 40/67)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13.4% (n = 9/67)</td>
<td>29.9% (n = 20/67)*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>6.0% (n = 4/67)</td>
<td>37.3% (n = 25/67)*</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>3.0% (n = 2/67)</td>
<td>23.9% (n = 16/67)*</td>
</tr>
</tbody>
</table>

*\(p < 0.01\) vs. baseline, \(\chi^2\) test.

Role of Sarcopenia in Frailty

Sarcopenia defined: Decreased muscle mass AND reduced muscle strength or function

Cruz-Jentoft AJ. Age Ageing 2010.
Importance of Sarcopenia in Advanced Lung Disease

• Individual elements of Sarcopenia studied

• In COPD patients; **Increased Mortality**
  
  - Low muscle mass \(^1\)
  
  - Mid-thigh cross-sectional area \(^2\)
  
  - Low Strength \(^3\)

Sarcopenia in Lung Transplant Patients

• Despite alleviation of cardio-respiratory limitations, improved HRQL,¹ and survival;² recipients have ++ VO₂ impairments³

• Majority of patients have impairments in muscle mass and strength pre- and post-transplant

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Low Muscle Mass (Fat Free Mass)

- Fat-free mass observed to be decreased pre- and post-transplant (using BIA)

(1) Low FFMI in 2/3 in the pre-transplant period and 1/3 of patients at 2 years post-transplant.

(2) Lower FFM in 12 recipients (~ 3 years post) compared to healthy age-matched controls

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Muscle Strength in Lung Transplant

**Systematic Review:**

- Quadriceps strength (QS) most common measure

- 14 out of 18 studies
  - Computerized Dynamometer (n = 10)
  - Hand-held Device (n = 4)

- Pre-Tx: Mean Range 49-86% (n=455)
- Post-Tx (< 3 months): 51-72% (n=126)
- Post-Tx (> 3 months): 58-101% (n=164)

Rozenberg D. Under review. Journal of Heart and Lung Transplantation
Muscular Function

• Lower body function: Sit-to-stand test (n=2)\textsuperscript{1,2}

• No studies assessed upper extremity function

1. Bossenbroek L. Respiration 2011
2. Bossenbroek L. Journal of Heart and Lung Transplantation 2009
Sarcopenia Measure Correlates

• QS correlates with ICU stay post transplant¹

• QS correlates with PA Measures:
  - Daily steps²
  - Peak VO₂³

• Lower body function (sit-to-stand)
  - Daily steps⁴

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Sarcopenia in Lung Transplant

• No lung transplant studies to date have used sarcopenia consensus definition

• Studies on clinical outcomes needed

• Patients with complex co-morbidities, myopathies, and hospitalizations excluded from many studies
Lung Transplant Candidates

Selection Process in 2014
Absolute Contraindications

- Malignancy in the last 2 years
- Advanced dysfunction of another organ
- Chronic extra-pulmonary infection
- Significant chest wall/spinal deformity
- Psychological/Non-adherence concerns
- Absence of Social support
- Substance Abuse

Relative Contraindications

• Age > 65 years old
• Unstable clinically (shock, ECMO)
• Limited functional status with poor rehab potential
• Colonization with virulent organisms
• Severe obesity
• Chronic Mechanical Ventilation

Lung Allocation Score

Waiting list mortality predictors:

- Age
- BMI
- Diabetes
- Functional status
- Forced vital capacity
- Systolic pulmonary artery pressure
- Supplemental oxygen requirement
- 6-min walk distance
- Arterial partial pressure of carbon dioxide
- Diagnosis

Doesn’t include:
- Psycho-social
- Sarcopenia

Figure: Hook JL. Expert Rev Respir Med. 2012
Data: Organ Procurement and Transplantation Network
Lung Allocation Score and Outcomes

- High LAS associated with decreased survival and prolonged hospitalization
- Improved mortality in the pre-transplant period but potentially selecting more frail candidates

Russo MJ. Chest 2010
Importance of Frailty and Sarcopenia

- Many of the listing criteria don’t necessarily capture the entire spectrum.
- Frailty, Sarcopenia and Psycho-social aspects in advanced lung disease may prove to be important.
Frailty as a Dynamic State

Potential Modifiable Factors
- BMI, Nutrition
- Muscle Mass, Strength
- Physical Activity
- Psycho-social Factors

Diagram Adapted from Fried LP. 1998
Summary

• Frailty and sarcopenia are prevalent in advanced lung disease

• Further study into the clinical implications of frailty and sarcopenia is needed in lung transplant candidates

• Rehabilitation strategies may play an important role