EVALUATION OF SARCOPENIA SCREENING AND DIAGNOSIS IN ACUTE AND CHRONIC CARE SETTINGS OF CARDIOVASCULAR DISEASE

Thesis Candidate:

Aayushi Joshi, BMSc

MSc Thesis Experimental Medicine, McGill University, Montreal

Division of Experimental Medicine, Department of Medicine

Version 1

Submitted August 2020

A thesis submitted to McGill University in partial fulfilment of the requirements of the degree of Master of Science in Experimental Medicine.

Table of Contents

English Abstract

Background: Sarcopenia is defined as an age-related loss of muscle strength and muscle mass and can be screened for and diagnosed in different ways in acute and chronic cardiovascular care. The main objectives of this thesis were to: 1) investigate the incremental prognostic value of sarcopenia diagnosis by DXA-based appendicular muscle mass index (AMMI) and performance-based muscle strength in older adults undergoing cardiac surgery, and 2) determine the prognostic value of sarcopenia screening by SARC-F questionnaire and muscle strength parameters in community-dwelling older adults with heart failure.

Methods: Following a literature review on sarcopenia in cardiovascular disease, two prospective cohort studies were performed. In the sub-study of the McGill Frailty Registry, older patients referred for coronary artery bypass or heart valve surgery who underwent a sarcopenia assessment involving a DXA scan prior to surgery were included. For the second multi-center prospective cohort study, FRAILTY HF, the cohort included older adults attending a heart failure clinic who completed a frailty assessment.

Results: From the first study of 141 cardiac surgery patients, the prevalence of low AMMI, slow chair rise time, and sarcopenia (low AMMI and slow chair rise time) was 24%, 57%, 13%, respectively. Adjusted multivariable regression indicated each standard deviation of decreasing AMMI and increasing chair rise time was associated with a hazard ratio of 1.84 (95% CI 1.18, 2.86) and 1.79 (95% CI 1.26, 2.54), respectively, for all-cause mortality. From the second study of 100 heart failure patients, prevalence of slow chair rise time and probable sarcopenia (worse SARC-F score and slow chair rise time) was 60% and 31%, respectively. Probable sarcopenia was

associated with a two-fold risk of all-cause mortality or worsening disability at 3-months (OR=2.7; 95% CI 0.87 to 8.42), although non-significant. However, probable sarcopenia was predictive of poor physical and mental health status at 3-months.

Conclusions: Lower-extremity muscle strength and DXA-based measures of muscle mass are indicative of sarcopenia and predictive of survival in older adults referred for cardiac surgery. Additionally, screening for sarcopenia among heart failure patients indicated that a positive screen is strongly predictive of poor health-related quality of life at 3-months. Validation of findings by optimizing thresholds for sarcopenia and determining best methods for screening and diagnosis in future studies are needed.

French Abstract

Introduction: La sarcopénie est définie comme une perte de force musculaire et de masse musculaire liée à l'âge et peut être dépistée et diagnostiquée de différentes manières dans les soins cardiovasculaires aigus et chroniques. Les principaux objectifs de cette thèse étaient de 1) étudier la valeur pronostique incrémentale du diagnostic de sarcopénie par l'indice de masse musculaire appendiculaire (AMMI) basé sur DXA et la force musculaire basée sur la performance chez les personnes âgées subissant une chirurgie cardiaque, et 2) déterminer la valeur pronostique de dépistage de la sarcopénie par questionnaire SARC-F et paramètres de force musculaire chez les personnes âgées vivant dans la communauté souffrant d'insuffisance cardiaque.

Méthodes: Suite à une revue de la littérature sur la sarcopénie dans les maladies cardiovasculaires, deux études prospectives de cohorte ont été effectuées. Dans la sous-étude du registre de fragilité de McGill, les patients âgés référés pour un pontage coronarien ou une chirurgie valvulaire cardiaque qui ont subi une évaluation de la sarcopénie impliquant un scan DXA avant la chirurgie ont été inclus. Pour la deuxième étude de cohorte prospective multicentrique, FRAILTY HF, la cohorte comprenait des adultes plus âgés fréquentant une clinique d'insuffisance cardiaque qui ont effectué une évaluation de la fragilité.

Résultats: D'après la première étude portant sur 141 patients en chirurgie cardiaque, la prévalence de l'AMMI faible, du temps de montée lente de la chaise et de la sarcopénie (faible AMMI et temps de montée lente de la chaise) était de 24%, 57% et 13%, respectivement. La régression multivariée ajustée a indiqué que chaque écart type de la diminution de l'AMMI et de l'augmentation du temps de montée du fauteuil était associé à un rapport de risque de 1.84 (IC à 95% 1.18 à 2.86) et 1.79

(IC à 95% 1.26 à 2.54), respectivement, pour la mortalité toutes causes confondues. D'après la deuxième étude portant sur 100 patients atteints d'insuffisance cardiaque, la prévalence du temps de montée lente et de la sarcopénie probable (pire score SARC-F et temps de montée lente) était de 60% et 31%, respectivement. La sarcopénie probable était associée à un double risque de mortalité toutes causes confondues ou d'aggravation de l'incapacité à 3 mois (OR = 2.7; IC à 95% 0.87 à 8.42), bien que non significatif. Cependant, une sarcopénie probable était prédictive d'un mauvais état de santé physique et mentale à 3 mois.

Conclusions: La force musculaire des membres inférieurs et les mesures de la masse musculaire basées sur la DXA sont indicatives de la sarcopénie et prédictives de la survie chez les personnes âgées référées pour une chirurgie cardiaque. De plus, le dépistage de la sarcopénie chez les patients atteints d'insuffisance cardiaque a indiqué qu'un dépistage positif est fortement prédictif d'une mauvaise qualité de vie liée à la santé à 3 mois. La validation des résultats en optimisant les seuils de sarcopénie et en déterminant les meilleures méthodes de dépistage et de diagnostic dans les études futures est nécessaire.

Acknowledgements

I would like to thank my thesis supervisor and thesis committee member Dr. Jonathan Afilalo for the tremendous amount of guidance he has provided me during my endeavors to pursue a MSc in Experimental Medicine. Not only has Dr. Afilalo's enthusiasm for clinical research, analytic knowledge and drive as clinician-scientist inspired me, but his teachings have provided me with the skills to progress in my own academic journey. The manuscripts presented in my thesis and other scholarly work were made possible under his direction and recommendations.

I am appreciative for my thesis committee members Drs. Michel and Sheppard as well as my academic advisor Dr. Lehoux at the Jewish General Hospital, who have provided valuable insights into the development of the FRAILTY-HF study and my thesis. Other members that I would like to thank are the heart failure nurses Delina Maghakian and Esther Laforest, and the Frailty Research Team coordinators that have helped this study run smoothly. I would also like to thank our collaborators Drs. Giannetti and Sharma at the Royal Victoria Hospital and Dr. Nguyen at Cite de la Santé Laval who were excited to get onboard and make our study into a multi-center collaborative effort.

Throughout my graduate studies I have been the proud recipient of the CIHR Fredrick Banting and Charles Best 2019 Canada Graduate Scholarships-Master's award valued at $17,500 and the Division of Experimental Medicine travel award valued at $1,250. These awards have given me financial support that has allowed me to produce meaningful research and scientific inquiry that I hope will translate into improve cardiovascular patient care in the future. Lastly, my success over the past two years would not have been possible without the encouragement from my parents, brother and close friends, all of whom have been my trusty reviewers and supporters on many occasions.

Contribution of Authors

Aayushi Joshi, BMSc

Thesis candidate. Performed literature review. Co-initiated and designed the FRAILTY-HF study which involved writing the protocol, creating baseline, follow up questionnaire forms, and consent forms, preparing and submitting study documentation to the institutional research ethics boards. Co-created the RedCap database for data collection purposes. Administered frailty assessments for patient recruitment. Developed the statistical approach and performed analyses pertaining to the two manuscripts for my thesis. Attended research team meetings, presented preliminary research findings to the Masters Thesis Committee and wrote the thesis document.

Rita Mancini, BSc

Graduate student collaborator. Co-initiated and designed the FRAILTY-HF study which involved writing the protocol, creating baseline, follow up questionnaire forms, consent forms, preparing and submitting study documentation to the institutional research ethics boards. Co-created the RedCap database for data collection purposes.

Jonathan Afilalo, MD, MSc, FACC, FRCPC

Thesis supervisor. Regularly provided support and input on study design for the FRAILTY-HF study and analytic approaches for other manuscripts. Attended all committee meetings. Critically reviewed and evaluated thesis document in addition to the two manuscripts for publication.

Caroline Michel, MD

Member of thesis committee. Attended all committee meetings and provided input on study design and methodology for the FRAILTY-HF study.

Richard Sheppard, MD

Member of thesis committee. Attended all committee meetings and provided input on study design and methodology for the FRAILTY-HF study.

Stephanie Lehoux, PhD

Academic advisor and member of thesis committee. Attended all committee meetings, provided input on study design and methodology for the FRAILTY-HF study, and helped navigate graduate degree administrative processes.

Jeff Wong, MD

Medical student. Assisted in medical chart reviews for the FRAILTY-HF study.

The following authors reviewed and contributed to the **McGill Frailty Registry manuscript**:

Rita Mancini, BSc, Stephan Probst, MD, Gad Abikhzer MD, Jonathan Afilalo MD, MSc

The following authors reviewed and contributed to the **FRAILTY HF manuscript**:

Rita Mancini, BSc, Jeffrey Wong MD, Caroline Michel MD, Richard Sheppard MD, Nadia Giannetti MD, Abhinav Sharma MD PhD, Viviane Nguyen MD MSc, Esther Laforest RN MSc, Delina Maghakian RN, Jonathan Afilalo, MD, MSc

CHAPTER 1: THESIS INTRODUCTION

The recognition of frailty as an independent prognostic indicator of adverse outcomes in older adults has only emerged in the past decade. Frailty is characterized as a geriatric syndrome associated with an increased vulnerability to physiologic stressors. As the frailty schema has developed, our conceptualization of its various phenotypes such as sarcopenia (muscle loss and weakness) has progressed[1]. The manifestation of sarcopenia in the frailty schema and development of standardized prognostic tools for sarcopenia assessment in cardiovascular disease is of interest as physically frail cardiovascular patients are a high-risk group for adverse outcomes.

Therefore, the objective of this thesis was to conduct a literature review of sarcopenia as it pertains to its pathophysiology, epidemiology, and methods of assessment. Additionally, the purpose was to perform two prospective cohort studies to evaluate different methods used to diagnose sarcopenia (appendicular muscle mass and muscle strength) and those used to screen for sarcopenia (self-reported questionnaire and muscle strength) for their prognostic power in determining all-cause mortality among acute cardiac surgery patients and community-dwelling older adults with heart failure, respectively.

Chapter 2 includes the definition of sarcopenia and current understanding of the pathophysiology of age-related and disease-related sarcopenia. The epidemiology of sarcopenia as a geriatric condition is reviewed, followed by a detailed description of tools currently used for the assessment of sarcopenia and their applicability in different care settings. Next, the scope of sarcopenia prevalence and impact on outcomes in cardiovascular disease is reviewed. The chapter is concluded by a discussion of the benefit of interventions and economic burden of untreated

sarcopenia, thus highlighting a need for establishing a gold standard evaluation method that will allow for appropriate interventional care to proceed.

Chapter 3 includes the first manuscript tilted, “Sarcopenia in Older Adults Undergoing Cardiac Surgery: Dual X-Ray Absorptiometry Analysis from the McGill Frailty Registry”, which explores sarcopenia measured by muscle mass and strength in predicting all-cause mortality at 12-months.

Chapter 4 involves a commentary on the limitations of sarcopenia diagnosis in different cardiovascular populations and suggests that screening for sarcopenia may meet the threshold for initiation of interventional care.

Chapter 5 includes the second manuscript titled, “FRAILTY HF: Sarcopenia Screening using the SARC-F Questionnaire and Muscle Strength Measures is Predictive of Poor Self-Reported Health in Community-Dwelling Heart Failure Patients”, which explores probable sarcopenia screened by self-reported questionnaire and muscle strength in predicting all-cause mortality at 3-months.

Lastly, Chapter 6 is the thesis conclusion which summarizes main findings, outlines the value added for the field of sarcopenia and provides an outline for target areas for where future research intersecting the fields of sarcopenia and cardiovascular sciences can aim.

CHAPTER 2: LITERATURE REVIEW – UNDERSTANDING SARCOPENIA

Pathophysiology of Sarcopenia

Sarcopenia has historically been known as muscle wasting that occurs in advanced age. The earliest operational definition of sarcopenia was defined in 1998 by Baumgartner et al, in which dual X-ray absorptiometry (DXA) was used to measure lean muscle mass[2]. Since then, several international organizations on sarcopenia research have established a consensus definition of sarcopenia. Sarcopenia is now widely recognized as a geriatric syndrome associated with a reduction in muscle quality (evidenced by low muscle strength) and muscle mass, with the presence of both criteria a requirement for its diagnosis[3-6].

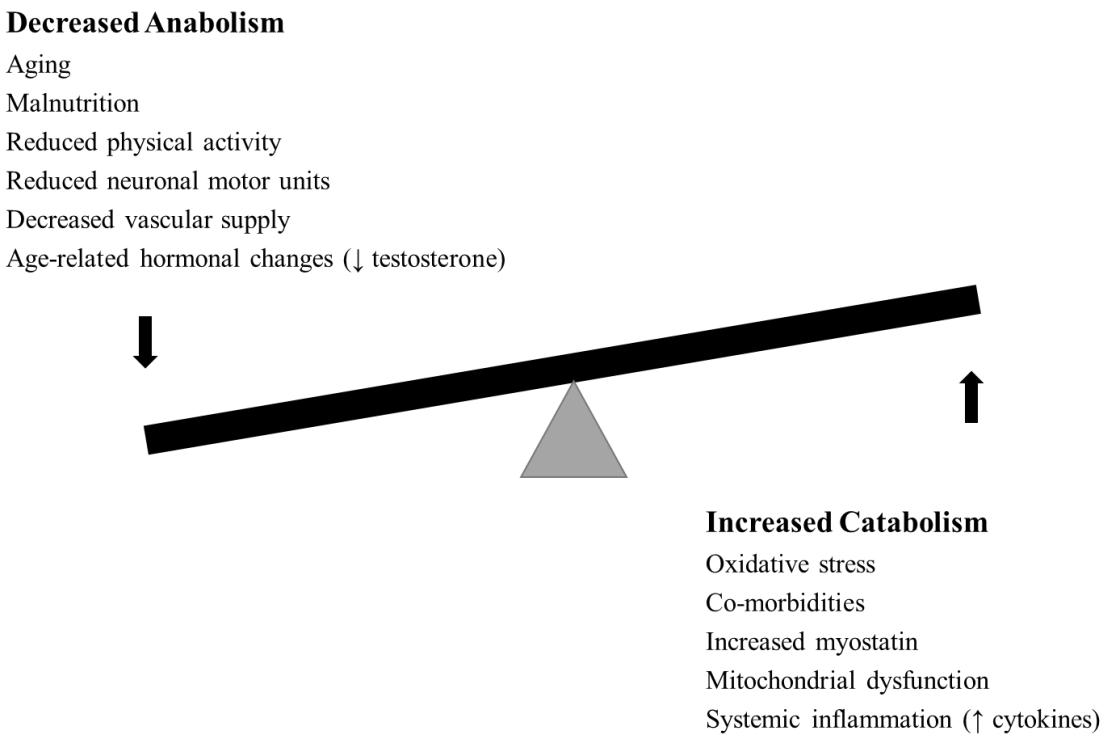
Sarcopenia is a multifactorial geriatric condition. The pathophysiology of sarcopenia involves many factors that are associated with age-related changes such as loss of muscle motor units, systemic inflammation due to increased cytokine activity, anorexia, decline in anabolic hormones (e.g.; growth hormone, insulin growth factor-1, testosterone), reduction in physical activity and increased sedentary lifestyle[7-10]. Reduction in lean muscle mass is mainly associated with protein degradation which is mediated by the ubiquitin-proteasome pathway, autophagy, and caspase signalling that leads to apoptosis[11]. When age-related risk factors are prominent, this is regarded as primary sarcopenia[3].

Sarcopenia can also be disease-related, which occurs when factors such as increased oxidative stress and inflammation are contributed by chronic diseases such as diabetes mellitus, cancer or heart failure (HF)[8, 9]. Sarcopenia is therefore classified as secondary when disease-related risk factors are the major contributors to progression of the condition[3]. Particularly in cardiovascular disease, a major cause of reduced exercise capacity is impaired endothelial function

leading to decreased vasodilation[12]. This inadequate vascular supply during physical exertion is thus highly prevalent in sarcopenic patients[12]. In the literature there has also been a bidirectional nature reported between sarcopenia and HF, with sarcopenia inducing endocrine abnormalities and myocyte contractile impairments[13, 14]. Reduction in skeletal muscle which is a major site of glucose storage can lead to insulin resistance which can contribute to endothelial dysfunction[15].

Ultimately, an imbalance of metabolism as a result of decreased anabolic processes and increased catabolic processes can lead to a presentation of muscle quantity and quality reduction (Figure 1).

Figure 1: Metabolic Derangement Leading to Sarcopenia



Epidemiology of Sarcopenia

Early work on muscle wasting reported a loss muscle mass of approximately 8% every 10 years in healthy adults over the age of 40, with an average loss of 24% between the ages 40 to 70[16]. The rate of muscle mass loss increased to 15% per decade among those over the age of 70[16]. As a major component of sarcopenia is muscle loss, this suggests prevalence of sarcopenia increases with age. It has also been emphasized by meta-analysis that weaker physical capability (grip strength, walking speed, chair rises, standing balance) are predictors of mortality in older community-dwelling populations[17]. More recent investigation includes the addition of muscle strength to sarcopenia evaluation, such as a 2014 systematic review by the European Working Group on Sarcopenia in Older People (EWGSOP) on prevalence and interventions for sarcopenia in ageing adults. According to the EWGSOP, the prevalence of sarcopenia in community-dwelling older adults ranged from 1-29%, in long-term care setting ranged from 14-33%, and in hospitalized care was 10%[18].

Methods of Assessment for Sarcopenia

A variety of tools currently exist that allow for the characterisation of sarcopenia. These assessment methods can be classified into either the screening or diagnosis category, with further sub-classification into self-reported questionnaire, tools for muscle strength measurement and tools for muscle mass measurement. The criteria and thresholds for widely used and validated assessment methods to evaluated sarcopenia among older adults is summarized below (Table 1).

Self-Reported Physical Functioning Assessment

The SARC-F questionnaire is one of the best tools available that can be used for case-finding individuals for pre-sarcopenia by measuring poor physical functioning[19]. Malmstrom et al. investigated the usefulness of the SARC-F across a total 5194 healthy adults from 3 studies (African American Health study, Baltimore Longitudinal Study of Aging, and National Health and Nutrition Examination Survey)[20]. A cut-off of ≥4 was shown to be internally consistent for detecting individuals at higher risk for recent hospitalizations and mortality from sarcopenia[20]. This SARC-F cut-off is consistently reported in other studies exploring screening for sarcopenia as it has been identified to produce high specificity, despite having low sensitivity[21-23].

Muscle Strength Assessment

Upper extremity strength is consistently measured by grip strength, with reduced grip strength being an indicator for falls, accelerated functional limitations, increased likelihood of discharge to skill-care facility following inpatient rehabilitation, and disability and mortality, in older adults[4, 24-26]. In a study involving patients with vascular disease, grip strength was recognized as a simple tool that overcomes limitations of walking-based measures as low grip strength was associated with increased comorbidity, cardiac risk and sarcopenia[27]. The chair rise test involves recording the time taken to perform 5 sit-to-stands from a chair as an accurate measure of lower extremity strength. Slow chair rise time has been shown to be a strong predictor of all-cause mortality in cardiac surgery patients[28, 29]. As such, the combination of grip strength and chair rise time serve as important biomarkers for sarcopenia as they are reflective of overall strength.

Muscle Mass Assessment

As anthropometric measurement has been deemed susceptible to error, more objective measures of body composition have been favored[18]. One method of discerning lean muscle mass is by measuring appendicular muscle mass by way of imaging technologies such as DXA as mentioned previously, but also by way of computed tomography (CT) scan, magnetic resonance imaging (MRI), and bioimpedance. Each of these 4 main techniques has associated advantages and disadvantages. CT-scans and MRI provide high accuracy and reproducibility in quantifying skeletal muscle mass, as well as enhanced discriminatory ability between different tissues, but this is offset by higher exposure to radiation, high cost, availability essentially low to scarce, requirement of operator experience, and high patient compliance[30-32]. Bioimpedance rests on the opposite end of the spectrum, providing non-invasive ability to discern muscle mass, good availability, efficient use as a portable device and no radiation exposure, however variation in hydration status of patients can drastically change results thereby decreasing its accuracy and reproducibility[30-32].

DXA fills the middle ground by covering the gaps in these 3 imaging technologies, but also having some similar disadvantages. In terms of advantages, DXA is a non-invasive method that provides high precision and reproducibility, ability to provide regional measures (fat mass, lean mass, bone density) while also being highly accessible, quick to use, and having low radiation exposure[30-33]. The disadvantages for DXA are that it requires more operator experience than bioimpedance and is affected by varying hydration status and body thickness making it less accurate than CT and MRI[30-33].

To note, the cut-off thresholds in DXA-based lean mass that indicate presence of weakness is varied slightly. In a pool cohort of older adults stratified by sex (7582 men and 3688 women),

one study of the Foundation for the National Institutes of Health Sarcopenia Project showed lean mass <19.75 kg in men and <15.02 kg in women to be most discriminatory for those who were weak compared to those who weren't[34, 35]. These thresholds are in line with those recommended by the EWGSOP 2019 guidelines. However, in past studies have used cut-offs ranging from 6.94 to 7.26 kg/m^2 in men and 5.4 to 6.1 kg/m^2 in women[2, 5, 36-38].

Another relatively novel surrogate for global muscle mass is psoas muscle area; measured in axial images of abdominopelvic CT-scan. Sarcopenia measured by psoas muscle area has been shown to improve discrimination for 6-month and 1-year mortality for patients undergoing transcatheter aortic valve replacement (TAVR)[39, 40]. In another cohort of TAVR patients, psoas muscle area was observed to be associated with midterm survival in women, after adjustment for Society of Thoracic Surgeons risk, but not men[41]. However, the psoas muscle being a minor muscle necessitates further studies to confirm its representation of overall sarcopenia, as is suggested by sarcopenia research groups.

Physical Performance Assessment

Physical performance tests that are consistently employed to test sarcopenia severity among older adults are the short physical performance batter (SPPB), gait speed and balance tests separately, 6-minute walk test, timed-up-and-go-test (TUG), and 400 m walk test.

A systematic review and meta-analysis of 17 studies determined the SPPB is associated with increased risk for mortality after adjustment for age, follow-up duration, and geographic area of participants[42]. The SPPB is more often used in research settings as it requires gait, balance and chair rise tests to be completed. For clinical settings where there is limited time, simple gait speed is sufficient. Gait speed alone has been identified as a reliable test for incrementally predicting

poor outcomes such as disability, falls, and mortality; all of which are sarcopenia-related[43-47]. The balance test is not robust enough on its own and is therefore conducted as part of the SPPB or in conjunction with tests such as the TUG[48, 49]. However, a meta-analysis indicates the TUG has limited ability to predict falling risk in older adults due to its low sensitivity and thus should be used in combination with other physical performance tests[49].

A 6-minute walk test is a common parameter measured in HF clinical practice, and thus can be readily incorporated as part of sarcopenia evaluation. The distance threshold of 300 m is cited in several studies of physical frailty among older adults with HF, such as the SOLVD (Studies of Left Ventricular Function) among others, as an indicator of poor functional performance and left ventricular function[50-52]. Nevertheless, the test data is often left on a continuous scale in order to distinguish severity of functional limitations.

Although these physical performance tests are relatively quick, in older adults these measures may be limited by presentation of gait or balance disorders or dementia as well as symptoms of fatigue or breathlessness in cardiovascular patients, especially those with HF.

Table 1: Summary of Sarcopenia Assessment Methods

Method	Criteria	Threshold for Sarcopenia
Self-Reported Physical Functioning		
SARC-F (Appendix A)	• Difficulty in lifting 10lbs • Difficulty in walking across room • Difficulty transferring from chair to bed • Difficulty in climbing 10 stairs • Number of falls in past year	Score ≥4 out of 10

Muscle Strength Assessment		
Grip strength	• Upper extremity strength	♀ <16 kg ♂ <27 kg
Chair rise test	• Lower extremity strength (time taken for 5 chair rises)	>15 s or inability to complete test
Muscle Mass Assessment		
DXA CT-scan MRI Bioimpedance	• Appendicular lean muscle mass (ASM) • Appendicular lean muscle mass (ASM/height^2) • Psoas muscle area (specifically CT-based)	♀ <15 kg ♂ <20 kg ♀ <5.5 kg/m^2 ♂ <7 kg/m^2 ♀ <11.8 cm^2 ♂ <20.3 cm^2
Physical Performance Assessment		
SPPB (Appendix B)	• Combined performance on gait speed, balance and chair rise tests	Score ≤8 out of 12
Gait speed	• 5 m walking test	≤0.8 m/s
Balance test	• Balance capacity (side-side, semi-tandem, full tandem)	<10 s for each position
6-minute walk test	• Walking capacity (distance covered in 6 minutes)	≤300 m
Timed Up and Go test	• Rising from chair, walking 3m then walking back and sitting down again	≥20 s
400 m walk test	• Walking endurance	Incomplete test or if completion takes ≥6 min

The feasibility of widely used sarcopenia assessment methods in either inpatient (acute) or outpatient care (community-dwelling) are identified below (Table 2). The attribution of each

method on a recommendation scale is based on several metrics including accessibility in setting, resources required to administer test, duration of test, costs, test robustness, associated negative factors like radiation exposure (if any), and appropriate-ness of test solely for sarcopenia evaluation[4, 30, 31].

Table 2: Feasibility of Sarcopenia Assessment Methods in Inpatient vs Outpatient Care Settings

	Feasibility in Inpatient Care	Feasibility in Outpatient Care
Self-Reported Physical Functioning		
SARC-F	xxx	xxx
Muscle Strength Assessment		
Grip strength	xxx	xxx
Chair rise test	xxx	xxx
Muscle Mass Assessment		
DXA	xxx	xxx
CT-scan	x	x
MRI	x	x
Bioimpedance	xx	xx
Physical Performance Assessment		
SPPB	xx	xxx
Gait speed	xxx	xxx
Balance test	x	x
6-minute walk test	xx	xx

Timed Up and Go test	xx	xx
400 m walk test	x	x

Categorizations of xxx = best recommended method, xx = useful alternative method, and x = least recommended method

Scope of Sarcopenia Evaluation in Patients with Cardiovascular Disease

Sarcopenia prevalence among older adults with cardiovascular disease and its impact on adverse outcomes varies considerably in current literature (Table 3). Over the last 5 years, publications relating to sarcopenia have increased, however the operational classification of sarcopenia has varied from diagnosis only based on muscle mass to diagnosis based on muscle mass and strength, thus contributing to different findings. This is evidenced by the fact that the following 7 studies cover 6 different sarcopenia assessment methods.

Bekfani et al., conducted a prospective cohort study aimed to describe sarcopenia in patients with heart failure with preserved ejection fraction and its relation to exercise capacity[53]. The study included 117 community-dwelling older adults and sarcopenia was defined by low appendicular muscle mass measured by DXA. Low appendicular muscle mass was independently associated with low exercise capacity on multivariable logistic regression (OR 1.2; CI 95% 1.03-1.33), after adjustment for echocardiography parameters and height. However, result was on the verge of non-significance.

Onoue et al., conducted a prospective cohort study aimed to evaluate the utility of a 3-component screening tool for sarcopenia (defined by age, grip strength, and calf circumference)[54]. The specific sarcopenia score calculation used has been previously defined by Ishii and colleagues

(Table 4). The study included 119 patients hospitalized due to their HF. Although multivariate cox proportional analysis showed sarcopenia score was an independent predictor of HF-related hospitalization or mortality (HR 1.03; 95% CI 1.01-1.05), the finding is only slightly significant. The addition of a sarcopenia score to brain natriuretic peptide levels (a key biomarker for HF severity), improved area under the curve for HF-related adverse events to 0.89 from 0.77 (sarcopenia alone) and 0.82 (brain natriuretic peptide alone). This alludes to the value of sarcopenia assessment, although the method may not be discriminatory enough for slight changes in muscle mass as no imaging technology was used.

Heidari et al., conducted a retrospective study to investigate the relation between sarcopenia and in-hospital adverse outcomes and mortality among patients undergoing TAVR[55]. The study captured 602 TAVR patients and defined sarcopenia by skeletal muscle mass measured by CT prior to surgery. Low muscle mass was not a predictor of poor in-hospital outcomes (eg; length of stay), however it was a predictor of all-cause mortality at 4-years (HR 1.46; 95% CI 1.06-2.14) following adjustment for post-TAVR predictors of mortality. Again, the findings are on the verge of significance. Furthermore, patients with low muscle mass were not more vulnerable to perioperative complications and morbidity which provides support for the safety of TAVR in sarcopenic patients.

Okamura et al., conducted a retrospective study aimed to explore the influence of sarcopenia on the post-operative outcomes of heart valve surgery[56]. The cohort analyzed consisted of 428 patients and sarcopenia was defined by psoas muscle area on preoperative CT scan. Although in-hospital mortality did not differ significantly between those with low psoas muscle area compared to normal, the former did have significantly greater rates of stroke, intra-aortic balloon pump or percutaneous cardiopulmonary support use, and low cardiac output syndrome.

On multivariable analysis, low psoas muscle area shown to be an independent predictor of mortality and major adverse cardiac and cerebrovascular events at 5-years (HR 2.22; 95% CI 1.26-3.92 and HR 2.8; 95% CI 1.24-6.32, respectively). The study did have some limitations, the first being it was a single center study and second it used a cut-off of psoas muscle area in lowest quartile among those ≥70 years of age which may not be applicable to younger patients.

Lopez et al., conducted a retrospective study aimed to clarify whether sarcopenia is associated with survival following acute hospitalization in HF with reduced ejection fraction (HFrEF) patients[57]. The cohort consisted of 160 patients who had a CT-scan during hospitalization. Sarcopenia was defined as lowest gender-based tertile of psoas muscle area. Initial multivariable regression suggested patients with low psoas muscle mass had an approximate 5-fold risk for post-discharge mortality at 1-year compared to those with normal psoas muscle mass (HR 4.5; 95% CI 1.78-11.76). However, through stratification of age and sex showed this association was limited to males and those <75 years of age. This suggests that HFrEF status in combination with low muscle mass poses great risk deterioration post-hospitalization. The lack association between psoas muscle mass and mortality in the very elderly may be explained by other factors such as cognitive, socioeconomic, and adherence to follow-up that exert greater influence. Another important factor to note, is that the CT-scan was performed for any clinical purpose during the acute hospitalization, and thus was likely not performed for the purpose of psoas muscle mass measurement.

Mamane et al., conducted a prospective cohort study aimed to assess the incremental prognostic value of sarcopenia in patients undergoing TAVR[39]. The study captured a total of 400 patients with pre-procedural CT-based psoas muscle area measurements. This is one of the few studies to have used both muscle mass and muscle strength (chair rise test) parameters in their definition of sarcopenia. Adjusted multivariable regression demonstrated that sarcopenia was

associated with significant 1-year mortality (OR 11.3; 95% CI 2.51-50.91) and worsening disability (OR 2.92; 95% CI 1.4-6.1). By integrating muscle strength into sarcopenia diagnosis, this study provided a more accurate classification of sarcopenia that is more concordant with older adults than surrogate measures of weight loss or muscle mass alone.

Teng et al., conducted a prospective cohort study to evaluate the influence of sarcopenia on changes in functional status after cardiac surgery[58]. The 242-sized cohort included a heterogenous population of cardiac surgery patients covering valve surgeries, coronary artery bypass graft (CABG) and combined procedures. Sarcopenia was defined by bioimpedance-based muscle mass and either grip strength or gait speed, thus taking into consideration muscle mass and strength measures. Following adjustment for cardiac operative risk factors, linear regression indicated sarcopenia patients had significantly longer length of stay (β=2.9; 95% CI 0.5-5.3) than non-sarcopenic patients. However, 1-year mortality (OR 0.7; 95% CI 0.1-4.1) and functional improvement was not associated with sarcopenia status, suggesting sarcopenia patients benefit greatly from surgery.

Although evaluation methods differed, overall, these studies demonstrate the negative impact of low muscle mass and/or low physical performance have on the short-term and long-term survival of older adults with cardiovascular disease. Alongside with a decline in survival rate, sarcopenia has been associated with a decline in quality of life in older individuals with various co-morbidities[59]. The downstream consequence of sarcopenia seems to be a limitation in functionality and deterioration of physical capacity, further limiting patients. These changes may exacerbate a patient's perception of their general health as a reduction in capability to accomplish activities of daily living can produce a lower quality of life.

Table 3: Studies Evaluating Sarcopenia in Cardiovascular Disease Patients

Study	N	Population / Setting	Assessment Method	% Sarcopenic	Primary Outcome(s)
Bekfani T. (2016)[53]	117	Symptomatic HFpEF, community-dwelling	DXA appendicular muscle mass	19.7	6-MWT <400m: OR 1.2 (95% CI 1.03-1.33)
Onoue Y. (2016)[54]	119	Hospitalized due to HF	Age, grip strength & calf circumference	68.9	HF-related hospitalization or mortality: HR 1.03 (95% CI 1.01-1.05)
Heidari B. (2018)[55]	602	Transcatheter aortic valve replacement	CT skeletal muscle mass	62.1	4-year mortality: HR 1.46 (95% CI 1.06-2.14)
Okamura H. (2018)[56]	428	Heart valve surgery	CT psoas muscle area	25.0	5-year mortality: HR 2.22 (95% CI 1.26-3.92) 5-year MACCE: HR 2.8 (95% CI 1.24-6.32)
Lopez P.D. (2019)[57]	160	HFrEF, discharged from acute hospitalization	CT psoas muscle area	32.5	6-month mortality: HR 3.85 (95% CI 1.55-9.95) 1-year mortality: HR 4.5 (95% CI 1.78-11.76)
Mamane S. (2019)[39]	400	Transcatheter aortic valve replacement	CT psoas muscle & chair rise test	21.0	1-year mortality: OR 11.3 (95% CI 2.51-50.91) Worsening disability: OR 2.92 (95% CI 1.4-6.1)
Teng C.H. (2019)[58]	242	Cardiac surgeries (CABG, valve replacement or combined procedures)	Bioimpedance muscle mass & grip strength or gait speed	27.7	1-year mortality: OR 0.7 (95% CI 0.1-4.1) Length of stay: β=2.9 (95% CI 0.5-5.3)

Abbreviations: HFpEF, Heart failure with preserved ejection fraction; 6-MWT, 6-minute walk test; MACCE, Major adverse cardiac and cerebrovascular events; HFrEF, Heart failure with reduced ejection fraction; CABG; Coronary artery bypass graft;

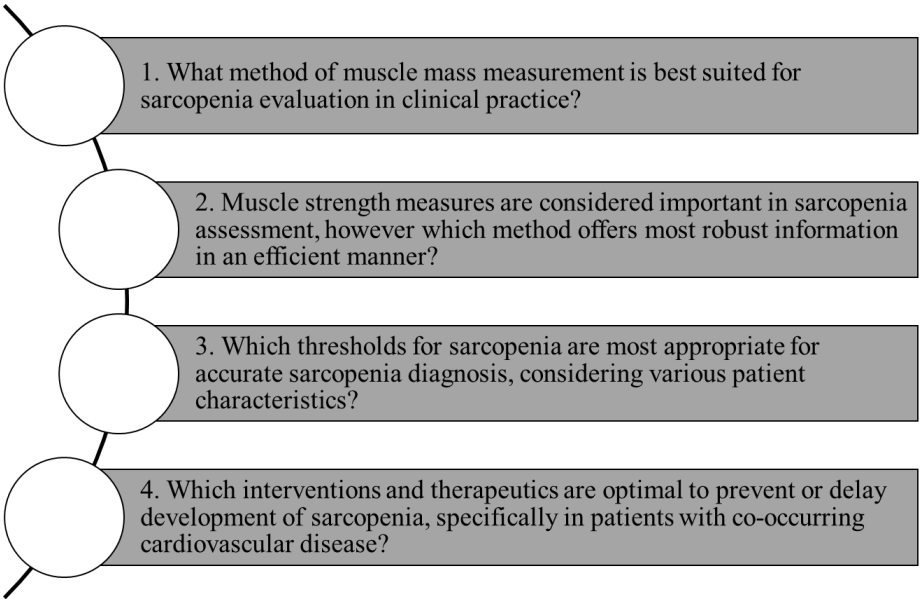
Table 4: The 3 Component Sarcopenia Score Calculation[60]

Sex	Calculation Formula
Male	0.62 x (age – 64) – 3.09 x (grip strength – 50) – 4.64 x (calf circumference – 42)
Female	0.80 x (age – 64) – 5.09 (grip strength – 34) – 3.28 x (calf circumference – 42)

A Need for a Gold Standard in Sarcopenia Assessment

Although the operational definition of sarcopenia has reached a consensus, due to the abundance of tools that exist for its evaluation, there is yet to be an identification of a gold standard protocol for its screening or diagnosis. In addition to a lack of standardized sarcopenia assessment, other areas that need to be addressed are determining which thresholds for tools should be consistently used and which interventions are best suited for patients with a co-burden of sarcopenia and cardiovascular disease (Figure 2).

Figure 2: Knowledge Gaps in Field of Sarcopenia



Importance of Assessing for Sarcopenia

The fact that sarcopenia is an actionable condition provides further impetus for consensus building for its assessment. Evidence to date on the impact of randomized trials for therapeutic interventions for frail elderly patients indicates a promising benefit.

A comprehensive review of 13 trails of exercise training, 4 trials of nutritional intervention, 7 trials of exercise and nutritional intervention, 8 trials of pharmaceutical intervention, 5 trials of multi-domain interventions, and 1 trial of home-based services provided an important analysis of the impact of interventions. Exercise training interventions have improved physical performance in frail older patients, and subsequent home-based exercise programs are effective in counteracting regression of functionality after supervised programming is completed[61]. Nutritional supplementation interventions have provided modest incremental value in terms of reversing the physical frailty phenotype[61]. Overall, recommendations have been put forth for multi-dimensional programs for improving patient outcomes. Specifically, in cardiovascular care, the heart team approach is one such interdisciplinary approach that considers global assessment of patient with consideration of body composition abnormalities[62].

Furthermore, sarcopenia-related healthcare costs are another reason as to why evaluation and treatment of sarcopenia is important. In the year 2000, the costs attributed to sarcopenia was estimated at $18.5 billion USD[63]. In the United States, a 10% reduction in sarcopenia prevalence was estimated to be associated with a saving of $1.1 billion per year[63]. Additionally, the costs associated with heart disease-related hospitalizations were approximately $55 billion per year[63, 64]. Among patients underdoing aortic valve replacement, a study demonstrated that 1% increase in Society of Thoracic Surgeons risk score is predictive of an added $3000 in hospital-associated charges and resource use[65]. Although these findings are based in the United States, they can be

applicable to Canada. This shows that not only does the combination of sarcopenia and cardiovascular disease pose a significant risk factor for adverse outcomes in older adults, it poses substantial economic burdens to healthcare institutions.

Sarcopenia screening alone provides an indicator of physical frailty in patients such that healthcare teams may initiate nutritional or exercise-related interventions as preventative actions. Thus, timely assessment and diagnosis of sarcopenia will not only provide useful information for patients' cardiovascular care, but can also lead to major cost-saving strategies.

CHAPTER 3: SARCOPENIA IN OLDER ADULTS UNDERGOING CARDIAC SURGERY: DUAL X-RAY ABSORPTIOMETRY ANALYSIS FROM THE MCGILL FRAILTY REGISTRY

This manuscript represents a planned analysis of a prospective study of sarcopenia among older adults undergoing cardiac surgery by DXA-based muscle mass and muscle strength parameters. A preliminary analysis was presented as a poster presentation at the Canadian Cardiovascular Congress in Montreal, Quebec in October 2019. This manuscript will be submitted for publication.

Sarcopenia in Older Adults Undergoing Cardiac Surgery: Dual X-Ray Absorptiometry Analysis from the McGill Frailty Registry

Aayushi Joshi, BMSc (1,2), Rita Mancini, BSc (1,2), Stephan Probst, MD (3), Jonathan Afilalo MD, MSc (1,2,4)

(1) Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada

(2) Division of Experimental Medicine, McGill University, Montreal, QC, Canada

(3) Department of Nuclear Medicine, Jewish General Hospital, McGill University, Montreal, QC, Canada

(4) Division of Cardiology, Jewish General Hospital, McGill University, Montreal, QC, Canada

Correspondence

Jonathan Afilalo, MD, MSc, FACC, FRCPC

Associate Professor, McGill University

Director, Geriatric Cardiology Fellowship Program

Co-Chair, ACC Geriatric Cardiology Section Research Working Group

Jewish General Hospital, 3755 Cote Ste Catherine Rd, E-222, Montreal, Quebec, H3T 1E2

Phone: (514) 340-8222 | Fax: (514) 221-3785 | Email: jonathan.afilalo@mcgill.ca

Funding

Dr. Jonathan Afilalo is supported by the Canadian Institutes of Health Research (CIHR) and the Fonds de recherche en santé du Québec (FRQ-S). Aayushi Joshi is supported by the Canadian Institutes of Health Research (CIHR CGS-M). Rita Mancini is supported by the Fonds de recherche en santé du Québec (FRQ-S).

Disclosures

None

ABSTRACT

Background: Sarcopenia is a biological hallmark of frailty that is associated with adverse health outcomes in older adults. Previous studies in the field of cardiac surgery have examined muscle mass using surrogate measures and results have been inconsistent. Dual x-ray absorptiometry (DXA) is a recommended modality to objectively measure muscle mass in clinical practice, which has the potential to be more accurate and predictive in this setting.

Objectives: To determine the prevalence and prognostic value of sarcopenia as measured by DXA-based muscle mass and performance-based muscle strength in older adults undergoing coronary artery bypass surgery or heart valve procedures.

Methods: A sample of older adults referred for cardiac surgery was prospectively enrolled at a single academic center. After a questionnaire and physical performance battery, patients underwent a DXA scan (GE Lunar) to measure their appendicular muscle mass index (AMMI). Patients were categorized as sarcopenic based on the European Working Group guidelines if they had low AMMI defined as <7 kg/m^2 in men or <5.5 kg/m^2 in women, and low muscle strength defined as 5 chair rises >15 seconds and/or low grip strength defined as <27 kg for men and <16 kg for women. Cox proportional hazards regression was used to test the association between sarcopenia and all-cause mortality over a median follow-up of 4.3 years.

Results: The cohort consisted of 141 patients with a mean age of 69.7 ± 10.0 years and 21% female. The procedures were isolated coronary bypass in 62%, heart valve surgery or other procedures in 31%, and decision not to proceed with surgery in 7%. The prevalence rates of low AMMI, slow chair rise time, and sarcopenia (low AMMI and slow chair rise time) were 24%, 57%, 13%, respectively. The 4-year survival rate was 79% in the non-sarcopenic group as

compared to 56% in the sarcopenic group (Log-rank P=0.01). After adjusting for covariates, each standard deviation of decreasing AMMI and increasing chair rise time was associated with a hazard ratio of 1.84 (95% CI 1.18, 2.86) and 1.79 (95% CI 1.26, 2.54), respectively, for all-cause mortality.

Conclusions: Lower-extremity muscle strength and DXA-based measures of muscle mass are indicative of sarcopenia and predictive of survival in older adults referred for cardiac surgery.

Keywords

Sarcopenia, Appendicular Muscle Mass Index, Chair Rise Time, Cardiac Surgery, DXA

Abbreviations

AMM – Appendicular Muscle Mass

AMMI – Appendicular Muscle Mass Indexed (height-squared)

DXA – Dual X-ray Absorptiometry

INTRODUCTION

Sarcopenia is defined as the age-related decline in skeletal muscle mass and strength – a cornerstone of the frailty syndrome. Clinical frailty scales do not typically include a direct measure of muscle mass, rather indirect (and often inaccurate) surrogates such as weight loss or body mass index[1]. To measure muscle mass, sarcopenia guidelines recommend dual x-ray absorptiometry scans (DXA), computed tomography scans (CT), magnetic resonance imaging (MRI), or bioimpedance. In patients undergoing transcatheter or surgical aortic valve replacement, CT-based psoas muscle area has been associated with higher midterm mortality[2-4]. In patients undergoing cardiac surgery, CT-based and bioimpedance-based muscle mass have been associated with prolonged postoperative length of stay[5, 6]. Therefore, early evidence suggests that sarcopenia appears to be a risk factor for adverse outcomes following cardiac surgery.

The evidence to-date has relied on opportunistic use of clinical CT scans to measure muscle mass[7], however, CT scans are acquired in a small subset of patients and cannot be broadly acquired solely for this indication due to concerns over ionizing radiation. DXA is another recommended modality that has trivial ionizing radiation, lower costs than CT, higher accuracy than bioimpedance, and accessibility in most hospitals for its role in bone density evaluation[8]. Despite the appeal of this modality, there has yet to be a study examining DXA-based muscle mass in the setting of cardiac surgery. This study aimed to determine the prevalence and incremental prognostic value of sarcopenia as measured by a combination of DXA-based muscle mass and performance-based muscle strength in older adults undergoing coronary artery bypass or heart valve surgery.

METHODS

Study Design

A prospective study nested within the McGill Frailty Registry was conducted between February 2013 and January 2017 at the Jewish General Hospital (Montreal, QC). Older patients referred for coronary artery bypass or heart valve surgery were screened; those that consented to participate underwent a comprehensive frailty assessment and DXA scan prior to surgery. Sarcopenia was operationally defined as low muscle mass by DXA and low muscle strength by physical performance tests. The primary outcome of all-cause mortality was assessed at 12 months. Ethics approval was obtained from the Jewish General Hospital's institutional review board.

Participants

Inclusion criteria were: (1) age 40 years or older, (2) referred for coronary artery bypass graft surgery (CABG) and/or heart valve repair or replacement surgery, (3) underwent a preoperative DXA scan, and (4) signed an informed consent form. Exclusion criteria were: clinical instability (unstable vital signs, refractory ischemia, acutely decompensated heart failure, uncontrolled arrhythmia), severe neuropsychiatric impairment, prohibitive language barrier, and logistical impediment to obtain a preoperative DXA scan such as scheduling issues or scanner availability.

Sarcopenia Definition

Based on the 2018 European Working Group on Sarcopenia in Older People (EWGSOP 2) guidelines[9, 10], the diagnosis of sarcopenia required demonstration of low muscle mass and strength. DXA was used to measure appendicular muscle mass index (AMMI) representing the

sum of fat-free mass for the extremities divided by the patient's height squared; low mass being AMMI <7.0 kg/m^2 for men and <5.5 kg/m^2 for women[9, 10]. Height was measured using a stadiometer. The chair rise and grip strength tests were used to measure muscle strength; low strength being a chair rise time >15 seconds or an inability to complete the test, and/or a grip strength <27 kg for men and <16 kg for women. The chair rise test was measured by recording the time taken to stand 5 times from a seated position without using arms[11]. The grip strength test was measured by recording the strongest of three trials using a Jamar dynamometer. Consistent with our previous study in which CT was used to measure muscle mass, sarcopenia was operationally defined as a combination of low muscle mass and slow chair rise time. Other definitions including grip strength and non-indexed muscle mass were examined in sensitivity analyses.

DXA Measurements

DXA computes the volume of fat and fat-free tissues as well as bone mineral content based on the penetrance of low-dose x-rays through the patient (estimated radiation dose 0.002 mSv, equivalent to 2% of a standard chest x-ray). Patients were asked to lie in a supine position on the DXA scanner table (GE Lunar; Madison, WI) for approximately 5 minutes. Regions of interest were automatically generated and manually adjusted by a trained observer to provide whole-body and regional measurements of the arms, legs, and trunk. AMM was calculated as the sum of fat-free tissue in the arms and legs. When accurate and complete measurement of one arm or leg was not feasible due to the patient's size relative to the DXA scanner table, the other arm or leg was substituted in its place. Patients with an amputated arm or leg were removed from the dataset (N=2).

Outcomes

The primary outcome was all-cause mortality at 12 months ascertained by a combination of medical records, linkage with administrative data sources, and contact with patients or their family members. The secondary outcome measures were all-cause mortality at 1 and 6 months, postoperative hospital length of stay (LOS), discharge to a skilled care facility, readmission at 1 month, and a composite outcome of all-cause mortality or incident disability at 12 months. Incident disability was defined as institutionalization or ≥2 new deficits in basic and instrumental activities of daily living (ADL, IADL) captured by the Older American Resources and Services tool[12].

Statistical Analyses

Descriptive statistics and distributional histograms were examined for variables of interest. Continuous variables were presented as sample means and compared using t-tests while categorical variables were presented as percentages and compared using chi-squared tests. The Kaplan-Meier method was used to generate survival curves. The Cox proportional hazards model was used to determine the association between sarcopenia and all-cause mortality after adjusting for age, sex, Charlson comorbidity index, left ventricular ejection fraction, type of surgical procedure, and DXA fat mass index; with the cohort entry set at the baseline assessment date (median of 4 days before the surgery date). The same model was repeated with AMMI and chair rise time entered as standardized continuous variables instead of the combined binary sarcopenia variable. Finally, a classification and regression tree (CART) analysis of the martingale residuals of a Cox proportional hazards model was used to explore a optimized cut-off for AMMI. Study data were managed using REDCap electronic data capture tools hosted at the Lady Davis Institute

Centre for Clinical Epidemiology (Jewish General Hospital; Montreal, QC). All analyses were completed using the STATA software package (version 16; College Station, TX).

RESULTS

Baseline Characteristics

The cohort consisted of 141 patients with a mean age of 69.7 ± 10.0 years and 21% females (Figure 1). The distribution of surgical procedures was as follows: isolated CABG in 88 patients (62%), heart valve surgery or other procedures in 44 patients (31%), no procedure in 10 patients (7%). AMM non-indexed and AMM indexed to height^2 (AMMI) were normally distributed with mean values of 24.0 ± 5.2 kg and 8.0 ± 1.8 kg/m^2 in men, 20.8 ± 5.2 kg and 8.4 ± 2.2 kg/m^2 in women (Figure 2). The prevalence rates of low AMMI, slow chair rise time, and sarcopenia (low AMMI plus slow chair rise time) were 24%, 59%, 13%, respectively. Sarcopenic patients were more likely to be older, have a history of falls, lower estimated glomerular filtration rates, lower albumin levels, and higher Essential Frailty Toolset and Short Physical Performance Battery scores (Table 1).

Crude Outcomes

A total of 34 all-cause deaths were observed. At 12 months, there were 13 deaths (11%) in the non-sarcopenic group and 4 deaths (21%) in the sarcopenic group (P=0.12). There were no statistically significant differences in readmission at 1 month or worsening disability at 12 months (Table 2). When patients were grouped by AMMI alone at 12 months, there were 11 deaths (10%) in the normal AMMI group and 6 deaths (18%) in the low AMMI group (P=0.25). When patients

were grouped by chair rise time alone at 12 months, there were 2 deaths (3%) in the normal chair rise time group and 15 deaths (18%) in the slow chair rise time group (P=0.009).

Survival Analysis

Median follow-up was 4.3 years and ascertainment of vital status was complete for all study patients. The 4-year survival rate was 79% (95% CI 71% to 86%) in the non-sarcopenic group as compared to 56% (95% CI 31% to 75%) in the sarcopenic group (Log-rank P=0.01) (Figure 3). In the first Cox proportional hazards model (Table 3), each standard deviation of decreasing DXA AMMI and increasing chair rise time was associated with an adjusted HR of 1.84 (95% CI 1.18, 2.86) and 1.79 (95% CI 1.26, 2.54), respectively, and each standard deviation of increasing DXA fat mass index was associated with an adjusted HR of 1.69 (95% CI 1.18, 2.86). In the second Cox proportional hazards model, sarcopenia as defined by the EWGSOP2 criteria was associated with an adjusted HR of 2.11 (95% CI 0.86, 5.17) for all-cause mortality.

Sensitivity Analysis

When sarcopenia was defined as low non-indexed AMM plus slow chair rise time, the prevalence of sarcopenia was 12% and it was associated with an adjusted HR of 2.29 (95% CI 0.94 to 5.62) for all-cause mortality. When sarcopenia was defined as low AMMI plus either slow chair rise time or low grip strength, the prevalence of sarcopenia was 15% and it was associated with an adjusted HF of 1.56 (95% CI 0.67 to 3.66) for all-cause mortality. When sarcopenia was defined as low AMMI with a cut-off of <8.0 kg/m^2 for men and women (optimal cut-off identified by the CART analysis; Figure 4) plus slow chair rise time, the prevalence of sarcopenia was 28% and it was associated with an adjusted HR of 2.98 (95% CI 1.37 to 6.45).

DISCUSSION

This study investigated the prevalence and prognostic value of sarcopenia defined by DXA-based muscle mass and chair-based muscle strength in older adults undergoing cardiac artery bypass or heart valve surgery. The main findings can be summarized as follows. At least one in seven patients had objective evidence of sarcopenia, which was co-prevalent with other indicators of frailty and geriatric risk. Sarcopenic patients had a twofold increase in hazard of all-cause mortality at a median of 4 years, although the statistical significance of this result was borderline when sarcopenia was classified according to the binary EWGSOP2 diagnostic criteria as opposed to when AMMI and chair rise time were interpreted as individual continuous variables. In addition to low AMMI, another DXA parameter – high fat mass index – was found to be associated with all-cause mortality.

Evidence for Muscle Strength as a Predictor in Cardiac Surgery

This study strengthens the existing body of evidence for lower extremity muscle strength, and specifically for the chair rise test, in cardiovascular patients. The chair rise test was recently reported as the best frailty screening method for patients undergoing aortic valve replacement (AVR)[13]. The chair rise test has demonstrated the greatest discriminatory power in comparison to other frailty tests[13]. In a cohort of 1020 AVR patients, slow chair rise time was associated with adverse outcomes[14]. In fact, lower extremity weakness assessed using chair rise time is a component of the essential frailty toolset, which demonstrated the strongest predictive value for worsening disability at 1 year and death at 30 days[14]. The chair rise test, as a measure of lower extremity muscle strength, is emerging as a strong predictor for adverse outcomes in cardiac surgery patients.

A correlation between low muscle area, low grip strength and Short Physical Performance Battery (SPPB) scores has been shown[6]. However, the risk prediction model derived by Zuckerman and colleagues achieved the greatest improvement when low psoas muscle area was combined with low grip strength. Therefore, muscle mass alone without evaluation of muscle quality may not be that useful in predicting outcomes. A recent study sought to investigate the association between sarcopenia and post-operative outcomes using CT-based muscle mass[15]. Although an association was found between psoas muscle area and mortality, their multivariable model did not adjust for muscle strength[15]. Given the recent evidence suggesting that muscle strength is an important risk factor in older adults undergoing cardiac surgery, we must disentangle muscle area from muscle strength to capture its true value as a risk predictor.

The value of psoas muscle mass as a surrogate for total body mass has been extensively studied in recent years. A systematic review of 20 studies concluded that CT was the most prominently used imaging modality, with psoas muscle cross-sectional area as the dominant method for sarcopenia assessment in acute injury[16]. Radiographically assessed sarcopenia was found to be significantly associated with mortality, morbidity, length of stay and in-hospital complications[16]. However, CT cannot be used as conventional method solely for muscle mass measurement in acute settings as it confers high ionizing radiation and is more costly. Therefore, the use of CT in these studies was opportunistic.

Limitations of DXA-based Measure of Skeletal Muscle Mass in Heart Failure or Edematous Patients

Sarcopenia is defined by an age-related reduction in muscle strength and skeletal muscle mass. Therefore, muscle mass measurements as a non-invasive and easily applicable marker is

pertinent for correct sarcopenia diagnosis. As such, there is a need for consensus on the best modality for muscle mass evaluation, especially in acute cardiac patients. However, DXA may be less accurate in hospitalized cardiac patients due to the confounding effects of peripheral edema and fluid shifts. DXA has been considered a reference standard for measuring muscle mass due to its feasibility, safety and modest costs[8]. However, it is by no means a gold standard given that hydration status abnormalities such as water retention due to heart, kidney or liver failure can affect muscle mass measures[8].

Patients with acutely decompensated heart failure (ADHF) present with peripheral edema and dynamic fluid status. There are limited studies evaluating the use of DXA for skeletal muscle mass measurement in patients with heart failure. Not only has sarcopenia (DXA-based low skeletal muscle index) been shown to be frequent in heart failure, it has also been associated with higher brain natriuretic peptide levels as a marker of increased heart failure severity[17]. However, DXA is not easily applicable in ADHF patients as most have difficulty with laying down in a supine position. This has contributed to uncertainty regarding the procedural and measurement accuracy of muscle mass using DXA in cardiac patients with a dynamic status.

Furthermore, DXA-based assessment of fat-free mass (sum of lean mass and bone mineral content) in stable heart failure patients has demonstrated an overestimation of fat-free mass compared to deuterium dilution as a reference standard[18]. The potential difference was not attributed to differences in body water compartments or bone mineral content between heart failure patients and controls[18]. The overestimation of fat-free mass by DXA corresponds with conclusions made by other studies among healthy participants[18-20]. A study comparing bioimpedance and DXA modalities demonstrated that DXA overestimates fat-free mass in the extremities rather than the trunk in healthy adults[19].

Prevalence of Sarcopenia Among Older Adult Women based on Diagnostic Criteria

In our study, only one woman was deemed sarcopenic among 30, which suggests a potential misclassification of women as non-sarcopenic. There is a potential for decompensated heart failure status in these acute cardiac patients causing inaccurate muscle mass measurements by DXA. Moreover, an overestimation of skeletal muscle mass by DXA can lead to lower estimate of sarcopenia prevalence.

Another explanation for the low prevalence of sarcopenia among women in our study could be based on the sarcopenia criteria used (Table 4). Prevalence of sarcopenia has been shown to vary considerably depending on the diagnostic criteria[9, 10, 21, 22]. The recommendation of an AMMI cut-off of 5.5 kg/m^2 for women by the EWGSOP2 is based on a study by Gould and colleagues among healthy Australian men and women[10]. The cut-offs for relative AMMI were generated based on T scores of –2.0 and –1.0 using data from young adult women aged 20-39 years enrolled in the study. In this cohort, the proportion of women aged ≥80 years with a T score less than –2.0 was 6.2%[23]. In other previous studies of healthy older adult women, an AMMI cutoff of 5.4 kg/m^2 resulted in a 22.7% prevalence of sarcopenia among those aged ≥65 years (Iannuzzi-Sucich and colleagues) and an AMMI cutoff of 5.45 kg/m^2 resulted in a 35.9% and 43.2% prevalence of sarcopenia among those aged 75-80 years and >80 years, respectively (Baumgartner and colleagues)[24, 25].

A study investigating the impact of 7 different diagnostic criteria for sarcopenia reported the prevalence of sarcopenia in women (mean age 61.8 years) ranging from 0% to 15.6%, 0% to 21.8%, and 0% to 25.8% among the lowest, middle and highest age category, respectively[21]. One prominent definition of sarcopenia used widely is defined as an AMMI less than 2 standard deviations below the mean of a reference population of young healthy adults[24]. This diagnostic

criterion is similar to that of osteopenia using bone mineral density. The use of this sarcopenia definition in a particular cohort of healthy older adult women corresponded to 6.1 kg/m^2 as the AMMI cutoff[26]. It was demonstrated that the prevalence of sarcopenia among those aged 60-69 years and >70 years was 9.4% and 12.3%, respectively[26]. The mean AMMI among these healthy women was 6.3 ± 0.7 kg/m^2 for the age decade 60-69 years (N=85) and 6.2 ± 0.8 kg/m^2 for the oldest age cohort >70 years (N=67)[26].

Limitations

A number of limitations should be acknowledged. First, the study sample was predominantly male, which is not unexpected given the high prevalence of coronary artery disease. Second, the study was conducted at a single academic centre with one type of DXA scanner. Third, the sample size was modest and confidence intervals in multivariable models were relatively wide for the prediction of all-cause mortality. Additional research is needed in multi-center cohorts with larger numbers of female patients to better define the optimal cut-offs for low AMMI and to validate the prognostic value with various types of DXA scanners. In the field of bone densitometry, there does not appear to be evidence of clinically relevant variability across DXA scanners on the market today.

Future Directions

Lower extremity strength represents a valuable predictor of the functional capabilities of older adults in activities of daily living. For older adults undergoing cardiac surgery, their mobility training and physiotherapy post-procedure is imperative to prevent deconditioning that occurs

during the post-operative course. Baseline evaluation of muscle strength prior to cardiac surgery thus provides an important prognostic tool.

As sarcopenia is known to be an age-related loss of muscle mass, it becomes a pertinent parameter to assess in older adults undergoing cardiac surgery who may be more vulnerable to adverse outcomes. Thus, the addition of muscle mass evaluation is involved in sarcopenia diagnosis. However, the limitations and uncertainty with regards to the accuracy of muscle mass evaluation by DXA in acute cardiac settings highlights a need for further study of imaging modalities best suited for this role. Further research is required to determine whether other measures of muscle mass and quality such as those provided by CT, MRI, or bioimpedance add incremental value above measures of muscle strength. This is necessary to justify the added costs and time required to perform these tests over the use of DXA-based muscle mass measurement. Lastly, consensus building with regards to appropriate AMMI cut-offs for older adult women in acute cardiac settings is imperative for accurate sarcopenia diagnosis. Future work must involve establishing a consistent definition of sarcopenia diagnosis.

CONCLUSIONS

Given the increasing age and comorbidity burden of patients undergoing cardiac surgery, assessment of frailty and sarcopenia have become core components of preoperative risk stratification. This study has shown that sarcopenia as measured by low chair rise strength and low AMMI is associated with a heightened risk of all-cause mortality up to 4 years following cardiac surgery. Our recommended approach is to start with the chair rise test to rapidly screen for physical frailty and sarcopenia. Patients that complete the test within <15 seconds are unlikely to be sarcopenic and have low procedural risk; those that cannot are evaluated further with additional

physical performance tests (gait speed, grip strength) and muscle mass testing. The added value of AMMI is most apparent in this subgroup of patients with low strength, although it must be carefully interpreted in light of the known sources of measurement error with DXA and the common disconnect between muscle mass and physical performance.

CLINICAL PERSPECTIVES

In a clinical setting where time and resources may be scarce, assessing muscle strength using a timed chair rise test is more feasible than a DXA scan. Findings suggests that lower extremity muscle strength may be prognostically superior to DXA-based measures. Thus, performing a simple test to assess muscle strength is clinically advantageous given its prognostic value. Moreover, muscular strength is actionable. Vulnerable patient populations may therefore benefit from exercise training to achieve significant risk reduction.

FIGURE LEGENDS

Figure 1: Flow Diagram

Total 148 patients received a DXA scan, out of which 2 were excluded due to significant amputation of arm(s) or leg(s) and 5 were excluded due to outpatient status with no indication of a surgery workup. This resulted in a study cohort of 141 patients for analysis.

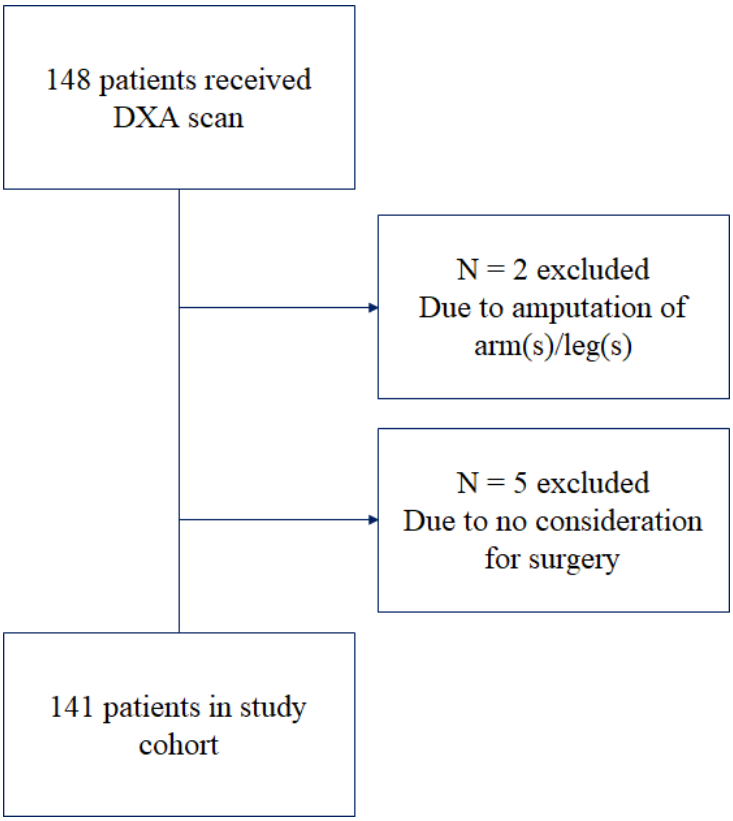
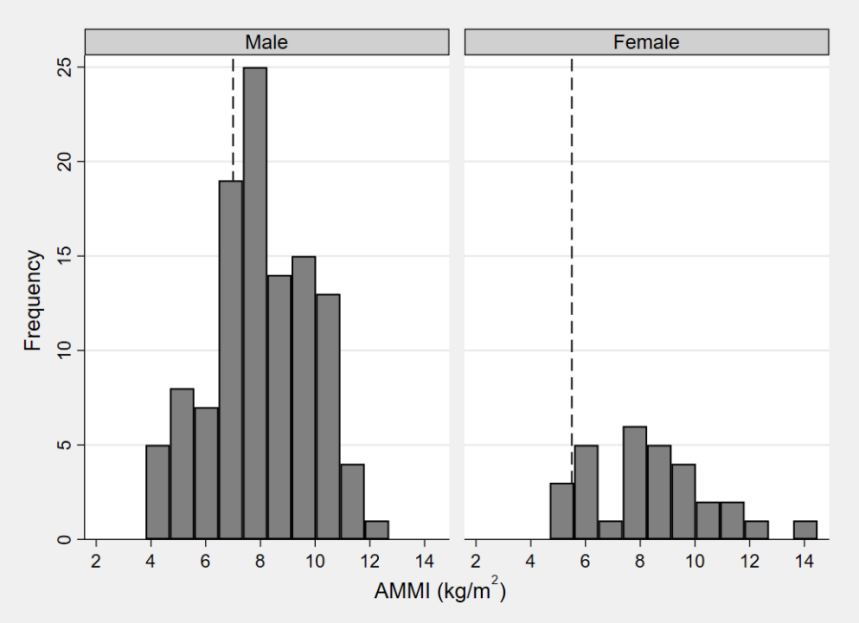


Figure 2: Appendicular Muscle Mass Index Distribution

Distribution of AMMI with sex-stratified sarcopenia cut-offs [dashed lines] of <7.0 kg/m^2 in men and <5.5 kg/m^2 in women based on the EWGSOP2.



Boxplot of AMMI for those who had mortality or worsening disability at 12-months compared to those who did not. Median AMMI was lower for those who had an event.

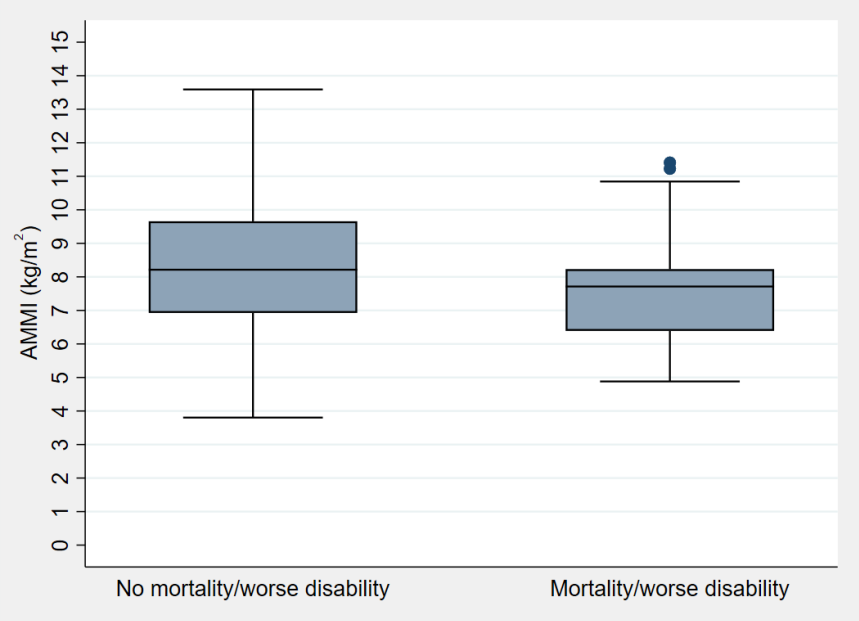


Figure 3: Kaplan-Meier Survival Curves by Sarcopenia Status

Kaplan-Meier survival estimates following the preprocedural assessment for study patients with sarcopenia [dashed line] and no sarcopenia [solid line].

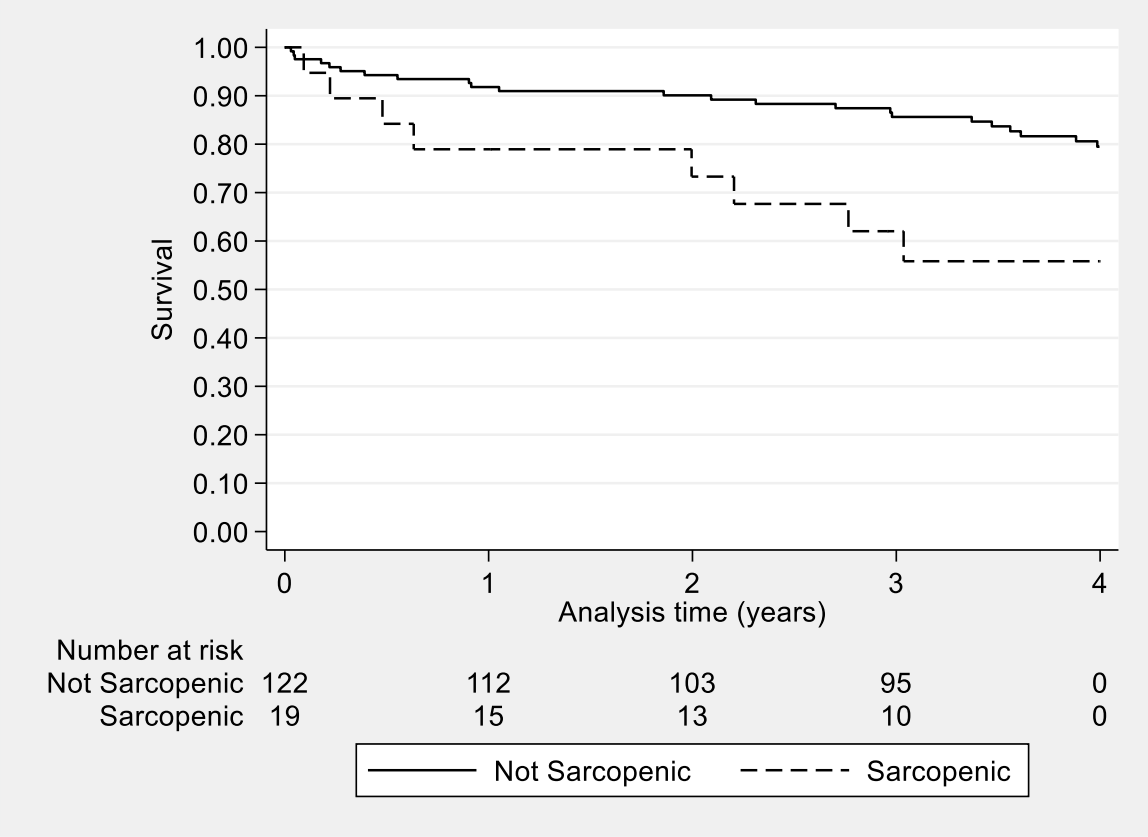


Figure 4: Classification Tree with Sarcopenia Parameters to Predict Mortality

Modified algorithm to identify sarcopenic patients at increased risk; the CART survival analysis identified the same chair rise cut-off of ≥15 seconds but a different AMMI cut-off of <8.0 kg/m^2 in men and women.

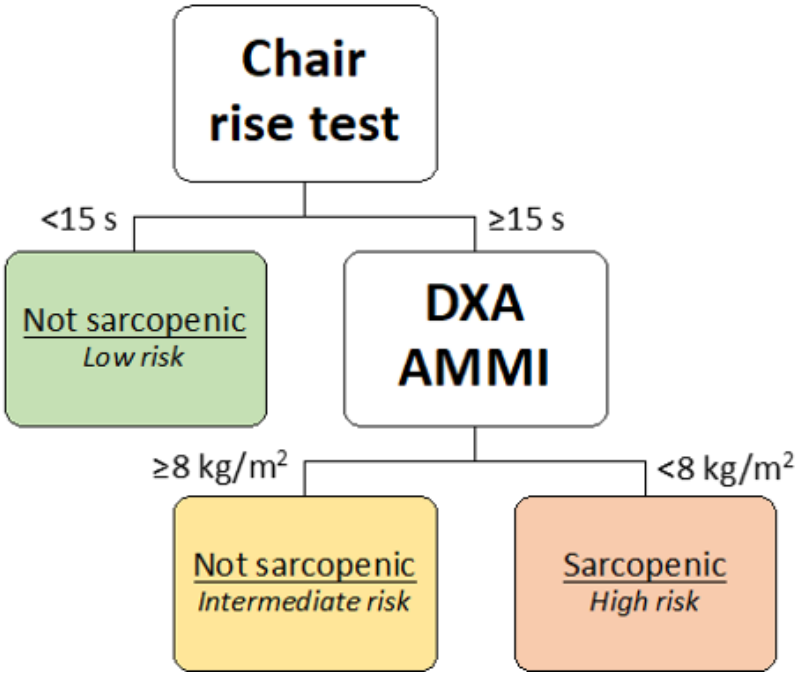


Table 1: Baseline Characteristics by Sarcopenia Status

	All Patients (N=141)	**No Sarcopenia (N=122)**	**Sarcopenia (N=19)**	**P-Value**
Demographics				
Age (years)	69.7 ± 10	68.7 ± 10	76.2 ± 9.4	<0.01*
Female	30 (21%)	29 (24%)	1 (5.3%)	0.07
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.8 ± 0.08	<0.01*
Weight (kg)	79.1 ± 17.3	78.3 ± 17.1	84.3 ± 18.1	0.08
BMI (kg/m^2)	27.1 ± 5.1	27.3 ± 5	26.5 ± 5.4	0.28
Underweight BMI < 18.5	3 (2%)	3 (2.5%)	0 (0%)	0.49
Obese BMI ≥30	42 (30%)	38 (31%)	4 (21%)	0.37
Body surface area (m^2)	1.93 ± 0.2	1.91 ± 0.2	2.0 ± 0.2	0.02*
Comorbidities				
LVEF (%)	51.3 ± 15.1	51.9 ± 15.4	47.9 ± 13.1	0.14
Charlson Comorbidity Index	2.6 ± 1.8	2.5 ± 1.8	3.1 ± 1.8	0.12
Heart Failure	48 (34%)	40 (33%)	8 (42%)	0.43
Coronary artery disease	120 (85%)	102 (84%)	18 (95%)	0.21
Peripheral arterial disease	15 (11%)	12 (10%)	3(16%)	0.43
COPD	9 (6%)	7 (6%)	2 (11%)	0.43
Diabetes	58 (41%)	52 (43%)	6 (32%)	0.36
Chronic kidney disease	39 (28%)	31 (25%)	8 (42%)	0.13
Glomerular filtration rate**	68.1 ± 17.2	69.3 ± 16.5	60.8 ± 20.2	0.02*
Falls	27 (19%)	20 (16%)	7 (37%)	0.04*

	All Patients (N=141)	No Sarcopenia (N=122)	Sarcopenia (N=19)	P-Value
Arthritis	58 (41%)	51 (42%)	7 (37%)	0.68
Osteoporosis	13 (9%)	12 (10%)	1 (5%)	0.52
Surgical Procedures				
CABG	112 (79%)	95 (78%)	17 (90%)	0.24
Mitral valve procedure	13 (9%)	11 (9%)	2 (11%)	0.83
Aortic valve procedure	31 (22%)	27 (22%)	4 (21%)	0.91
Geriatric/Frailty Domains				
Fried Frailty Scale	1.5 ± 1.4	1.5 ± 1.4	1.7 ± 1.3	0.51
Clinical frailty scale (/9)	2.9 ± 1	2.9 ± 1	2.9 ± 0.9	0.96
SPPB score (/12)	8.1 ± 3	8.3 ± 3.1	6.9 ± 2.5	0.02*
Gait speed (cm/s)	89.9 ± 30	90.9 ± 30.3	84.1 ± 27.9	0.18
Max grip strength (kg)	33.8 ± 12	33.6 ± 12.2	34.7 ± 10.5	0.36
Chair time (max 60 s)	25.5 ± 19.6	24.9 ± 19.7	29± 15.6	0.2
Chair rise time (>15 s)	83 (59%)	64 (52%)	19 (100%)	<0.01*
Essential frailty toolset score (/5)**	1.5 ± 1.2	1.4 ± 1.2	2.2 ± 1	<0.01*
MMSE (<24)	11 (8%)	10 (8%)	1 (5%)	0.66
Geriatric depression scale	32 (23%)	30 (25%)	2 (11%)	0.17
Mini nutritional assessment	11.2 ± 2.6	11.1 ± 2.5	11.7 ± 3	0.23
Disability score (/14)	0.4 ± 1.3	0.5 ± 1.3	0.1 ± 0.5	0.23

*Significant P-value (<0.05)

**EFT score for N=139; Glomerular filtration rate for N=139; Clinical frailty scale for N=139

Abbreviations: BMI, Body Mass Index; AMMI, Appendicular Muscle Mass Index; LVEF, Left Ventricular Ejection Fraction; COPD, Chronic Obstructive Pulmonary Disease; CABG, Coronary Artery Bypass Graft; SPPB, Short Physical Performance Battery; MMSE, Mini-Mental State Examination

Table 2: Unadjusted Outcomes by Sarcopenia Status

	All Patients (N=141)	**No Sarcopenia (N=122)**	**Sarcopenia (N=19)**	**P-Value**
6-Month Mortality	14 (10%)	10 (8%)	4 (21%)	0.08
12-Month Mortality	17 (12%)	13 (11%)	4 (21%)	0.12
12-Month Mortality or Worsened Disability*	25 (19%)	19 (17%)	6 (32%)	0.14
Discharge to Skilled Care Facility or In-Hospital Death	43 (30%)	37 (30%)	6 (32%)	0.91
30-Day Readmission	12 (9%)	9 (7%)	3 (16%)	0.22

*11 patients did not complete the disability questionnaire at 12-months and were excluded from analysis

Table 3: Cox Proportional Hazards Model for All-Cause Mortality

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age (per +1 year)	1.06 (1.01, 1.12)	1.07 (1.01, 1.12)	1.08 (1.03, 1.13)
Female sex	1.35 (0.60, 3.03)	1.46 (0.68, 3.16)	1.12 (0.53, 2.40)
Left ventricular ejection fraction (per +1 %)	0.98 (0.96, 1.00)	0.99 (0.96, 1.01)	0.99 (0.97, 1.01)
Charlson comorbidity index	1.27 (0.98, 1.65)	1.20 (0.95, 1.52)	1.12 (0.88, 1.43)
Procedure: Isolated coronary artery bypass	1 (referent)	1 (referent)	1 (referent)
Procedure: Valve or other cardiac surgery	1.54 (0.66, 3.57)	1.31 (0.57, 3.01)	1.01 (0.43, 2.35)
Procedure: None	2.73 (0.91, 8.19)	3.59 (1.16, 11.13)	2.75 (0.90, 8.36)
DXA fat mass index (per +1 SD)	1.69 (1.20, 2.37)	1.38 (1.00, 1.91)	1.39 (1.00, 1.95)
DXA appendicular muscle mass index (per -1 SD)	1.84 (1.18, 2.86)	–	–
Chair rise time (per +1 SD)	1.79 (1.26, 2.54)	–	–
Sarcopenia: EWGSOP2 definition	–	2.11 (0.86, 5.17)	–
Sarcopenia: Modified definition	–	–	2.98 (1.37, 6.45)

Abbreviations: DXA, Dual X-ray Absorptiometry; EWGSOP2 European Working Group on Sarcopenia in Older People 2; SD, Standard Deviation.

Table 4: Prevalence of Low Appendicular Muscle Mass among Healthy Older Adult Women based on Diagnostic Criteria

	Gould et al (EWGSOP2) **N=960**	**Iannuzzi-Sucich et al** **N=195**	**Baumgartner et al** **N=382**	**Tanko et al** **N=754**
Low AMMI (kg/m^2) Cutoff for Women	5.5	5.4	5.45	6.1
Low AMMI Prevalence in Women (%)	6.2 (≥80 years)	22.7 (≥65 years)	35.9 (75-80 years) 43.2 (>80 years)	9.4 (60-69 years) 12.3 (>70 years)

REFERENCES

1. Fried LP TC, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McGurnie MA for the Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-M56.

2. Hawkins RB, Mehaffey JH, Charles EJ, Kern JA, Lim DS, Teman NR, et al. Psoas Muscle Size Predicts Risk-Adjusted Outcomes After Surgical Aortic Valve Replacement. Ann Thorac Surg. 2018;106(1):39-45.

3. Krishnan A, Suarez-Pierre A, Zhou X, Lin CT, Fraser CD, 3rd, Crawford TC, et al. Comparing Frailty Markers in Predicting Poor Outcomes after Transcatheter Aortic Valve Replacement. Innovations (Phila). 2019;14(1):43-54.

4. Mamane S, Mullie L, Lok Ok Choo W, Piazza N, Martucci G, Morais JA, et al. Sarcopenia in Older Adults Undergoing Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2019;74(25):3178-80.

5. Teng CH, Chen SY, Wei YC, Hsu RB, Chi NH, Wang SS, et al. Effects of sarcopenia on functional improvement over the first year after cardiac surgery: a cohort study. Eur J Cardiovasc Nurs. 2019;18(4):309-17.

6. Zuckerman J, Ades M, Mullie L, Trnkus A, Morin JF, Langlois Y, et al. Psoas Muscle Area and Length of Stay in Older Adults Undergoing Cardiac Operations. Ann Thorac Surg. 2017;103(5):1498-504.

7. Soud M, Alahdab F, Ho G, Kuku KO, Cejudo-Tejeda M, Hideo-Kajita A, et al. Usefulness of skeletal muscle area detected by computed tomography to predict mortality in patients undergoing transcatheter aortic valve replacement: a meta-analysis study. Int J Cardiovasc Imaging. 2019;35(6):1141-7.

8. Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. J Cachexia Sarcopenia Muscle. 2018;9(2):269-78.

9. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(4):601.

10. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.

11. Guralnik JM SE, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol A Biol Sci Med Sci. 1994;49(2):M85-M94.

12. Fillenbaum GG SM. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. J Gerontol. 1981;36(4):428-34.

13. Hosler QP, Maltagliati AJ, Shi SM, Afilalo J, Popma JJ, Khabbaz KR, et al. A Practical Two-Stage Frailty Assessment for Older Adults Undergoing Aortic Valve Replacement. J Am Geriatr Soc. 2019;67(10):2031-7.

14. Afilalo J, Lauck S, Kim DH, Lefevre T, Piazza N, Lachapelle K, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. J Am Coll Cardiol. 2017;70(6):689-700.

15. Okamura H, Kimura N, Tanno K, Mieno M, Matsumoto H, Yamaguchi A, et al. The impact of preoperative sarcopenia, defined based on psoas muscle area, on long-term outcomes of heart valve surgery. J Thorac Cardiovasc Surg. 2018.

16. Zumsteg DM, Chu CE, Midwinter MJ. Radiographic assessment of sarcopenia in the trauma setting: a systematic review. Trauma Surg Acute Care Open. 2020;5(1):e000414.

17. Tsuchida K, Fujihara Y, Hiroki J, Hakamata T, Sakai R, Nishida K, et al. Significance of Sarcopenia Evaluation in Acute Decompensated Heart Failure. Int Heart J. 2018;59(1):143-8.

18. Uszko-Lencer NH, Bothmer F, van Pol PE, Schols AM. Measuring body composition in chronic heart failure: a comparison of methods. Eur J Heart Fail. 2006;8(2):208-14.

19. Kyle U.G. SDO, Pichard C. Underestimation of fat-free mass in women, but not men, by dual-energy x-ray absorptiometry. Ann N Y Acad Sci. 2006;904(1):126-7.

20. Fogelholm M. vMLW. Comparison of body composition methods: A literature analysis. Eur J Clin Nutr. 1997;51:495-503.

21. Bijlsma AY, Meskers CG, Ling CH, Narici M, Kurrle SE, Cameron ID, et al. Defining sarcopenia: the impact of different diagnostic criteria on the prevalence of sarcopenia in a large middle aged cohort. Age (Dordr). 2013;35(3):871-81.

22. Newman A.B. KV, Visser M., Simonsick E.M., Goodpaster B.H., Kritchevsky S.B., Tylavsky F.A., Rubin S.M., Harris T.B. on Behalf of the Health, Aging and Body Composition Study Investigators. Strength, but not muscle mass, is associated with mortality in the Health, Aging and Body Composition study cohort J Gerontol A Biol Sci Med Sci. 2006;61:72-7.

23. Gould H, Brennan SL, Kotowicz MA, Nicholson GC, Pasco JA. Total and appendicular lean mass reference ranges for Australian men and women: the Geelong osteoporosis study. Calcif Tissue Int. 2014;94(4):363-72.

24. Baumgartner R.N. KKM, Gallagher D., Romero L., Heymsfield S.B., Ross R.R., Garry P.J., Lindeman R.D. . Epidemiology of sarcopenia among the elderly in new mexico. Am J Epidemiol. 1998;147(8):755-63.

25. Iannuzzi-Sucich M. PKM, Kenny A.M. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci. 2002;57(12):772-7.

26. Tanko LB, Movsesyan L, Mouritzen U, Christiansen C, Svendsen OL. Appendicular lean tissue mass and the prevalence of sarcopenia among healthy women. Metabolism. 2002;51(1):69-74.

CHAPTER 4: TRANSITION SECTION AND PROSPECTIVE COHORT STUDY

Commentary on Sarcopenia Evaluation in Acute vs Chronic Cardiovascular Disease Settings

Acute hospitalization settings are different from outpatient clinic settings in cardiovascular disease in terms of the clinical presentation of patients as well as accessibility and appropriateness of sarcopenia assessment methods. As such it is imperative that discussion regarding sarcopenia evaluation consider the inherent constraints and context regarding these different settings, as previous review of the feasibility of assessment methods alluded to. Furthermore, the manifestation of sarcopenia may have a different impact in acute cardiac compared to chronic HF patients.

Our study with the McGill Frailty Registry on sarcopenia diagnosis in cardiac surgery patients by way of DXA-based muscle mass and physical performance-based muscle strength provides insight into the value of these assessments in acute cardiovascular care settings. DXA is highly accessible as most hospitals are equipped with it for regular body composition and bone densitometry analysis. Along with higher accessibility, DXA imparts relatively more advantages than CT, MRI such as lower radiation exposure and resources required for its use. Our study suggests DXA-based sarcopenia assessment although objective, needs to be supplemented with chair rise test to improve model prognostic ability for all-cause mortality.

The conclusions from the first manuscript do align with findings from previous studies regarding the performance of muscle mass compared to muscle strength in predicting outcomes. A review of 9 studies, including the National Health and Nutrition Examination Survey III, did not find evidence of a consistent association between low muscle mass and disability, as was found

for low muscle strength[66]. These findings are suggestive of the transition of sarcopenia definition to emphasize physical performance. Considering that patients who are referred for cardiac surgery are an already highly vulnerable population, CT or MRI may not be clinically indicated and thus would be inappropriate use of hospital resources for sarcopenia evaluation. This study therefore adds to body of research supporting the use of muscle strength measures to provide accurate sarcopenia diagnosis in acute cardiovascular patients referred for cardiac surgery.

Following initial analysis of sarcopenia among this sample of cardiac surgery candidates, it was deemed important to investigate sarcopenia in community-dwelling older adults with HF as HF is seen to be clinically correlated with sarcopenia in older adults admitted for hospitalization[67, 68]. This supports the trend in cardiovascular care in the past decade towards recognizing the frailty phenotypes in this population as evidenced by the 2017 Canadian Cardiovascular Society update for the management of HF[69]. In this update the Society recommended patients with known or suspected HF to be assessed for frailty among multimorbidity and cognitive impairment as they can affect treatment, adherence to therapy, follow-up or prognosis[69]. Sarcopenia being a core component of physical frailty, then would be necessary to evaluate in this population.

Several studies have explored what body composition changes occur in HF patients and the impact of these changes on outcomes. An early investigation of muscle wasting involving patients with both HF with reduced and preserved ejection fraction showed a sarcopenia prevalence of 19.5% and sarcopenia identified as an independent predictor of reduced exercise capacity[70]. Another prospective cohort study demonstrated that sarcopenia affects a clinically relevant portion (19.7%) of heart failure patients with preserved ejection fraction, with strong association between low appendicular muscle mass and reduced muscle strength, exercise capacity and quality of life in these patients[53]. The Health, Aging, and Body Composition study followed

nondisabled adults over a span of 6 years to compare those who developed incident HF with those who did not[71]. This integral study demonstrated loss of appendicular muscle mass remained disproportionately greater in those with HF even after adjusted for weight change, especially in men[71]. This places further emphasize on the value of incorporating body composition evaluation as part of sarcopenia protocol in HF care.

Thus, sarcopenia screening methods were included as part of the comprehensive frailty assessment conducted on participants enrolled in the FRAILTY HF study (Appendix C). Now, as previously discussed, Onoue et al. evaluated the clinical utility of a 3 component sarcopenia screening tool (age, grip strength, calf circumference) in HF patients and demonstrated that this sarcopenia score is a strong independent indicator of adverse events in HF patients[54]. Although this is a simple tool, using calf circumference for HF patients, especially those with decompensated HF can pose inaccurate muscle mass measurements due to fluid buildup. For instance, the impact of edema on calf circumference in 2101 older adults revealed edema can contribute to an approximate increase in calf circumference of 2 cm[72]. For FRAILTY HF, although we had an exclusion criteria of decompensated HF status or administration of Lasix within the past 3 months from baseline assessment, it was decided that calf circumference was not a robust enough measure.

Therefore, when determining which methods to analyze, it was decided that the screening protocol recommended by the European Working Group should be used, based on many reasons. First and foremost, this was based on the Group's evidence that initial screening for sarcopenia provides pertinent information that meets the threshold for initiating interventions for patients with a positive screen. This protocol included administration of the SARC-F questionnaire for physical functioning, chair rise test, and grip strength test. Secondly, due to the nature of HF clinics without quick access to a DXA scan and the fact that one of our centers was a community-based clinic

without access to a DXA scan, we focused our efforts on sarcopenia screening rather than complete diagnosis. With regards to the outcomes assessed, in addition to more objective clinical endpoints such as mortality, hospitalizations, and length of stay for hospitalizations, we also assessed self-reported worsening disability and quality of life. Specifically, we planned to assess both physical and mental health at follow-up. Although these measures are more subjective, they are arguably even more important endpoints from a patient-centered perspective as older HF patients may highly value their day-to-day functionality and quality of life.

Adoption of the European Working Group's protocol would allow us to investigate whether a simple and rapid sarcopenia screening protocol can be widely implemented into HF clinics. Through these discussions, the FRAILTY HF study was planned and implemented at two academic hospitals and one community-based clinic across Montreal, Quebec.

FRAILTY HF: SARCOPENIA SCREENING USING THE SARC-F QUESTIONNAIRE AND MUSCLE STRENGTH MEASURES IS PREDICTIVE OF POOR HEALTH IN COMMUNITY-DWELLING HEART FAILURE PATIENTS

This manuscript represents a multi-center prospective cohort study (FRAILTY HF) of probable sarcopenia in older adults with heart failure. The manuscript will be submitted for publication.

FRAILTY HF: Sarcopenia Screening using the SARC-F Questionnaire and Muscle Strength Measures is Predictive of Poor Health in Community-Dwelling Heart Failure Patients

Aayushi Joshi BMSc (1,2), Rita Mancini, BSc (1,2), Jeffrey Wong MD (3), Caroline Michel MD (3), Richard Sheppard MD (3) , Nadia Giannetti MD (4), Abhinav Sharma MD PhD (4), Viviane Nguyen MD MSc (5), Esther Laforest RN MSc (3), Delina Maghakian RN (3), Jonathan Afilalo, MD, MSc (1,2,3)

(1) Centre for Clinical Epidemiology, Jewish General Hospital, Montreal, QC, Canada

(2) Division of Experimental Medicine, McGill University, Montreal, QC, Canada

(3) Division of Cardiology, Jewish General Hospital, McGill University, Montreal, QC, Canada

(4) Division of Cardiology, McGill University Health Centre, McGill University, Montreal, QC, Canada

(5) Division of Cardiology, Hôpital Cité de la santé de Laval, Laval, QC, Canada

Correspondence

Jonathan Afilalo, MD, MSc, FACC, FRCPC

Associate Professor, McGill University

Director, Geriatric Cardiology Fellowship Program

Co-Chair, ACC Geriatric Cardiology Section Research Working Group

Jewish General Hospital, 3755 Cote Ste Catherine Rd, E-222, Montreal, Quebec, H3T 1E2

Phone: (514) 340-8222 | Fax: (514) 221-3785 | Email: jonathan.afilalo@mcgill.ca

Funding

Dr. Jonathan Afilalo is supported by the Canadian Institutes of Health Research (CIHR) and the Fonds de recherche en santé du Québec (FRQ-S). Aayushi Joshi is supported by the Canadian Institutes of Health Research (CIHR CGS-M). Rita Mancini is supported by the Fonds de recherche en santé du Québec (FRQ-S).

Disclosures

None

ABSTRACT

Background: The co-burden of sarcopenia and heart failure (HF) among older adults is associated with poor outcomes such as mortality and HF-related hospitalizations. It is recognized that sarcopenia definition requires measurement of both muscle mass and strength. However, the appropriate and efficient protocol for screening sarcopenia in clinical settings has not been established.

Objectives: The aim was to evaluate the prevalence of probable sarcopenia among community-dwelling older adults with HF and clarify whether probable sarcopenia defined by SARC-F questionnaire and muscle strength parameters as per European Working Group guidelines is independently predictive of all-cause mortality.

Methods: FRAILTY-HF is prospective cohort study in which patients attending one of 3 heart failure clinics (Jewish General Hospital, Royal Victoria Hospital, and Cité- de-la-Santé) were enrolled to participate and underwent a frailty assessment. Probable sarcopenia was classified as a SARC-F score (≥4) and low muscle strength by 5 chair rises >15 seconds and/or grip strength <27 kg for men and <16 kg for women. Multivariable regression was used to test the association between probable sarcopenia and all-cause mortality.

Results: The cohort consisted of 100 patients with a mean age of 77.1 ± 7.9 years and was 34% female. The prevalence of slow chair rise time and probable sarcopenia (worse SARC-F score and slow chair rise time) was 60% and 31%, respectively. Probable sarcopenia was associated with a two-fold risk of all-cause mortality or worsening disability at 3-months (OR=2.7; 95% CI 0.87 to 8.42), although non-significant. However, probable sarcopenia was predictive of poor physical (β=-0.43) and mental (β=-0.35) health status at 3-months. For adjusted models, Harrell's c-statistic

was 0.82 for worse SARC-F score and slow chair rise time. The addition of low grip strength improved model prognostic power for all-cause mortality with a Harrell's c-statistic of 0.86.

Conclusions: Positive screen for sarcopenia by SARC-F and muscle strength parameters in HF patients is strongly predictive of poor health-related quality of life at 3-months and can serve as a rapid screening method in clinical practice.

Keywords

Heart Failure, Community-Dwelling Older Adults, SARC-F Questionnaire, Sarcopenia, Chair Rise Time, Grip Strength

Abbreviations

HF – Heart Failure

PCS – SF-36 Physical Component Score

MCS – SF-36 Mental Component Score

INTRODUCTION

Sarcopenia is a condition in which muscle quality and muscle mass decline with age. As such, it remains a pertinent hallmark of the frailty phenotype[1]. Chronic heart failure (HF) is the leading cause of mortality, morbidity and hospitalizations in older adults, with an incidence rate of 1% at age 65 that doubles with each decade of age[2]. The characteristic HF symptoms are dyspnea and fatigue as well as a marked reduction in exercise tolerance attributable to advanced age and/or comorbid conditions[3].

Due to the chronic nature of HF and associated deterioration of functional status, the co-occurrence of sarcopenia is clinically relevant as it poses an enhanced vulnerability to poor health outcomes. The prevalence of sarcopenia among older individuals with HF is approximately 20%, higher than in age-matched individuals without HF[4]. Sarcopenia in HF patients has been associated with reduced exercise capacity and quality of life as well as disease severity[4, 5].

Accordingly, sarcopenia is becoming an increasingly valuable measure of prognosis and an indicator of mortality and health-related outcomes among older adults with HF. However, in the absence of accessible muscle mass imaging technologies or contraindications in HF patients with pacemakers and/or defibrillators, evaluation of muscle mass in these patients may be deemed more difficult. Furthermore, HF patients often have difficulty in laying in the supine position for DXA scans, making body composition analysis a rarity in HF care[6]. As such, International groups such as the Society on Sarcopenia, Cachexia and Wasting Disorders (SCWD), have emphasized muscle strength measures among disease-related sarcopenia studies[7].

There are several metrics by which muscle strength and physical functioning can be assessed. The SARC-F questionnaire is a self-reported measure of physical functioning and a validated rapid screening tool for probable sarcopenia[7, 8]. Other muscle strength measures to

supplement the SARC-F are time chair rise and grip strength tests. These physical performance measures remain easily assessible and have consistently proven to provide incremental prognostic value in cardiovascular patients[9-11]. Although the importance of sarcopenia evaluation has emerged, there is a lack of sarcopenia studies in HF using a combination of muscle strength measures.

The objective of this study was to determine the prevalence of probable sarcopenia among community-dwelling older adults with HF and determine whether probable sarcopenia as assessed by SARC-F questionnaire and muscle strength parameters (either chair rise time or grip strength) is predictive of all-cause mortality and quality of life.

METHODS

Study Design

FRAILTY-HF is a multicentre, longitudinal cohort study involving three institutions in Quebec, Canada (Jewish General Hospital, Royal Victoria Hospital, and Cité- de-la-Santé). The study began in April 2019 and the cohort to-date represents recruitment up to February 2020. Community-dwelling older adults who were in attendance at heart failure clinics were screened and those that consented to participate underwent a multi-domain frailty and geriatric assessment. Probable sarcopenia was determined by SARC-F score and low muscle strength by physical performance tests.

Participants

Inclusion criteria included: 1) community-dwelling older adults, 2) aged 60 years or older, 3) diagnosed with HF with preserved or reduced ejection fraction for a minimum of 3 months, and 4) signed informed consent form.

Exclusion criteria included: 1) a hospital admission within 3 months, 2) acutely decompensated HF status at the time visit, 3) intravenous diuretics or inotropes received within 3 months, 4) a moribund health status with life expectancy less than 3 months, 5) major surgical or percutaneous procedure scheduled within 3 months, 6) cardiac resynchronization therapy implantation within the past 3 months or intent to place, 7) a history of heart transplantation, current inclusion in a transplant list or a left ventricular device implantation, 8) severe neuropsychiatric impairments, and 9) non -English or French speaking.

Probable Sarcopenia Definition

Evaluation of probable sarcopenia was operationalized through administration of SARC-F questionnaire and muscle strength parameters such as chair rise test and grip strength, according to the EWGSOP 2 guidelines[10, 12]. All three evaluations were assessed as part of the comprehensive frailty assessment at baseline. The EWGSOP 2 also provide an algorithm for finding cases, making a diagnosis and quantifying the severity of sarcopenia in clinical practice.

The initial screening phase involved administration of the SARC-F questionnaire. The SARC-F questionnaire evaluated five self-reported physical components: 1) Strength – difficulty in lifting 10 lbs, 2) assistance walking – difficulty in walking across a room, 3) Transferring – difficulty in transferring from chair or bed, 4) Climbing stairs – difficulty in climbing a flight of 10 stairs, and 5) Falls – number of falls in the past year[8]. The first four components were rated

from 0 (no difficulty), 1 (some difficulty) to 2 (a lot of difficulty or unable). The falls component was rated from 0 (no falls), 1 (1 to 3 falls) to 2 (4 or more falls). A SARC-F score ≥ 4 out of a maximum of 10 was predictive of sarcopenia and poor outcomes[13].

The assessment phase involved muscle strength evaluation by chair rise test and grip strength. Low strength was defined as a chair rise time >15 seconds or an inability to complete the test, and/or a grip strength of <27 kg for men and <16 kg for women. The chair rise test was conducted by recording the time taken to stand 5 times from a seated position without the use of arms[13]. The grip strength was conducted by recording the strongest of three trials using a Jamar dynamometer. The presence of a high SARC-F score in addition to either slow chair rise time or low grip strength was indicative of probable sarcopenia.

Outcomes

The primary outcome variable is all-cause mortality, which was determined by medical records or contact with patients or their family members.

The secondary outcome variables were unplanned hospitalization at 3 months, 3-month mortality or worsening disability, and health-related quality of life at 3 months measured using the SF-36 physical and mental component scores (PCS and MCS, respectively). The SF-36 PCS encompassed physical functioning, role physical, bodily pain and general health domains. The SF-36 MCS encompassed vitality, social functioning, role emotional, and mental health domains. Incident disability was defined as institutionalization or ≥ 2 new deficits in basic and instrumental activities of daily living (ADL, IADL) captured by the Older American Resources and Services tool[14]. Worsening disability was defined as a positive change in disability score at 3 months from baseline.

Statistical Analyses

Descriptive statistics and distributional histograms were examined for variables of interest. Continuous variables were presented as sample means (± standard deviation) and compared using t-tests. Categorical variables were presented as percentages and compared using chi-squared tests. Multivariable logistic regression was used to determine the association between probable sarcopenia and all-cause mortality as well as secondary outcome variables, after adjusting for age, sex, and Charlson comorbidity index. The Kaplan-Meier method was used to generate survival curves. Cox proportional hazards model was used to determine the survival time as a function of probable sarcopenia, age, sex, and Charlson comorbidity index. Cohort entry for the adjusted Cox proportional hazards model was defined as the frailty assessment date and cohort exit was defined as a 1-year follow-up time subsequent to the assessment. REDCap electronic data capture tools were used to manage study data which was hosted at the Lady Davis Institute Centre for Clinical Epidemiology. Statistical analyses were completed using the STATA software package (version 15; College Station, TX).

RESULTS

Baseline Characteristics

The cohort consisted of 100 patients with a mean age of 77.1 ± 7.9 years and 34% females (Figure 1). Key parameters of HF include a mean left ventricular ejection fraction of 36.7 ± 15.1 and 31% of patients had a New York Heart Association (NYHA) classification of 3 of 4, indicating marked or severe limitation of physical activity leading to symptom exacerbation, respectively. The mean SARC-F score was 1.95 ± 2.1 in men and 3.74 ± 2.1 in women (Figure 2). The prevalence of slow chair rise time and probable sarcopenia (worse SARC-F score and slow chair

rise time) was 60% and 31%, respectively. When low grip strength was incorporated as a muscle strength measure, prevalence of probable sarcopenia increased to 35%.

Patients with a screen of probable sarcopenia were significantly more likely to be older, female, NYHA class 3 or 4, have a history of falls, higher comorbidity burden, worse frailty status by all frailty scales tested (Table 1).

Unadjusted Primary and Secondary Outcomes

Overall, there were 7 deaths, 3 deaths (10%) observed in the probable sarcopenic group and 4 deaths (6%) observed in the non-sarcopenic group ($p=0.45$). There were no significant differences in all-cause mortality, all-cause mortality or worsening disability, number of hospitalizations at 3-months from baseline, and overall length of stay between probable sarcopenic and non-sarcopenic groups (Table 2). The SF-36 physical component and mental component scores at 3-months were significantly lower among those screened with probable sarcopenia, indicating a worse health status, compared to those that were considered non-sarcopenic ($p<0.01$) (Table 2).

Adjusted Secondary Outcomes

Adjusted multivariable regression model indicated probable sarcopenia was associated with a greater than two-fold risk of all-cause mortality or worsening disability at 3-months, although non-significant (OR=2.7; 95% CI 0.87 to 8.42) (Table 3). After accounting for disability and NYHA class, association of sarcopenia with mortality or worsening disability was reduced (OR=1.59; 95% CI 0.44 to 5.72). Multivariable linear regression models accounting for age, sex, Charlson comorbidity index, disability, NYHA class, and SARC-F score, explained 57%

variability in the SF-36 physical component score (F(6, 74); P<0.01) and 34% variability in the SF-36 mental component score (F(6, 74); P<0.01). Probable sarcopenia could significantly predict physical health (β coefficient: -0.43) and mental health (β coefficient: -0.35) at 3-months.

Survival Analysis

Mean follow-up time was 4-months for 89 patients, with 11 patients lost to follow-up. Among those classified as non-sarcopenic, the survival rate was 93% (95% CI 0.76 to 0.98) and those screened with probable sarcopenia had a survival rate of 91% (95% CI 0.52 to 0.98) (Log-rank P=0.49) (Figure 3). The Cox models were adjusted for age, sex, and Charlson comorbidity index. Probable sarcopenia was associated with an adjusted hazard ratio of 0.45 (95% CI 0.06 to 3.33) for all-cause mortality (Table 4). Worse SARC-F score was associated with an adjusted hazard ratio of 1.06 (95% CI 0.16 to 7.01) for all-cause mortality. Slow chair rise time alone was associated with an adjusted hazard ratio of 1.04 (95% CI 0.99 to 1.08) for all-cause mortality. The Harrell's c-statistic was 0.80 and 0.82 for adjusted models with worse SARC-F score and slow chair rise time alone, and both, respectively.

Sensitivity Analysis

Probable sarcopenia was also defined as a worse SARC-F score and either slow chair rise time or low grip strength. When using this definition, the prevalence of probable sarcopenia was 35% and it was associated with an adjusted hazard ratio of 1.06 (95% CI 0.16 to 7.05) for all-cause mortality. The inclusion of grip strength as a muscle strength parameter in the adjusted model resulted in a Harrel's c-statistic of 0.86.

Comparison of SARC-F to Gold Standard Physical Performance Tests

The self-reported SARC-F score with a cut-off of ≥ 4 has a sensitivity of 64.2% and specificity of 95.7% of predicting poor physical performance by short physical performance battery (SPPB). The SARC-F score has a ROC area of 0.85 (95% CI 0.78 to 0.92) (Figure 4).

DISCUSSION

This study aimed to determine the prevalence of probable sarcopenia among community-dwelling older adults with HF and determine whether probable sarcopenia as assessed by SARC-F and muscle strength (either chair rise time or grip strength) is predictive of all-cause mortality. The findings indicate that approximately one in three patients had a positive screen for sarcopenia. Probable sarcopenia (worse SARC-F score and slow chair rise time) was associated with a two-fold risk of all-cause mortality or worsening disability at 3-months, although results were non-significant. Furthermore, probable sarcopenia was predictive of poor self-reported health status, both physically and mentally at 3-months. The addition of low grip strength as an indicator of poor muscle strength improves model prognostic power for all-cause mortality.

Validity of SARC-F Questionnaire for Sarcopenia Screening

Although muscle mass was not measured, it has been recommended that in clinical practice, a screening of probable sarcopenia meets the threshold for evaluation of causes and introduction of interventions[10, 12]. The SARC-F questionnaire, a key aspect of the EWGSOP 2 screening protocol, has been established for its validity as it serves as a simple and inexpensive sarcopenia screening tool beneficial in clinical practice[7, 15]. The SARC-F score has been identified

as a significant predictor of adverse events after discharge and useful predictor of high risk physical limitations among older adults[16]. A meta-analysis of studies involving a total of 12,800 participants demonstrated that although sensitivity for the SARC-F was low, its specificity was high, thereby concluding that the value of SARC-F is in its ability to quickly screen patients for sarcopenia[17].

This study's findings demonstrate that among older, stable HF patients, the SARC-F has a low sensitivity and high specificity for physical limitations, thus aligning with previous findings. This results in the SARC-F score correctly classifying 79% of HF patients with physical limitations compared to the standard SPPB. Therefore, the SARC-F score is consistently seen as a valid measure screening tool for sarcopenia.

Muscle Strength as a Predictor of Poor Outcomes Among Cardiovascular Patients

Lower extremity strength as measured by chair rise time is a highly validated physical performance measure[18]. The essential frailty toolset, of which a core component is lower extremity muscle strength, has been identified as the strongest predictor of mortality and worsening disability at 1-year in patients undergoing aortic vale replacement[9]. Many studies report slow chair rise time as a strong predictor of mortality and poor recovery among patients with cardiovascular disease[19, 20]. Additionally, grip strength evaluation has been incorporated into frailty assessment of older adults as it has been deemed an important discriminator of slowness[21]. Low grip strength has been identified to independently predict falls, self-reported mobility limitations and mortality in community-dwelling older adults[21]. Among hospitalized older adults with significant coronary artery disease, poor grip strength (≤25 kg) was a strong predictor of 6-month mortality[20].

Specifically, in those with HF, physically frail patients (i.e.; with more physical limitations) show a higher risk of mortality at 1-year, HF-related hospitalizations, and impaired quality of life[22].

In another cohort of HF patients, low grip strength capability conferred a 16% increase in predictive risk of hospitalizations due to HF symptom exacerbation[23]. These findings suggest that the inclusion of grip strength to SARC-F and chair rise test has incremental prognostic power in sarcopenia screening, which is consistent with the reported findings in this study.

Difficulty of Muscle Mass Assessment in Heart Failure Patients

The HF patients in this study had no clinical indication for undergoing radiographic imaging (e.g.; Dual X-ray absorptiometry, bioimpedance, computed tomography, magnetic resonance imaging) solely for the purpose of muscle mass evaluation. Therefore, self-reported physical functioning and muscle strength measures on their own were deemed appropriate for sarcopenia screening. Although unstable HF patients were excluded in this study, there remains a possibility for hydration abnormalities to affect the measurement of muscle mass by technologies such as dual X-ray absorptiometry. This can be due to clinical feature of fluid overload or congestion in HF patients not always being evident through clinical examination[24]. As such, sarcopenia diagnosis would require optimal monitoring of the HF status of patients to ensure decompensation has not occurred prior to muscle mass evaluation.

Limitations

The mean follow-up time for the cohort studied was 4 months, which is a short follow-up time in terms of determining clinically important adverse outcomes such as hospitalizations and all-cause mortality. Furthermore, 11 patients were deemed lost to follow-up, 5 of which were considered positive for sarcopenia screening. This resulted in loss of valuable data on the outcomes for potentially sarcopenic patients.

Future Directions

In order to validate the complete EWGSOP 2 algorithm for sarcopenia diagnosis, future research should incorporate muscle mass measurement and disease severity testing through additional physical performance tests such as gait speed and SPPB. Additional research regarding primary and secondary outcomes should be done with a longer follow-up time of 1 year and longer to assess for long-term outcomes.

CONCLUSIONS

As a simple questionnaire with high specificity, SARC-F is deemed a rapid method for preliminary screening of sarcopenia that can then be supplemented with muscle strength and mass evaluations to confirm the diagnosis. Rapid assessment of sarcopenia serves a particularly important role as evidence shows that early intervention can improve outcomes. This method of sarcopenia screening in HF patients demonstrates utility in predicting short-term health-related quality of life, that serves as an indicator of future worsening of outcomes in the long-term.

CLINICAL PERSPECTIVES

The evaluation of sarcopenia can involve multiple self-reported questionnaires, physical performance tests, and imaging technologies for muscle mass measurement. The abundance of different methods may serve as an obstacle for the implementation of sarcopenia assessment in HF clinical care as it poses time and resource constraints. The SARC-F questionnaire, being a relatively rapid and simple screening tool for sarcopenia, addresses this problem as it can be easily administered in community healthcare or other clinical settings. Muscle strength measures such as chair rise time and grip strength are not only quick tests, but they are also highly predictive of

adverse outcomes, and thus also provide high value as components of sarcopenia screening. As such, this study demonstrated the feasibility of the EWGSOP 2 algorithm in assessment of community-dwelling older adults with HF. Given the high prevalence of probable sarcopenia among this population, timely determination of probable sarcopenia status in HF patients may serve as important evaluation to prompt early interventions.

FIGURE LEGENDS

Figure 1: Study Flow Diagram

Overall, 104 patients were recruited to participate across the 3 hospital sites. Two were excluded from analysis due to incomplete baseline assessments and another two developed cognitive impairments after baseline assessment and were thus excluded from future follow-up, resulting in a study cohort of 100 patients.

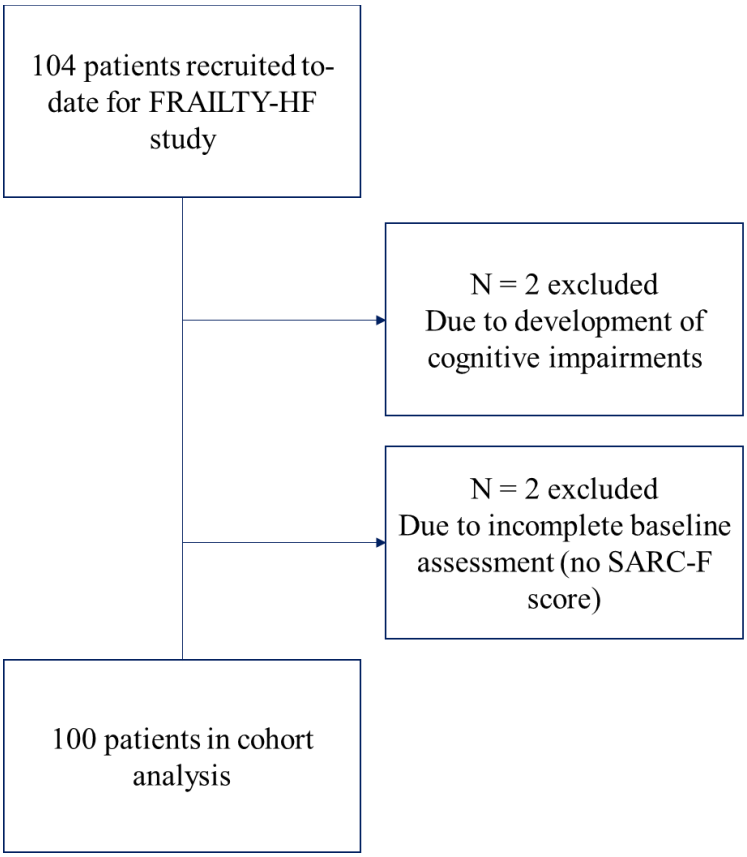
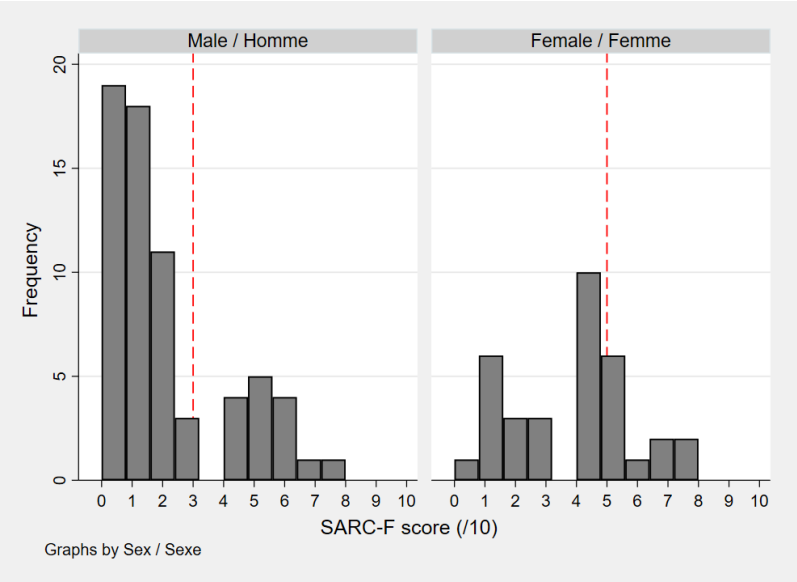


Figure 2: Distribution of SARC-F Scores

Distribution of SARC-F score in men and women with highest quartile values [red dashed lines; 3 for men, 5 for women]. A SARC-F score of ≥4 out of a maximum of 10 indicates positive sarcopenia screening.



Boxplot of SARC-F scores by those who had mortality or worsening disability at follow-up compared to those who did not. Median SARC-F score is higher for those who had an event.

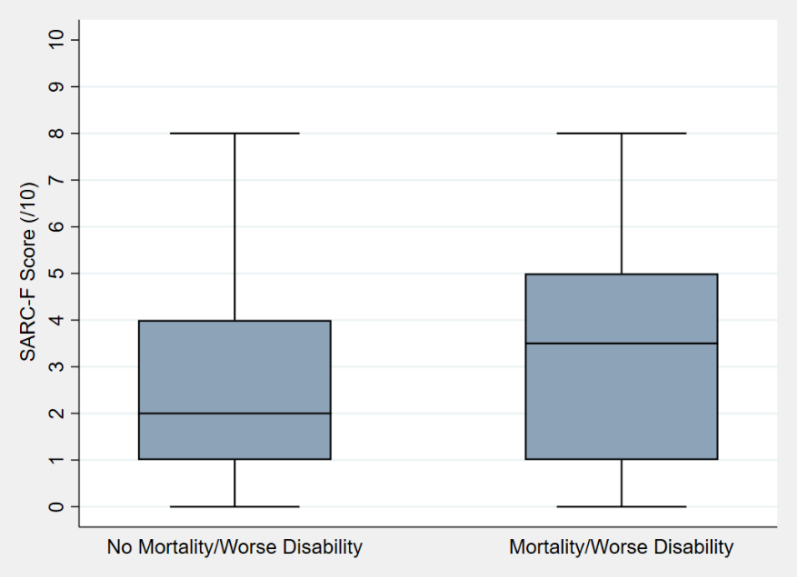


Figure 3: Kaplan-Meier Survival Curve by Probable Sarcopenia Status

Kaplan-Meier survival estimates for community-dwelling older adults with heart failure with probable sarcopenia [dashed line] and no sarcopenia [solid line]. Follow-up time of an average of 4 months from baseline assessment.

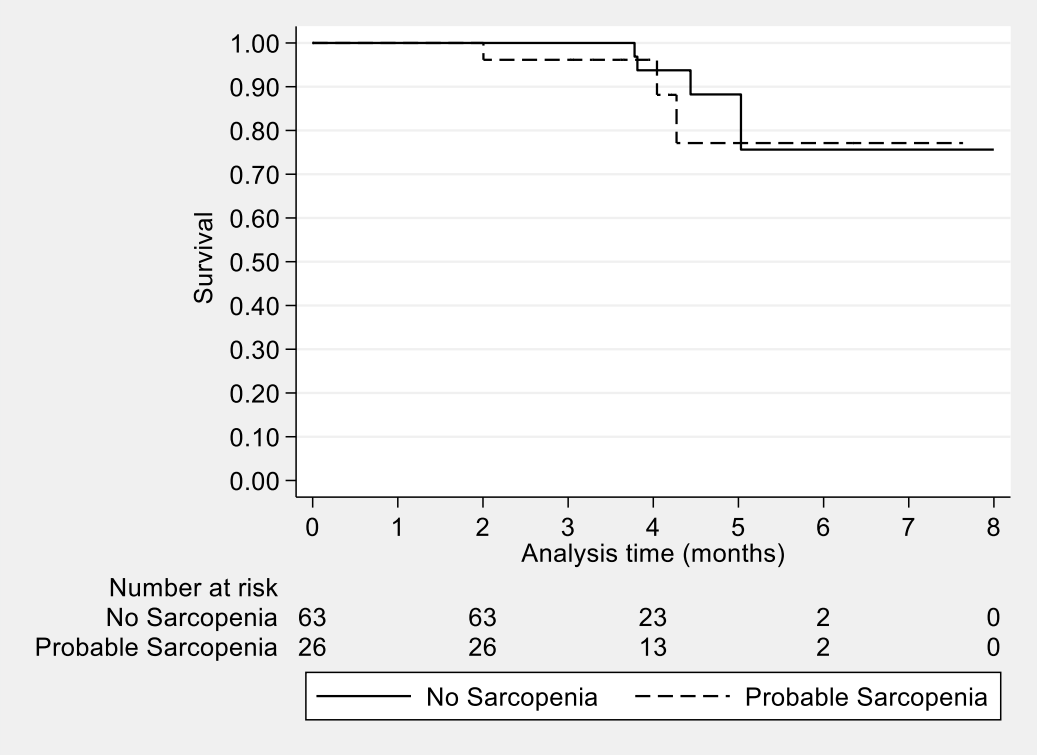


Figure 4: ROC curve for SARC-F to Predict Physical Performance

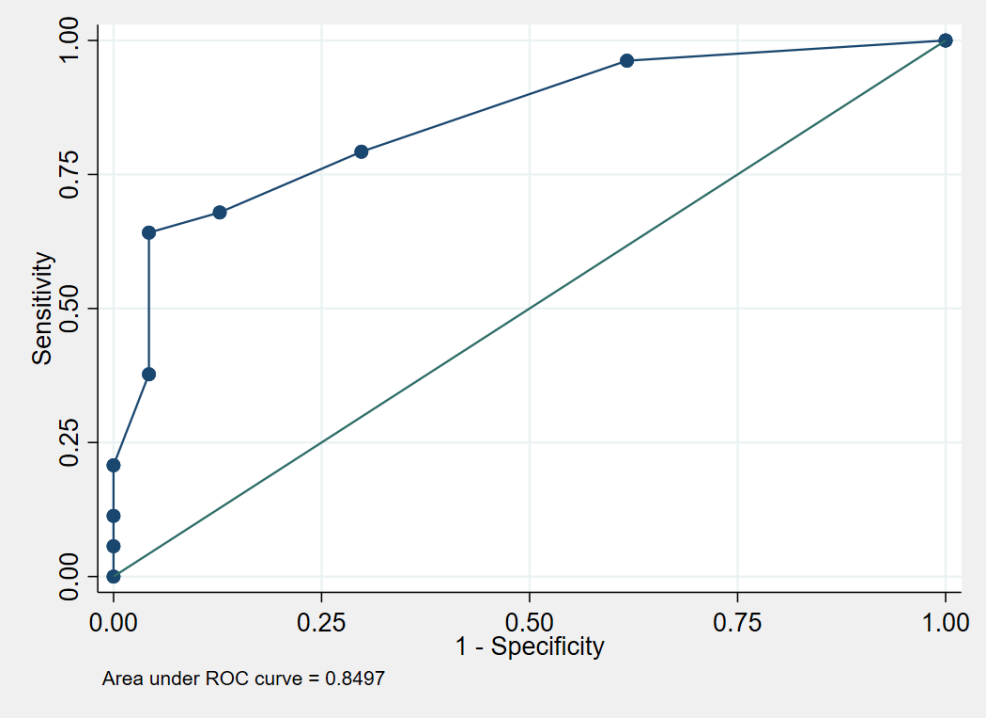


Table 1: Baseline Characteristics by Probable Sarcopenia Status

	All Patients (N=100)	**No Sarcopenia (N=69)**	**Probable Sarcopenia (N=31)**	**P-Value**
Demographics				
Age (years)	77.1 ± 7.9	75.2 ± 7.6	81.2 ± 7.2	<0.01*
Female	34 (34%)	15 (22%)	19 (61%)	<0.01*
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.03*
Weight (kg)	80.1 ± 18.2	79.8 ± 14.9	80.8 ± 24.3	0.40
BMI (kg/m^2)	28.2 ± 6.4	27.7 ± 4.8	29.5 ± 8.8	0.09
Underweight BMI < 18.5	2 (2%)	0 (0%)	2 (6%)	0.03*
Obese BMI ≥30	32 (32%)	18 (26%)	14 (45%)	0.06
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.3	0.32
LVEF (%)**	36.7 ± 15.1	34.6 ± 13.4	41.2 ± 17.8	0.02*
HFpEF**	39 (39%)	24 (35%)	15 (48%)	0.22
NYHA classification	2.1 ± 0.7	1.9 ± 0.6	2.6 ± 0.5	<0.01*
Comorbidities				
Hypertension	78 (78%)	54 (78%)	24 (77%)	0.96
Dislipidemia	62 (62%)	43 (62%)	19 (61%)	0.92
Myocardial Infarction	40 (40%)	31 (45%)	9 (29%)	0.13
Coronary artery disease	51 (51%)	40 (58%)	11 (35%)	0.04*
Peripheral arterial disease	7 (7%)	4 (6%)	3 (10%)	0.48
COPD	16 (16%)	6 (9%)	10 (32%)	<0.01*
Cerebrovascular accident	10 (10%)	9 (13%)	1 (3%)	0.13

	All Patients (N=100)	No Sarcopenia (N=69)	Probable Sarcopenia (N=31)	P-Value
Diabetes	41 (41%)	23 (33%)	18 (58%)	0.02*
Chronic renal failure	30 (30%)	18 (26%)	12 (39%)	0.20
Falls	0.4 ± 0.6	0.3 ± 0.5	0.6 ± 0.7	0.03*
Arthritis	26 (26%)	10 (14%)	16 (52%)	<0.01*
Osteoporosis	7 (7%)	6 (9%)	1 (3%)	0.32
Charlson comorbidity index	6.1 ± 1.9	5.8 ± 1.8	6.9 ± 1.9	<0.01*
Prior Procedures/Hospitalizations				
Priory surgery number	0.4 ± 0.6	0.5 ± 0.6	0.3 ± 0.5	0.07
Prior PCI**	28 (28%)	22 (32%)	6 (19%)	0.18
Prior hospitalization in past year	48 (48%)	28 (41%)	20 (65%)	0.03*
Geriatric/Frailty Domains				
Clinical frailty scale (/9)	3.5 ± 1.4	2.9 ± 1	4.8 ± 1.2	<0.01*
Fried Frailty Scale	1.7 ± 1.3	1.2 ± 1	2.8 ± 1.1	<0.01*
SPPB score (/12)	7.6 ± 3.3	9 ± 2.4	4.5 ± 2.6	<0.01*
6MWT distance (m)	247.5 ± 157	311.6 ± 131.3	104.8 ± 108.5	<0.01*
Gait speed (m/s)	0.8 ± 0.4	1 ± 0.3	0.5 ± 0.3	<0.01*
Max grip strength (kg)	23.9 ± 10.4	27 ± 9.3	16.8 ± 9.3	<0.01*
Chair time (max 60 s)	27.5 ± 20.2	19.2 ± 14.4	46.2 ± 19.1	<0.01*
Chair rise time (>15 s)	60 (60%)	29 (42%)	31 (100%)	<0.01*
EFT score (/5)	1.7 ± 1.3	1.2 ± 1.1	2.7 ± 0.9	<0.01*
Disability score (/14)	12.4 ± 2.2	13.2 ± 1.5	10.6 ± 2.4	<0.01*

	All Patients (N=100)	No Sarcopenia (N=69)	Probable Sarcopenia (N=31)	P-Value
Mini-Cog score	3.3 ± 1.6	3.7 ± 1.5	2.5 ± 1.5	<0.01*
Screen II nutritional scale	44.9 ± 7.9	46.7 ± 6.9	41 ± 8.7	<0.01*

*Significant P-value (<0.05)

**LVEF for N=99; HFpEF N=99; Prior PCI N=99;

Abbreviations: BMI, Body Mass Index; LVEF, Left Ventricular Ejection Fraction; Heart Failure with Preserved Ejection Fraction; NYHA, New York Heart Association; COPD, Chronic Obstructive Pulmonary Disease; PCI, Percutaneous Coronary Intervention; SPPB, Short Physical Performance Battery; 6MWT, 6-Minute Walk Test; EFT, Essential Frailty Toolset

Table 2: Unadjusted Outcomes by Probable Sarcopenia Status

	All Patients (N=100)	No Sarcopenia (N=69)	Probable Sarcopenia (N=31)	P-Value
All-Cause Mortality**	7 (7%)	4 (6%)	3 (10%)	0.45
All-Cause Mortality or Worsened Disability**	30 (35%)	17 (28%)	13 (50%)	0.05
Number of Hospitalizations since Baseline**	0.2 ± 0.5	0.2 ± 0.6	0.2 ± 0.5	0.96
Overall LOS	1.6 ± 4.9	1.3 ± 4.2	2.2 ± 6.3	0.20
3-Month Physical Component Score**	55.4 ± 23	62.6 ± 21.4	38.3 ± 17.1	<0.01*
3-Month Mental Component Score**	74.5 ± 17.9	79.2 ± 14.8	63.4 ± 20	<0.01*

*Significant P-value (<0.05)

**All-cause mortality N=99; 3-Month mortality/worsened disability N=86; Number of hospitalizations since baseline N=98; 3-Month Physical Component Score N=81; 3-Month Mental Component Score N=81;

Lower SF-36 physical and mental component score indicates lower health status

Table 3: Adjusted Outcomes by Probable Sarcopenia Status

	Probable Sarcopenia (N=31)	**P-Value**
All-Cause Mortality**	OR 0.63 (0.09, 4.29)	0.63
3-Month Mortality or Worsened Disability**	OR 2.7 (0.87, 8.42)	0.08
Number of Hospitalizations since Baseline**	$F(4,93) = 2.53$, $p = 0.05$, $R^2=0.098$	0.70
Overall LOS	$F(4, 95) = 0.84$, $p = 0.50$, $R^2=0.034$	0.69
3-Month Physical Component Score**	$F(4, 76) = 10.07$, $p<0.01$, $R^2=0.346$	<0.01*
3-Month Mental Component Score**	$F(4, 76) = 5.40$, $p<0.01$, $R^2=0.221$	0.02*

*Significant P-value (<0.05)

**3-Month Physical Component Score N=24; 3-Month Mental Component Score N=24;

Table 4: Survival Analysis

Variable	Hazard Ratio	95% Confidence Interval
Age	1.12	0.99 – 1.26
Female Sex	3.23	0.39 – 26.79
Charlson comorbidity index	1.37	0.77 – 2.45
SARC-F score (≥4)	2.51	0.26 – 24.70
Chair rise time (>15s)	0.08	0.007 – 0.921

N=89; 11 patients did not complete 3-month questionnaire (loss to follow-up)

REFERENCES

1. Fried LP TC, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McGurnie MA for the Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-M56.

2. Mozaffarian D, Benjamin E.J., Go, A.S., Arnett D.K., Blaha M.J., Cushman M., de Ferranti S., Despres J.P., Fullerton H.J., Howard V.J., et al. Heart disease and stroke statistics—2015 update. Circulation. 2015;131(4):e29-e322.

3. Butrous H, Hummel SL. Heart Failure in Older Adults. Can J Cardiol. 2016;32(9):1140-7.

4. Fulster S, Tacke M, Sandek A, Ebner N, Tschope C, Doehner W, et al. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). Eur Heart J. 2013;34(7):512-9.

5. Bekfani T, Pellicori P, Morris DA, Ebner N, Valentova M, Steinbeck L, et al. Sarcopenia in patients with heart failure with preserved ejection fraction: Impact on muscle strength, exercise capacity and quality of life. Int J Cardiol. 2016;222:41-6.

6. Forman DE, Santanasto AJ, Boudreau R, Harris T, Kanaya AM, Satterfield S, et al. Impact of Incident Heart Failure on Body Composition Over Time in the Health, Aging, and Body Composition Study Population. Circ Heart Fail. 2017;10(9).

7. Bauer J, Morley JE, Schols A, Ferrucci L, Cruz-Jentoft AJ, Dent E, et al. Sarcopenia: A Time for Action. An SCWD Position Paper. J Cachexia Sarcopenia Muscle. 2019;10(5):956-61.

8. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle. 2016;7(1):28-36.

9. Afilalo J, Lauck S, Kim DH, Lefevre T, Piazza N, Lachapelle K, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. J Am Coll Cardiol. 2017;70(6):689-700.

10. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(4):601.

11. Zuckerman J, Ades M, Mullie L, Trnkus A, Morin JF, Langlois Y, et al. Psoas Muscle Area and Length of Stay in Older Adults Undergoing Cardiac Operations. Ann Thorac Surg. 2017;103(5):1498-504.

12. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.

13. Guralnik JM SE, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol A Biol Sci Med Sci. 1994;49(2):M85-M94.

14. Fillenbaum GG SM. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. J Gerontol. 1981;36(4):428-34.

15. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013;14(8):531-2.

16. Tanaka S. KK, Hamazaki N., Matsuzawa R., Nozaki K., Ichinosawa Y., Harada M., Nakamura T., Maekawa E., Noda C., Yamaoka-Tojo M., Matsunaga A., Masuda T., Ako J. SARC-F questionnaire identifies physical limiations and predictors post discharge outcomes in elderly patients with cardiovascular disease. J Cachexia Sarcopenia Muscle. 2018;3(1):1-10.

17. Ida S, Kaneko R, Murata K. SARC-F for Screening of Sarcopenia Among Older Adults: A Meta-analysis of Screening Test Accuracy. J Am Med Dir Assoc. 2018;19(8):685-9.

18. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol. 2014;63(8):747-62.

19. Hosler QP, Maltagliati AJ, Shi SM, Afilalo J, Popma JJ, Khabbaz KR, et al. A Practical Two-Stage Frailty Assessment for Older Adults Undergoing Aortic Valve Replacement. J Am Geriatr Soc. 2019;67(10):2031-7.

20. Purser JL, Kuchibhatla MN, Fillenbaum GG, Harding T, Peterson ED, Alexander KP. Identifying frailty in hospitalized older adults with significant coronary artery disease. J Am Geriatr Soc. 2006;54(11):1674-81.

21. Bhasin S, Travison TG, Manini TM, Patel S, Pencina KM, Fielding RA, et al. Sarcopenia Definition: The Position Statements of the Sarcopenia Definition and Outcomes Consortium. J Am Geriatr Soc. 2020.

22. Lupón J. GB, Santaeugenia S., Altimir S., Urrutia A., Más D., Díez C., Pascual T., Cano L., Valle V. Prognostic implications of frailty and depressive symptoms in an outpatient population with heart failure. Rev Esp Cardiol. 2008;61(8):835-42.

23. Chaudhry SI, McAvay G, Chen S, Whitson H, Newman AB, Krumholz HM, et al. Risk factors for hospital admission among older persons with newly diagnosed heart failure: findings from the Cardiovascular Health Study. J Am Coll Cardiol. 2013;61(6):635-42.

24. Pellicori P, Kaur K, Clark AL. Fluid management in patients with chronic heart failure. Card Fail Rev. 2015;1(2):90-5.

CHAPTER 5: THESIS CONCLUSION

An exploration of sarcopenia prevalence and impact on older adults with cardiovascular disease was conducted in this thesis. Sarcopenia remains highly relevant to study among older adults with coronary artery disease and/or valve damage requiring cardiac surgery as well as those with chronic HF due to added risk of mortality and worsening disability. Given the high prevalence of sarcopenia in cardiovascular patients, it is pertinent that sarcopenia assessment is incorporated into clinical care.

The literature review on sarcopenia outlined the current knowledge available in the field with regards to condition progression and scope of research conduced in cardiovascular disease populations. Prevalence of sarcopenia ranges from 21-62% in acute cardiac surgery patients prior to surgery and from 20-69% among community-dwelling heart failure patients. In comparison, prevalence of sarcopenia in hospitalized older adults is approximately 10% and in community-dwelling older adults it ranges from 1-29%, further emphasizing the added vulnerability of older adults with cardiovascular disease who also present with reduced muscle mass and strength. Although, broad comparisons are difficult to make due to different classifications and methods used to evaluate sarcopenia. Furthermore, the review of the landscape of assessment methods available ultimately suggests that it may be appropriate for sarcopenia assessment protocols to differ based on whether care setting is acute compared to outpatient.

The prognostic value of sarcopenia in those with cardiovascular disease was based on a limited number of studies. Overall, most studies showed sarcopenia was a significant risk factor for all-cause mortality at 1-year and more long-term 5-year follow up period for patients undergoing cardiac surgery and patients with heart failure. Some also demonstrated sarcopenic

heart failure patients with significantly reduced physical functioning. Among cardiac surgery patients, sarcopenic significantly contributed to increased major adverse cardiac or cerebrovascular events and greater length of stay post-procedure. However, some studies also reported opposing findings; that sarcopenia was only a slightly significant risk for heart failure-related hospitalization or mortality or that it was not associated with mortality in cardiac surgery patients.

According to the findings from the first manuscript, at least one in seven patients had evidence of sarcopenia (measured by DXA-based muscle mass and chair rise test), which was associated with indicators of frailty. The 4-year survival rate between sarcopenic and non-sarcopenic patients differed significantly from 56% and 79%, respectively. Sarcopenic patients had a two-fold increase in post-procedural mortality at a mean of 4 years, although the statistical significance of this result was borderline. Therefore, it was concluded that lower-extremity muscle strength and DXA-based measures of muscle mass, is strongly predictive of adverse outcomes in hospitalized older adults referred for cardiac surgery.

The findings from the second manuscript demonstrated that approximately one in three older adults with heart failure had a positive screen for sarcopenia. Although probable sarcopenia was non-significantly associated with a two-fold risk of all-cause mortality or worsening disability at 3-months, it was significant risk factor for poor quality of life at 3-months. The model's prognostic power for all-cause morality was improved by the addition of grip strength as an indicator of poor muscle. Therefore, it was concluded that a positive screen for sarcopenia by SARC-F and muscle strength parameters in heart failure patients is strongly predictive of poor health-related quality of life at 3-months and can serve as a rapid screening method in clinical practice.

Discussion of these studies must also be followed by consideration of the associated limitations from an epidemiological perspective. One such limitation being that a relatively small sample size (141 patients from the McGill Frailty Registry and 100 patients from FRAILTY HF study) reduces the power and external validity of the study by decreasing generalizability of results. However, for the FRAILTY HF study this was taken into consideration by making it a multi-center prospective cohort study capturing heart failure patients from academic hospital clinics and a community-base clinic. As a counterbalance, lower sample size and multi-center nature of the study increased its internal validity by reducing confounding.

As research intersecting the fields of sarcopenia and cardiovascular disease continues to develop in the upcoming decade, there are several take homes messages this thesis provides that can contribute to said research approaches. Sarcopenia is highly prevalent in cardiovascular disease patients. Sarcopenia measured by muscle mass and physical performance tests provides valuable prognostic information, however, the best method for muscle mass measurement needs to be further clarified. DXA-based muscle mass is a promising predictor of adverse events, however measurement in cardiovascular patients it may pose several challenges. DXA may be the optimal method of measuring muscle mass in cardiovascular patients, however optimal age and sex-associated thresholds need to be consolidated. Chair rise test and grip strength on the other hand have been shown to be strong predictors of adverse outcomes, further supporting previous literature. Screening for sarcopenia by SARC-F questionnaire and muscle strength parameters although not predictive of conventional endpoints such as mortality in the short-term follow up, are predictive of worsening health status and thus may be sufficient for initiation of interventions.

Furthermore, research progression in this topic should consider the value in measuring disability and quality of life outcomes in older adults as functionality and their perception of health

are important factors to their care. These patient-centered endpoints should be measured in addition to the conventional endpoints such as mortality and hospitalizations in future sarcopenia research. Ultimately, more studies focused on validation and integration of pertinent risk factors must be conducted to provide evidence-based information for incorporation of sarcopenia screening, diagnosis, and related-interventions into routine clinical cardiovascular practice.

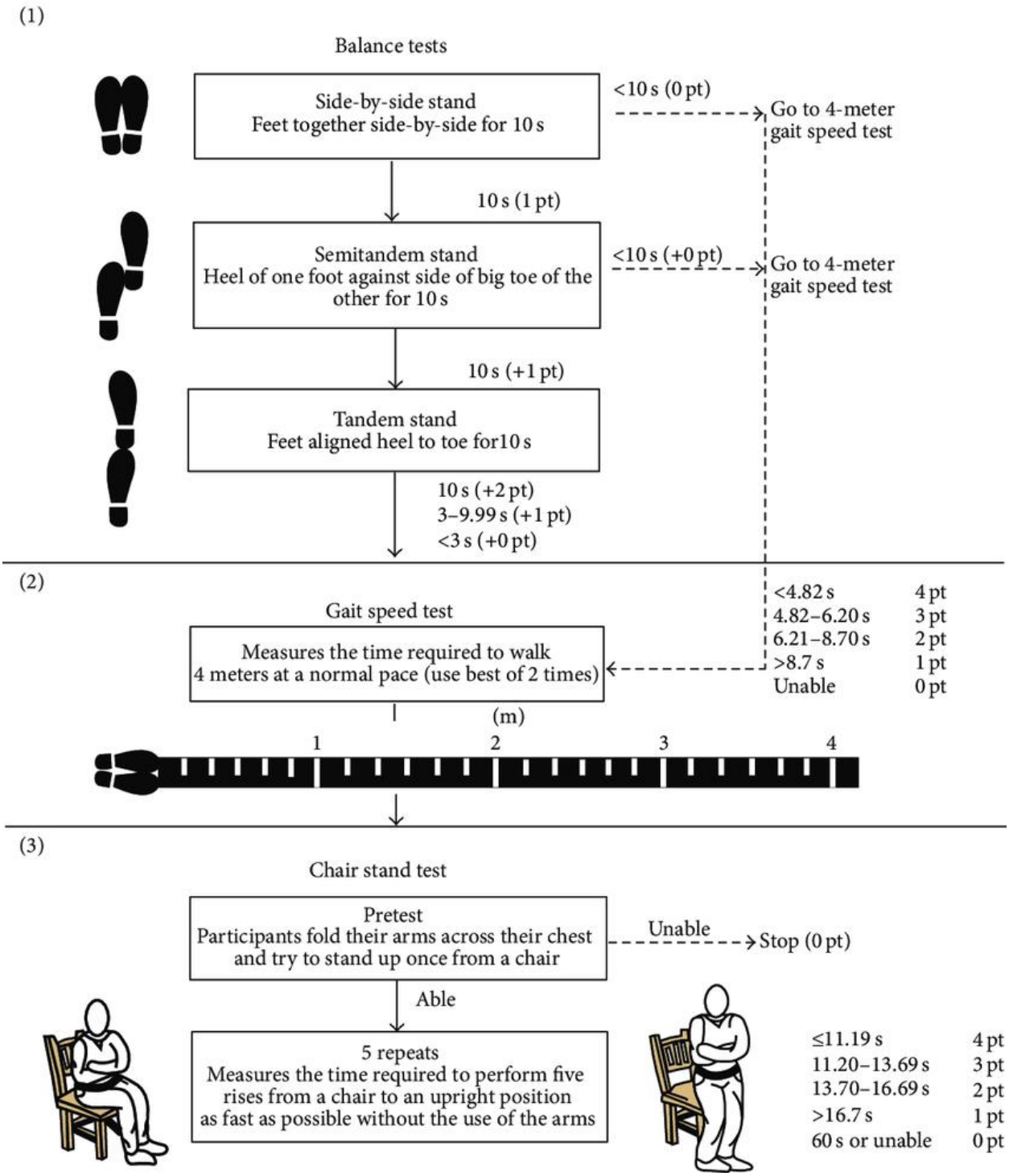
APPENDICES

Appendix A: SARC-F Questionnaire[19]

SARC-F Screen for Sarcopenia

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1−3 falls = 1 4 or more falls = 2

Appendix B: Short Physical Performance Battery[73]



Appendix C: Comprehensive Frailty Assessment Protocol in the FRAILTY HF Study

	Baseline Visit	3-Month Phone Call	12-Month Phone Call
SARC-F	✓		
International physical activity questionnaire	✓	✓	✓
OARS disability questionnaire	✓	✓	✓
SCREEN II nutrition assessment	✓	✓	✓
Mini-Cog (cognition)	✓		
Whisper test (hearing)	✓		
Snellen test (vision)	✓		
Self-care of heart failure index	✓		
SF-36 quality of life questionnaire	✓	✓	✓
SPPB	✓		
6-minute walk test	✓		
Grip strength	✓		
Blood test	✓		
Medical chart review	✓	✓	✓

REFERENCES (Chapters 1, 2, 4 - Commentary, 5)

1. Fried LP TC, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McGurnie MA for the Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-M56.

2. Baumgartner R.N. KKM, Gallagher D., Romero L., Heymsfield S.B., Ross R.R., Garry P.J., Lindeman R.D. . Epidemiology of sarcopenia among the elderly in new mexico. Am J Epidemiol. 1998;147(8):755-63.

3. Bauer J, Morley JE, Schols A, Ferrucci L, Cruz-Jentoft AJ, Dent E, et al. Sarcopenia: A Time for Action. An SCWD Position Paper. J Cachexia Sarcopenia Muscle. 2019;10(5):956-61.

4. Bhasin S, Travison TG, Manini TM, Patel S, Pencina KM, Fielding RA, et al. Sarcopenia Definition: The Position Statements of the Sarcopenia Definition and Outcomes Consortium. J Am Geriatr Soc. 2020.

5. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.

6. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc. 2020;21(3):300-7 e2.

7. Clark B.C. MTM. Sarcopenia ≠ Dynapenia. J Gerontol A Biol Sci Med Sci. 2008;63A(8):829-34.

8. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. J Lab Clin Med. 2001;137(4):231-43.

9. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, et al. Sarcopenia: an overview. Aging Clin Exp Res. 2017;29(1):11-7.

10. Dodds RM, Roberts HC, Cooper C, Sayer AA. The Epidemiology of Sarcopenia. J Clin Densitom. 2015;18(4):461-6.

11. Glass DJ. Signaling pathways perturbing muscle mass. Curr Opin Clin Nutr Metab Care. 2010;13(3):225-9.

12. Dos Santos MR, Saitoh M, Ebner N, Valentova M, Konishi M, Ishida J, et al. Sarcopenia and Endothelial Function in Patients With Chronic Heart Failure: Results From the Studies Investigating Comorbidities Aggravating Heart Failure (SICA-HF). J Am Med Dir Assoc. 2017;18(3):240-5.

13. Kinugasa Y, Yamamoto K. The challenge of frailty and sarcopenia in heart failure with preserved ejection fraction. Heart. 2017;103(3):184-9.

14. Biolo G, Cederholm T, Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. Clin Nutr. 2014;33(5):737-48.

15. Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2013;10(4):401-10.

16. Grimby G. SB. The ageing muscle. Clin Physiol. 1983;3:209-18.

17. Cooper R, Kuh D, Hardy R, Mortality Review G, Falcon, Teams HAS. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. BMJ. 2010;341:c4467.

18. Cruz-Jentoft AJ, Landi F, Schneider SM, Zuniga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing. 2014;43(6):748-59.

19. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013;14(8):531-2.

20. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. J Cachexia Sarcopenia Muscle. 2016;7(1):28-36.

21. Ida S, Kaneko R, Murata K. SARC-F for Screening of Sarcopenia Among Older Adults: A Meta-analysis of Screening Test Accuracy. J Am Med Dir Assoc. 2018;19(8):685-9.

22. Tanaka S. KK, Hamazaki N., Matsuzawa R., Nozaki K., Ichinosawa Y., Harada M., Nakamura T., Maekawa E., Noda C., Yamaoka-Tojo M., Matsunaga A., Masuda T., Ako J. SARC-F questionnaire identifies physical limiations and predictors post discharge outcomes in elderly patients with cardiovascular disease. J Cachexia Sarcopenia Muscle. 2018;3(1):1-10.

23. Woo J, Leung J, Morley JE. Validating the SARC-F: a suitable community screening tool for sarcopenia? J Am Med Dir Assoc. 2014;15(9):630-4.

24. Rantanen T. GJM, Foley D., Masaki K., Leveille S., Curb D., White L., . Midlife hand grip strength as a predictor of old age disability. JAMA. 1999;281(6):558-60.

25. Taekema DG, Gussekloo J, Maier AB, Westendorp RG, de Craen AJ. Handgrip strength as a predictor of functional, psychological and social health. A prospective population-based study among the oldest old. Age Ageing. 2010;39(3):331-7.

26. Roberts HC, Syddall HE, Cooper C, Aihie Sayer A. Is grip strength associated with length of stay in hospitalised older patients admitted for rehabilitation? Findings from the Southampton grip strength study. Age Ageing. 2012;41(5):641-6.

27. Reeve TEt, Ur R, Craven TE, Kaan JH, Goldman MP, Edwards MS, et al. Grip strength measurement for frailty assessment in patients with vascular disease and associations with comorbidity, cardiac risk, and sarcopenia. J Vasc Surg. 2018;67(5):1512-20.

28. Afilalo J, Lauck S, Kim DH, Lefevre T, Piazza N, Lachapelle K, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. J Am Coll Cardiol. 2017;70(6):689-700.

29. Hosler QP, Maltagliati AJ, Shi SM, Afilalo J, Popma JJ, Khabbaz KR, et al. A Practical Two-Stage Frailty Assessment for Older Adults Undergoing Aortic Valve Replacement. J Am Geriatr Soc. 2019;67(10):2031-7.

30. Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. J Cachexia Sarcopenia Muscle. 2018;9(2):269-78.

31. Guglielmi G, Ponti F, Agostini M, Amadori M, Battista G, Bazzocchi A. The role of DXA in sarcopenia. Aging Clin Exp Res. 2016;28(6):1047-60.

32. Tosato M, Marzetti E, Cesari M, Savera G, Miller RR, Bernabei R, et al. Measurement of muscle mass in sarcopenia: from imaging to biochemical markers. Aging Clin Exp Res. 2017;29(1):19-27.

33. Morgan SL, Prater GL. Quality in dual-energy X-ray absorptiometry scans. Bone. 2017;104:13-28.

34. Cawthon PM, Peters KW, Shardell MD, McLean RR, Dam TT, Kenny AM, et al. Cutpoints for low appendicular lean mass that identify older adults with clinically significant weakness. J Gerontol A Biol Sci Med Sci. 2014;69(5):567-75.

35. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014;69(5):547-58.

36. Iannuzzi-Sucich M. PKM, Kenny A.M. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci. 2002;57(12):772-7.

37. Tanko LB, Movsesyan L, Mouritzen U, Christiansen C, Svendsen OL. Appendicular lean tissue mass and the prevalence of sarcopenia among healthy women. Metabolism. 2002;51(1):69-74.

38. Gould H, Brennan SL, Kotowicz MA, Nicholson GC, Pasco JA. Total and appendicular lean mass reference ranges for Australian men and women: the Geelong osteoporosis study. Calcif Tissue Int. 2014;94(4):363-72.

39. Mamane S, Mullie L, Lok Ok Choo W, Piazza N, Martucci G, Morais JA, et al. Sarcopenia in Older Adults Undergoing Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2019;74(25):3178-80.

40. Saji M, Lim DS, Ragosta M, LaPar DJ, Downs E, Ghanta RK, et al. Usefulness of Psoas Muscle Area to Predict Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement. Am J Cardiol. 2016;118(2):251-7.

41. Mamane S, Mullie L, Piazza N, Martucci G, Morais J, Vigano A, et al. Psoas Muscle Area and All-Cause Mortality After Transcatheter Aortic Valve Replacement: The Montreal-Munich Study. Can J Cardiol. 2016;32(2):177-82.

42. Pavasini R, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, et al. Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. BMC Med. 2016;14(1):215.

43. Guralnik J. FL, Pieper C.F., Leveille S.G., Markides K.S., Ostir G.V., Studenski S., Berkman L.F., Wallace R.B. . Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci. 2000;55A(4):M221-M31.

44. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. J Gerontol A Biol Sci Med Sci. 2013;68(1):39-46.

45. Studenski S. PS, Patel K., Rosano C., Faulkner K., Inzitari M., Brach J., Chandler J., Cawthon P., Connor E.B., Nevitt M., Visser M., Kritchevsky S., Badinelli S., Harris T., Newman A.B., Cauley J., Ferrucci L., Guralnik J. Gait speed and survival in older adults. JAMA. 2011;305(1):50-8.

46. Afilalo J, Kim S, O'Brien S, Brennan JM, Edwards FH, Mack MJ, et al. Gait Speed and Operative Mortality in Older Adults Following Cardiac Surgery. JAMA Cardiol. 2016;1(3):314-21.

47. Afilalo J, Eisenberg MJ, Morin JF, Bergman H, Monette J, Noiseux N, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. J Am Coll Cardiol. 2010;56(20):1668-76.

48. Podsiadlo D. RS. The timed "up & go": A test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142-8.

49. Barry E. GR, Keogh C., Horgan F., Fahey T. Is the timed up and go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta- analysis. BMC Geriatr. 2014;14:1-14.

50. Bittner V. WDH, Yusuf S., Rogers W.J., McIntyre K.M., Bangdiwala S.I., Kronenberg M.W., Kostis J.B., Kohn R.M., Guillotte M., Greenberg B., Woods P.A., Bourassa M.G. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. JAMA. 1993;270(14):1702-7.

51. Rostagno C. OG, Comeglio M., Boddi V., Banchelli M., Galanti G., Gensini G.F. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. Eur J Heart Fail. 2003;5(3):247-52.

52. Society AT. ATS statement: Guidelines for the six-minute walk test Am J Respir Crit Care Med. 2002;166:111-7.

53. Bekfani T, Pellicori P, Morris DA, Ebner N, Valentova M, Steinbeck L, et al. Sarcopenia in patients with heart failure with preserved ejection fraction: Impact on muscle strength, exercise capacity and quality of life. Int J Cardiol. 2016;222:41-6.

54. Onoue Y, Izumiya Y, Hanatani S, Tanaka T, Yamamura S, Kimura Y, et al. A simple sarcopenia screening test predicts future adverse events in patients with heart failure. Int J Cardiol. 2016;215:301-6.

55. Heidari B, Al-Hijji MA, Moynagh MR, Takahashi N, Welle G, Eleid M, et al. Transcatheter aortic valve replacement outcomes in patients with sarcopaenia. EuroIntervention. 2019;15(8):671-7.

56. Okamura H, Kimura N, Tanno K, Mieno M, Matsumoto H, Yamaguchi A, et al. The impact of preoperative sarcopenia, defined based on psoas muscle area, on long-term outcomes of heart valve surgery. J Thorac Cardiovasc Surg. 2018.

57. Lopez PD, Nepal P, Akinlonu A, Nekkalapudi D, Kim K, Cativo EH, et al. Low Skeletal Muscle Mass Independently Predicts Mortality in Patients with Chronic Heart Failure after an Acute Hospitalization. Cardiology. 2019;142(1):28-36.

58. Teng CH, Chen SY, Wei YC, Hsu RB, Chi NH, Wang SS, et al. Effects of sarcopenia on functional improvement over the first year after cardiac surgery: a cohort study. Eur J Cardiovasc Nurs. 2019;18(4):309-17.

59. Rizzoli R, Reginster JY, Arnal JF, Bautmans I, Beaudart C, Bischoff-Ferrari H, et al. Quality of life in sarcopenia and frailty. Calcif Tissue Int. 2013;93(2):101-20.

60. Ishii S, Tanaka T, Shibasaki K, Ouchi Y, Kikutani T, Higashiguchi T, et al. Development of a simple screening test for sarcopenia in older adults. Geriatr Gerontol Int. 2014;14 Suppl 1:93-101.

61. Bibas L, Levi M, Bendayan M, Mullie L, Forman DE, Afilalo J. Therapeutic interventions for frail elderly patients: part I. Published randomized trials. Prog Cardiovasc Dis. 2014;57(2):134-43.

62. Holmes DR, Jr., Rich JB, Zoghbi WA, Mack MJ. The heart team of cardiovascular care. J Am Coll Cardiol. 2013;61(9):903-7.

63. Janssen I. SDS, Katzmarzyk P.T., Roubenoff R. The healthcare costs of sarcopenia in the United States. JAGS. 2004;52:80-5.

64. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018;137(12):e67-e492.

65. Arnaoutakis GJ, George TJ, Alejo DE, Merlo CA, Baumgartner WA, Cameron DE, et al. Society of Thoracic Surgeons Risk Score predicts hospital charges and resource use after aortic valve replacement. J Thorac Cardiovasc Surg. 2011;142(3):650-5.

66. Manini TM, Clark BC. Dynapenia and aging: an update. J Gerontol A Biol Sci Med Sci. 2012;67(1):28-40.

67. Bianchi L, Abete P, Bellelli G, Bo M, Cherubini A, Corica F, et al. Prevalence and Clinical Correlates of Sarcopenia, Identified According to the EWGSOP Definition and Diagnostic Algorithm, in Hospitalized Older People: The GLISTEN Study. J Gerontol A Biol Sci Med Sci. 2017;72(11):1575-81.

68. Joyce E. Frailty in Advanced Heart Failure. Heart Fail Clin. 2016;12(3):363-74.

69. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol. 2017;33(11):1342-433.

70. Morley JE, Anker SD. Myopenia and precision (P4) medicine. J Cachexia Sarcopenia Muscle. 2017;8(6):857-63.

71. Forman DE, Santanasto AJ, Boudreau R, Harris T, Kanaya AM, Satterfield S, et al. Impact of Incident Heart Failure on Body Composition Over Time in the Health, Aging, and Body Composition Study Population. Circ Heart Fail. 2017;10(9).

72. Ishida Y, Maeda K, Nonogaki T, Shimizu A, Yamanaka Y, Matsuyama R, et al. Impact of edema on length of calf circumference in older adults. Geriatr Gerontol Int. 2019;19(10):993-8.

73. Guralnik JM SE, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol A Biol Sci Med Sci. 1994;49(2):M85-M94.