Frailty Measurement: Where We Stand

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Introduction
Whither “frailty measurement”?

• “Geronmetrics”
  – a.k.a.: econometrics, psychometrics, biometrics
  – e.g.: generalized inflammation; frailty; aging

• Essential to
  – Sensitivity, specificity for genetic, other discovery
  – Theory operationalization, testing
  – Correctly targeted, evaluated interventions

• Is frailty worth measuring?
  – If not, pursuing items under the last bullet makes little sense
Geronmetric Measurement

- Proposition: Most effective when attacked “from both ends”
  - Mechanisms / basic science
  - Phenotype / validity
    - Face
    - Content
    - Predictive / Criterion
    - Construct: Convergent, Divergent
      Internal, External
Frailty phenotype
Where we stand: Strengths

• Face validity
  – Criteria reflect geriatric impression
  – WHAS I: prevalence increases with age
  – WHAS: prevalence higher among more disabled (25.4%) than overall (11.3%)

• Cross validity
  – Prevalence similar across cohorts (11.3% in WHAS; 11.6% in age-matched CHS women)
Frailty phenotype
Where we stand: Strengths

• Criterion / Predictive validity
  – Phenotype strongly predicts adverse geriatric outcomes: severe disability onset; falls; NH admission; death
  – Phenotype predicted by signs of systemic dysregulation: inflammatory, immunological, hormonal, nutritional
Frailty phenotype
Where we stand: Strengths

- Convergent internal construct validity
- Criterion onset—Drs. Fried & Xue
- Criteria manifestation is syndromic
  “a group of signs and symptoms that occur together and characterize a particular abnormality”
  - Method: Latent class analysis
Syndrome validation
Latent class analysis

• Seeks clinically homogeneous subgroups
• Features that characterize each group
  – Prevalence in overall population
  – Percentage manifesting each criterion
• If criteria characterize syndrome:
  – At least two groups (otherwise, no co-occurrence)
  – No subgrouping of symptoms (otherwise, more than one abnormality characterized)
Table 3
Conditional Probabilities of Meeting Criteria in Latent Frailty Classes
WHAS

<table>
<thead>
<tr>
<th>Criterion</th>
<th>2-Class Model</th>
<th>3-Class Model</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL. 1 NON-FRAIL</td>
<td>CL. 2 FRAIL</td>
<td>CL. 1 ROBUST</td>
<td>CL. 2 INTERMED.</td>
<td>CL. 3 FRAIL</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>.073</td>
<td>.26</td>
<td>.072</td>
<td>.11</td>
<td>.54</td>
</tr>
<tr>
<td>Weakness</td>
<td>.088</td>
<td>.51</td>
<td>.029</td>
<td>.26</td>
<td>.77</td>
</tr>
<tr>
<td>Slowness</td>
<td>.15</td>
<td>.70</td>
<td>.004</td>
<td>.45</td>
<td>.85</td>
</tr>
<tr>
<td>Low Physical Activity</td>
<td>.078</td>
<td>.51</td>
<td>.000</td>
<td>.28</td>
<td>.70</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>.061</td>
<td>.34</td>
<td>.027</td>
<td>.16</td>
<td>.56</td>
</tr>
<tr>
<td>Class Prevalence (%)</td>
<td>73.3</td>
<td>26.7</td>
<td>39.2</td>
<td>53.6</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Bandeen-Roche et al., 2006
Frailty phenotype
Where we stand: Content validity

- Missing pieces?
  - Cognitive decline?
  - Depression / anxiety?
- Improvement re existing pieces?
  - Exhaustion; weight loss?
  - Different cutoffs or scaling?
- Physiotype rather than phenotype?
- Value of aggregate over components?
- A beta version, or a proof of principle?
Frailty phenotype
Where we stand: Prediction

- ...i.e. utility for screening, diagnosing & targeting adverse geriatric outcomes

- Needed
  - Rigorous delineation of predictive accuracy
  - Comparison to competitors
  - Threshold relationships?

- Is this the primary goal?
  - If so: Why genetic, physiological discovery?
Frailty phenotype
Where we stand: Construct validity

• Discriminant: What is frailty not?

• External
  - Multisystemic dysregulation
  - Specificity re vulnerability to stressors
    • WHAS II challenge study

• Refinement of the construct?
  - “Vulnerable” vs. “already broken” (Ferrucci)
  - Placement in pathology-to-disability path?
Identifying Frailty
Latent Variable Paradigm

\[ \begin{align*}
Y_1 & \quad \text{Determinants} \\
\ldots & \\
Y_p & \\
\end{align*} \]

Frailty

Construct validity

Adverse outcomes

Determinants

D

\[ \begin{align*}
e_1 & \quad \text{theory} \\
e_p & \\
\end{align*} \]
Data on Content Validity
More than Component Parts

• WHAS: Disease-adjusted analysis, mobility disability vs. components
  – Slowness=strongest predictor
    \[ \text{OR} = 17, \text{95% CI [7.8, 38]} \] vs.
    \[ 6.6, \text{95% CI [2.2, 20]} \] for weakness
  – All but weight loss predict (multiply)

• InCHIANTi: “Frailty” specifically associated with generalized inflammatory dysregulation, as opposed to components
Discriminant Validity Data
More than disease (WHAS)

• Frail, # diseases associated, not redundant
  – “Frail” rare if no (2%) or 1 (5%) disease
  – “Intermediate” not rare these cases (>29%)
  – Many with comorbid diseases robust (>28%)

• Frailty strongly predicts mobility disability, independently of age, # diseases
  – OR for severe disability = 29 (95% CI [9.3,88])
  – Little interaction w disease: not severity marker
### Discriminant Validity Data
More than disease (WHAS)

- Mortality analysis with propensity scoring

<table>
<thead>
<tr>
<th>ADJUSTMENT</th>
<th>FRAILTY OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.42 (1.81, 3.24)</td>
</tr>
<tr>
<td>Disease count, age</td>
<td>1.81 (1.33, 2.45)</td>
</tr>
<tr>
<td>Cluster-based C/D/S vars.</td>
<td>1.74 (1.28, 2.36)</td>
</tr>
<tr>
<td>Elements of score</td>
<td>1.69 (1.23, 2.30)</td>
</tr>
<tr>
<td>Propensity score</td>
<td>1.67 (1.22, 2.28)</td>
</tr>
<tr>
<td>P. Score: Mid-90</td>
<td>1.51 (1.07, 2.13)</td>
</tr>
</tbody>
</table>
Frailty: Aims & Status

• Sensitivity and specificity: A measure tied explicitly to systemic dysregulation

• Validate theory that frailty is:
  – More than a marker of disease
  – More than severe disability
  – A syndrome: more than component parts
  – A result of vulnerability to stressors & loss of reserve

• Product: A target for interventions
  – Deliverable: A refined summary variable
  – Either: A causal intermediary or measured surrogate

• Much accomplished; much worthwhile to do
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