La sindrome da Fragilità
Moving Frailty Toward Clinical Practice: NIA Intramural Frailty Science Symposium

• “The lack of general consensus on the language used to describe frailty, and the differing theories on the nature of frailty, present ongoing barriers to researchers and may discourage clinicians considering using frailty assessment in clinical practice”
Moving Frailty Toward Clinical Practice:
NIA Intramural Frailty Science Symposium

• ....the confusion as to what frailty is and how it can be best captured by a specific assessment....

• ...The lack of clarity may be connected in part by the use of the word “frailty” to indicate disparate conceptual frameworks, risk predictors, and assessments...

• ... Furthermore, related-and as of now, loosely defined-concepts of “vulnerability” and “resiliency” have further confused clinicians and researchers alike...
Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/NIA Research Conference on Frailty in Older Adults

“A state of increased vulnerability to stress due to age-related declines in physiologic reserves across neuromuscular, metabolic, and immune systems”

Watson J et al JAGS 2006
Few examples

Progressive decline in anatomical integrity and function across multiple physiological systems

Frailty as accelerated decline in anatomical integrity and function across multiple physiological systems

Testosterone
Estrogens
IGF-1
Cytokines and APR (higher)
ROS / Antioxidants
Complexity of CV reflexes

Physiological Parameter

Age

65  100
Interactions between age-related changes and chronic diseases

Chronic Diseases

- CHD, CHF, CVD, diabetes, COPD, obesity, osteoarthritis, depression, dementia

↓ Functional reserve

Aging Process

- Progressive decline in anatomical integrity and function of multiple physiological systems

Frailty

- Functional decline
- Falls
- Disability
- Cognitive impairment
- Institutionalization
- Death

65 yrs  Age  100 yrs
Clarification of conceptual frameworks for commonly used Frailty models

1. **Physical Frailty**
   ✓ CHS (Fried)
   ✓ SOFT
   ✓ others

2. **Deficit accumulation Frailty**
   ✓ CSA Frailty Index
   ✓ MPI
   ✓ Silver code
   ✓ others

3. **Pre-disability state**
   ✓ SPPB
   ✓ Physical Frailty and sarcopenia
   ✓ others
Physical Frailty Phenotype

- Physical Activity
- Muscle Strength
- Energy Level
- Walking Speed
- Weight Loss
The Cycle of Frailty

Neuroendocrine Dysfunction
- Anorexia of aging
- Inadequate intake of protein and energy; micronutrient deficiencies
- Total Energy Expenditure
- Activity
- Walking Speed
- Disability
- Dependency

Chronic Undernutrition
- Negative Energy Balance
- Negative Nitrogen Balance
- Weight Loss

Aging: Senescent musculoskeletal changes
- Loss of muscle mass
- Sarcopenia

Resting Metabolic Rate
- Strength & Power
- VO2 max

Disease
Fried LP. J Gerontol Med Sci 2001

<table>
<thead>
<tr>
<th>Frailty Status at Baseline</th>
<th>Died</th>
<th>First Hospitalization</th>
<th>First Fall</th>
<th>Worsening ADL Disability</th>
<th>Worsening Mobility Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>3 yr %</td>
<td>7 yr %</td>
<td>3 yr %</td>
<td>7 yr %</td>
</tr>
<tr>
<td>Not Frail</td>
<td>2469</td>
<td>3</td>
<td>12</td>
<td>33</td>
<td>79</td>
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<tr>
<td>Intermediate</td>
<td>2480</td>
<td>7</td>
<td>23</td>
<td>43</td>
<td>83</td>
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<tr>
<td>Frail</td>
<td>368</td>
<td>18</td>
<td>43</td>
<td>59</td>
<td>96</td>
</tr>
</tbody>
</table>

*p*: 7-year estimates are only available for the first cohort.

*Only those evaluable for frailty are included.

*The p value is based on the 2 degree of freedom log rank test using all available follow-up.
Clarification of conceptual frameworks for commonly used Frailty models

- Physical Frailty
  - CHS (Fried)
  - SOFT
  - others

2. Deficit accumulation Frailty
   - CSA Frailty Index
   - MPI
   - Silver code
   - others

3. Pre-disability state
   - SPPB
   - Physical Frailty and sarcopenia
   - others
Frailty Index
**Appendix 1: List of variables used by the Canadian Study of Health and Aging to construct the 70-item CSHA Frailty Index**

- Changes in everyday activities
- Head and neck problems
- Poor muscle tone in neck
- Bradykinesia, facial
- Problems getting dressed
- Problems with bathing
- Problems carrying out personal grooming
- Urinary incontinence
- Mood problems
- Feeling sad, blue, depressed
- History of depressed mood
- Tiredness all the time
- Depression (clinical impression)
- Sleep changes
- Restlessness
- Memory changes
- Seizures, partial complex
- Seizures, generalized
- Syncope or blackouts
- Headache
- Cerebrovascular problems
- History of stroke
- History of diabetes mellitus
- Arterial hypertension

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**Ratio between the number of deficits detected and the number of conditions evaluated**

- Sucking problems
- Problems going out alone
- Impaired mobility
- Musculoskeletal problems
- Bradykinesia of the limbs
- Poor muscle tone in limbs
- Poor limb coordination
- Poor coordination, trunk
- Poor standing posture
- Irregular gait pattern
- Falls
- Paranoid features
- History relevant to cognitive impairment or loss
- Family history relevant to cognitive impairment or loss
- Impaired vibration
- Tremor at rest
- Postural tremor
- Intention tremor
- History of Parkinson’s disease
- Family history of degenerative disease
- Lung problems
- Respiratory problems
- History of thyroid disease
- Thyroid problems
- Skin problems
- Malignant disease
- Breast problems
- Abdominal problems
- Presence of snout reflex
- Presence of the palpmential reflex
- Other medical history
Frailty in Relation to the Accumulation of Deficits

Kenneth Rockwood\textsuperscript{1,2} and Arnold Mitnitski\textsuperscript{2}

![Graph showing frailty index versus age](image)
Kaplan–Meier medium-term survival curves (adjusted for age and sex) for individuals with different values

Clarification of conceptual frameworks for commonly used Frailty models

• Physical Frailty
  • CHS (Fried)
  • SOFT
  • others

• Deficit accumulation Frailty
  • CSA Frailty Index
  • MPI
  • others

3. Pre-disability state
   ✓ SPPB
   ✓ Physical Frailty and sarcopenia
   ✓ others
Short Physical Performance Battery

1. Balance Tests
   - Side-by-Side Stand
     Feet together side-by-side for 10 sec
     - < 10 sec (0 pt)
     - 10 sec (1 pt)
     Go to 4-Meter Gait Speed Test
   - Semi-Tandem Stand
     Heel of one foot against side of big toe of the other for 30 sec
     - < 10 sec (4 pt)
     Go to 4-Meter Gait Speed Test
     - 10 sec (3 pt)
     - 3-9.99 sec (2 pt)
     - 10 sec (1 pt)
   - Tandem Stand
     Feet aligned heel to toe for 10 sec
     - < 10 sec (2 pt)
     - 10 sec (1 pt)
     Go to 4-Meter Gait Speed Test
     - 10 sec (0 pt)

2. Gait Speed Test
   - Measure the time required to walk 4 meters at a normal pace (use best of 2 times)
   - 4.82 sec or less (4 pt)
   - 4.83-6.20 sec (3 pt)
   - 6.21-8.70 sec (2 pt)
   - >8.7 sec (1 pt)
   - Unable (0 pt)

3. Chair Stand Test
   - Pre-test
     Participants fold their arms across their chest and try to stand up once from a chair
     unable Step (0 pt)
   - 5 repeats
     Measures the time needed to perform five rises from a chair to an upright position as fast as possible without the use of the arm
     <11.19 sec (4 pt)
     11.20-13.69 sec (3 pt)
     13.70-16.08 sec (2 pt)
     >16.7 sec (1 pt)
     >60 sec or unable (0 pt)
SPPB and risk of Mobility and ADL disability over 4-year FU (EPESE)

SPPB and all-cause Mortality: Systematic Review and Meta-analysis


<table>
<thead>
<tr>
<th>Study</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnaud et al. 2015</td>
<td>0.52</td>
<td>0.19</td>
<td>3.1%</td>
<td>1.68 [1.16, 2.44]</td>
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<tr>
<td>Brown et al. 2015</td>
<td>0.30</td>
<td>0.28</td>
<td>6.3%</td>
<td>2.29 [1.55, 3.39]</td>
</tr>
<tr>
<td>Csesari et al. 2008</td>
<td>1.46</td>
<td>0.52</td>
<td>1.2%</td>
<td>4.31 [1.55, 11.93]</td>
</tr>
<tr>
<td>Csesari et al. 2013</td>
<td>0.56</td>
<td>0.09</td>
<td>8.8%</td>
<td>0.57 [0.15, 2.21]</td>
</tr>
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<td>Chianantini et al. 2010</td>
<td>0.63</td>
<td>0.08</td>
<td>5.1%</td>
<td>1.51 [0.41, 5.60]</td>
</tr>
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<td>Corsello et al. 2012</td>
<td>0.77</td>
<td>0.59</td>
<td>12.0%</td>
<td>2.16 [0.68, 6.86]</td>
</tr>
<tr>
<td>Ennfilde et al. 2013</td>
<td>0.61</td>
<td>0.11</td>
<td>3.6%</td>
<td>2.25 [1.81, 2.89]</td>
</tr>
<tr>
<td>Greene et al. 2014</td>
<td>1.07</td>
<td>0.34</td>
<td>2.0%</td>
<td>2.92 [1.50, 5.68]</td>
</tr>
<tr>
<td>Kim et al. 2015</td>
<td>1.87</td>
<td>0.35</td>
<td>1.2%</td>
<td>3.94 [1.84, 11.38]</td>
</tr>
<tr>
<td>Lai et al. 2014</td>
<td>0.73</td>
<td>1.17</td>
<td>0.3%</td>
<td>2.08 [0.21, 20.56]</td>
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<td>Legrand et al. 2014</td>
<td>0.53</td>
<td>0.22</td>
<td>2.9%</td>
<td>1.70 [1.10, 2.61]</td>
</tr>
<tr>
<td>Menecci et al. 2015</td>
<td>0.61</td>
<td>0.27</td>
<td>2.5%</td>
<td>2.25 [1.32, 3.82]</td>
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<td>Rolland et al. 2006</td>
<td>0.67</td>
<td>0.11</td>
<td>3.8%</td>
<td>1.95 [1.58, 2.42]</td>
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<tr>
<td>Sterneholt et al. 2013</td>
<td>1.02</td>
<td>0.19</td>
<td>3.1%</td>
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<tr>
<td>Taalbaek et al. 2014</td>
<td>0.74</td>
<td>0.25</td>
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<td>1.0%</td>
<td>4.57 [1.50, 13.57]</td>
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<td>Volpato et al. 2011</td>
<td>1.68</td>
<td>1.28</td>
<td>0.3%</td>
<td>2.94 [0.24, 16.15]</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.00$; $Q_{df = 16} = 16 (P = 0.51)$; $I^2 = 0$

Test for overall effect: $Z = 13.71 (P < 0.00001)$

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<td>3.3%</td>
<td>1.36 [0.98, 1.90]</td>
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<td>Brown et al. 2015</td>
<td>0.26</td>
<td>0.17</td>
<td>3.3%</td>
<td>1.30 [0.93, 1.81]</td>
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<td>Csesari et al. 2008</td>
<td>0.47</td>
<td>0.55</td>
<td>1.1%</td>
<td>1.60 [0.54, 4.70]</td>
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<td>Csesari et al. 2013</td>
<td>0.10</td>
<td>0.88</td>
<td>0.6%</td>
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<td>Chianantini et al. 2010</td>
<td>0.04</td>
<td>0.68</td>
<td>0.8%</td>
<td>0.87 [0.23, 3.30]</td>
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<td>0.47</td>
<td>0.62</td>
<td>0.9%</td>
<td>1.60 [0.47, 5.59]</td>
</tr>
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Heterogeneity: $I^2 = 0.02$; $Q_{df = 16} = 16 (P = 0.51)$; $I^2 = 27$

Test for overall effect: $Z = 6.29 (P < 0.00001)$
The Assessment of Scales of Frailty and Physical Performance Improves Prediction of Major Adverse Cardiac Events in Older Adults with Acute Coronary Syndrome

From December 2014 to October 2016:
2837 patients admitted with Acute Coronary Syndrome

- n=55 did not receive coronary artery angiography
- n=31 died before coronary artery angiography

2751 (97%) patients underwent coronary artery angiography

- n=378 with indication to surgical revascularization
- n=53 died after angiography
- n=1558 age <70 years

762 (28%) patients were eligible for inclusion

- n=89 transfer from cardiology unit to other clinics (e.g. long-term care)
- n=68 SPMSQ <4
- n=95 did not guarantee follow-up
- n=51 refused to participate
- n=57 unable to stay upright

402 (53%) patients respected inclusion/exclusion criteria and were included
The Assessment of Scales of Frailty and Physical Performance Improves Prediction of Major Adverse Cardiac Events in Older Adults with Acute Coronary Syndrome

Table 4. Multivariable Analysis Including Scales of Frailty and Physical Performance and Incremental Value

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR (95% CI)*</th>
<th>Δ C-Statistic</th>
<th>p Value</th>
<th>IDI</th>
<th>p Value</th>
<th>NRI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACCE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPPB</td>
<td>0.79 (0.70–0.89)</td>
<td>0.044</td>
<td>.04</td>
<td>0.054</td>
<td>.001</td>
<td>0.752</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Columbia</td>
<td>1.17 (1.03–1.33)</td>
<td>0.019</td>
<td>.2</td>
<td>0.016</td>
<td>.2</td>
<td>0.248</td>
<td>.1</td>
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<tr>
<td>Edmonton</td>
<td>1.34 (1.15–1.56)</td>
<td>0.017</td>
<td>.4</td>
<td>0.073</td>
<td>&lt;.0001</td>
<td>0.505</td>
<td>.001</td>
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<tr>
<td>Grip strength (kg)</td>
<td>0.96 (0.92–0.99)</td>
<td>0.008</td>
<td>.6</td>
<td>0.018</td>
<td>.04</td>
<td>0.316</td>
<td>.052</td>
</tr>
<tr>
<td>Fried</td>
<td>1.36 (1.04–1.79)</td>
<td>0.011</td>
<td>.5</td>
<td>0.019</td>
<td>.02</td>
<td>0.319</td>
<td>.047</td>
</tr>
<tr>
<td>Rockwood CFS</td>
<td>1.07 (0.76–1.49)</td>
<td>0.001</td>
<td>.9</td>
<td>0.001</td>
<td>.4</td>
<td>0.100</td>
<td>.5</td>
</tr>
<tr>
<td>MPI</td>
<td>1.61 (2.70–9.61)</td>
<td>0.020</td>
<td>.1</td>
<td>0.020</td>
<td>.1</td>
<td>0.277</td>
<td>.08</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPPB</td>
<td>0.74 (0.63–0.85)</td>
<td>0.063</td>
<td>.02</td>
<td>0.61</td>
<td>&lt;.0001</td>
<td>1.022</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Columbia</td>
<td>1.13 (0.97–1.30)</td>
<td>0.005</td>
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<td>.05</td>
<td>0.012</td>
<td>.9</td>
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<td>Edmonton</td>
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<td>0.037</td>
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<td>0.045</td>
<td>.004</td>
<td>0.646</td>
<td>.0003</td>
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<tr>
<td>Grip strength (kg)</td>
<td>0.98 (0.94–1.02)</td>
<td>−0.008</td>
<td>.4</td>
<td>0.010</td>
<td>.01</td>
<td>0.358</td>
<td>.047</td>
</tr>
<tr>
<td>Fried</td>
<td>1.58 (1.14–2.18)</td>
<td>0.020</td>
<td>.3</td>
<td>0.033</td>
<td>.002</td>
<td>0.371</td>
<td>.035</td>
</tr>
<tr>
<td>Rockwood CFS</td>
<td>1.34 (0.94–1.92)</td>
<td>0.005</td>
<td>.7</td>
<td>0.015</td>
<td>.08</td>
<td>0.420</td>
<td>.017</td>
</tr>
<tr>
<td>MPI</td>
<td>1.25 (0.01–1.13)</td>
<td>−0.001</td>
<td>.5</td>
<td>0.0002</td>
<td>.78</td>
<td>−0.061</td>
<td>1</td>
</tr>
</tbody>
</table>

*Note: CFS = Clinical frailty scale; IDI = Integrated discrimination improvement; MACCE = Major adverse cardiac cerebrovascular event; MPI = Multidimensional prognostic index; NRI = Net reclassification improvement; OR = Odds ratio; SPPB = Short physical performance battery.

*Multivariable analysis obtained after the insertion of the scale in the baseline model (Table 3).

Δ C-Statistic, IDI, NRI: the values are referred for the comparison between the baseline model (Table 3) and the same model with the addition of frailty scale.
The Assessment of Scales of Frailty and Physical Performance Improves Prediction of Major Adverse Cardiac Events in Older Adults with Acute Coronary Syndrome

![Graphs showing sensitivity and specificity for MACCE and all-cause mortality]

<table>
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<tr>
<th></th>
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<th>Δ C-Statistic</th>
<th>IDI</th>
<th>NRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRACE</td>
<td>0.620 (0.581-0.663)</td>
<td>0.143</td>
<td>0.083 (p&lt;0.001)</td>
<td>0.853 (p&lt;0.001)</td>
</tr>
<tr>
<td>GRACE + SPPB</td>
<td>0.763 (0.726-0.801)</td>
<td>0.158</td>
<td>0.083 (p&lt;0.001)</td>
<td>0.692 (p&lt;0.001)</td>
</tr>
<tr>
<td>TIMI</td>
<td>0.610 (0.574-0.644)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI + SPPB</td>
<td>0.765 (0.736-0.803)</td>
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![Graphs showing sensitivity and specificity for MACCE and all-cause mortality]

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<tbody>
<tr>
<td>GRACE</td>
<td>0.640 (0.601-0.683)</td>
<td>0.176</td>
<td>0.115 (p&lt;0.001)</td>
<td>1.050 (p&lt;0.001)</td>
</tr>
<tr>
<td>GRACE + SPPB</td>
<td>0.816 (0.777-0.859)</td>
<td>0.228</td>
<td>0.102 (p&lt;0.001)</td>
<td>0.937 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

![Graphs showing sensitivity and specificity for MACCE and all-cause mortality]
Ability to discriminate haemorrhagic events of risk scores and scales of frailty or physical performance

<table>
<thead>
<tr>
<th></th>
<th>BARC 3-5</th>
<th></th>
<th>BARC 2</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>C-statistic (95%CI)</td>
<td>p-value</td>
<td>C-statistic (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Risk scores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paris</td>
<td>0.74 (0.61-0.86)</td>
<td>0.002</td>
<td>0.52 (0.46-0.57)</td>
<td>0.817</td>
</tr>
<tr>
<td>PRECISE-DAPT</td>
<td>0.79 (0.66-0.91)</td>
<td>&lt;0.001</td>
<td>0.55 (0.50-0.61)</td>
<td>0.332</td>
</tr>
<tr>
<td>BleeMACS</td>
<td>0.77 (0.60-0.93)</td>
<td>&lt;0.001</td>
<td>0.54 (0.50-0.60)</td>
<td>0.434</td>
</tr>
<tr>
<td><strong>Scales of frailty/physical performance</strong></td>
<td></td>
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<td></td>
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<tr>
<td>SPPB</td>
<td>0.75 (0.64-0.86)</td>
<td>0.002</td>
<td>0.53 (0.47-0.58)</td>
<td>0.632</td>
</tr>
<tr>
<td>Columbia</td>
<td>0.67 (0.54-0.80)</td>
<td>0.013</td>
<td>0.53 (0.48-0.59)</td>
<td>0.555</td>
</tr>
<tr>
<td>Edmonton</td>
<td>0.75 (0.62-0.89)</td>
<td>&lt;0.001</td>
<td>0.50 (0.44-0.55)</td>
<td>0.961</td>
</tr>
<tr>
<td>Grip strength, (Kg)</td>
<td>0.64 (0.53-0.76)</td>
<td>0.088</td>
<td>0.57 (0.51-0.62)</td>
<td>0.189</td>
</tr>
<tr>
<td>Fried</td>
<td>0.66 (0.55-0.78)</td>
<td>0.067</td>
<td>0.55 (0.50-0.61)</td>
<td>0.343</td>
</tr>
<tr>
<td>Rockwood CFS</td>
<td>0.71 (0.58-0.84)</td>
<td>0.005</td>
<td>0.57 (0.52-0.62)</td>
<td>0.225</td>
</tr>
<tr>
<td>MPI</td>
<td>0.60 (0.44-0.76)</td>
<td>0.243</td>
<td>0.56 (0.51-0.61)</td>
<td>0.267</td>
</tr>
</tbody>
</table>
SARCOPENIA
- Skeletal muscle loss
- Poor muscle quality

PHYSICAL FUNCTION IMPAIRMENT
- Weak muscle strength
- Slow gait speed
- Poor balance

FRAILTY
- Deficits accumulation
- Fatigue
- Sedentary behaviour
- Weight loss
- Cognitive impairment
- Social isolation

Cesari M et al. Front Aging Neurosci 2014
ROBUSTNESS

SPPB ≥10/12
No sarcopenia
No mobility disability

Probable few benefits from interventions against disability

FRAILTY

SPPB between 3/12 and 9/12
Sarcopenia
No mobility disability

Possible interventions for PREVENTING disability

DISABILITY

SPPB <3/12
Sarcopenia (cachexia?)
Mobility disability

Possible interventions for TREATING disability
Exhaustion of endogenous reserves for restoring robustness

PF&S

Limit posed by the low SPPB impairment (ceiling effect)

Limit posed by the mobility disability (floor effect)
Using Frailty models in clinical practice:

1. Frailty as a preclinical state: a condition that can be prevented, slowed or even reversed

2. Frailty as a prognostic and stratification factor that orients the treatment plan

3. Use different model according to the clinical aim