Frailty: Pathobiology and Implications in the ICU – Are Chronic Critical illness and Frailty the Same?

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Scientific Director, Canadian Frailty Network (CFN)
Disclosure

- Scientific Director for the Canadian Frailty Network
  - Funded by Networks of Centers of Excellence (NCE)
Aging and critical care in Ontario and Manitoba

- 144,000 patients admitted to Ontario ICUs in 2014-15
  - Over 40% of patients were 70+ y.o.
  - ≈ 20% were > 80 y.o.

- Mean age: 64.5 ± 16.4
- Median: 66 (IQR 54 – 76)

Garland et al, Crit Care 2016
Canada and Internationally

- Canadian Institute of Health Information
  - Care in Canadian ICUs 2016
  - 52% over age of 65
    (44% in the 65 – 84 age group)

- Intensive Care Over Nations (ICON) audit
  - Ages of ICU patients varied widely with lowest ages in resource challenged regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of centres</th>
<th>Number of patients (%)</th>
<th>Mean age, years (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>317</td>
<td>4335 (43.1%)</td>
<td>63 (17)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>87</td>
<td>1110 (11.9%)</td>
<td>60 (17)</td>
</tr>
<tr>
<td>South America</td>
<td>109</td>
<td>993 (9.9%)</td>
<td>59 (20)</td>
</tr>
<tr>
<td>North America</td>
<td>23</td>
<td>730 (7.2%)</td>
<td>59 (18)</td>
</tr>
<tr>
<td>East and southeast Asia</td>
<td>91</td>
<td>946 (9.4%)</td>
<td>60 (18)</td>
</tr>
<tr>
<td>South Asia</td>
<td>36</td>
<td>982 (9.8%)</td>
<td>55 (17)</td>
</tr>
<tr>
<td>Oceania</td>
<td>20</td>
<td>439 (4.4%)</td>
<td>58 (18)</td>
</tr>
<tr>
<td>Middle East</td>
<td>36</td>
<td>393 (3.9%)</td>
<td>55 (20)</td>
</tr>
<tr>
<td>Africa</td>
<td>11</td>
<td>141 (1.4%)</td>
<td>48 (19)</td>
</tr>
<tr>
<td>GNI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low and lower-middle income</td>
<td>62</td>
<td>1209 (12.0%)</td>
<td>55 (17)</td>
</tr>
<tr>
<td>Upper-middle income</td>
<td>237</td>
<td>2504 (24.9%)</td>
<td>58 (18)</td>
</tr>
<tr>
<td>High income</td>
<td>431</td>
<td>6356 (63.1%)</td>
<td>62 (18)</td>
</tr>
</tbody>
</table>

Vincent et al, Lancet Respir Med 2014
Shift in the Aging Curve

Function

Age

Healthy Aging

Frailty

Multi-morbidity, Loss of functional capacity

Canadian Frailty Network

Réseau canadien des soins aux personnes fragilisées
The Frailty Health State

• Frailty is defined as a state of increased vulnerability resulting from reduced physiological reserve and loss of function across multiple systems reducing the ability to cope with normal or minor stressors.

• ‘Minor’ events trigger major changes in health status

• Associated with increased risk of physical, cognitive and functional decline, adverse health outcomes and mortality

Frailty in Canadians

• Aging and Frailty are not synonymous but frailty becomes increasingly common as age advances

• Decline in health status and higher health care use driven more by frailty than age

Sources:
2. statcan.gc.ca/pub/82-003-x/2013009/article/11864-eng.htm
Frailty Measurement

• Pathophysiology of frailty is reduced function in the neuromuscular, neuroendocrine and immunological systems
  – Increased risk of inability to maintain homeostasis
  – Scales reflect the underlying pathophysiology

• At least 25 frailty scales are available
  – No consensus (clinically or in research)
  – Data collection burden vs. reliability vs. validity

• Measured in ICU populations: Frailty Phenotype, Frailty Index, Clinical Frailty Scale

Viña et al, 2016, Molecular Aspects of Medicine 50; 88–108
## Frailty Phenotype Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weight loss/Sarcopenia</td>
<td>&gt; 10 lb weight loss/year</td>
</tr>
<tr>
<td>2. Weakness</td>
<td>Grip strength</td>
</tr>
<tr>
<td>3. Slowness</td>
<td>15 feet Walking time</td>
</tr>
<tr>
<td>4. Low Activity Level</td>
<td>Kcal/week expended</td>
</tr>
<tr>
<td>5. Exhaustion</td>
<td>Self-reported</td>
</tr>
</tbody>
</table>

Frailty: > 3 Criteria Present  
Pre-Frail: 2 Criteria Present
Frailty – Accumulation of Deficits

Frailty Index =

Number of deficits in an individual
Total number of potential deficits measured

e.g. in a dataset with 50 health measures, a person with 10 things wrong (10 deficits) has a frailty index of $\frac{10}{50} = 0.20$.

Searle et al. BMC Geriatrics 2008, 8:24
Clinical Frailty Scale

1. Very Fit — People who are robust, active, energetic and motivated. They are among the fittest for their age.
2. Well — People who have no active disease symptoms but are less fit than Category 1. Often, they exercise or are very active occasionally, say seasonally.
3. Managing Well — People whose medical problems are well controlled, but are not regularly active beyond routine walking.
4. Vulnerable — While not dependent on others for daily help, often symptoms limit activities. A common complaint is being “sloshed up,” and for being tired during the day.
5. Mildly Frail — Those people often have more evident slowing, and need help in high order ADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.
6. Moderately Frail — People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (sitting, standing) with dressing.
7. Severely Frail — Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).
8. Very Severely Frail — Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.
9. Terminally III — Approaching the end of life. This category applies to people with a life expectancy < 6 months, who are not otherwise evidently frail.

Where dementia is present, the degree of frailty usually corresponds to the degree of dementia:
- Mild dementia — includes forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.
- Moderate dementia — recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.
- Severe dementia — they cannot do personal care without help.

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Rockwood et al, CMAJ 173 (5): 489
• Included patients admitted to ICU > 50 y.o. and were expected to stay in ICU > 24 hours
• Clinical Frailty Scale > 4 was defined as frail
• Frailty prevalence was 33%
• Compared to fit individuals, frailty was associated with increased morbidity, mortality, adverse events
• Also associated with greater impairment of health related Quality of Life, reduced functional dependence and disability post discharge

Bagshaw et al, CMAJ 2014
Bagshaw et al, CCM 2015
Frailty in ICU: Mortality

Overall mortality: 33.7% (frail) vs. 20.0% (fit)
Measurement of Frailty at Discharge

The feasibility of measuring frailty to predict disability and mortality in older medical intensive care unit survivors

- Frailty measured in 22 survivors of critical illness (ventilation > 24 hrs)
- Frailty status determined at hospital discharge using Fried’s criteria was feasible and was associated with adverse outcomes
- Increasing frailty associated with disability at 1 month and 6 month mortality

Baldwin et al, J Crit Care 2014
## Biochemical Characteristics of Frailty

<table>
<thead>
<tr>
<th>Frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased inflammatory cytokines (TNF-a, IL-6, IL-1B, CRP)</td>
</tr>
<tr>
<td>Evidence of mitochondrial dysfunction</td>
</tr>
<tr>
<td>Increased levels of markers of endothelial dysfunction (ADMA)</td>
</tr>
<tr>
<td>Increased markers of Oxidative Damage</td>
</tr>
<tr>
<td>Low levels of Vitamin D</td>
</tr>
<tr>
<td>Immunosuppression and Increased risk of infection (lower levels of IL-12, p70, Il-23)</td>
</tr>
<tr>
<td>Increased transferrin, haptoglobin, fibrinogen</td>
</tr>
</tbody>
</table>

*Vina et al, Mol Asp Med 2016*
Chronic critical illness (CCI)

- Poorly defined
- Common features:
  - Prolonged ICU stay
  - Organ dysfunction
- Age and chronic medical problems correlate with CCI
- Poor outcomes
- Frailty and CCI have similar constellation of manifestations

Nelson et al, AJRCCM 2010
Chronic Critical Illness and Persistent Inflammation, Immunosuppression and Catabolism Syndrome

- Inflammation
- Catabolism/cachexia
- Immunosuppression
- Adverse Outcomes


Vanzant et al, J Trauma Acute Care Surgery 2014
Mira J, Crit Care Med 2016
## PICS and Frailty

<table>
<thead>
<tr>
<th>PICS (Definition)</th>
<th>Described in Frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Illness &gt; 14 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Persistent Inflammation</td>
<td>✓</td>
</tr>
<tr>
<td>• Increased CRP (&gt; 50 ug/dL)</td>
<td>✓</td>
</tr>
<tr>
<td>• Low Retinol Binding Protein (&lt; 1 mg/dL)</td>
<td>✓</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>✓</td>
</tr>
<tr>
<td>• Low lymphocyte levels (&lt; 0.8 X 10^9)</td>
<td>✓</td>
</tr>
<tr>
<td>Catabolic State</td>
<td>✓</td>
</tr>
<tr>
<td>• Low Albumin Levels (&lt; 30 g/L)</td>
<td>✓</td>
</tr>
<tr>
<td>• Creatinine height index (&lt;80%)</td>
<td>X</td>
</tr>
<tr>
<td>• Weight Loss (&gt; 10% or BMI &lt; 18)</td>
<td>✓</td>
</tr>
</tbody>
</table>

Gentile, J Trauma Acute Care Surg 2012
Frailty, Sarcopenia and critical illness

- Sarcopenia common both in frailty and critical illness
- Sarcopenia results from altered muscle metabolism, mitochondrial dysfunction and chronic catabolism
- Mediated by inflammation (TNF-a, IL6)
- Enhanced by insult of critical illness
- Sarcopenia shown to be predictor of outcome in critically ill including increased mortality, LOS and mechanical ventilation

Hanna et al, JPEN 2015
Moisey et al, Crit Care 2013
Possible Interaction between Frailty and Critical Illness

Fit

Environmental Inflammatory Stimulus
Inability to Turn Off Inflammatory Process
Chronic Inflammation

Frail

Severe Acute Inflammatory Insult of Critical Illness
Amplification of chronic inflammation
Inability to Turn Off Inflammation

Persistent Inflammation

Recovery

Environmental Inflammatory Stimulus
Ability to Turn Off Inflammatory Process

Acute inflammation
Ability to Turn Off Inflammation
Conclusions

• Frailty is a determinant of ICU outcomes
• Chronic critical illness and frailty have similar manifestations
• Chronic critical illness and frailty maybe situational phenotypes of the same underlying pathophysiological process
• Need for better evidence
Canadian Frailty Network is an interdisciplinary network dedicated to improving care of Canada’s frail elderly by:

- Increasing frailty recognition and assessment
- Increasing evidence for decision making, and
- Advocating for change in the health care system to ensure that the needs of this vulnerable population are met.