Supplemental Material

Sarcopenia Definition: Detailed Historical Perspective

Rosenberg was not the first to recognize the phenomenon of dramatic loss of muscle mass and function in connection with aging, but the age-related muscle mass loss was previously encountered long before it constituted a clinical condition. In 1931, Macdonald Critchley, a neurologist from London, described the age-related muscle loss as a senile myotrophy that manifests as wasting.[26] In the 1970s, multiple publications from The Baltimore Longitudinal Study, further defined the physiologic changes that is associated with aging.[27,28] Nathan Shock noted a progressive decline in many cellular functions including the loss of muscle cells.[27] Tzankoff and Norris attributed the age-related reduction in basal metabolic rate to decreased muscle mass observed with aging.[28] However, it was the name "sarcopenia" that drew more attention to the phenomenon, causing investigators to study its biologic mechanism and significance in more detail.[8] Despite this attention, there was no consistent tool to measure sarcopenia. In 1998, Baumgartner and colleagues proposed the first operational definition of sarcopenia to estimate its prevalence.[9] Sarcopenia was defined as height-adjusted appendicular skeletal muscle mass (ASM) that is two standard deviations below the mean of a reference group.[9] However, mounting evidence underscored low muscle function as an essential factor in defining sarcopenia – weakness and impaired mobility were noted to be better predictors of mortality and disability than low muscle mass alone.[10,11,29] In 2010, the Special Interest Group (SIG) on cachexia-anorexia in chronic wasting diseases [16] and the European Working Group on Sarcopenia in Older People (EWGSOP) [15] were among the initial to propose consensus definitions for sarcopenia. The EWGSOP recommended the inclusion of low muscle function (low muscle strength or physical performance) to low muscle mass in the diagnostic criteria of

sarcopenia. However, there was no consensus on specific diagnostic tools to define low muscle mass, strength, or performance which prompted the Asian Working Group for Sarcopenia (AWGS) in 2014 to propose a similar consensus definition with defined cutoff points specific for Asian populations.[20]

The mounting evidence emphasizes the clinical significance of low muscle function when defining sarcopenia. Weakness and mobility impairment were noted to be better predictors for mortality and disability than low muscle mass alone. In 2011, the International Working Group on Sarcopenia (IWGS) [17] and the Society of Sarcopenia, Cachexia and Wasting Disorders (SCWD) [18] proposed consensus definitions highlighting low physical function as an important prognostic factor in sarcopenia and suggesting low gait speed as a diagnostic criterion in addition to low muscle mass. In 2014, The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium Sarcopenia Project used data pooled from nine longitudinal studies to construct evidence-based cutoff points and provide consensus recommendations.[19] The FNIH found that weakness is associated with future mobility disability irrespective of muscle mass, and muscle mass alone is not consistently associated with adverse outcomes; it does only when muscle weakness co-exists. Based on their finding, the FNIH recommended handgrip strength and appendicular muscle mass adjusted for body mass index (BMI) for diagnosing clinically significant muscle weakness and low muscle mass, respectively. Compared to the preceding operational criteria, the FNIH criteria were highly specific in ruling out sarcopenia but had a low agreement for the diagnosis.

Search Strategy

PubMed electronic database was searched using the keywords “sarcopenia” and “cardiovascular disease”, “sarcopenia definition”, “sarcopenia pathophysiology”, “sarcopenic obesity”, “sarcopenia” and “heart failure”, “sarcopenia” and “coronary artery disease” or “myocardial infarction”, “sarcopenia” and “transcatheter aortic valve replacement” or “TAVR”, “sarcopenia” and “cardiovascular surgery” “prehabilitation”, “sarcopenia” and “therapeutic” or “treatment”. We excluded studies on sarcopenia and cardiovascular outcomes in other chronic diseases such as chronic kidney disease, hemodialysis, chronic obstructive lung disease, and cancer. We also excluded studies on sarcopenia and congenital heart diseases as the focus of this review is on older adults.

Supplemental Table 1. Diagnostic Criteria of Cardiac Cachexia.

Author (Year)	Definition	Diagnostic Criteria
Freeman and Roubenoff (1994) [30]	Cardiac Cachexia	Loss of at least 10% of lean tissue
Anke Anker et al. (1997) [31]	Cardiac Cachexia: "In patients with CHF of at least 6 months' duration without signs of other primary cachectic states (e.g., cancer, thyroid disease, or severe liver disease), cardiac cachexia can be diagnosed when weight loss of >7.5% of the previous normal weight is observed. This weight loss should usually be observed over a period of >6 months."	Early or moderate cachexia defined as >7.5% to ≤15% weight loss, or >7.5% weight loss and ≥85% of ideal body weight. Severe cachexia defined as >15% weight loss, or >7.5% weight loss and <85% of ideal body weight.
Anker et al. (2003) [32]	Updated the diagnostic cut-off point of weight loss to ≥6% at any time, which found to be the strongest predictor of mortality.	
Evans et al. (2008) [33]	Cachexia: "Cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. Cachexia is	Weight loss of at least 5% in 12 months or less (or BMI <20 kg/m^2) **Plus** 3 of 5 criteria: ▪ Decreased muscle strength ▪ Fatigue ▪ Anorexia ▪ Low fat-free mass index ▪ Abnormal biochemistry o Increased inflammatory markers (CRP, IL-6) o Anemia (Hb <12 g/dL) Low serum albumin (<3.2 g/dL)

	distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption, and hyperthyroidism and is associated with increased morbidity."	
SIG (2010) [19]	Introduced "Pre-Cachexia"	Pre-cachexia is defined based on the presence of all the following criteria: 1. Underlying chronic disease, 2. Unintentional weight loss ≤5% of usual body weight during the last 6 months, 3. Chronic or recurrent systemic inflammatory response, and Anorexia or anorexia-related symptoms.

Abbreviation: CHF = chronic heart failure; CRP = C-reactive protein; HB = hemoglobin; IL = interleukin; SIG = Special Interest Groups.

Supplemental Table 2. Sarcopenia in Heart Failure.

Type	Name / NCT	Observation/ Intervention	Subjects	Sarcopenia	Outcomes
Prospective Observational [97]	Part of SICA-HF NCT0187 2299	Sarcopenia prevalence in HF and its impact on clinical status and functional capacity	200 participants with stable chronic HF < 3 months with LVEF ≤ 40% or LVEF > 40% with LA dimension ≥ 4.0 cm.	Muscle mass 2 SD below the mean of a healthy young reference group aged 18-40 years. ASMI was calculated from DEXA scan	Sarcopenia was found in 39 (19.5%). Sarcopenic participants have significantly lower handgrip and quadriceps strength, lower total peak oxygen consumption (pVO_2, 1173 vs 1622 mL/min, *P*< 0.001), lower exercise time (7.7 vs 10.22 min, *P*< 0.001), lower 6MWT distance, lower gait speed on 4-m walk test (*P*< 0.05), lower LVEF, and increased IL-6 levels (*P*= 0.001)
Prospective observational [98]	Part of SICA-HF	Diagnostic value of C-terminal agrin-fragment (CAF) for muscle wasting in HF	196 with HF (LVEF ≤ 40%, LAD > 2.5cm/m ht, LAD > 4.0cm, NTpro-BNP > 400 pg/mL or BNP > 150 pg/mL) and serum CAF levels at baseline	Muscle mass 2 SD below the mean of a healthy young reference group aged 18-40 years. ASMI was calculated from DEXA scan	38 (19.4%) had sarcopenia. Sarcopenic participants have higher CAF values (125.1 pmol/L vs 103.8 pmol/L, *P*= 0.01) with the optimal value for diagnosis being > 87.5 pmol/L, (78.9% sensitivity, 43.7% specificity). Higher CAF was associated with worse handgrip (r = − 0.17, *P*= 0.03) and quadriceps strength

					(r = − 0.31, p < 0.0001), pVO_2 (r = − 0.5, < 0.0001), 6MWT distance (r = − 0.32, *P*< 0.0001), and gait speed (r = − 0.2, *P*= 0.001).
Cohort study [94]	N/A	Clinical utility of a sarcopenic screening test in hospitalized older adults with HF	119 consecutive patients > 65-year hospitalized for HF	Ishii et al 3 variable calculated score from age, grip strength, and calf circumference; sarcopenia if score ≥ 105 in men and ≥120 in women	82 (68.9%) had sarcopenia. LVEF was lower (53.8 vs 58.8%, *P*= 0.04), and BNP (182.6 vs 72.7 pg/mL, *P*< 0.01) and hs-TnT (0.026 vs 0.011 ng/mL, *P*= 0.01) were higher in sarcopenic than those without it. HF event-free survival rate was significantly lower in the sarcopenia group. Sarcopenia with high BNP (>100 pg/mL) correlated with higher probability of HF events (*P*< 0.01).
Prospective Observational [100]	Part of SICA-HF	Sarcopenia in HFpEF participants and its impact on exercise capacity and QoL	117 symptomatic outpatient pts with HF symptoms, EF ≥% ***and*** LA dilation (LAVI ≥ 34 ml/m2) or diastolic dysfunction on tissue doppler (septal e' < 8 or lateral e' < 10)	ASMI < 7.26 kg/m^2 for men and < 5.45 kg/m^2 for women ASMI was calculated from DEXA scan	19.7% had sarcopenia and lower 6MWT distance (307 m vs 404 m, *P*= 0.003) and lower absolute peak VO_2 (1211 ml/min vs 1579 ml/min, *P*< 0.05). Participants with E/e' > 15 had the lowest muscle strength and ASM compared to those with E/e' values of ≤ 8 or 9-14.

					Lower ASM and muscle strength correlated with worse QoL (P< 0.005).
Cross Sectional Study [101]	N/A	Incidence of muscle wasting (sarcopenia) in younger patients with dilated cardiomyopathy (DCM)	55 consecutive pts with non-ischemic DCM, LVEF ≤40%, NYHA class I-III, on GDMT for at least 3 months, and < 55-year.	ASMI < 7.26 kg/m^2 for men and < 5.45 kg/m^2 for women	66 (47.3%) met criteria for muscle wasting. Sarcopenic had lower BMI (22.4 vs 26.1 kg/m2, P< 0.001), 6MWT distance (338 vs 440 m, P= 0.003), LVEF (P= 0.001), and higher NYHA class (P= 0.01), and higher rates of hospitalization over 3 months (P= 0.008).
Prospective Observational Cohort [102]	N/A	Sarcopenia impact in ADHF	38 consecutive patients hospitalized for ADHF	ASMI 2 SD below the mean for healthy young subjects	Sarcopenic with ADHF had significantly higher BNP levels compared to those without sarcopenia (1666 vs 429 pg/mL, P< 0.0001). Sarcopenia is a predictor of higher BNP levels (OR = 18.4; 95% CI 1.86-181.27, P=0.013) and hence associated with increased disease severity in ADHF.
Prospective Observational [96]	Part of SICA-HF	Overlap between sarcopenia and cachexia in HF and compare their functional impact	207 males with HF of at least 3 months with EF ≤ 40% or EF > 4% and LA diameter ≥ 4.0 cm	ASMI < 7.26 kg/m^2 for men. ASMI was calculated from DEXA scan.	138 (66%) had no wasting; 44 (21.3%) had sarcopenia: 30 (14.4%) without cachexia and 14 (6.7%) with both sarcopenia and cachexia. 39 (18.8%) had cachexia: 25 (12.1%) without sarcopenia.

					Men with any sarcopenia (±cachexia) had lower handgrip strength, quadriceps strength, peak VO_2, 6MWT distance, and QoL compared to those with no muscle wasting or cachexia alone. Men with both sarcopenia and cachexia had the lowest strength and function out of any of the other groups.
Prospective Cohort Study [103]	N/A	Determine predictors of cardiac events including sarcopenia in older adults with HF and if they differed in those with and without symptoms	191older that 60-year who were previously admitted for HF or were on therapy for HF	Asian Working Group for Sarcopenia –***presence of both*** low muscle function (gait speed <0.8 m/s or grip strength < 26 kg for men and <18 kg for women) and low ASMI.	20 (10.5%) had sarcopenia and there were 20 cardiac events. Multivariate analysis showed that sarcopenia was significantly associated with cardiac events only in NYHA class II-IV (HR 4.44, *P*= 0.04).
Cross-sectional study [104]	N/A	Impact of autonomic modulation on sarcopenia in male HF patients	116 males with HF with LVEF <40%	Sum of ASM divided by height (m^2) ***and*** handgrip strength	33 (28%) had sarcopenia. Sarcopenic men had lower delta heart rate recovery (dHRR) at both the 1st minute (15 vs 22 beats/min, *P*< 0.001) and the 2nd minute (25 vs 35 beats/min, *P*= 0.017) after exercise than those without sarcopenia. ASM positive correlated with dHRR at both time

					points (r = 0.26 [*P*= 0.017] and r = 0.25 [*P*= 0.008]) and negatively correlated with muscle sympathetic nerve activity (r = – 0.029, *P*= 0.003).
Cross-Sectional Controlled Study [105]	N/A	Prevalence of pre-sarcopenia and sarcopenia in HFrEF	79 selected from database of the Echocardiographic Service with LVEF ≤ 40% confirmed with 2 consecutive echocardiograms at least 6 months apart, and 143 controls	EWGSOP definition with cut-off points of the Foundation for the National Institute of Health	Pre-sarcopenia was found in 30.4%, and sarcopenia in 10.1%. Pre-sarcopenia (*P*= 0.04) and sarcopenia (*P*= 0.008) were independently associated with aging.
Prospective Observational [106]	N/A	Identify factors determining exercise capacity in older adults with HF ± sarcopenia	186 consecutive HF patients > 60-year with no physical disability and hospitalized for ADHF	Simplified Japanese Geriatric Society criteria - ***2 or more of the following***: gait speed <0.8 m/s, grip strength <26 kg for men and <18 kg for women, and BMI <18.5	Sarcopenia found in 77 (41.2%). 6MWT distance strongly correlated with age, grip strength, gait speed, and knee extensor muscle strength (*P*< 0.05). In multivariate analysis, gait speed was an independent factor determining distance in both sarcopenic and non-sarcopenic. Knee extensor muscle strength was an independent factor only in the sarcopenic group.
Cross-sectional study [107]	N/A	Prevalence of sarcopenia by three methods and	168 ambulatory males with stable HFrEF	3 methods – Baumgartner [B] method (ASMI), Newman [N]	66 (39.3%) had sarcopenia by at least one method; 35 by [B], 36 BY [N], and 36

		compare body composition for overweight and obese with HF		method (calculation using lean mass, height, and total fat mass), and Studenski [S] method (ASM/BMI). Cut off values for sarcopenia defined as lower 20th percentile of the distribution of each method (7.03 kg/m2 by [B], -2.32 by [N], and 0.76 by [S] respectively).	by [S] – some identified exclusively by 1 method: 8 by [B], 6 by [N], 19 by [S]. 25 (14.9%) were classified in 2 of 3 methods and 8 (4.8%) were classified by all 3 methods. Regardless of method, sarcopenic were older and had higher hs-CRP. Weight, BMI, and height were lower in sarcopenic compared with non-sarcopenic. In patients with BMI ≥ 25 kg/m^2, [N] and [S] were more likely to detect sarcopenia than [B] (both P< 0.005), with [S] being more feasible. All sarcopenic groups had lower total lean mass, but sarcopenic obese had higher total lean mass than lean sarcopenic patients.
Systematic Review and Meta-Analysis [92]	N/A	Estimate overall prevalence of sarcopenia and HF	11 articles and a total of 1742 HF patients	Sarcopenia	Pooled prevalence of sarcopenia in HF is 34% (95% CI 22%-47%) and ranged from 10%-69%. Significant heterogeneity between studies (P< 0.001) but not in the method used to define sarcopenia. With statistically significant

					heterogeneity between subgroups, there was pooled prevalence of sarcopenia of 55% (95% CI 43%-66%) in hospitalized patients with HF and 26% (95% CI 16%-37%) for outpatient.
Prospective Cohort [108]	N/A	Prevalence in ADHF patients	140 patients hospitalized for ADHF	EWGSOP1 criteria, bioimpedance analysis	91 (65%) had sarcopenia. Sarcopenia was associated with lower handgrip strength (22.4kg vs 27.4kg, *P*= 0.007), 4-m gait speed (0.56m/s vs 0.80m/s, *P*< 0.001) and autonomy based on IADL. At 4-year follow-up, sarcopenia was associated with time to first non-CV hospitalization (*P*= 0.014) but not with other hospitalization or mortality endpoint.

Abbreviation: 6MWT = 6-minute walking test; ADHF = acute decompensated heart failure; ASMI = appendicular skeletal muscle mass index; BMI = body mass index; BNP = B-type nitric peptide; CV = cardiovascular; DEXA = dual energy X-ray absorptiometry; EWGSOP = European Working Group on Sarcopenia in Older People; GDMT = guideline directed medical therapy; HFrEF = heart failure with reduced ejection fraction; hs-CRP = high sensitivity C-reactive protein; hs-TnT = high sensitivity troponin; IADL = instrumental activities of daily living; LVEF = left ventricular ejection fraction; NYHA = New York heart association; QoL = quality of life; SPPB = Short Physical Performance Battery.

Supplemental Table 3. Sarcopenia and Coronary Artery Disease.

STUDY	SUBJECTS	SARCOPENIA DEFINITION	OUTCOMES
Kang et al. (Cohort) [115]	475 patients with CAD and sarcopenia undergoing PCI (Percutaneous Coronary Intervention), 2004-2014	CT measurement of the skeletal muscle area (SMA)	Low SMA increased 3-year all-cause mortality, 3-year major adverse cardiovascular events (MACE) within 30 days of receiving PCI.
Lee et al. (Sub-Cohort) [116]	1,086 patients older than 65 who underwent PCI with complete 3 year follow up	Serum creatinine/serum cystatin C ratio (Sarcopenia Index: SI)	Lower SI associated with increased risk of MACE at 3 years in this population
Campos et al. (Cross Sectional) [117]	208 patients aged 80 or older who had never manifested CAD.	European Consensus on Definition and Diagnosis of Sarcopenia (Gait speed, Handgrip strength, Muscle mass, Muscle mass Index)	The decline of body mass and strength are predictors of subclinical atherosclerosis using coronary calcium score (CCS).
Lin et al. (Prospective Cohort) [118]	722 patients >65 from 1997-2003 with a primary diagnosis of CAD from ET-CHD registry in Taiwan	Low BMI <21 kg/m2	Patients with low BMI had the highest mortality
Dierks et al. (Prospective Cohort) [119]	80845 patients with positive cardiac markers and/or ischemic ST-segment changes	Low BMI<18.5 kg/m2	Higher incidence of death and reinfarction in low BMI
Goal et al. (Prospective Cohort) [120]	9,394 >65 yrs. underwent PCI 2000-2011	Low BMI <20kg/m2	Low BMI increases long-term cardiovascular and non-cardiovascular mortality
Uchida et al. (Retropective Cohort)	321 patients >65 yrs. old	Gait speed, quadriceps isometric strength	Sarcopenia associated with intima-media thickness (IMT) as a parameter of atherosclerosis
Okamura et al. (Observational) [111]	304 patients underwent elective CABG from Oct 2008-Aug 2013	Lowest sex-specific quartile of the psoas muscle area index	Pre-operative sarcopenia associated with late mortality after CABG
Xia et al. (Cross Sectional) [114]	2432 patients from Shangfeng Study	Height-adjusted appendicular skeletal muscle mass	Sarcopenia associated with myocardial infarction.

Liestner et al. (Prospective Cohort) [122]	990 patients older than 88 undergoing PCI from Jan 2009- Dec 2017	Low BMI<24.1	In elderly patients undergoing PCI, low BMI is associated with increased mortality mainly in ACS.
Li et al. (Analytical, Cross Sectional) [123]	36,374 patients	Skeletal Muscle Mass (SMM)	There is a significant independent association between SMM and arteriosclerosis.
Ko et al. (Cross Sectional) [112]	31,108 patients who underwent cardiac tomography estimation of CAC (coronary artery calcium) scores between 2012 and 2013.	Skeletal Muscle Mass Index (SMI)	SMI was negatively associated with coronary calcification, supporting low muscle mass as an independent risk for CAD
Jun et al. (Cross Sectional) [113]	19,728 adults free of CVD who underwent computed tomographic estimation of CAC scores.	SMM	Low SMM is significantly associated with elevated risk of CAC.
Zhang et al. (Prospective Cohort) [109]	345 patients with CAD >65 from Peking Union Medical College Hospital from Dec 2017-Nov 2018	Asian Working Group of Sarcopenia in 2014 (Walking speed <0.8m/s and grip strength<26kgin males and <18 in females)	There is a high prevalence of sarcopenia among hospitalized adults with CAD. There is also a shorter MACE free survival time in this group.
Nicholes et al. (Cross Sectional) [124]	60 male patients enrolled in the CARE CR study, (recently discharged following an admission for stable angina, myocardial infarction, coronary artery bypass grafting or PCI)	Dual X-ray absorptiometry and SMI	There was a strong association between SMI and peak VO2/HR in patient with CAD.
Liu et al. (Observational) [125]	Body lean mass (n:331.291), handgrip, left (n:335,821), right (n:184,305)	BIA, Hand grip strength	Decreased muscle mass leads to increased risk of CAD in sarcopenia.
Wand et al. (Prospective Cohort) [126]	402 patients>65, after PCI receiving cardiopulmonary exercise testing during Feb 2014-Dec 2016 in Dep Cardiology at Peking University	SMM	SMM correlates with exercise capacity in these patients. This can be used as an important criterion for predicting and guiding rehabilitation exercise in patients with CAD

Abbreviation: CAD = Coronary Artery Disease; SMI = Skeletal Muscle Mass; SMM = Skeletal Muscle Mass; ACS = Acute Coronary Syndrome; PCI = Percutaneous Coronary Intervention; MACE = Major Adverse Cardiovascular Outcome; CCS = Coronary Calcium Score; SI = Sarcopenia Index; CABG Surgery = Coronary Artery Bypass Graft Surgery; BIA = Bioelectrical Impendence Absorbometry.

Supplemental Table 4. Sarcopenia and Aortic Valve Disease.

Study	Measure of Sarcopenia	Definition of Sarcopenia	Study Outcomes
Damluji et al. [135]	SMI cm^2 of skeletal mass/m^2 of BSA from the cross-sectional CT image at L3 vertebra	Men < 55 cm^2/m^2 Women < 39 cm^2/m^2	Higher SMI associated with shorter LOS and better 1-year QOL
Furzan et al. [141]	PMD PMI at L3 vertebra	PMD <25 HU PMI <4 cm^2/m^2	Higher 90 day and 1 year mortality.
Gallone et al. [143]	PMA at L4 vertebra SMI at L3 vertebra	PMA Men <20.3 cm^2 Women <11.8 cm^2 SMI Men <55.4 cm^2/m^2 Women <38.9 cm^2/m^2	PMA-sarcopenia predicted increased 2-year mortality.
Dahya et al. [144]	SMI	Men < 55 cm^2/m^2 Women < 39 cm^2/m^2	Low SMI predicted higher LOS.
Garg et al. [137]	PMA indexed to BSA	Men <4.15 cm^2/m^2 Women <3.47 cm^2/m^2	Sarcopenia associated with early poor outcome, increased 1 year mortality and high resource utilization.
Heidari et al. [145]	SMI at L3 vertebra	Men <55.4 cm^2/m^2 Women <38.9 cm^2/m^2	Similar in hospital clinical outcomes but higher mid-term mortality.
Kleczynski et al. [146]	PMA PMV	Median PMA normalized for BSA 25.81 (22.15-26.55) cm^2/m^2	At 12 months, all-cause mortality and new-onset atrial fibrillation were highest in the lowest tertile of normalized PSA.

		Median of normalized PMV 338.8 (288.1-365.6) cc/m^2	
Krishnan et al. [147]	PMA PVMA	PMA Men <12 cm^2/m^2 Women <8 cm^2/m^2 Indexed PVMA Men <50 cm^2/m^2 Women <35 cm^2/m^2	PMA associated with increased 2-year mortality on univariate and multivariate analysis. Reduced PMVA associated with higher. mortality on univariate analysis.
Lee et al. [148]	Indexed SMA	Men <41.2 cm^2/m^2 Women <33 cm^2/m^2	Sarcopenia associated with high 30-day in hospital events, and 30-day and 1-year mortality.
Luetkens et al. [149]	FMF (ratio of fatty and lean muscle)	Low <37.3% Medium 51.8-37.3% High >51.8%	High FMF strongly associated with high 1,2- and 3-year mortality and remained independent predictor of 1 year mortality.
Mamane et al. [139]	PMA	Men <20.3 cm^2 Women <11.8 cm^2	Low PMA is associated with higher 1-Year mortality, worsening disability and discharge to a skilled nursing facility.
Mok et al. [132]	SMI Fat mass	SMI Men <55.4 cm^2/m^2 Women <38.9 cm^2/m^2	Sarcopenia predicted cumulative mortality (30-day and midterm, median 12 months mortality). No association of FM with clinical outcomes.
Nemec et al. [133]	SMI at T12 Vertebra VF tissue area	SMI Men <42.6 cm^2/m^2 Women <30.6 cm^2/m^2	Sarcopenia at T12 is associated with prolonged hospital stay VF associated with 30-day mortality
Saji et al. [150]	Total cross-sectional PMA at L4 level indexed to BSA	Men: Tertile 1 (17.08 to 11.78 cm^2/m^2) Tertile 2 (11.76 to 10.11 cm^2/m^2) Tertile 3 (10.09 to 5.87 cm^2/m^2) Women:	Tertile 3 had higher mortality rate than tertile 1 at 6 months

		Tertile 1 (14.36 to 9.62 cm^2/m^2) Tertile 2 (9.52 to 8.07 cm^2/m^2) Tertile 3 (8.06 to 5.27 cm^2/m^2)	
Sakuyama et al. [140]	PMV PMA TMV at L3 vertebra	Median of the normalized PMV: Men 96.3 cm^3/m^2 Women 68.0 cm^3/m^2 Median of the MA of the normalized PMV Men 41.8 HU Women 36.4 HU	Low PMV and MA had higher incidence of all cause readmission
Tokuda et al. [134]	SMI SMD by CT	SMI Men <55.4 cm^2/m^2 Women <38.9 cm^2/m^2 SMD Men < 33.4 HU Women <29.5 HU	Increased 1-year mortality with low density alone and in combination with sarcopenia.
Tzeng et al. [136]	PMA PMI PMD measured at L3 vertebra	PMD <29.68 ± 6.25 HU	Low PMD associated with increased LOS (>14 days).
Uchida et al. [151]	PMI	Men <79.8 cm^3/m^2 Women <60 cm^3/m^2	Low PMI associated with MACE.
Mourik et al. [152]	PMA indexed to BSA at L3 vertebra (Muscle area traced in a range of -29 and 150)	Men: Tertile 1 (1,708 to 1,178 mm^2/m^2) Tertile 2 (1,176 to 1,011 mm^2/m^2) Tertile 3 (1,009 to 587 mm^2/m^2) Women: Tertile 1 (1,436 to 962 mm^2/m^2)	Low indexed PMA in women independent predictor of 1-and 2-year mortality in women.

		Tertile 2 (952 to 807 mm^2/m^2) Tertile 3 (806 to 527 mm^2/m^2)	
Walpot et al. [153]	CSA both psoas muscles Mean attenuation coefficient (Psoas Mean HU) - HDM (30-100HU) /LDM ratio (0-29 HU) - CSA LDM (%)		Psoas Mean HU, HDM/LDM ratio, CSA LDM (%) are independent and incremental predictors of all-cause mortality.
Yoon et al. [154]	SMI (SMA demarcated using -29 to 190 HU, at L3 level indexed to BSA)	Men: Low ≤38.9 cm^2/m^2 Mid >38.9 cm^2/m^2 to ≤43.9 cm^2/m^2 High >43.9 cm^2/m^2 Women: Low ≤31.3 cm^2/m^2 Mid >31.3 cm^2/m^2 to ≤36.8 cm^2/m^2 High >36.8 cm^2/m^2	Low tertile SMI independent predictor of all cause 1-year mortality.

Abbreviations: BSA = body surface area; CSA = circumferential surface area; FMF = fatty muscle fraction; HDM = high density mass; HU = hounsfield units; LDL= low density mass; LOS = length of stay; MACE = major adverse cardiac events; PMA = Psoas muscle area; PMD = psoas muscle density; PMI = psoas muscle cross sectional area indexed to BSA; PMV = psoas muscle volume; PVMA = paravertebral muscle area; QOL = quality of life; SMA -skeletal muscle area; SMD = skeletal muscle density; SMI = skeletal muscle index; PMV = psoas muscle volume; TMV = total muscle area at a vertebral level; VF = visceral fat.

Supplemental Table 5. Sarcopenia and Cardiac Surgery.

Study	Study Population	Measure of Sarcopenia	Outcomes
Lee et al. [148]	Patients aged ≥65 years who underwent surgical aortic valve replacement	Total skeletal muscle area was calculated using height squared ($cm2/m^2$)	Sarcopenia was independently associated with higher 30-day mortality, 30-day in-hospital events, and 1-year mortality
Okamura et al. [156]	Patients aged >70 years undergoing non emergent elective heart valve surgery	Psoas muscle area	The incidence of stroke and intra-aortic balloon pump/percutaneous cardiopulmonary support use was greater in the sarcopenia group. The patients with sarcopenia had significantly decreased long-term survival and decreased freedom from major adverse cardiac and cerebrovascular events. Sarcopenia was an independent predictor for decreased survival.
Hawkins et al. [157]	Moderate to high-risk (predicted risk of mortality [PROM] >3%) patients > 80 years of age who underwent surgical AVR with or without coronary bypass	Psoas muscle index (mean psoas cross-sectional area was divided by the body surface area)	Patients with sarcopenia had higher 1-year mortality (31.9% vs 16.9% p = 0.03). Psoas index significantly predicted risk-adjusted 1-year mortality (odds ratio 0.84, p = 0.02) and long-term mortality (hazard ratio 0.92, p = 0.04), as well as risk-adjusted major morbidity, prolonged ventilation, length of stay, discharge to a facility, and hospital cost.

Iwasaki et al. [159]	Patients aged ≥ 75 years who underwent elective cardiovascular surgery	Psoas Muscle Index	PMI cut-off of 3.24 had a specificity, sensitivity, positive predictive value, and negative predictive value of 0.86, 0.63, 0.58, and 0.87 for predicting worse outcome (death or discharge to a rehabilitation facility) at discharge.
Kiriya et al. [160]	Patients over 75 years old undergoing non emergent cardiac surgery	Total psoas muscle index (TPI) and intra-muscular adipose tissue content (IMAC). Patients were classified into high- (HT) and low- (LT) TPI groups and low- (LI) and high- (HI) IMAC	More respiratory complications in the LT group (HT 0% vs. LT 6.3%, P = 0.002). More surgical site infections in the HI group than in the LI group (LI 0.8% vs. HI 7.1%, P = 0.014). Low TPI and high IMAC significantly predicted more major complications than other combinations (odds ratio [OR] 2.375; 95% confidence interval [CI] 1.152-5.783; P = 0.036)
Yamashita et al. [161]	Patients undergoing cardiac surgery, mean age 65.5 years	Psoas muscle density	The psoas SMD cut-off estimated by the Youden index was 45 HU with high sensitivity and moderate specificity for all-cause mortality. EuroSCORE II, preoperative and postoperative physical status, psoas SMD cut-off was predicted for mortality (HR 2.42, 95% CI 1.32–4.45). The psoas SMD cut-off was significantly associated with postoperative sarcopenia and provided additional prognostic information to EuroSCORE II on ROC

			curve analysis (AUC 0.627 vs 0.678, P = 0.011).
Yamashita et al. [162]		Psoas muscle attenuation (MA) and visceral adipose tissue (VAT) were measured as metrics of sarcopenia and obesity, respectively. Sarcopenia was defined as low MA (below median), while obesity was defined as high VAT (103 cm^2 for males and 69 cm^2 for females).	Sarcopenic obesity was associated with increased risk of mortality after adjusting for EuroSCORE (HR, 3.04; 95% CI, 1.25-7.40).
Wittman et al. [163]	Patients with end stage heart failure receiving Left Ventricular Assist Device (LVAD) therapy	Psoas mean area (PMAi): calculated using psoas mean area with BSA using the Dubois formula (BSA = $0.007184 * Height^{0.725} * Weight^{0.425}$) High or moderate: women, >635 mm^2/m^2; men, >856 mm^2/m^2 Low: women, ≤635 mm^2/m^2; men, ≤856 mm^2/m^2	30-day mortality was higher in patients with low muscle mass compared to with high/moderate muscle mass (15% vs 3.5%; $p = 0.045$). Estimated 30-day survival calculated using the Kaplan-Meier estimator showed higher mortality in patients with low PMAi ($p = 0.04$) Low PMAi independent predictors of mortality in the first 30 days (high/moderate vs. low, HR: 27.3, 95% CI: 2.736–272.797; $p = 0.005$)
Thurston et al. [164]	Patients > 50 years of age undergoing endovascular aneurysm repair (EVAR)	Psoas area normalized for patient height with sarcopenia defined as total psoas area of <500 mm2/m2	Sarcopenic patients had poorer survival (HR, 2.37; P = .011). Sarcopenia patients had increased hospital duration of stay (4.0 days vs 3.0 days; P = .008)

			Sarcopenic patients were more likely to self-report as unfit (12.4% vs 33.3%; P = .004). Sarcopenia did not correlate with an increased rate of post procedure complications.
Teng et al. [165]	Adult patients who underwent elective or non-elective cardiac surgery (i.e., CABG, valve replacement, and combined procedures)	Sarcopenia was defined as low muscle mass with either low muscle strength or poor physical performance. Low muscle mass: lean body mass divided by height squared, < 14.6 kg/m^2 for women and <16.7 kg/m^2 for men. Low muscle strength: grip strength < 30 kg for men and < 20kg for women Poor physical performance: Gait speed < 0.8 m/s.	Sarcopenia group had a significantly longer length of hospital stay than the non-sarcopenia group (19.4 vs. 15.3 days; β=2.9, P=0.02) but 1-year mortality (3.4 vs. 3.9% for non-sarcopenia group) was comparable. Independent of EuroSCORE II, changes in physical activity levels, walking distance and grip strength did not differ significantly between the sarcopenia and non-sarcopenia groups 1, 3, 6 and 12 months after surgery.
Morimoto et al. [166]	Adult patients undergoing CV surgery	Sarcopenia was defined as a short physical performance battery score of <9.5	Sarcopenia was a significant factor to the POD of first rehabilitation (β=0.20; p=0.013), independence in 100 walking (β=0.89; p=0.003), and first exercise at rehabilitation gym (β=1.93; p=0.003) but

			was not a significant factor to the LOS in the hospital.
Lim et al. [167]	Patients aged >65 years undergoing minimally invasive cardiac surgery	PMA index	No significant differences in early mortality (sarcopenia vs non-sarcopenia; 2.2% vs 2.5%, *P* = 1.000) Overall survival and freedom from late composite outcome were similar between the two groups
Yuenyongchaiwat et al. [168]	Patients between the age of 35 to 80 years undergoing CV surgery	Sarcopenia was defined as low muscle mass with either low muscle strength or poor physical performance. Muscle mass was measured through bioelectrical impedance analysis (BIA). muscle mass was calculated: Skeletal muscle mass (Kg) = [(Ht2/BIA resistance x 0.401) + (gender x 3.825) + (afe x -0.071)] + 5.102 Low muscle mass: Skeletal muscle mass divided by height squared, < 7 kg/m2 for women and <5.7 kg/m2 for men.	Post operatively, the incidence of sarcopenia increased by 20.92%. Sarcopenia patients spent more time on mechanical ventilator (872.2 ± 287.9 min and 723.7 ± 293.5 min, p < 0.001) Sarcopenia patients had longer length of stay (9.3 ± 3.8 days and 7.2 ± 2.0 days, *p* < 0.001)

	Low muscle strength: grip strength < 26 kg for men and < 18 kg for women Poor physical performance: Gait speed < 0.8 m/s	

Supplemental Table 6. Management of sarcopenia

Type of Intervention	Study Design	Intervention	Subjects	Measured Parameters	Outcome
Physical					
	Retrospective Harada et al. [205]	Comprehensive cardiac rehabilitation program including physical, nutritional and pharmacological management	Total=322 inpatients with CVD, sarcopenia = 90, without sarcopenia= 232	Muscle mass (bioelectric impedance assay), muscle strength (hand grip strength), physical performance (balance and gait speed)	Improvement in handgrip strength and leg weight bearing index, improved gait speed and balance after exercise training in both patient with and without sarcopenia
	Single blind RCT Liang et al. [195]	25-mins Resistance exercise and 25-mins balance exercise including rise from chair, walk for 3 meters, turn around and walk back for 12-weeks	≥80 years with sarcopenia defined by AWGS Total=60 Intervention= 30 Control= 30	Performance of activity of daily living (ADL) using the Barthel Index Overall physical performance through assessing gait, speed, hand grip strength, and Berg balance score.	Mean increase of 9.5 points on the Barthel Index (BI) for the resistance and balance group Mean increase of 6.5 points on the Barthel Index for the resistance only group
	Single blind Pilot RCT Bellomo et al. [227]	Three arms of interventions: balance exercise (20 mins, 2-sessions per week in the first 8 weeks, followed by 3-sessions for the	Total= 40 older adults with sarcopenia defined by a muscle mass index [muscle mass(kg)/height(m)^2] < 2SD below the	Maximal isometric strength test	Muscle strength increased significantly, specifically knee extensor strength, in the resistance exercise, balance, and vibratory therapy groups.

		last 4-weeks); resistance exercise (10 mins with an intensity 60% of maximum HR, 1 session in the first 8-weeks, followed by 3-sessions in the last 4-weeks); and vibratory therapy intervention (15 mins, 1session per week in the first 8 weeks, followed by 3-sessions per week for the last 4-weeks)	mean of a young reference group. Intervention arm=30 (10 in each arm), control arm= 10		
Nutrition					
Amino Acids	Double-blind placebo-controlled trial Murphy et al.[228]	Three parallel arms randomized into either: twice daily/24-week 1. LEU-PRO (3g leucine, 10g protein), 2. LEU-PRO plus long chain n-3 PUFAs (0.8g EPA, 1.1g DHA; LEU-PRO+n-3), or 3. An isoenergetic control	107 men and women ≥65 y with low muscle mass and/or strength, 76 enrolled in two arms of intervention and 31 enrolled in placebo arm	Hand grip strength, physical strength, appendicular lean muscle mass, circulating metabolic acid, physical and performance were measured pre- and post-intervention	No difference in hand strength, leg strength, appendicular lean muscle mass, or physical performance across the 3 groups

	Double-blind placebo-controlled trial Martínez-Arnau et al. [229]	Leucine (6g/day) or placebo (lactose, 6g/day)	≥ 65 y, living in nursing homes Total= 100, 50 enrolled in the intervention arm and, 50 enrolled in the control arm	Sarcopenia (defined by EWGSOP criteria), respiratory muscle function, and changes in the geriatric evaluation scales, such as cognitive function, functional impairment and nutritional assessments	Consumption of Leucine improved sarcopenia parameters and physical performance measured by walking and lean muscle index. Leucine-treated group also observed an improvement in maximum static expiratory force compared to the placebo
	RCT Aleman-Mateo et al. [230]	Intervention group: 210g/day of ricotta cheese plus the habitual diet, control group: habitual diet only for 3 months	Total= 40 patients with sarcopenia age >60 years, intervention= 20, control= 20	Total ASM by DEXA and muscle strength	The addition of 210 g of ricotta cheese to the habitual diet didn't significantly change ASM or muscle strength at 3-month follow-up period. However, there was a signal toward significance in muscle strength ($P = 0.06$).
	Prospective nested case-control Gray-Donald et al. [231]	The intervention consisted of different categories of protein intake classified as low [<0.8 g/(kg · d)], moderate [0.8–<1.0 g/(kg · d)], high [1.0–<1.2 g/(kg ·	Total=422, cases=211 control=211 matched by sex and age	Age, weight, protein intake, body weight, % change of body weight, and BMI was measured	Low protein intake (< 0.8 g/kg/day) was associated with harmful weight loss when compared to participants with moderate (0.8-1.0 g/kg/day) to high protein intake (>1.2 g/kg/day)

		d)], and very high [≥1.2 g/(kg · d)].			
	Multicenter double blind RCT Bauer et al. [232]	For 13 weeks, the intervention group was given a vitamin D and leucine-enriched whey protein nutritional supplement to take twice daily. For 13 weeks, the control group (n = 196) was given an isocaloric control product to consume twice daily.	Older adults ≥65 years with mild to moderate physical function limitation (SPPB 4-9) and low SMI Total= 380, intervention group= 184, control group= 196	Primary outcomes: Short physical performance battery test (SPPB) and handgrip strength. Secondary outcome: appendicular muscle mass by DEXA	A 13-week intervention with a vitamin D and leucine-enriched whey protein oral nutritional supplement improved chair-stand test compared with the control group, (Difference between groups −1.01 seconds [95% CI −1.77, −0.19], *P* = .01) Intervention group also observed a greater gain in muscle mass than the control group (Difference between groups 0.17 kg [95% CI 0.004, 0.338], *P* = .045)
Combined Resistance exercise and nutrition supplement	Double-blind placebo-controlled trial [233]	Resistance exercise (eight lifting, resistance leg and shoulder exercise) combined with essential amino-acid supplements	Total= 26; milk (n=8), soy (n=8), rice-milk (n=10)	Physical capacity (walking speed, time up and go,	Improvement in functional capacity (char stand, walk speed, time up and go test), and increase in fat- free mass, with no differences across groups that consumed or did not consume essential amino acids

	Randomize, placebo-controlled trial [234]	Four groups: progressive resistance exercise training, multi-nutrient supplementation, both interventions, and placebo activity and supplement	Total= 100, exercise group (n=25), exercise plus supplement (n=25), supplements only group (n=25), placebo group (n=25)	Gait velocity, muscle strength, stair climbing, body potassium, CT scan of midthigh,	Muscle strength, stair climbing, and gait velocity improved in the exercise groups, as opposed to the supplement-only and placebo group. Cross-sectional muscle thigh increased in the exercise groups but declined in the nutrition-only and placebo groups. Nutritional supplement had no effect on any primary outcome measure
Pharmacotherapy					
Testosterone	RCT Travison et al. [218]	Daily Testosterone gel 10g for 6 months	209 men > 65 years with mobility limitations	Leg press test, chest-press strength, stair-climb, 40-m walk, muscle mass, physical activity, self-reported function, and fatigue	Increased leg press strength, chest press strength, stair climb power, but no change in physical activity, walking speed, self-reported function, or fatigue.
Selective androgen receptor modulators	RCT Dalton et al. [220]	Enobosarm (Selective androgen receptor modulators (SARM))	120 healthy elderly men age >60 and postmenopausal women	total lean body mass assessed by dual energy X-ray absorptiometry, physical function, body weight, and insulin resistance	Enobosarm resulted in increase in total LBM and physical function.

ACE-I	Observational study Onder et al. [226]	ACE-I	641 older women with hypertension	knee extensor muscle strength and walking speed	lower mean 3-year decline in muscle strength among participants who took ACE-I
	Cohort study Schellenbaum et al. [235]	ACE-I	5888 older adults from Cardiovascular Health Study (CHS) with heart failure or treated hypertension	Weight change, grip strength	ACE-I was not associated with maintenance of muscle strength but was associated with maintenance of weight.

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor; ADL = activity of daily living; AMI = appendicular skeletal muscle mass index; DEXA = dual energy X-ray absorptiometry; EWGSOP = European Working Group on Sarcopenia in Older People; LEU-PRO = Leucine protein; RCT = randomized control trial.