Sarcopenia in critically ill patients

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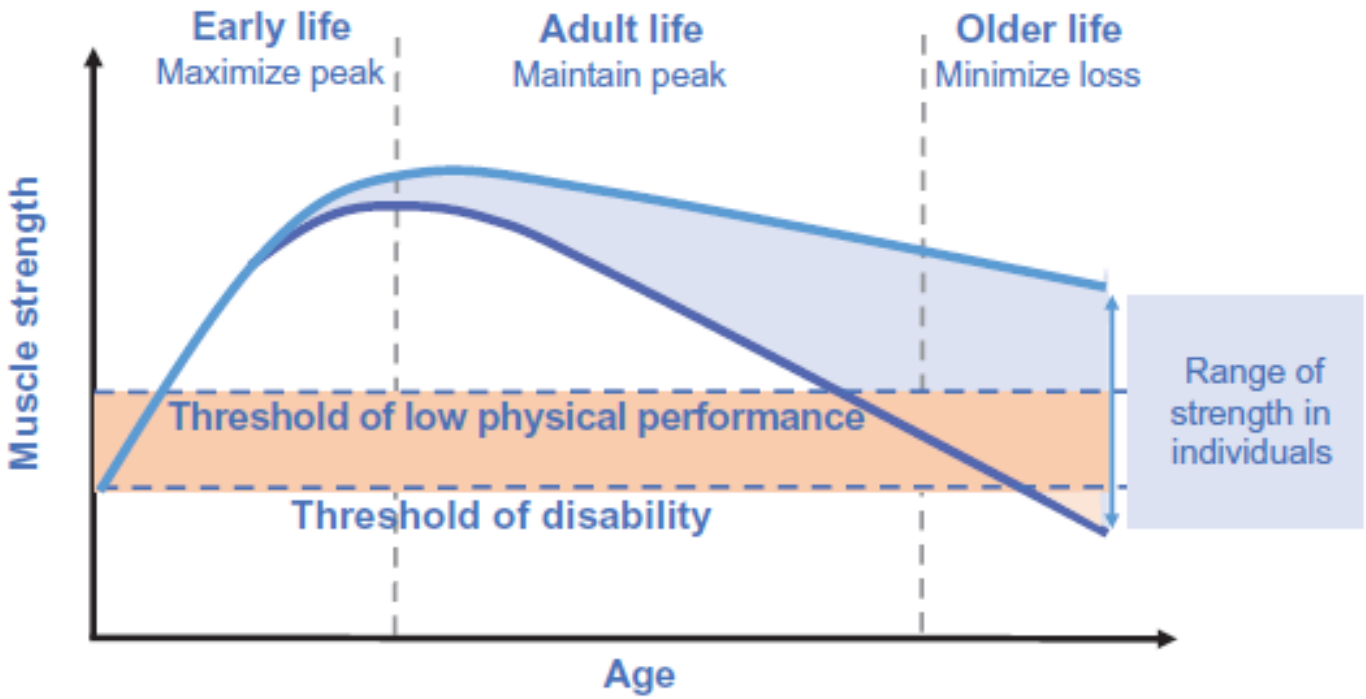
Sarcopenia

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

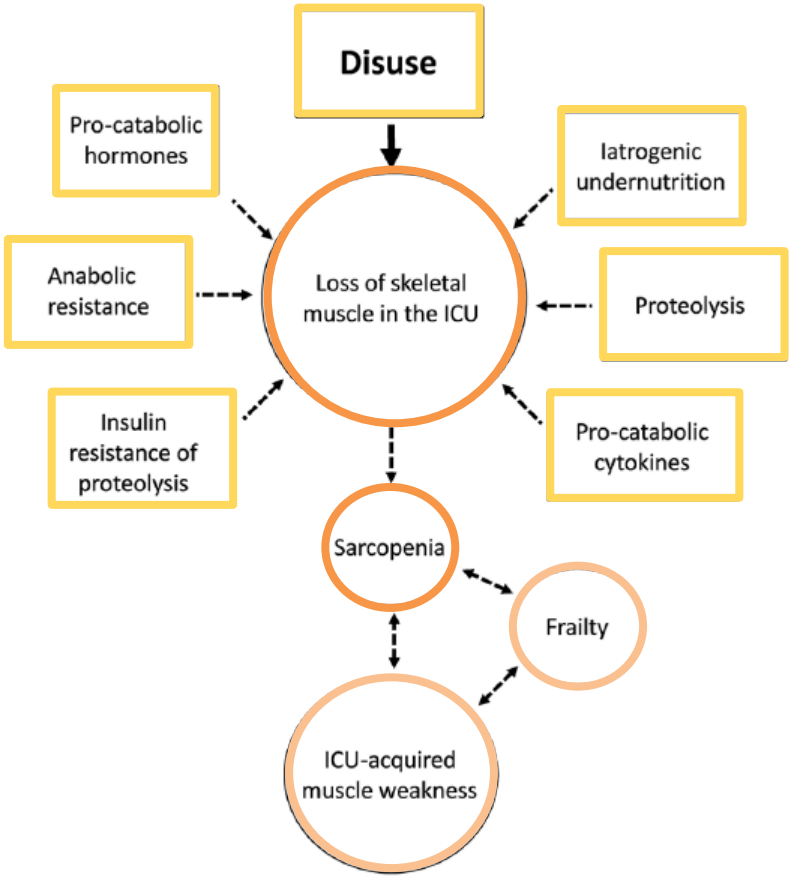

Super-aged Society
Homo Hundred Era
Life expectancy
≒ Healthy life years + 10 years

Increase of the admission to the ICU of elderly patients in Korea from 2003 to 2010

Variable	Total	2003	2004	2005	2006	2007	2008	2009	2010	β (P-value)[a]
Total of ICU admission	25,400 (2.31)	2,938 (0.29)	3,091 (0.30)	2,947 (0.29)	3,089 (0.31)	3,296 (0.32)	3,315 (0.33)	3,412 (0.34)	3,312 (0.33)	0.007 (0.001)
Sex										
Male	14,721 (57.96)	1,607 (54.7)	1,753 (56.71)	1,769 (60.03)	1,805 (58.43)	1,965 (59.62)	1,949 (58.79)	1,952 (57.21)	1,921 (58.00)	0.27 (0.337)
Female	10,679 (42.04)	1,331 (45.3)	1,338 (43.29)	1,178 (39.97)	1,284 (41.57)	1,331 (40.38)	1,366 (41.21)	1,460 (42.79)	1,391 (42.00)	−0.27 (0.337)
Age (yr)										
20–29	787 (3.10)	121 (4.12)	125 (4.04)	87 (2.95)	90 (2.91)	94 (2.85)	112 (3.38)	91 (2.67)	67 (2.02)	−0.24 (0.008)
30–39	1,565 (6.16)	232 (7.90)	254 (8.22)	207 (7.02)	172 (5.57)	191 (5.79)	169 (5.10)	157 (4.60)	183 (5.53)	−0.47 (0.003)
40–49	3,286 (12.94)	421 (14.33)	470 (15.21)	416 (14.12)	383 (12.40)	417 (12.65)	398 (12.01)	408 (11.96)	373 (11.26)	−0.52 (0.001)
50–59	4,607 (18.14)	550 (18.72)	545 (17.63)	507 (17.20)	560 (18.13)	583 (17.69)	617 (18.61)	632 (18.52)	613 (18.51)	0.08 (0.390)
60–69	6,275 (24.70)	757 (25.77)	795 (25.72)	763 (25.89)	791 (25.61)	795 (24.12)	789 (23.80)	782 (22.92)	803 (24.25)	−0.38 (0.009)
70–79	5,952 (23.43)	605 (20.59)	616 (19.93)	645 (21.89)	728 (23.57)	810 (24.58)	824 (24.86)	902 (26.44)	822 (24.82)	0.85 (0.001)
≥80	2,928 (11.53)	252 (8.58)	286 (9.25)	322 (10.93)	365 (11.82)	406 (12.32)	406 (12.25)	440 (12.90)	451 (13.62)	0.69 (0.001)
Age (yr), mean±SD	62.15±15.37	60.02±15.58	59.95±15.76	61.54±15.42	62.59±15.13	62.74±15.32	62.79±15.34	63.53±15.03	63.63±14.92	0.56 (0.001)
Household income										
High	7,740 (30.47)	904 (30.77)	948 (30.67)	852 (28.91)	942 (30.50)	977 (29.64)	999 (30.14)	1,075 (31.51)	1,043 (31.49)	0.14 (0.329)
Middle	9,674 (38.09)	1,113 (37.88)	1,243 (40.21)	1,139 (38.65)	1,208 (39.11)	1,272 (38.59)	1,256 (37.89)	1,237 (36.25)	1,206 (36.41)	−0.39 (0.043)
Low	7,986 (31.44)	921 (31.35)	900 (29.12)	956 (32.44)	939 (30.40)	1,047 (31.77)	1,060 (31.98)	1,100 (32.24)	1,063 (32.10)	0.24 (0.169)
CCI										
0	3,961 (15.59)	550 (18.72)	593 (19.18)	462 (15.68)	454 (14.70)	474 (14.38)	480 (14.48)	483 (14.16)	465 (14.04)	−0.73 (0.005)
1	6,901 (27.17)	802 (27.30)	924 (29.89)	855 (29.01)	864 (27.97)	880 (26.70)	880 (26.55)	870 (25.50)	826 (24.94)	−0.56 (0.013)
2	4,934 (19.43)	545 (18.55)	535 (17.31)	563 (19.10)	603 (19.52)	691 (20.96)	634 (19.13)	676 (19.81)	687 (20.74)	0.34 (0.040)
≥3	9,604 (37.81)	1,041 (35.43)	1,039 (33.61)	1,067 (36.21)	1,168 (37.81)	1,251 (37.96)	1,321 (39.85)	1,383 (40.53)	1,334 (40.28)	0.95 (0.001)

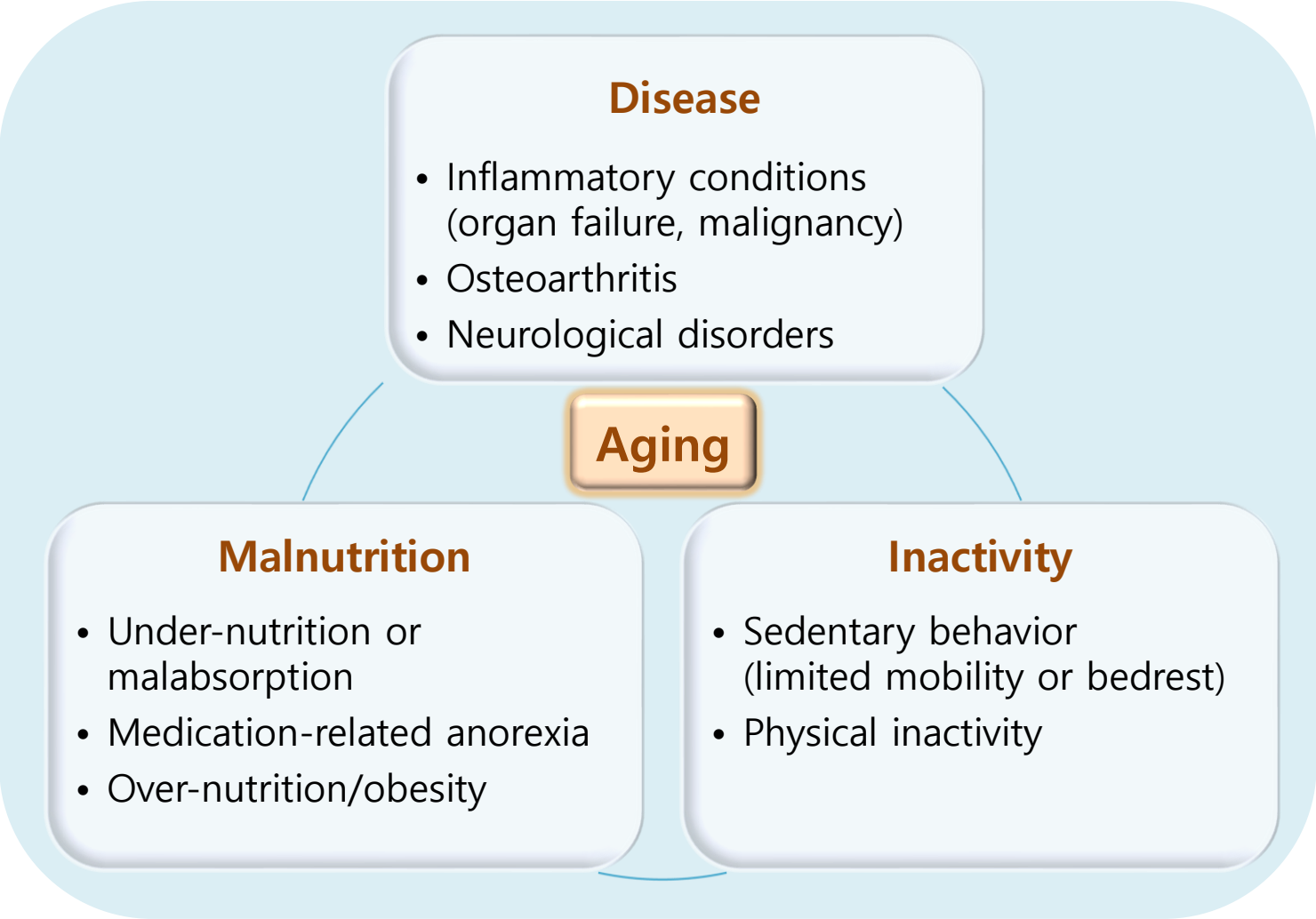
Heo et al. *Acute and Critical Care* 2018 33(3):135-145

Multiple factors contributing to rapid loss of muscle mass in the older ICU patient



Phillips SM et al. *Nutr Clin Pract*. 2017 ;32:112S-120S

Factors contributing to sarcopenia



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

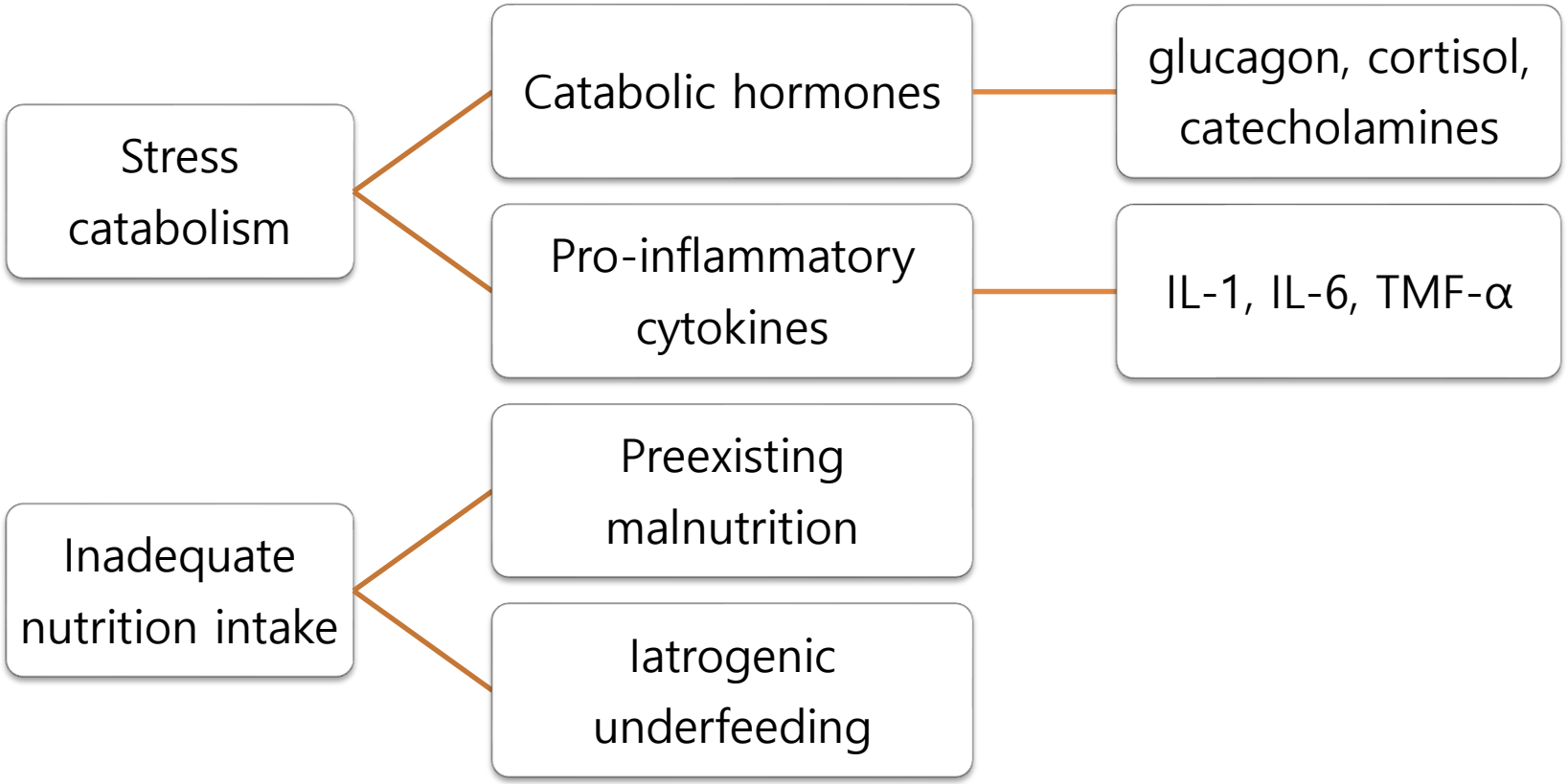
Sarcopenia categories

- 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

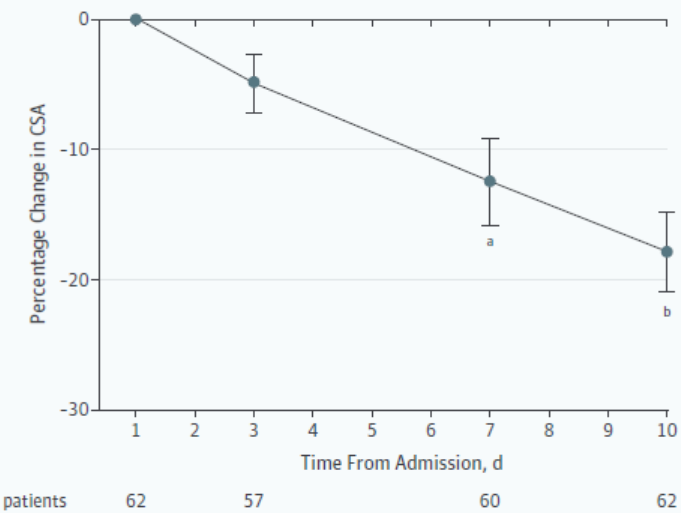


LEE Zyet al. *Nutr Clin Pract* 2019;34(1):96-111

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

Change in rectus femoris cross-sectional area over 10 days



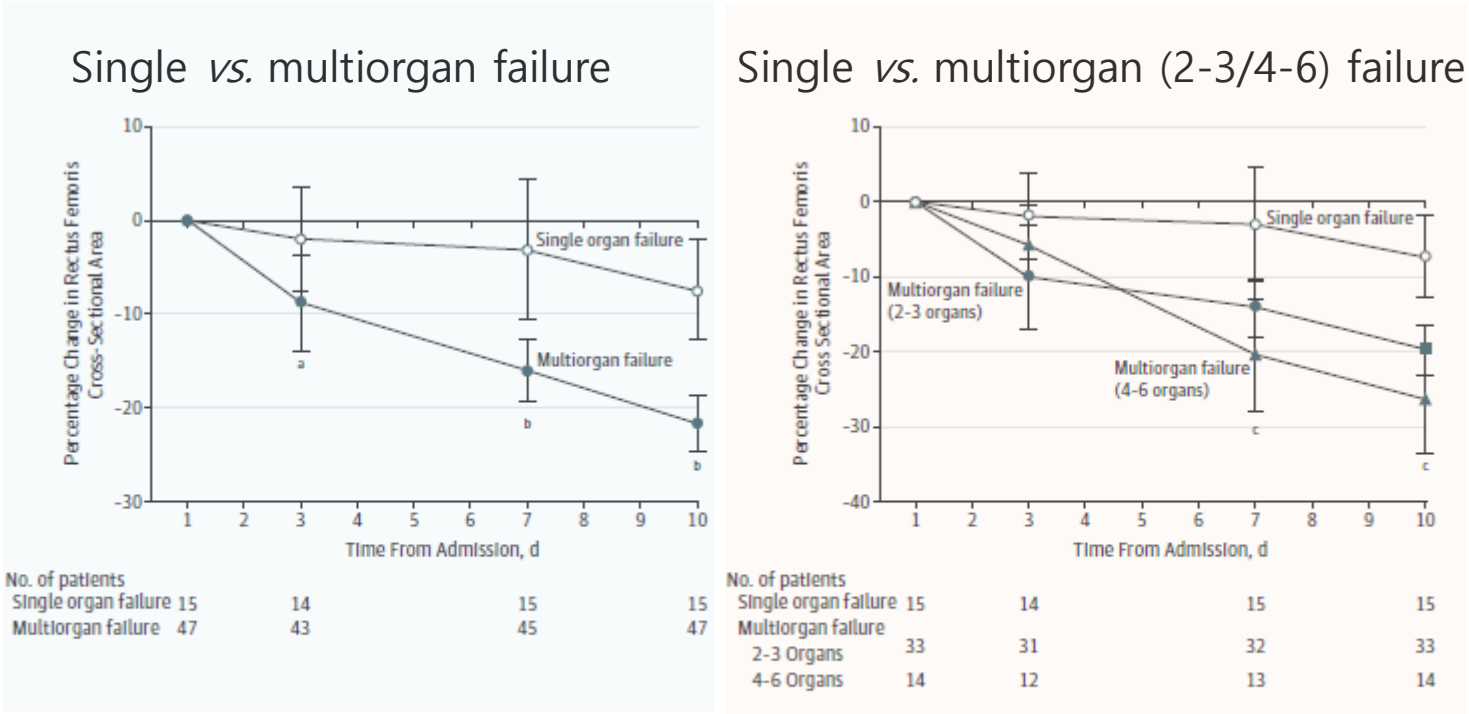
Summary data (dark circles) are expressed as means and 95% confidence intervals.

[a] P=.002 for change from day 1 to day 7 by repeated measures 2-way analysis of variance.

[b] P<.001 for change from day 1 to day 10.

Puthucheary ZA et al. *JAMA* 2013 16;310(15):1591-600.

Measurements of muscle wasting during critical illness by organ failure



Data are expressed as means and 95% confidence intervals.

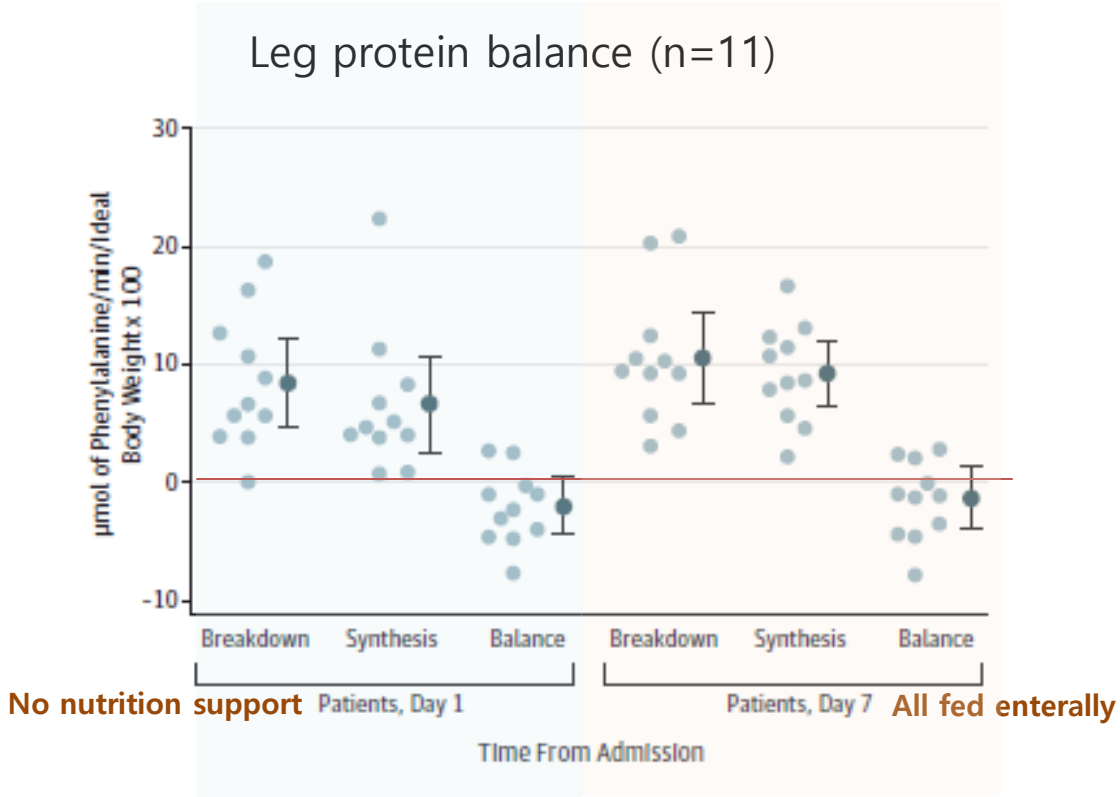
[a] $P=.03$ for change from day 1 to day 3 in multiorgan failure vs single organ failure.

[b] $P<.001$ for change from day 1 to day 7 and day 1 to day 10 in multiorgan failure vs single organ failure.

[c] $P<.001$ for difference between failure of 2-3 organs and 4-6 organs from day 1 to day 7 and day 10.

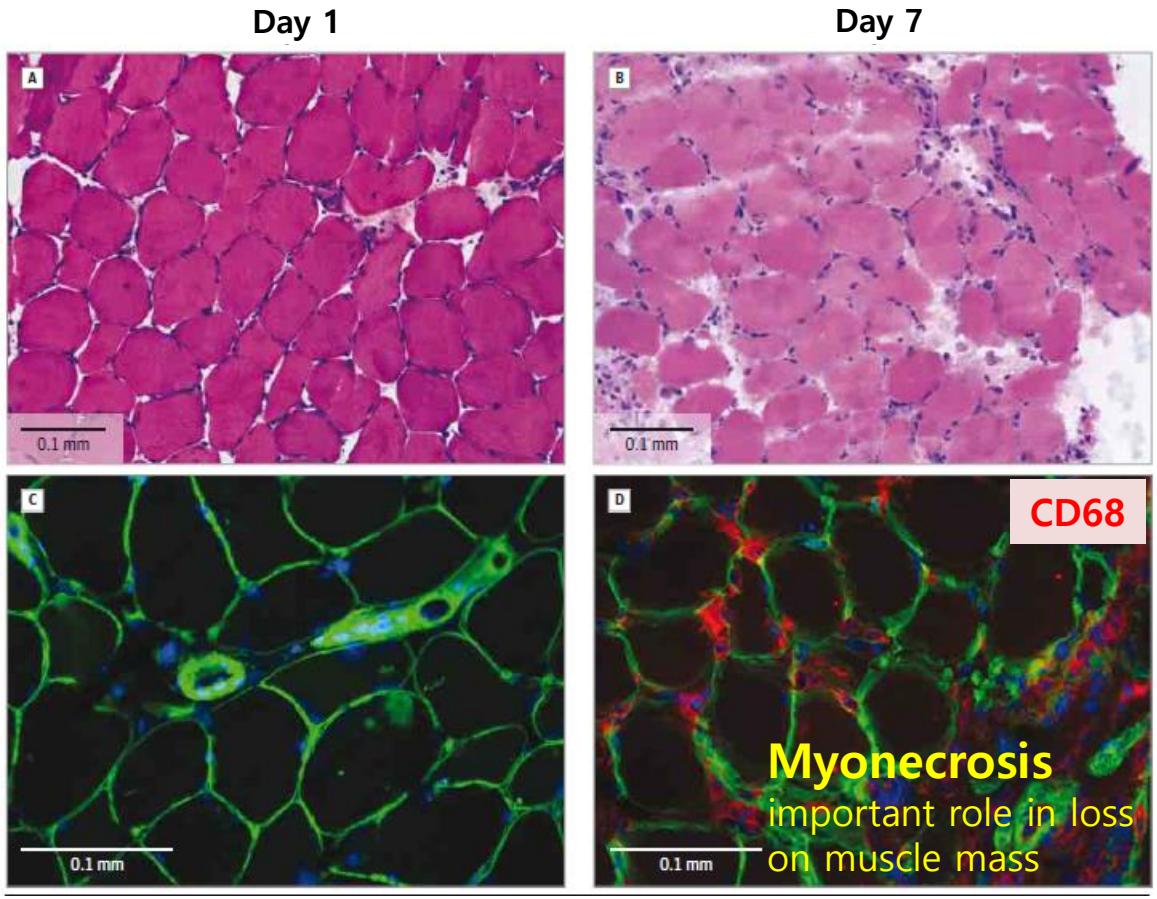
Puthucheary ZA et al. *JAMA* 2013 16;310(15):1591-600.

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



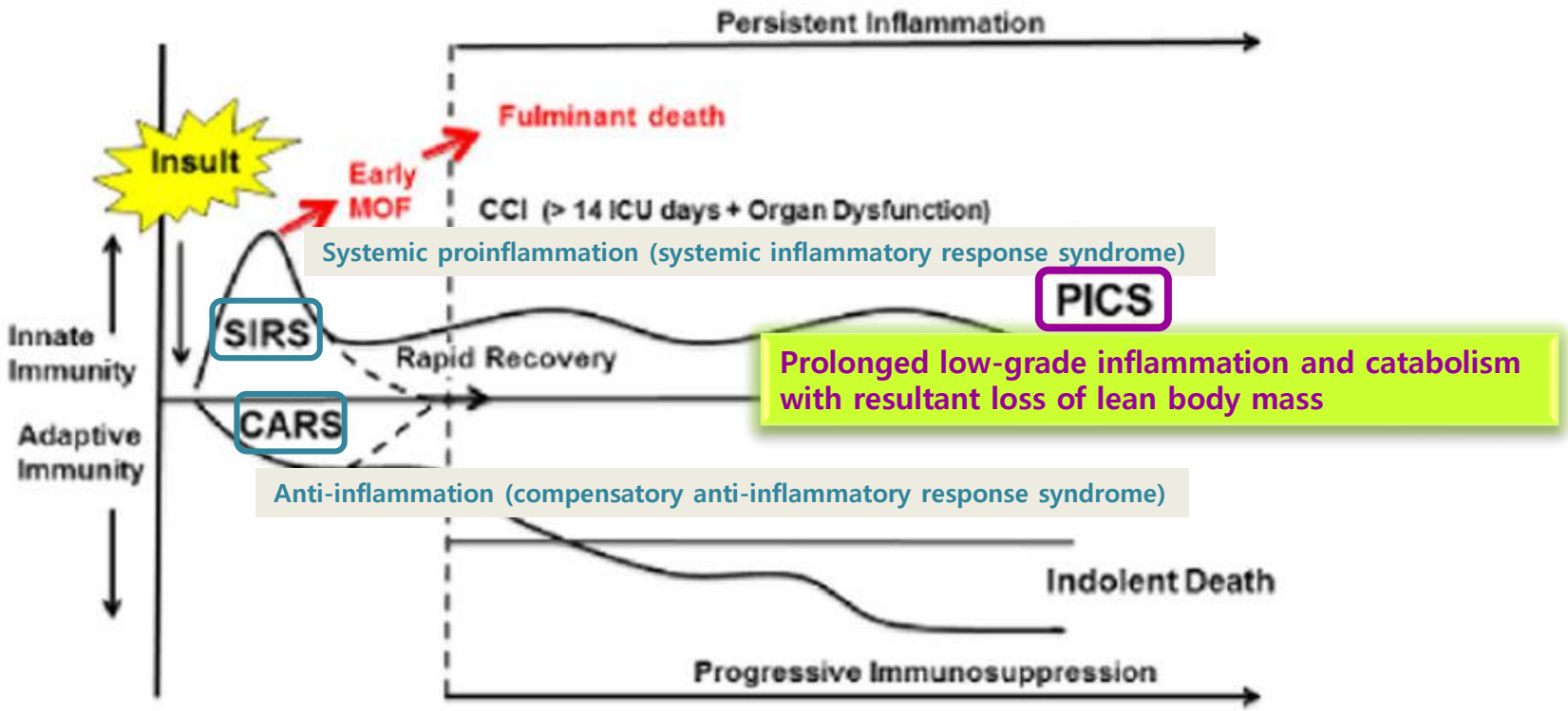
Puthucheary ZA et al. *JAMA* 2013 16;310(15):1591-600.

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



Puthucheary ZA et al. *JAMA* 2013 16;310(15):1591-600.

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



Moore FA et al. *Nutr Clin Pract*. 2017;32(1): 121S–127S

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
Weijs PJ et al. *Crit Care* 2014 Jan 13;18(2):R12.
Gariballa S et al. *Clin Nutr* 2013 Oct;32(5):772–6
Heyland DK et al. *Clin Nutr* 2016;35:1196-1206

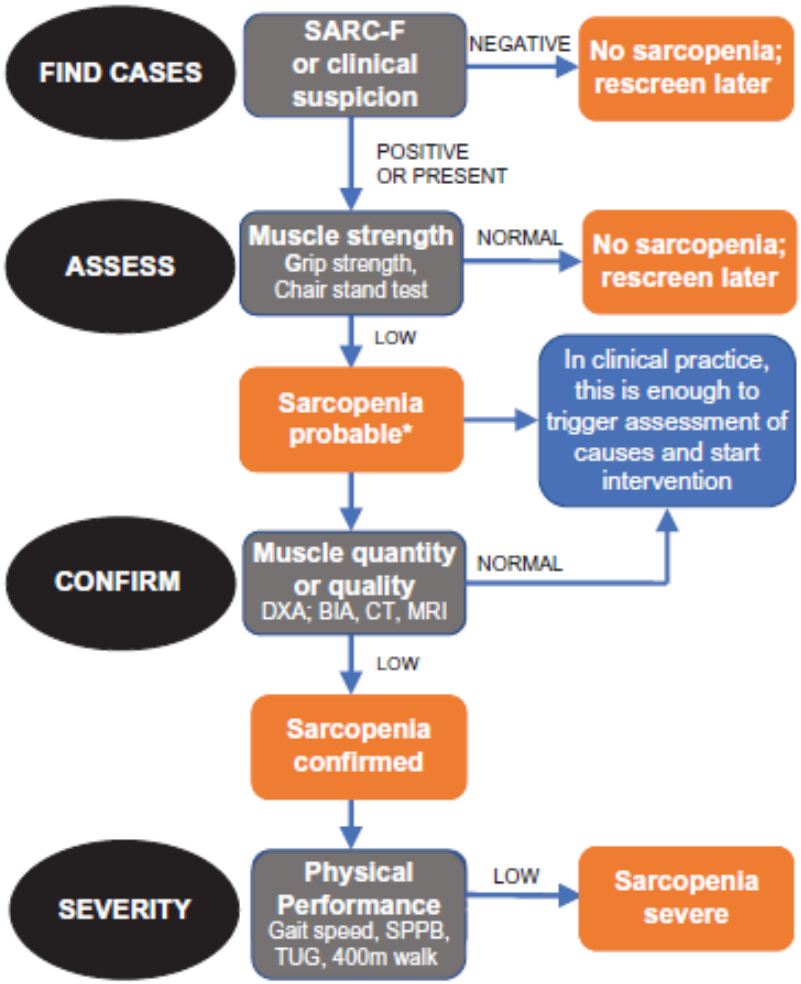
2018 operational definition of sarcopenia

- **Low muscle strength**

+ Low muscle quantity or quality

+ Low physical performance

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



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

EWGSOP2 Sarcopenia cut-off points

Table 3. EWGSOP2 sarcopenia cut-off points

Test	Cut-off points for men	Cut-off points for women	References
EWGSOP2 sarcopenia cut-off points for low strength by chair stand and grip strength			
Grip strength	<27 kg	<16 kg	Dodds (2014) [26]
Chair stand	>15 s for five rises		Cesari (2009) [67]
EWGSOP2 sarcopenia cut-off points for low muscle quantity			
ASM	<20 kg	<15 kg	Studenski (2014) [3]
ASM/height^2	<7.0 kg/m^2	<6.0 kg/m^2	Gould (2014) [125]
EWGSOP2 sarcopenia cut-off points for low performance			
Gait speed	≤0.8 m/s		Cruz-Jentoft (2010) [1] Studenski (2011) [84]
SPPB	≤8 point score		Pavasini (2016) [90] Guralnik (1995) [126]
TUG	≥20 s		Bischoff (2003) [127]
400 m walk test	Non-completion or ≥6 min for completion		Newman (2006) [128]

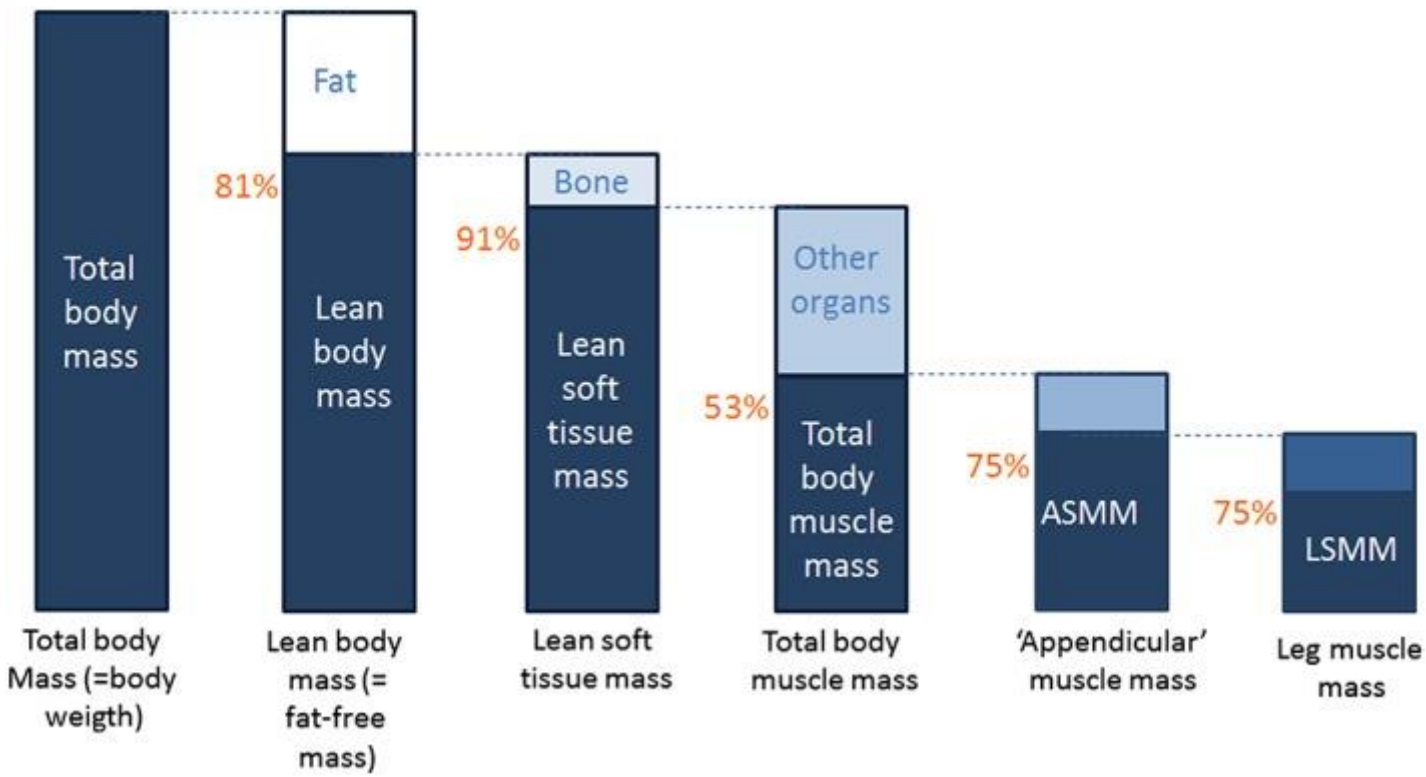
ASM (Appendicular skeletal muscle mass)

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

TUG (Timed-up-and-go test)

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

Body compartments

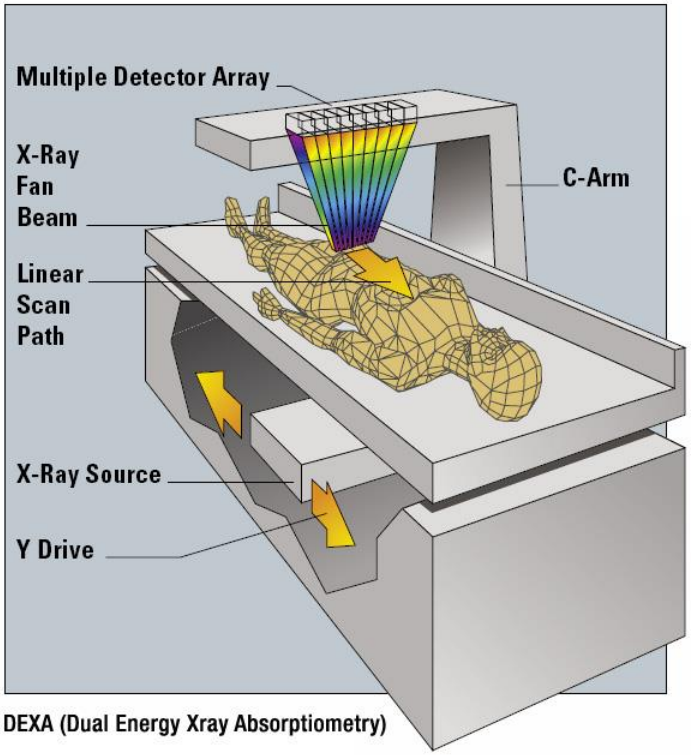


Buckins F et al. *J Cachexia Sarcopenia Muscle* 2018;9(2):269-278.

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)



DEXA (Dual Energy Xray Absorptiometry)

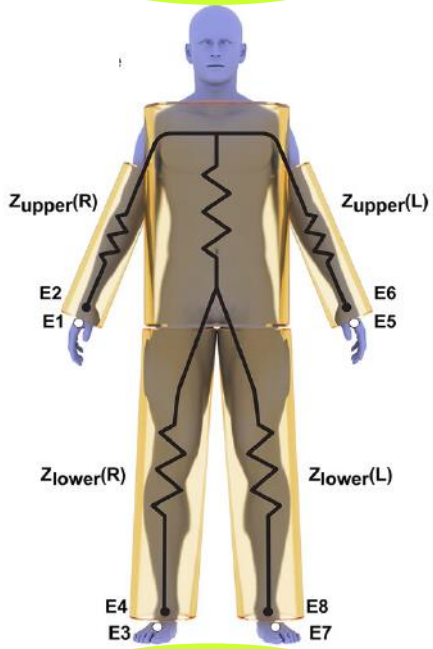
- Non-invasive with small doses of radiation
- Relatively cheap
- Well validated tool, low precision errors

- 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

Buckins F et al. *J Cachexia Sarcopenia Muscle* 2018;9(2):269-278.

Bioimpedance analysis (BIA)

Muscle, blood



Fat, bone,
air-filled spaces

- 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
Buckins F et al. *J Cachexia Sarcopenia Muscle* 2018;9(2):269-278.

BIA-ICU outcomes

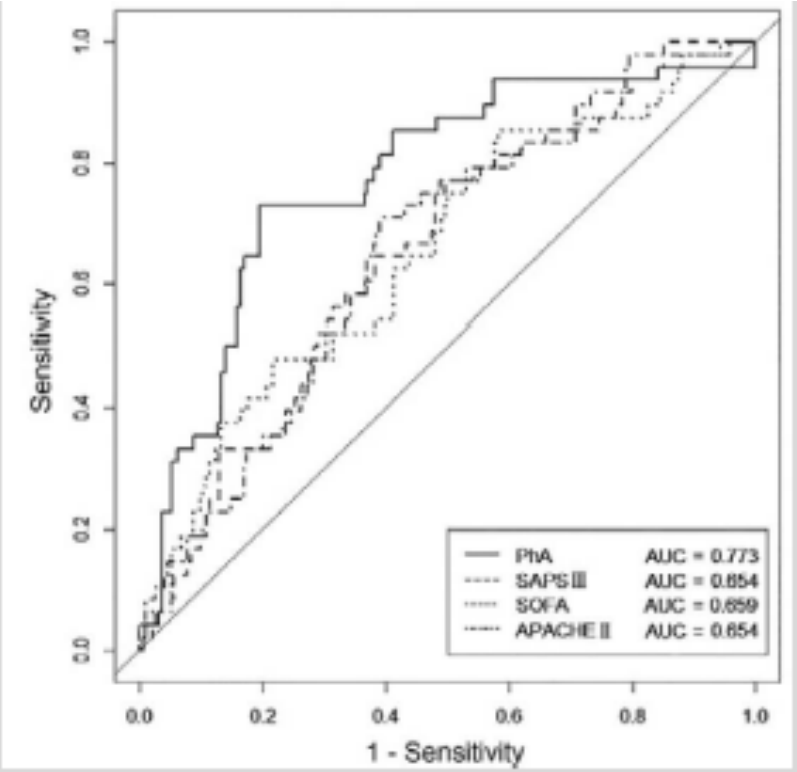


Fig. 1. Covariate-adjusted ROC curves for BIA values (Wholebody phase angle) and severity scorings (APACHE II, SOFA, and SAPS III) as mortality predictive tools. (Adjusted values; age, gender, BMI)

241 critically ill surgical patients

- **Phase angle**

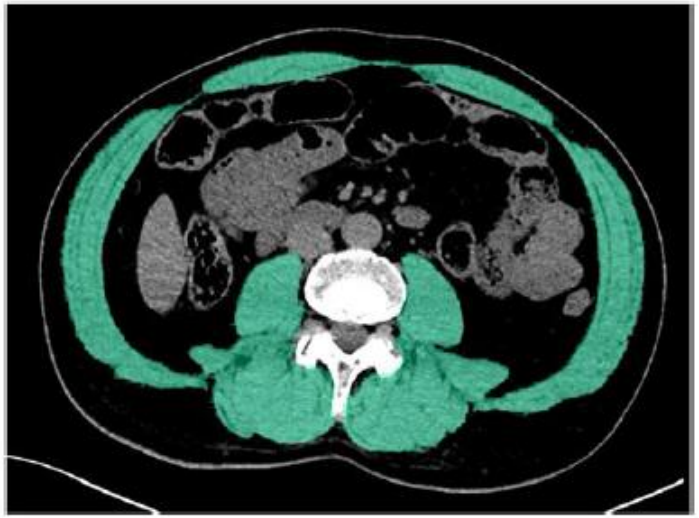
✓ Indicator of **membrane integrity** and **water distribution**

✓ **Prognostic indicator**, **positive association with survival** in patients with HIV, malignancy, hemodialysis, and **critical illness**

Lee YH et al. *J Crit Care* 40(2017) 103-107

Buckins F et al. *J Cachexia Sarcopenia Muscle* 2018;9(2):269-278.

Computed tomography (CT)



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

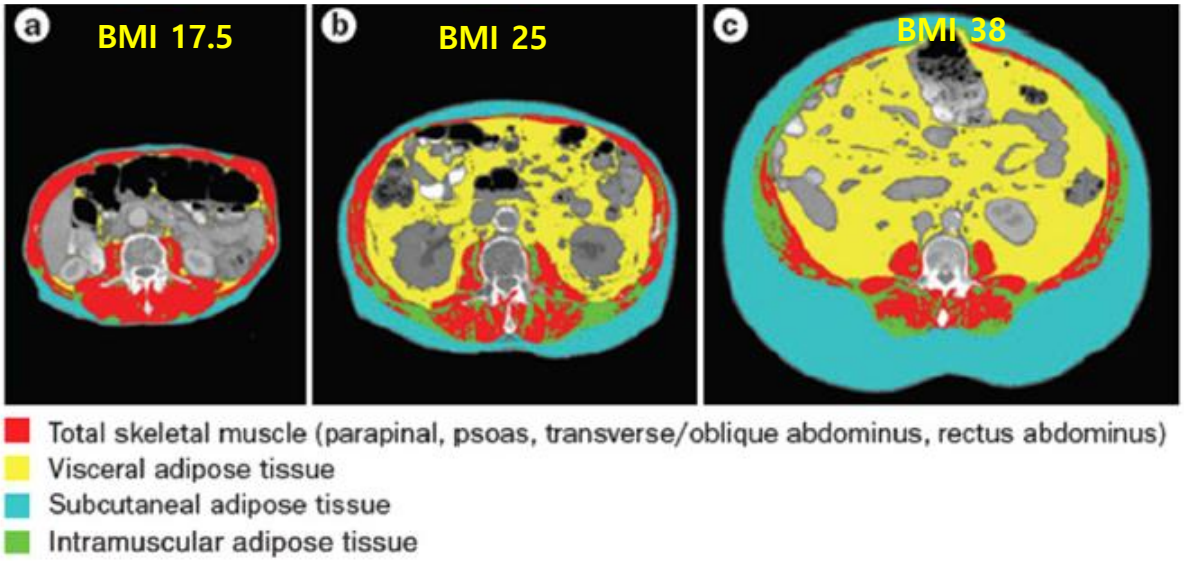
- **Differentiate organs, skeletal muscle, and adipose tissue**
- Differentiate abnormal muscles from normal muscle

- **High radiation exposure**
- Analysis is time-consuming and requires special software

Mundi MS et al. *Nutr Clin Pract* 14(1) 48-58
Koga Y et al. *J Crit Care* 47(2018)153-158

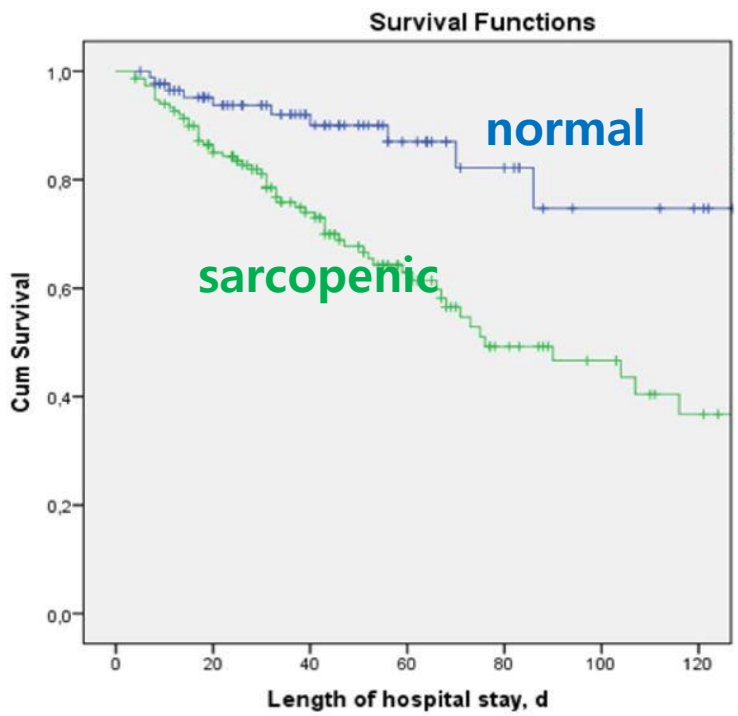
Lumbar 3rd vertebra imaging correlated significantly with whole-body muscle

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



Fearon K et al. *Nat Rev Clin Oncol*. 2013;10(2):90-99.

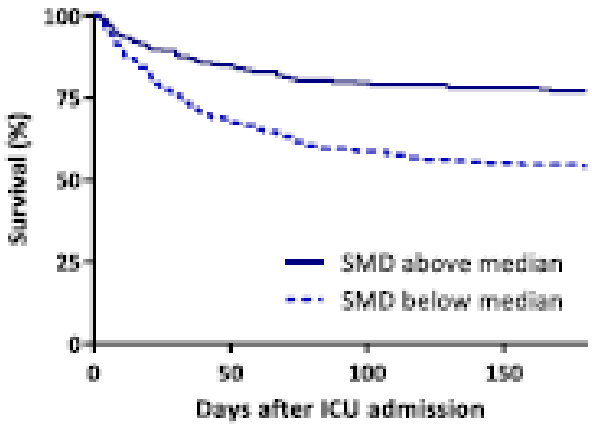
CT-ICU outcomes



- 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%)

Weijs PJ et al. *Crit Care*. 2014;18(1):R12.

CT-ICU outcomes



Number at risk					
SMD above median	245	187	174	170	167
SMD below median	246	165	144	135	132

Skeletal muscle density (SMD)

- 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), $p < 0.001$

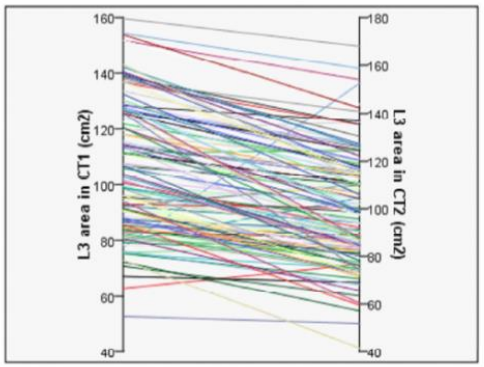
Looijaard WG et al *Crit Care* 2016(20):386

CT-ICU outcomes

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

Variables	aHR	P value
Malignancy (HCC)	2.245	0.004
Alcoholic LC	2,704	0.007
APACHE II	1.064	< 0.001
Accelerated L_3 mass loss (WBMI loss >2%/year)	1.032	0.028

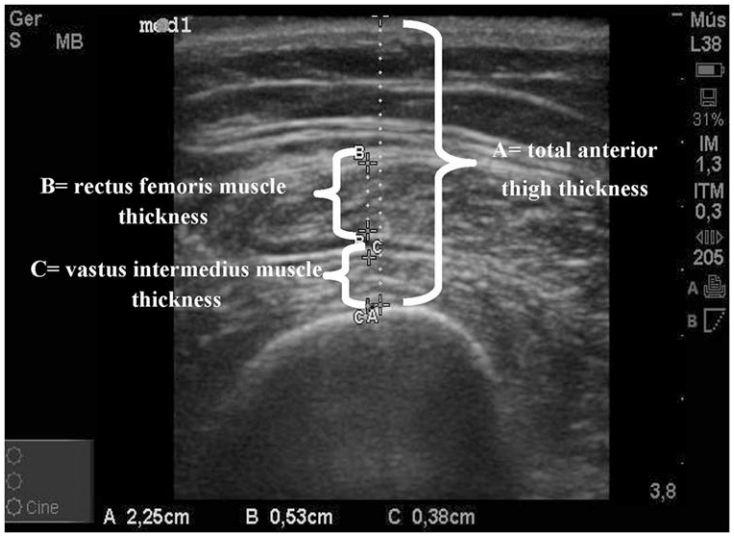
Figure 1. Change in cross-sectional area at the L_3 level between CT1 and CT2 scans



- 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.

Ju S et al. *J Intensive Care Med* 2018 Jan 1

Ultrasound

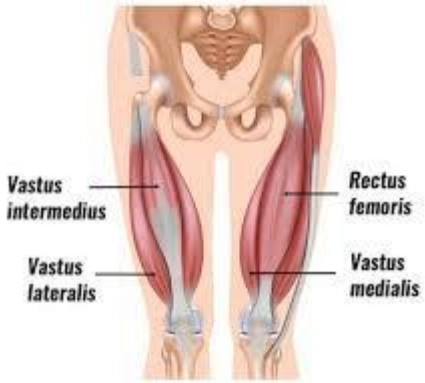


- **No radiation exposure**
- Accessible **at the bedside**
- Assess **quantity** and **quality** of muscle
- Lack of protocol consensus for method and site of measurement

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)

Mourtzakis M et al. *Ann Am Thorac Soc.* 2017 Oct;14(10):1495-1503.

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)

Parry SM et al. *J Crit Care* 30 (2015)1151.e9–1151.e14

Sarcopenia index

(serum creatinine/serum cystatin C) x 100

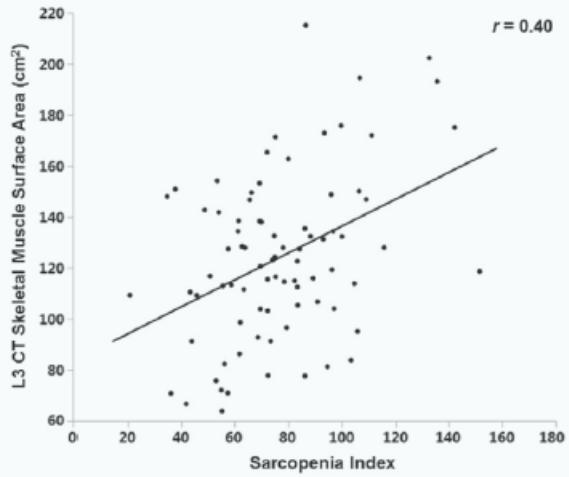


Fig. 1. Correlation between sarcopenia index and skeletal muscle surface area at the L3 level in the 81 patients with an available abdominal CT scan ($r = 0.40$).

- 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

Kashani et al. *Crit care med* 2017;45(1):e23-e29.
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.

Koga Y et al. *J Crit Care* 47(2018)153-158

- Early nutritional deficits were correlated with muscle quality deterioration.
  - Inpatient gain in psoas density is associated with shorter hospital stay.

Yeh DD et al. *J Crit Care* 45(2018)7-13

Table 2
Background characteristics and outcomes of patients with or without early enteral nutrition.

	Non-sarcopenia (n = 100)		P value	Sarcopenia (n = 91)		P value
	EEN (n = 43)	DEN (n = 57)		EEN (n = 35)	DEN (n = 56)	
Age (years)	72 (66–79)	70 (62–77)	0.273	75 (67–82)	74 (66–79)	0.540
Sex (female)	18 (42)	19 (33)	0.382	10 (29)	18 (32)	0.720
APACHE II score	19 (13–26)	20 (16–24)	0.544	23 (17–30)	23 (18–29)	0.867
SOFA score						
Day 1	9 (4–12)	10 (8–12)	0.064	7 (6–11)	9 (6–11)	0.505
Day 3	6 (3–10)	9 (6–12)	0.013	7 (4–11)	8 (5–10)	0.412
JAAM-DIC score	3 (2–6)	5 (3–7)	0.024	4 (2–5)	3 (2–5)	0.370
Septic shock	19 (44)	33 (58)	0.174	15 (43)	35 (63)	0.067
Multiple vasopressor use	11 (26)	17 (30)	0.640	6 (17)	16 (29)	0.215
Lactate on admission (mmol/l)	2.4 (1.5–4.6)	2.8 (1.8–4.3)	0.480	2.1 (1.5–5.1)	2.8 (1.3–5.4)	0.543
Infection source			<0.001			0.001
Respiratory	18 (42)	10 (18)		19 (54)	20 (36)	
Abdominal	1 (2)	22 (39)		0 (0)	20 (36)	
Urinary tract	8 (19)	1 (2)		10 (29)	6 (11)	
Soft tissue	11 (26)	8 (14)		4 (11)	6 (11)	
Others	5 (12)	16 (28)		2 (6)	4 (7)	
Time to antibiotics (hr)	2.5 (1.5–3.5)	2.2 (1.0–3.0)	0.685	2.0 (1.5–3.5)	2.6 (2.0–4.5)	0.118
Mortality						
ICU	6 (14)	9 (16)	0.799	3 (9)	14 (25)	0.043
In-hospital	7 (16)	9 (16)	0.947	3 (9)	19 (34)	0.005

Values are numbers (percentages) of patients or medians (interquartile ranges).
BMI, body mass index; NUTRIC, Nutrition Risk in the Critically Ill; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation.

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

Table 3
Factors associated with in-hospital mortality.

a. Non-sarcopenic patients	OR	95% CI	P value
SOFA score on day 3 (per point)	1.34	(1.12–1.60)	0.002
Sex (female)	7.24	(1.72–30.53)	0.007
Time to antibiotics (per hr)	1.39	(1.10–1.76)	0.006

b. Sarcopenic patients	OR	95% CI	P value
SOFA score on day 3 (per point)	1.24	(1.06–1.46)	0.008
EEN	0.18	(0.05–0.71)	0.014

SOFA, Sequential Organ Failure Assessment; EEN, early enteral nutrition; OR, odds ratio; CI, confidence interval.

Koga Y et al. *J Crit Care* 47(2018)153-158

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

- Aging sarcopenia with recommendation to provide 1.5 g/kg/d of protein.

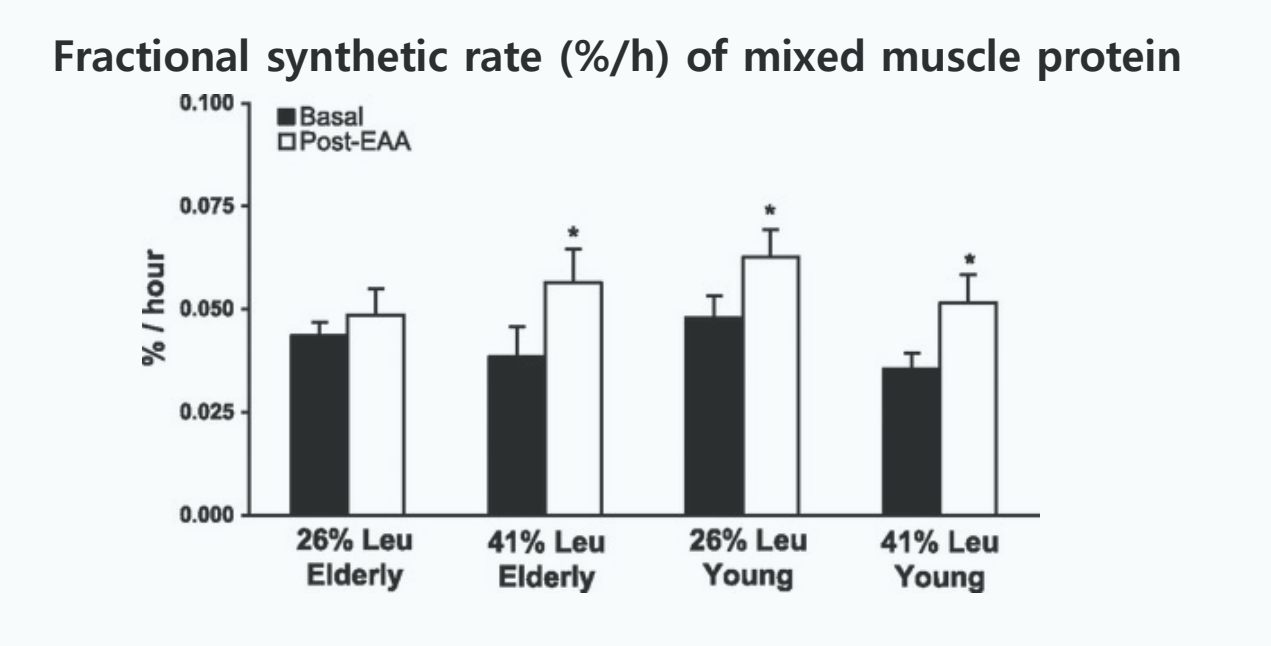
  Wolfe RR et al. *Clin Nutr.* 2008 Oct;27(5):675-84.

- 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

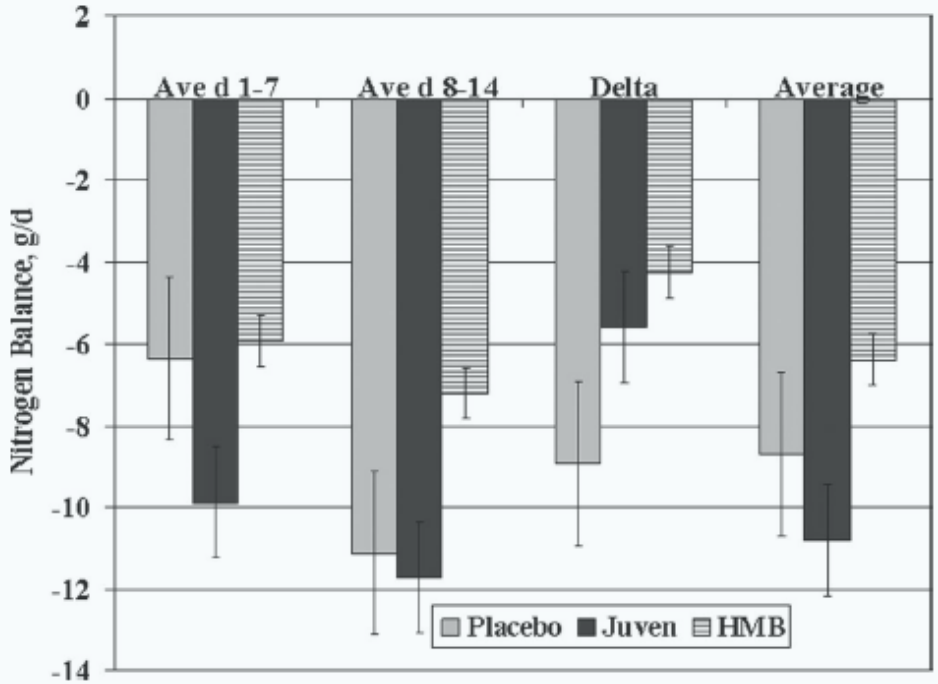


Katsanos CS et al. *Am J Physiol*. 2006; 291:E381-E387
Moore FA et al. *Nutr Clin Pract*. 2017; 32: 121S-127S

β-hydroxy-β-methylbutyrate

- Leucine metabolite
- Stimulate protein synthesis or prevent proteolysis

*14-day nitrogen balance measurements



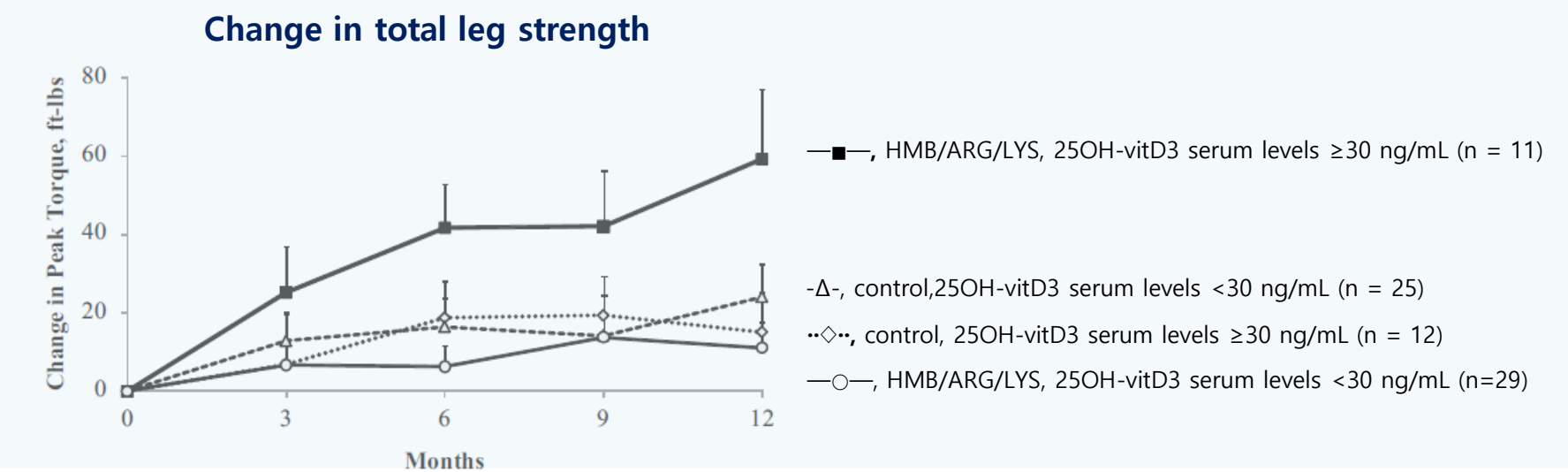
<HMB> β-hydroxy-β-methylbutyrate

<Juven> HMB + L-arginine + L-glutamine

Kuhls et al. *J Trauma* 2007;62(1):125-31

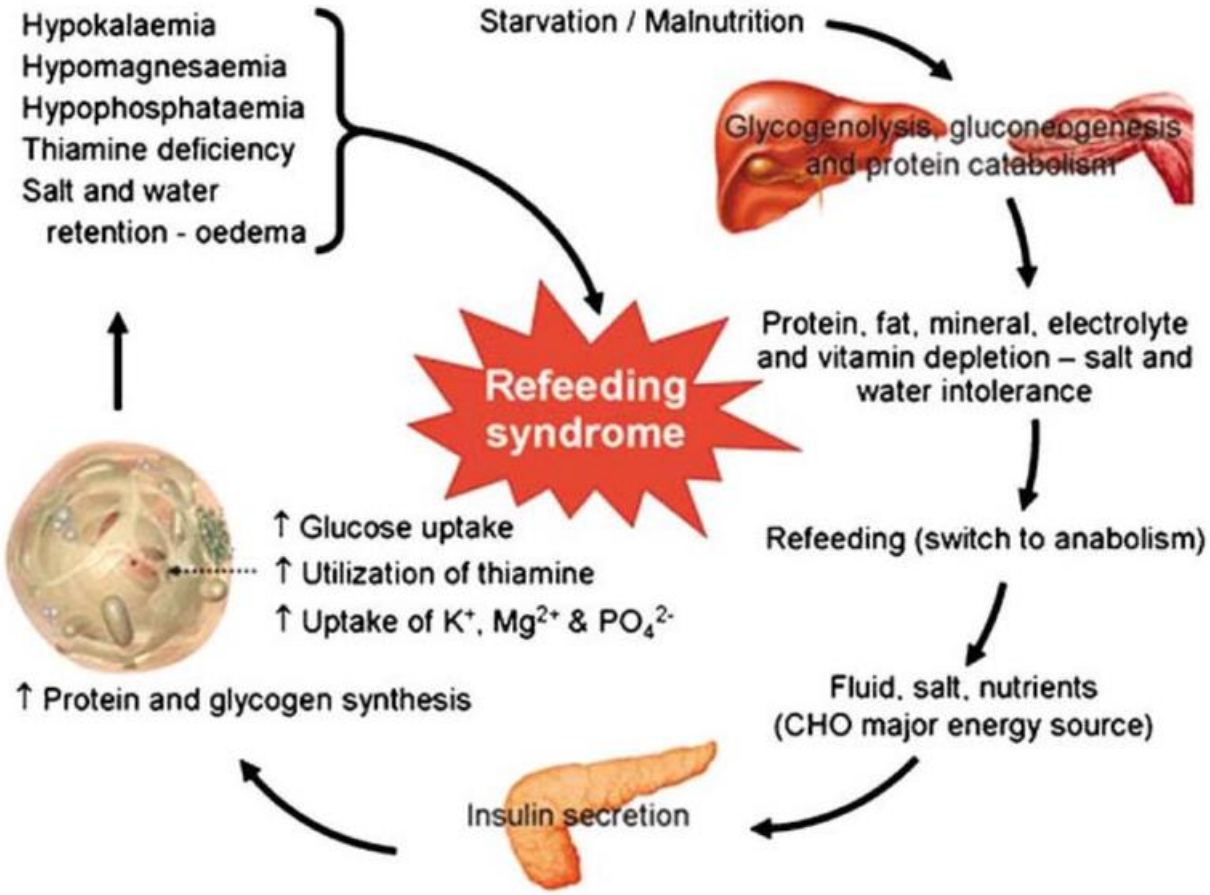
Vitamin D supplement

- 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.



Simpson RU et al. *J Biol Chem* 260, 8882–8891.
Beuadart C et al. *J Clin Endocrinol Metab* 99, 4336–4345.
Fuller JC et al. *JPEN* 35, 757–762.

Pathogenesis and features of the refeeding syndrome



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

P. Singer et al. *Clin Nutr* 2019 Feb;38(1):48-79.

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 : L_3 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!