Sarcopenia in critically ill patients

Gyeongsang national university hospital
Department of internal medicine
Division of pulmonology and critical care medicine
Sunmi Ju
Sarcopenia

$Sarx$ (flesh) + $penia$ (loss)

- Rosenberg, 1989 -

Age-related loss of skeletal muscle mass and function
Muscle strength and the life course

Cruz-Jentoft et al. *Age and Ageing* 2019; 48: 16–31
Super-aged Society

Homo Hundred Era

Life expectancy

\[ \approx \text{Healthy life years} + 10 \text{ years} \]
Increase of the admission to the ICU of elderly patients in Korea from 2003 to 2010

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>β (P-value)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total of ICU admission</td>
<td>25,400 (2.31)</td>
<td>2,938 (0.29)</td>
<td>3,091 (0.30)</td>
<td>2,947 (0.29)</td>
<td>3,089 (0.31)</td>
<td>3,296 (0.32)</td>
<td>3,315 (0.33)</td>
<td>3,412 (0.34)</td>
<td>3,312 (0.33)</td>
<td>0.007 (0.001)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14,721 (57.96)</td>
<td>1,607 (54.7)</td>
<td>1,753 (56.71)</td>
<td>1,769 (60.03)</td>
<td>1,805 (58.43)</td>
<td>1,966 (59.62)</td>
<td>1,949 (58.79)</td>
<td>1,952 (57.21)</td>
<td>1,921 (58.00)</td>
<td>0.27 (0.337)</td>
</tr>
<tr>
<td>Female</td>
<td>10,679 (42.04)</td>
<td>1,331 (45.3)</td>
<td>1,338 (43.29)</td>
<td>1,178 (39.97)</td>
<td>1,284 (41.57)</td>
<td>1,331 (40.38)</td>
<td>1,366 (41.21)</td>
<td>1,460 (42.79)</td>
<td>1,391 (42.00)</td>
<td>-0.27 (0.337)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>787 (3.10)</td>
<td>121 (4.12)</td>
<td>125 (4.04)</td>
<td>87 (2.95)</td>
<td>90 (2.91)</td>
<td>94 (2.85)</td>
<td>112 (3.38)</td>
<td>91 (2.67)</td>
<td>67 (2.02)</td>
<td>-0.24 (0.008)</td>
</tr>
<tr>
<td>30-39</td>
<td>1,565 (6.16)</td>
<td>232 (7.50)</td>
<td>254 (8.22)</td>
<td>207 (7.02)</td>
<td>172 (5.57)</td>
<td>191 (5.79)</td>
<td>169 (5.10)</td>
<td>157 (4.60)</td>
<td>183 (5.53)</td>
<td>-0.47 (0.003)</td>
</tr>
<tr>
<td>40-49</td>
<td>3,286 (12.94)</td>
<td>421 (14.33)</td>
<td>470 (15.21)</td>
<td>416 (14.12)</td>
<td>383 (12.40)</td>
<td>417 (12.65)</td>
<td>396 (12.01)</td>
<td>408 (11.96)</td>
<td>373 (11.26)</td>
<td>-0.52 (0.001)</td>
</tr>
<tr>
<td>50-59</td>
<td>4,607 (18.14)</td>
<td>550 (18.72)</td>
<td>545 (17.63)</td>
<td>507 (17.20)</td>
<td>560 (18.13)</td>
<td>583 (17.69)</td>
<td>617 (18.61)</td>
<td>632 (18.52)</td>
<td>613 (18.51)</td>
<td>0.08 (0.390)</td>
</tr>
<tr>
<td>60-69</td>
<td>6,275 (24.70)</td>
<td>757 (25.77)</td>
<td>795 (25.72)</td>
<td>763 (25.89)</td>
<td>791 (25.61)</td>
<td>795 (24.12)</td>
<td>789 (23.80)</td>
<td>782 (22.92)</td>
<td>803 (24.25)</td>
<td>-0.38 (0.009)</td>
</tr>
<tr>
<td>70-79</td>
<td>5,952 (23.43)</td>
<td>605 (20.59)</td>
<td>616 (19.93)</td>
<td>645 (21.89)</td>
<td>728 (23.57)</td>
<td>810 (24.58)</td>
<td>824 (24.86)</td>
<td>902 (26.44)</td>
<td>822 (24.82)</td>
<td>0.85 (0.001)</td>
</tr>
<tr>
<td>≥80</td>
<td>2,928 (11.53)</td>
<td>252 (8.58)</td>
<td>288 (9.25)</td>
<td>322 (10.93)</td>
<td>365 (11.82)</td>
<td>406 (12.32)</td>
<td>406 (12.25)</td>
<td>440 (12.90)</td>
<td>451 (13.62)</td>
<td>0.69 (0.001)</td>
</tr>
<tr>
<td>Age (yr), mean±SD</td>
<td>62.15±15.37</td>
<td>60.02±15.58</td>
<td>59.95±15.76</td>
<td>61.54±15.42</td>
<td>62.59±15.13</td>
<td>62.74±15.32</td>
<td>62.79±15.34</td>
<td>63.53±15.03</td>
<td>63.63±14.92</td>
<td>0.56 (0.001)</td>
</tr>
<tr>
<td>Household income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>7,740 (30.47)</td>
<td>904 (30.77)</td>
<td>948 (30.67)</td>
<td>852 (28.91)</td>
<td>942 (30.50)</td>
<td>977 (29.64)</td>
<td>999 (30.14)</td>
<td>1,075 (31.51)</td>
<td>1,043 (31.49)</td>
<td>0.14 (0.329)</td>
</tr>
<tr>
<td>Middle</td>
<td>9,674 (38.09)</td>
<td>1,113 (37.88)</td>
<td>1,243 (40.21)</td>
<td>1,139 (38.65)</td>
<td>1,208 (39.11)</td>
<td>1,272 (38.59)</td>
<td>1,256 (37.89)</td>
<td>1,237 (36.25)</td>
<td>1,206 (36.41)</td>
<td>-0.39 (0.043)</td>
</tr>
<tr>
<td>Low</td>
<td>7,986 (31.44)</td>
<td>921 (31.35)</td>
<td>900 (29.12)</td>
<td>956 (32.44)</td>
<td>939 (30.40)</td>
<td>1,047 (31.77)</td>
<td>1,060 (31.98)</td>
<td>1,100 (32.24)</td>
<td>1,063 (32.10)</td>
<td>0.24 (0.169)</td>
</tr>
<tr>
<td>CCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3,961 (15.59)</td>
<td>550 (18.72)</td>
<td>593 (19.18)</td>
<td>462 (15.68)</td>
<td>454 (14.70)</td>
<td>474 (14.38)</td>
<td>480 (14.48)</td>
<td>483 (14.16)</td>
<td>465 (14.04)</td>
<td>-0.73 (0.005)</td>
</tr>
<tr>
<td>1</td>
<td>6,901 (27.17)</td>
<td>802 (27.30)</td>
<td>924 (29.89)</td>
<td>855 (29.01)</td>
<td>864 (27.97)</td>
<td>880 (26.70)</td>
<td>880 (26.55)</td>
<td>870 (25.50)</td>
<td>826 (24.94)</td>
<td>-0.56 (0.013)</td>
</tr>
<tr>
<td>2</td>
<td>4,934 (19.43)</td>
<td>545 (18.55)</td>
<td>535 (17.31)</td>
<td>563 (19.10)</td>
<td>603 (19.52)</td>
<td>691 (20.96)</td>
<td>634 (19.13)</td>
<td>676 (19.81)</td>
<td>687 (20.74)</td>
<td>0.34 (0.040)</td>
</tr>
<tr>
<td>≥3</td>
<td>9,604 (37.81)</td>
<td>1,041 (35.43)</td>
<td>1,039 (33.61)</td>
<td>1,067 (36.21)</td>
<td>1,168 (37.81)</td>
<td>1,251 (37.96)</td>
<td>1,321 (39.85)</td>
<td>1,383 (40.53)</td>
<td>1,334 (40.28)</td>
<td>0.95 (0.001)</td>
</tr>
</tbody>
</table>

Heo et al. *Acute and Critical Care* 2018 33(3):135-145
Multiple factors contributing to rapid loss of muscle mass in the older ICU patient

Factors contributing to sarcopenia

Disease
- Inflammatory conditions (organ failure, malignancy)
- Osteoarthritis
- Neurological disorders

Aging

Malnutrition
- Under-nutrition or malabsorption
- Medication-related anorexia
- Over-nutrition/obesity

Inactivity
- Sedentary behavior (limited mobility or bedrest)
- Physical inactivity

Cruz-Jentoft et al. Age and Ageing 2019; 48: 16–31
Sarcopenia categories

- **Primary**: aging
- **Secondary**: disease, inactivity, and malnutrition
- **Acute**: lasting < 6 months
- **Chronic**: lasting ≥ 6 months

Cruz-Jentoft et al. *Age and Ageing* 2019; 48: 16–31
Malnutrition in critically ill patients

Stress catabolism

- Catabolic hormones: glucagon, cortisol, catecholamines
- Pro-inflammatory cytokines: IL-1, IL-6, TMF-α

Inadequate nutrition intake

- Preexisting malnutrition
- Iatrogenic underfeeding

Acute skeletal muscle wasting in critical illness

- Prospective study, August 2009 - April 2011, England
- 63 patients, mean age 54.7 years, APACHE II score of 23.5
- > 48 hours of MV, >7 days in ICU

Measurements of muscle wasting during critical illness by organ failure

Elevation in leg protein breakdown relative to protein synthesis resulting in a net catabolic state

Muscle biopsy specimens from a critically ill patient on day 1 and day 7

Day 1

Day 7

Myonecrosis important role in loss on muscle mass

Persistent inflammation, immunosuppression, and catabolism syndrome (PICS) paradigm

Effects of sarcopenia in ICU

- Delayed cessation of mechanical ventilation
- Longer hospital stay
- Increased risk of mortality
- Greater readmission rate
- Worse long-term physical function and QOL
- Increased care-giver burden

Moisey et al. *Crit Care* 2013; 17:R206
2018 operational definition of sarcopenia

- Probable sarcopenia
  - Low muscle strength

- Sarcopenia
  - Low muscle quantity or quality

- Severe sarcopenia
  - Low physical performance

Cruz-Jentoft et al. *Age and Ageing* 2019; 48: 16–31
### EWGSOP2 Sarcopenia cut-off points

<table>
<thead>
<tr>
<th>Test</th>
<th>Cut-off points for men</th>
<th>Cut-off points for women</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>EWGSOP2 sarcopenia cut-off points for low strength by chair stand and grip strength</td>
<td>Grip strength: &lt;27 kg</td>
<td>&lt;16 kg</td>
<td>Dodds (2014) [26]</td>
</tr>
<tr>
<td></td>
<td>Chair stand: &gt;15 s for five rises</td>
<td></td>
<td>Cesari (2009) [67]</td>
</tr>
<tr>
<td>EWGSOP2 sarcopenia cut-off points for low muscle quantity</td>
<td>ASM: &lt;20 kg</td>
<td>&lt;15 kg</td>
<td>Studenski (2014) [3]</td>
</tr>
<tr>
<td></td>
<td>ASM/height²: &lt;7.0 kg/m²</td>
<td>&lt;6.0 kg/m²</td>
<td>Gould (2014) [125]</td>
</tr>
<tr>
<td>EWGSOP2 sarcopenia cut-off points for low performance</td>
<td>Gait speed: ≤0.8 m/s</td>
<td></td>
<td>Cruz-Jentoft (2010) [1]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Studenski (2011) [84]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pavarini (2016) [90]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Guralnik (1995) [126]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bischoff (2003) [127]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Newman (2006) [128]</td>
</tr>
</tbody>
</table>

**SPPB** (Short physical performance battery) – gait speed, balance test, and chair stand test

**TUG** (Timed-up-and-go test)

ASM (Appendicular skeletal muscle mass)
Body compartments

Modalities of measurement for muscle mass

- Dual-energy x-ray absorptiometry (DEXA)
- Bioimpedance analysis (BIA)
- Computed tomography (CT)
- Ultrasound
Dual-energy x-ray absorptiometry (DEXA)

- Non-invasive with small doses of radiation
- Relatively cheap
- Well validated tool, low precision errors
- Not portable
- Body thickness and abnormalities in hydration status (e.g. water retention, heart, kidney, or liver failure) can affect muscle measure.
- Cannot quantify fatty infiltration of muscle

Bioimpedance analysis (BIA)

- Inexpensive
- **No radiation exposure**
- Accessible and can be performed **at the bedside**
- Need of age, gender, and ethnic-specific equation
- Sensitive to subjects’ conditions such as **hydration**, recent activity, and time being horizontal

Mundi MS et al. *Nutr Clin Pract* 14(1) 48-58
BIA-ICU outcomes

- **Phase angle**
  - Indicator of membrane integrity and water distribution
  - Prognostic indicator, positive association with survival in patients with HIV, malignancy, hemodialysis, and critical illness

Fig. 1. Covariate-adjusted ROC curves for BIA values (Wholebody phase angle) and severity scorings (APACHE II, SOFA, and SAPS III) as mortality predictive tools. (Adjusted values; age, gender, BMI)

241 critically ill surgical patients

Computed tomography (CT)

- Differentiate organs, skeletal muscle, and adipose tissue
- Differentiate abnormal muscles from normal muscle
- High radiation exposure
- Analysis is time-consuming and requires special software

Skeletal muscle: $-29$ to $150$ HU
Visceral, subcutaneous, intramuscular adipose tissue: $-150$ to $-50$ HU

Mundi MS et al. *Nutr Clin Pract* 14(1) 48-58
Lumbar 3\textsuperscript{rd} vertebra imaging correlated significantly with whole-body muscle

Psoas, erector spinae, quadrates lumborum, transverse abdominus, external and internal obliques, and rectus abdominus

CT-ICU outcomes

- Retrospective analysis
- 240 mechanical ventilated patients
- Abdomen CT on clinical indication between 1 day before and 4 days after admission
- Hospital mortality was significantly higher in those with sarcopenia compared with normal muscle area.
  - females (47.5% vs 20.0%)
  - males (32.3% vs 7.5%)

Retrospective study
• 491 mechanically ventilated critically ill adult patients
• Abdomen CT scan, 1 day before to 4 days after ICU admission
• Higher skeletal muscle density was associated with a lower 6-month mortality. HR/10 HU, 0.640 (95% CI, 0.552–0.742), p < 0.001

Looijaard WG et al *Crit Care* 2016(20):386
CT-ICU outcomes

- Cox proportional hazards regression multivariate analysis of in-hospital mortality of 125 cirrhotic patients admitted to ICU

<table>
<thead>
<tr>
<th>Variables</th>
<th>aHR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy (HCC)</td>
<td>2.245</td>
<td>0.004</td>
</tr>
<tr>
<td>Alcoholic LC</td>
<td>2.704</td>
<td>0.007</td>
</tr>
<tr>
<td>APACHE II</td>
<td>1.064</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Accelerated L3 mass loss (WBMI loss &gt;2%/year)</td>
<td>1.032</td>
<td>0.028</td>
</tr>
</tbody>
</table>

- 125 patients with liver cirrhosis admitted in MICU
- Two separate occasions before admission to the MICU
- 113 patients (90.4%) - sarcopenia
- Rapid muscle decline (WBMI loss >2%/year) is correlated with increased ICU mortality and in-hospital mortality in critically ill patients with cirrhosis.

Ultrasound

- No radiation exposure
- Accessible at the bedside
- Assess **quantity** and **quality** of muscle
- Lack of protocol consensus for method and site of measurement

Mundi MS et al. *Nutr Clin Pract* 14(1) 48-58
Guerreiro AC et al. *Front Med* 2017;31(4)122
Ultrasound

- No standardization of specific muscles
  - Rectus femoris (CSA or thickness)
  - Vastus lateralis (thickness)
  - Limb thickness (rectus femoris + vastus intermedius)
  - Individual muscle groups

- Unknown image acquisition site
  - Midthigh, 2/3, and 3/5 of femur length
    (for the quadriceps)

Rapid muscle wasting in the ICU

Detection changes in the quality and quantity of muscle
→ Relation with muscle strength and function

| Percentage change in ultrasound muscle parameters over the first 10 days of the ICU admission |
|---------------------------------------------|-----|-----|-----|-----|
| US muscle parameter measured                | Day 3 | Day 5 | Day 7 | Day 10 |
| RF thickness                                | −8.7% | −16.6%| −24.9%| −30.4%|
| VI thickness                                | −1.3% | −18.1%| −20.0%| −29.7%|
| VL thickness                                | −0.2% | −5.7% | −6.0% | −14.1%|
| RF CSA                                      | −1.0% | −11.8%| −16.8%| −29.9%|
| RF echogenicity                             | +2.8% | +8.8% | +9.6% | +12.7%|
| VI echogenicity                             | +4.0% | +7.1% | +13.6%| +25.2%|
| VL pennation angle                          | +4.9% | +18.9%| +1.4% | −7.3% |
| Subcutaneous tissue thickness               | +7.3% | +15.7%| +30.4%| +39.4%|

Day 3 measure is a percentage change from baseline.

vastus intermedius (VI)
rectus femoris (RF)
cross-sectional area (CSA)

Sarcopenia index

(serum creatinine/serum cystatin C) x 100

- Significant correlation with measured muscle mass via CT scan
- Independent predictor of the hospital and 90-day mortality rates (area under ROC, 0.8)
- Correlation with mechanical ventilation

Barreto et al. *Clinical nutrition* 2018
Interventions

- **Nutritional supports**
  - Early nutritional support
  - High-protein support
  - Leucine
  - β-Hydroxy-β-Methylbutyrate
  - Vitamin D supplement

- **Physiotherapy**
  - Neuromuscular electrical stimulation (NMES)
  - Exercise

- Reduction of sedatives and opioids
Early nutritional support

• Early enteral nutrition reduced in-hospital mortality from sepsis in patients with sarcopenia.
  

• Early nutritional deficits were correlated with muscle quality deterioration.
  – Inpatient gain in psoas density is associated with shorter hospital stay.
  
Single-center retrospective analysis - septic patients
Yamaguchi University Hospital ICU
January 2010-August 2017
Skeletal muscle area (SMA) at the level of the third lumbar vertebra was measured with CT on admission
Sarcopenia: SMA < 80% of the predicted value
High-protein support

Protein requirements are expected to be in the range of **1.2–2.0 g/kg actual body weight per day** and may likely be even higher in burn or multitrauma patients.

2014 ASPEN guideline

During critical illness, **1.3 g/kg protein equivalents per day** can be delivered progressively.

**1.2-1.5 g protein/kg/day** in older people who are malnourished or at risk of malnutrition because they have acute or chronic illness, with even high protein intake for individuals with severe illness or injury.

2018 ESPEN guideline
High-protein support

- Sarcopenic ICU patients benefit more from protein intake > 1.2 g/kg per day. Looijaard et al. *Crit Care* 2016;20:386


- Older patients in the ICU were able to achieve nitrogen equilibrium but only with protein intakes that approached 2–2.5 g/kg/d. Dickerson RN et al. *JPEP J Parenter Enteral Nitr.* 2015;39:282-290
Leucine

- Promote muscle protein synthesis by stimulating the mammalian target of rapamycin (mTOR) signaling pathway

**β-hydroxy-β-methylbutyrate**

- Leucine metabolite
- Stimulate protein synthesis or prevent proteolysis

*14-day nitrogen balance measurements

\(<\text{HMB}>\) β-hydroxy-β-methylbutyrate

\(<\text{Juven}>\) HMB + L-arginine + L-glutamine

Vitamin D supplement

- Vitamin D receptor on muscle
- Vitamin D deficiency → muscle pain and weakness
- Vitamin D supplementation can improved muscle strength, in particular in those most deficient.

Change in total leg strength

Pathogenesis and features of the refeeding syndrome

- Hypokalaemia
- Hypomagnesaemia
- Hypophosphataemia
- Thiamine deficiency
- Salt and water retention - oedema

Starvation / Malnutrition

Glycogenolysis, gluconeogenesis and protein catabolism

Protein, fat, mineral, electrolyte and vitamin depletion – salt and water intolerance

Refeeding (switch to anabolism)

Fluid, salt, nutrients (CHO major energy source)

↑ Glucose uptake
↑ Utilization of thiamine
↑ Uptake of K⁺, Mg²⁺ & PO₄²⁻

↑ Protein and glycogen synthesis

Insulin secretion
Patients of high risk of refeeding syndrome

Either the patient has one or more of the following:
- Body mass index (kg/m²) < 16
- Unintentional weight loss > 15% in the past three to six months
- Little or no nutritional intake for > 10 days
- Low levels of potassium, phosphate, or magnesium before feeding

Or the patient has two or more of the following:
- Body mass index < 18.5
- Unintentional weight loss > 10% in the past three to six months
- Little or no nutritional intake for > 5 days
- History of alcohol misuse or drugs, including insulin, chemotherapy, antacids, or diuretics

Malabsorptive syndrome (such as inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, short bowel syndrome)
- Long term users of antacids (magnesium and aluminium salts bind phosphate)
- Long term users of diuretics (loss of electrolytes)

Mehanna HM et al. BMJ 2008;336:1495-8
Prevention of the refeeding syndrome

• Immediately vitamin (thiamine) supplementation

• Close monitoring and correction of phosphate, potassium, calcium, and magnesium
  – Once daily for the first week
  – Refeeding hypophosphatemia: < 2.0 mg/dl, ▼ 0.5 mg/dl

• Slow progression to energy target during the first 72 h

Conclusions

• **Definition of sarcopenia**
  – Low muscle strength + low muscle quantity or quality

• **Pathophysiology of sarcopenia in ICU**
  – Primary: aging
  – Secondary: stress catabolism, inactivity, and malnutrition

• **Effect of sarcopenia in critically ill patients**
  – Increased mortality
  – Longer hospital stay
  – Longer MV days
  – Worse long-term physical function and QOL
Conclusions

• **Modalities to measure muscle mass**
  - **BIA**: accessible at the bedside, phase angle – prognostic factor
  - **CT**: L₃ vertebrae level, measuring quantity and quality of muscle
  - **US**: Rectus femoris & vastus intermedius mm., no radiation, accessible at the bedside, measuring quantity and quality of muscle

• **Prevention or reducing muscle wasting**
  - Early nutritional supports, high-protein support, leucine, β-hydroxy-β-methylbutyrate (HMB), vitamin D (in deficient case)
  - Rehabilitation, reduction of sedatives and opioids

• **Refeeding syndrome**
  - Close monitoring and correction of serum levels of electrolytes, especially phosphate
  - Slow progression of nutrition in patients of high risk
Thank you for your attention!