Frailty
Searching for a Relevant and Evidence Based Framework

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Canadian Initiative on Frailty and Aging / Initiative canadienne sur la fragilité et le vieillissement
www.frail-fragile.ca
Core feature of frailty is increased vulnerability to stressors due to impairments in multiple, inter-related systems that lead to decline in homeostatic “reserve” and resiliency

The main consequence is an increased risk for multiple adverse health-related outcomes
- disability, morbidity, falls, hospitalisation, institutionalisation, death

a syndrome encountered in older persons with diverse predisposing, precipitating, enabling and reinforcing factors

Frailty and disability: while related and with overlap, are distinct concepts

Survival According to Frailty Status
Cardiovascular Health Study

Frailty: A Complex Syndrome of Increased Vulnerability
A Framework

Prevent/Delay Frailty
Health Promotion and Prevention

Delay Onset

Delay/Prevent adverse outcomes, care

FRAILTY

Candidate markers
- Nutrition
- Mobility
- Activity
- Strength
- Endurance
- Cognition
- Mood

Adverse outcomes
- Disability
- Morbidity
- Hospitalization
- Institutionalization
- Death

Biological, Psychological, Social, societal
modifiers/assets and deficits

Bergman H, Hogan D, Karunananthan S.

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Explosion of frailty models

- The single analysis and the single meeting models
- Every year, new models of frailty are being proposed in the literature:
  - Extensive literature that is difficult to interpret:
    - Range of the reported crude prevalence of frailty based on a systematic review: 1% to 98%
- The leap from frailty as a risk to frailty as a predictive clinical tool
Objectives

To examine the associations among 7 candidate frailty domains: nutrition; physical activity; mobility; strength; cognition; mood


To test the ability of the domains, individually and in combination, to predict adverse outcomes
International Database Inquiry on Frailty (FrData Project)

- Includes data from many longitudinal studies on aging:
  - The Montreal Unmet Needs Study [C Wolfson]
  - The Canadian Study of Health and Aging [C Wolfson]
  - The System of Integrated Services for Older Persons [F Beland, H. Bergman]
  - NuAGE [H Payette]
  - The Mexican Health and Aging Study [L Gutiérrez-Robledo]
  - The Longitudinal Aging Study Amsterdam [D Deeg]
  - Established Populations for Epidemiologic Studies of the Elderly [J Guralnik]
Contribution of frailty deficits in explaining differences among individuals across five samples of older persons

Literature on predictive accuracy of frailty

- Some recent papers in predictive accuracy of frailty
  
  Studenski Survival *JAMA*. 2011

- Studies tested specific frailty models or markers or within specific clinical populations

- Studies did not investigate how much frailty adds to the predictive accuracy of readily available medical data (age, sex, number of chronic diseases)
FrData : Testing the predictive accuracy of the frailty domains

- Test all possible combinations of the 7 frailty domains + Fried phenotype model
  129 models in all

- Objectives:
  #1: Determine model with best prediction for incident ADL disability
  #2: Determine the contribution of the frailty markers over and above age, sex and the number of chronic diseases

- Predictive accuracy measured with c-statistic
7-year survival by frailty phenotype group in EPESE East Boston sample

![Product-Limit Survival Function Estimates](image)

**Table: Survival Estimates**

<table>
<thead>
<tr>
<th>Frailty Group</th>
<th>No. of Subjects</th>
<th>Event (%)</th>
<th>Censored (%)</th>
<th>Median Survival (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Frail</td>
<td>1247</td>
<td>18% (226)</td>
<td>82% (1021)</td>
<td>NA ( NA NA )</td>
</tr>
<tr>
<td>2 Pre-Frail</td>
<td>1710</td>
<td>30% (510)</td>
<td>70% (1200)</td>
<td>NA ( NA NA )</td>
</tr>
<tr>
<td>3 Non-Frail</td>
<td>585</td>
<td>56% (329)</td>
<td>44% (256)</td>
<td>69.20 ( 62.93 80.03)</td>
</tr>
</tbody>
</table>

1= Frail, 2=Pre-Frail, 3=Non-Frail
### Prediction of incident ADL disability in EPESE East Boston

<table>
<thead>
<tr>
<th>Best model (lowest AIC):</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>1.44 [1.21-1.70]</td>
</tr>
<tr>
<td>Mobility</td>
<td>2.16 [1.44-3.24]</td>
</tr>
<tr>
<td>Nutrition</td>
<td>1.63 [1.36-1.94]</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>1.88 [1.50-2.36]</td>
</tr>
<tr>
<td>Strength</td>
<td>2.00 [1.65-2.43]</td>
</tr>
</tbody>
</table>

| AIC                             | 3635.70           |
| C-statistic                     | 76.4%             |

<table>
<thead>
<tr>
<th>Fried et al. model</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-frail vs non-frail</td>
<td>1.90 [1.59-2.28]</td>
</tr>
<tr>
<td>Frail vs non-frail</td>
<td>6.53 [4.71-9.06]</td>
</tr>
</tbody>
</table>

| AIC                             | 3679.42           |
| C-statistic                     | 75.9%             |
Increase in predictive accuracy by addition of frailty variables

- Addition of frailty variables:
  - "Best" Model
    - Age, sex, disease: 73.1%
    - Addition of frailty variables: 3.1%
  - Phenotype Model
    - Age, sex, disease: 73.1%
    - Addition of frailty variables: 2.8%
Hierarchical contribution of model variables to predictive accuracy in EPESE-Boston

- Disease: 59.1%
- Frailty: 68.0%
- Age + sex: 69.1%
- Disease + frailty: 69.8%
- Age + sex + disease: 73.1%
- Age + sex + frailty: 75.3%
- Age + sex + disease + frailty: 76.4%
Contribution of model variables by age group
EPESE - Boston

- Frailty contribution *increases* from 4.3% to 8.8%
- Chronic disease contribution *decreases* from 11.4% to 0.7%
Prediction Is Very Hard

Especially about the future
Confusion in the literature between explanatory and predictive ability

- Most of the research in frailty has consisted of analyzing the explanatory ability, i.e. testing frailty as a significant risk factor for adverse outcomes within a given sample.

- Little is known on the true predictive ability of frailty to predict accurate outcomes in new, out-of-sample subjects.

- Explanatory ability often wrongly used to infer predictive ability.

- Even highly significant risk factors can make poor predictors for a prognostic tool.
  - determinants of current market stock prices vs prediction future stock prices.
  - Application of a prediction model is sensible, if the model is able to provide useful additional information for clinical decision making.

Siontis, Tzoulaki, Ioannidis ARCH INTERN MED/VOL 2011
Grady, Berkowitz. Why is a good clinical prediction rule hard to find?. Editorial Arc inter med 2011
Summary of prediction results

- Frailty markers were found to be significant risk factors at the population level.
- However, as a prognostic clinical tool to optimally predict disability in new subjects, the addition of frailty may add very little to the predictive accuracy beyond age, sex and chronic disease.
- But impact with age.
- Age, number of chronic diseases and sex are not modifiable. Frailty markers are.
- Reducing risk, even by a few % may be important.
- IF there is an intervention that will change the outcome.
Summary of prediction results

- Risk and Prediction vary depending on the
  - Population studied: socio-economic status, ethnic origin, age etc
  - Setting: clinical (eg Oncology, surgery, primary care), general population
  - Outcomes studied (onset of disability, falls, admissions, death etc)

Siontis, Tzoulaki, Ioannidis ARCH INTERN MED/VOL 2011
Grady, Berkowitz. Why is a good clinical prediction rule hard to find?. Editorial Arch inter med 2011
Frailty is an integral component of risk prediction in elderly patients undergoing cardiac surgery.

- The single measure of gait speed outperformed multi-item frailty scales.
- Disability as measured by ADL’s and IADL’s are uncommon and insensitive.
- Higher-level functioning as captured by Nagi items add more to risk prediction.

Afilalo et al. Submitted 2011
Afilalo J, Eisenberg M, Bergman H et al.
Gait Speed as an Incremental Predictor of Mortality and Major Morbidity in Elderly Patients Undergoing Cardiac Surgery.
Journal of the American College of Cardiology. 2010
Frailty is an integral component of risk prediction in elderly patients undergoing cardiac surgery.

Risk prediction in elderly cardiac surgery patients can be optimized by considering a combination of:

- **5-meter gait speed** for frailty,
- **Nagi items** for higher-level disability
- **Parsonnet score** for comorbidities and illness severity.

“I had come to an entirely erroneous conclusion, which shows my dear Watson, how dangerous it always is to reason from insufficient data.”

Sherlock Holmes in “The speckled band”
Conclusion

◆ Frailty research and debate has opened new horizons in understanding
  - the aging process and the heterogeneity of older persons and
  - the potential to identify independent vulnerable older adults and prevent/delay adverse consequences

◆ Still working towards an understanding of frailty; its place as a clinical instrument
  - Frailty markers as markers of vulnerability in independent older persons may be more important than a model
    » Number of markers; different markers depending on pathway

◆ Need for research on predictive capacity of frailty in different population and settings and for different outcomes of interest
  - One size may not fit all

◆ Need for intervention research: delay onset of frailty; delay onset of adverse outcomes
  - Ultimately will only be relevant we succeed in identifying effective health promotion, prevention, treatment, rehabilitation, and care interventions.

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