Physical Resilience after Orthopedic Surgery in Older Adults

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Disclosures and Funding

- **NIA UH2 AG056925-01** (Colon-Emeric and Whitson, MPI)
- Consultant for Amgen (CEC Chair), Novartis (DMC Chair) Musculoskeletal Programs including myostatin inhibitor
- U.S. patent 20104717 “Bisphosphonate compositions and methods for treating heart failure”, and 61560328 “Bisphosphonate compositions and methods for treating and/or reducing cardiac dysfunction”
- Equity owner of BisCardia, Inc.
Objectives

1. Describe **resilient phenotypes** following hip fracture using 2 different approaches
2. Identify **biomarkers** that predict resilient phenotypes
   - Hypotheses for underlying pathways
Recovery Phenotype Approach

• Descriptive
• Multiple parameters
• Can summarize multiple outcomes simultaneously
  - Latent Class Trajectory Analysis
  - Factor Analysis
  - Principle Components Analysis
• Driven by age, pre-stressor status
Expected Recovery Differential Approach

- Quantifies how much outcome differed from expected
- Requires predictive model from large cohort
- Accounts for baseline status, stressor factors, environment etc.
Applying Phenotype Approaches after Hip Fracture

- 3 Cohorts of the Baltimore Hip Studies
  - N=541
- Latent Class Profile analysis
  - Complete Case Analysis
  - Multiple Imputation
  - Death as covariate

Jay Magaziner, PhD
University of Maryland
Latent Profile Analysis trajectory group

- Lowest resilience
- - - Medium resilience
- - - - - Highest resilience
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lowest N=136</th>
<th>Intermediate N=242</th>
<th>Highest N=163</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yrs)</td>
<td>83.1</td>
<td>81.1</td>
<td>78.2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>33.1</td>
<td>14.5</td>
<td>13.5</td>
</tr>
<tr>
<td># Comorbidities</td>
<td>1.6</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>≤ High School (%)</td>
<td>65.4</td>
<td>62.3</td>
<td>50.5</td>
</tr>
<tr>
<td>Depressed (%)</td>
<td>49.3</td>
<td>37.6</td>
<td>35.0</td>
</tr>
<tr>
<td>Cognitive Impairment (%)</td>
<td>25.0</td>
<td>5.0</td>
<td>0</td>
</tr>
<tr>
<td>Any alcohol use (%)</td>
<td>47.4</td>
<td>48.8</td>
<td>61.1</td>
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<tr>
<td>Prior weight loss (%)</td>
<td>19.9</td>
<td>12.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Trochanteric fracture (%)</td>
<td>52.9</td>
<td>40.9</td>
<td>33.7</td>
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<tr>
<td>General Anesthesia (%)</td>
<td>86.8</td>
<td>35.3</td>
<td>22.6</td>
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<tr>
<td>Hospital Infection (%)</td>
<td>16.9</td>
<td>6.6</td>
<td>7.4</td>
</tr>
</tbody>
</table>
Factors Associated with Resilience

Model Predicting High vs. Low/Medium Resilience

AUC for Variable Chunk

- Stressor Factors
- Environment
- Comorbidities
- Demographics
- Psychosocial
- Pre-stressor function

AUC values:
- Stressor Factors: 0.6
- Environment: 0.6
- Comorbidities: 0.61
- Demographics: 0.67
- Psychosocial: 0.67
- Pre-stressor function: 0.84
Expected Recovery Differential (ERD) After Hip Fracture

- Mixed Model with random effects predicting outcome for each individual
  - 10 outcomes
- Difference from actual outcome = ERD
- Average across all outcomes for Total ERD
Expected Recovery Differentials Correlated Across Most Outcomes
Pathway Analysis of Biomarkers Significantly Associated with ERD

Adjusted Canonical Correlation 0.58

- Cytokine-cytokine receptor interaction
- TNF Signaling

Pathways regulating pluripotency of stem cells

- P35 signaling pathway
- Jak-STAT signaling pathway

Transcriptional misregulation in cancer

- FoxO pathway
- PI3K-Akt pathway
- mTOR pathway
- Adipocytokine pathway
- Insulin signaling pathway
- Non-alcoholic fatty liver disease
Hypotheses Generated

Are biomarkers associated with physical resilience?

High Resilience
- ↓ Cellular Senescence
- ↓ Inflammation
- ↑ Mitochondrial Function
- ↑ Skeletal Muscle Metabolism

Low Resilience
- ↑ Cellular Senescence
- ↑ Inflammation
- ↓ Mitochondrial Function
- ↓ Skeletal Muscle Metabolism

miRNAs, free amino acids, acylcarnitines, IL-6, TNFR-I, TNFR-II, sVCAM-1, IGF-1
Thank you and Questions

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