The prognostic role of sarcopenia in older adults undergoing transcatheter aortic valve replacement

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Abstract

Background: Sarcopenia is the "biologic substrate of frailty" defined as an age-related syndrome characterized by the loss of skeletal muscle mass and a decrease in muscle function. Our objective was to explore the role of sarcopenia in the pre-procedural evaluation of older adults undergoing transcatheter aortic valve replacement (TAVR) and to determine its incremental prognostic value above established risk stratification tools.

Methods: After reviewing the literature on sarcopenia in the peri-operative setting, focusing on the use of CT-scan skeletal muscle cross-sectional area as a measure of muscle mass, we developed a novel software tool and methodology for measuring psoas muscle area (PMA). In the first study, we validated this tool in the retrospective two-center Montreal-Munich cohort study evaluating the predictive role of PMA on outcomes in older adults undergoing TAVR. In the second study, we conducted a pre-planned analysis of the prospective multicentre FRAILTY-AVR cohort study to evaluate the prognostic value of sarcopenia as measured by a combination of low PMA and low lower extremity muscle performance, deriving a sarcopenia score including muscle mass and function.

Results: PMA measured on single axial image at the level of the L4 vertebrae correlated well with psoas muscle volume ($r=0.91$, $p<0.001$). Inter-observer mean difference ranged from -0.15 to -0.53 cm^2. In the Montreal-Munich cohort, PMA was independently associated with cumulative all-cause mortality in woman (HR 0.88 per cm^2, CI 0.78-0.99). Addition of PMA improved STS risk prediction (C-statistic 0.62 to 0.67). In the FRAILTY-AVR cohort, PMA was independently associated with length of stay (LOS) (-0.32 days per cm^2, CI -0.56 to -0.08) and disability (-0.14 deficits per cm^2, CI -0.26 to -0.01). Sarcopenia was independently and incrementally associated with mortality at 6 months (OR 11.6, CI 1.49 to 90.16), ΔAIC 6.8, and at 12 months (OR 5.61, CI 5.61 to 19.91), ΔAIC 6.2. Sarcopenia was also independently and incrementally associated with LOS (4.8 days per point, CI 1.97 to 7.68), ΔAIC 11.6, and disability (3.3 deficits per point, CI 1.74 to 4.85).

Conclusion: Measuring PMA from peri-procedural CT-scan is feasible and reliable, and represents a prognostic surrogate measure for muscle mass. Low muscle mass and sarcopenia are associated with poorer outcomes after TAVR. Thus, the pre-TAVR evaluation of sarcopenia should dually include complementary measures of muscle mass and function. Further research is needed to determine if sarcopenia is a viable therapeutic target peri-procedurally.

Résumé

Introduction: La sarcopénie est l'aspect biologique de la fragilité et se définit comme un syndrome caractérisé par une perte de masse musculaire squelettique ainsi qu'une diminution de la fonction musculaire. Notre objective était d'explorer le rôle de la sarcopénie dans l'évaluation péri-opératoire du remplacement trans-cathéter de la valve aortique (RTVA) chez les patients âgés afin de déterminer sa valeur incrémentale au-dessus des outils établis de stratification de risques.

Méthodes: Après avoir réalisé une révision brève de la littérature sur la sarcopénie dans le contexte péri-opératoire, en focalisant sur l'utilisation de l'aire transversale des muscles squelettiques sur CT-scan comme mesure de masse musculaire, nous avons développé un logiciel original et la méthodologie en lien avec la mesure de l'aire musculaire du psoas (AMP). Dans la première étude, nous avons validé cet outil dans l'étude de cohorte rétrospective et bicentrique « Montréal-Munich » qui évaluait le rôle prédictif de l'AMP dans le contexte du RTVA. Dans la deuxième étude, nous avons effectué une analyse planifiée de l'étude de cohorte prospective et multicentrique « FRAILTY-AVR » afin d'évaluer la valeur pronostique de la sarcopénie. Afin de dériver un score de sarcopénie, la valeur pronostique de la sarcopénie a été mesurée en combinant l'AMP et la performance musculaire du bas du corps.

Résultats: L'AMP mesuré sur un image axial solitaire au niveau du vertèbre L4 corrélait bien avec le volume du muscle psoas ($r=0.91$, $p<0.001$). La différence moyenne entre observateurs s'étalait entre -0.15 et -0.53 cm^2. Dans la cohorte Montréal-Munich, l'AMP était associée indépendamment avec la mortalité cumulative toute-cause chez les femmes (HR 0.88 par cm^2, CI 0.78 à 0.99). L'addition de l'AMP a amélioré la prédiction de risque STS (statistique-C 0.62 à 0.67). Dans la cohorte FRAILTY-AVR, l'AMP était associée indépendamment avec la durée de séjour (-0.32 jour par cm^2, CI -0.56 à -0.08) et l'invalidité (-0.14 déficits par cm^2, CI -0.26 à -0.01). La sarcopénie était indépendamment et de façon incrémentale associée avec la mortalité à 6 mois (OR 11.6, CI 1.49 à 90.16), ΔAIC 6.8, et à 12 mois (OR 5.61, CI 5.61 à 19.91), ΔAIC 6.2. La sarcopénie était aussi indépendamment et de façon incrémentale associée avec la durée de

séjour (4.8 jours par point, CI 1.97 à 7.68), ΔAIC 11.6, et l'invalidité (3.3 déficits par point, CI 1.74 à 4.85).

Conclusion : La mesure péri-opératoire de l'AMP au CT-scan est non seulement facile à réaliser et fiable, mais elle représente aussi un substitut prognostique pour mesurer la masse musculaire. La faible masse musculaire et la sarcopénie sont associées avec de moins bons résultats après le RTVA. Ainsi, l'évaluation de la sarcopénie pré-RTVA devrait inclure une mesure de masse musculaire et une mesure de fonction musculaire de façon complémentaire. Plus de recherches sont nécessaires afin de déterminer si la sarcopénie est une cible thérapeutique applicable dans le cadre péri-opératoire.

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Chapter 1 – Introduction

1.1 – Aortic Stenosis

Aortic Stenosis is among the leading causes of valvular heart diseases in the industrialized world (1, 2) and a disease that primarily affects older adults (3). A recent meta-analysis found that 12.4% of patients >75 years old have at least mild AS, and 3.4% already have severe AS (4). As the population continues to age, the prevalence of AS is increasing (5) and has become a significant focus, as symptomatic severe AS carries a poor prognosis if left untreated with a median survival of 5 years or less (6-8). Despite a multitude of trials, no medical therapy has been able to convincingly slow the progression of AS or to improve prognosis (9). As such, surgical aortic valve replacement (SAVR) has remained the standard of care for the treatment of symptomatic severe AS. However, in both cohort studies (10) and randomized controlled studies (RCT) (11), those deemed too high risk for surgery had a mean survival of only 1 year.

1.2 – Transcatheter Aortic Valve Replacement (TAVR)

To treat high-risk patients, transcatheter aortic valve replacement (TAVR) was developed as a less invasive treatment strategy. In 2010, the first RCT (PARTNER trial) comparing TAVR vs medical treatment showed a marked 20% absolute survival advantage for those treated with TAVR, translating into a number needed to treat (NNT) of only 5 (11). Less than a year later, the same PARTNER trial investigators showed that TAVR was equivalent to SAVR in high risk patients (12). Consequently, the rate of TAVR began to rapidly rise (13) and questions regarding cost-effectiveness surfaced (14). In non-surgical and high risk patients, TAVR is felt to be a cost-effective intervention (15), but it remains a very costly intervention nonetheless and it is estimated that that almost 30,000 patients in North America and Europe are eligible candidates

for TAVR annually (4) with an associated cost well over 2 billion dollars per year (16). In addition to the growing costs, it also stands to reason that not all patients will benefit equally (17). Despite a technical success rate of >95% in patients undergoing TAVR (18), more than one third of patients do not achieve improvement in quality of life or reduction in physical limitation (19, 20), and many suffer midterm death despite early post-procedural survival (17, 21). As such, patient selection has become an important focus. Most risk stratification tools focus on patient comorbidities, including the Society of Thoracic Surgeons (STS) score (22) which is the most well accepted (23) and widely used in TAVR. The STS risk prediction models include over 40 variables, and were derived and validated in a large American cohort of >65,000 patients undergoing SAVR from 2002-2006, for several outcomes including mortality (STS-PROM), major morbidity (STS-PROMM) and prolonged length of stay (STS-PLOS) (22).

However, Clinicians and investigators soon realized that TAVR cohorts were older, with a mean age >80 years old (18) and having other geriatric conditions that affected prognosis. It was also becoming increasingly evident that while there was a clear mortality benefit for many patients, some patients faired poorly, and could expect only modest improvements in quality of life (QOL) and disability (24, 25).

Given the growing octogenarian population and the cost of TAVR, a search for prognostic indicators became increasingly important in order to determine pre-hoc in whom the procedure could be considered futile (17). In the initial years of TAVR, surgeons and cardiologists alike relied on the so-called “eye-ball test” (26), but realized quickly that there was a need to integrate geriatric assessment into pre-procedural TAVR evaluation and risk assessment. The traditional myopic view of AS treatment broadened to appreciate the complex

framework of host factors in older adults that could affect outcomes (5); the primary focus was on frailty.

1.3 – Frailty in Peri-procedural Assessment of Older Adults

1.3.1 – Defining Frailty

Frailty is a geriatric syndrome of decreased resilience and vulnerability to physiologic stressors (27, 28). Frailty is a systemic syndrome that is thought to affect about 40% of people ≥80 years old (29). The most widely accepted description of the frailty phenotype stems from Fried et al., who characterized the syndrome as involving 5 domains: shrinking, weakness, exhaustion, slowness and low activity, where a score of ≥3 constitutes clinical frailty (30). These criteria have since been modified in some cases to include the domains of cognition and mood (31). It should be noted that another school of thought defines frailty as the additive accumulation of disease, comorbidities, deficits and disabilities over time (32). Subsequently, a wealth of literature has emerged regarding the various tools to measure the different domains of frailty.

1.3.2 – Measuring Frailty

Many functional performance tests aimed at testing the different domains of frailty have been proposed, each primarily testing one domain of frailty, and with specific cut-off values that have been validated in different cohorts. For example, weakness can be measured in the upper extremity using handgrip strength as measured by a dynamometer with sex-specific or BMI specific cut-offs (30). A test of weakness in the lower extremity is chair rises. Slowness is traditionally tested by gait speed. In order to examine several domains at once, certain tests have been used in combination, for example the Short Physical Performance Battery which includes a

measurement of gait speed, balance and chair rises (33) (appendix 1). Some of the other domains can be tested using detailed questionnaires, such as the Paffenbarger Physical Activity Score (34) for estimation of physical activity or the Mini-Mental Status Exam (MMSE) to assess cognition (35).

Searching to simplify frailty assessment, Rockwood et al. built upon their initial definition and developed the Clinical Frailty Scale (CFS), which focuses primarily on the observer's subjective global assessment of the patient's overall health status, level of activity and disability, rather than the specific domains of frailty (36). Although the CFS is predictive of poor outcomes in patients undergoing TAVR (37), it identifies patients who are already extremely disabled in which TAVR may provide little benefit, rather than identifying frail patients who can be targeted for intervention (38).

1.3.3 – Frailty and Outcomes after TAVR

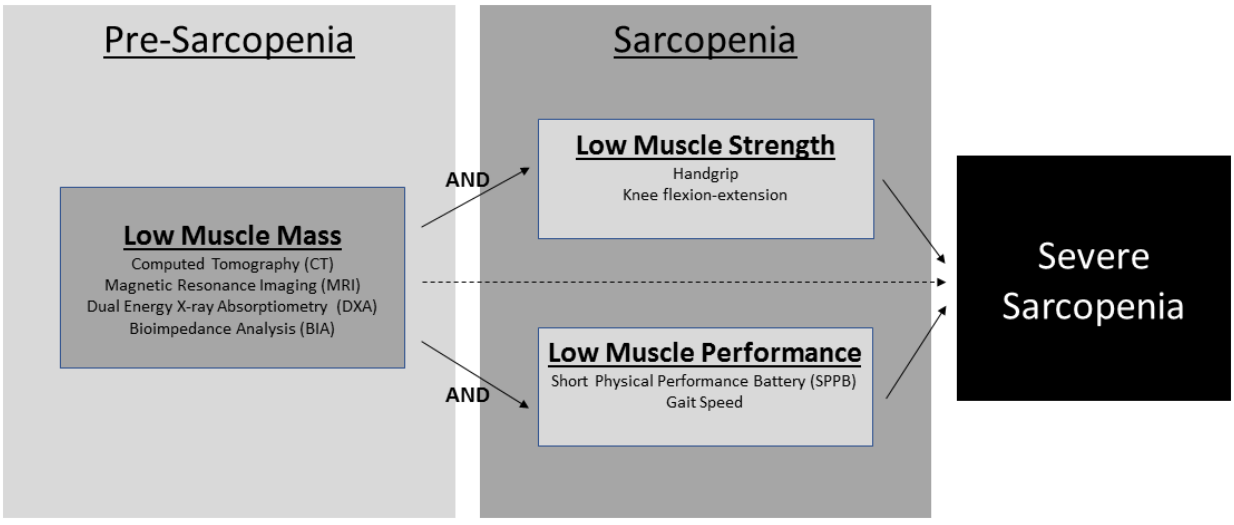
Frailty in older adults is associated with poor physical fitness (39), disability post-hospitalization (40), high resource utilization in hospitalized patients (41), falls (42), poor surgical outcomes (43) and all-cause mortality (44, 45). More specifically, in patients undergoing TAVR, frailty is a strong predictor of functional decline (46), major adverse cardiac events (47), 1-year and cumulative mortality (21, 37), and overall poorer outcomes (48). Consequently, there has been a successful push to integrate frailty and geriatric assessment into cardiac surgery and TAVR risk scores (49-51). However, frailty testing in patients undergoing TAVR focuses on physical performance testing, which cannot be completed in 10-35% of patients (28), and does not measure muscle mass, which is a core component of frailty that is often overlooked (29). While frailty overall remains a strong prognostic indicator, its traditional measures provide less insight into the biologic substrate of frailty, known as sarcopenia.

1.4 – Sarcopenia in Periprocedural Assessment of Older Adults

1.4.1 – Defining Sarcopenia

Sarcopenia is an age-related syndrome characterized by progressive loss of skeletal muscle mass and function (52), and is a core component of frailty (53). The European Working Group on Sarcopenia in Older People (EWGSOP) recommends that a diagnosis of sarcopenia include documentation of both loss of muscle mass, and muscle function as defined by loss of strength (ie: low handgrip strength) or performance (ie: low SPPB score) (52). Furthermore, they go on to conceptualize the stages of sarcopenia, defining pre-sarcopenia as low muscle mass in isolation, sarcopenia as low muscle mass in combination with low muscle strength or performance, and severe sarcopenia as low muscle mass in combination with low muscle strength and performance. This definition and conceptual framework is summarized in Figure 1 (52).

Figure 1: Sarcopenia definition and framework



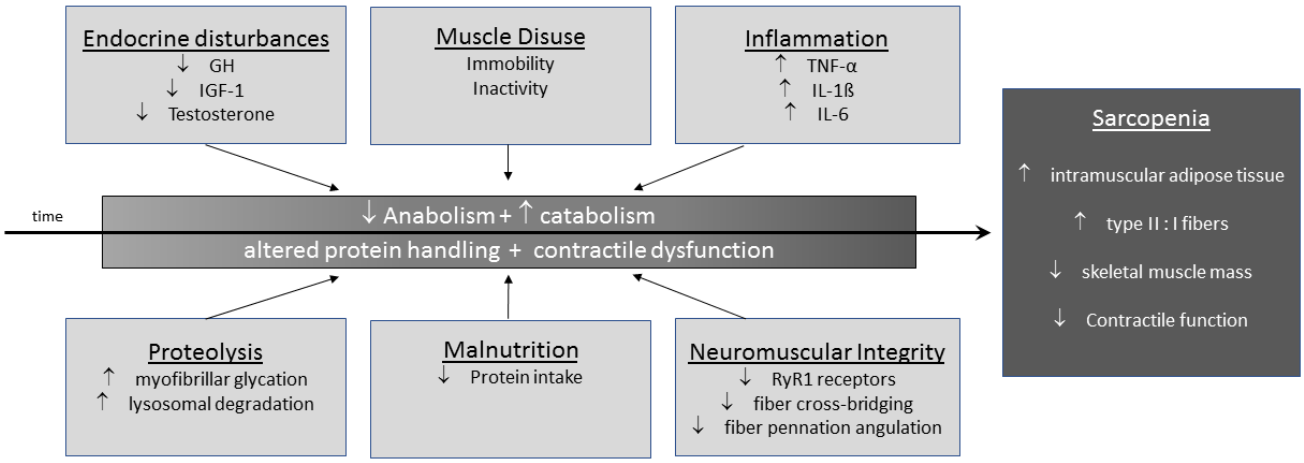
As one would expect, there is significant overlap in the assessment of sarcopenia and frailty given that frailty is a phenotypic manifestation of underlying sarcopenia. The evaluation of sarcopenia often involves a varying combination of assessing muscle mass, muscle strength, muscle performance and biological markers (54). The prevalence of sarcopenia increases with age, with 12-50% of the population ≥80 years old meeting criteria for clinical sarcopenia, depending on the definition (55).

1.4.2 – Pathophysiology of Sarcopenia

The causes of sarcopenia are multifactorial and can include muscle disuse, changing endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies (28, 52, 56). The term sarcopenia is relatively new and until the late 1990's had been used by it's literal definition from the greek 'sark' meaning flesh and 'penia' meaning deficiency, focusing primarily on the age-related reduction in muscle mass (57-59). Although they are sometimes discussed together, it should be noted that sarcopenia is distinct from cachexia. Cachexia is a multifactorial syndrome that can occur in children or adults, that is characterized by severe body weight loss and protein catabolism, driven by inflammation and anorexia (60, 61). Patients that are cachectic, are usually sarcopenic in that they have low muscle mass, but most sarcopenic patients are not cachectic (52). In the discussion of sarcopenia throughout this text, I apply the diagnostic label of sarcopenia refers to the former age-related muscle loss, primarily in patients ≥65 years old. The distinction between cachexia and sarcopenia is often more difficult than meets the eye, as many older adults have chronic conditions which may contribute to inflammation and cachexia-related muscle loss beyond the expected age-related muscle loss. However, discerning which is the primary driver of muscle loss and dysfunction remains a difficult task.

The mechanisms driving sarcopenia are varied and although the sarcopenia process is universal, it remains heterogenous between individuals (59). Figure 2 (52, 56, 59, 62) presents a concise schematic summary of the complex interplay of contributors which converge into the final pathway of sarcopenia; the hallmarks include increased adipose tissue (63), reduction in the size of type-II skeletal muscle fibers (64), a shift from fast-to slow-type muscle fibers (65), and decreased contractile function (59).

Figure 2: Pathophysiology of sarcopenia



1.4.3 – Targeting Sarcopenia for Intervention

Sarcopenia is the biologic substrate of frailty and believed to be the principal driver underlying the frailty phenotype. As such, therapeutic interventions aimed to curtail frailty are ultimately targeted at preventing the development of sarcopenia, treating low muscle mass, or improving muscle function. Many therapies focused on targeting the mechanisms briefly detailed above have been proposed, including nutritional supplementation, exercise programs, hormone replacement therapy and other pharmaceutical agents (66). Exercise acts at many levels to slow muscle decay and to improve muscle function (67). It has long been known that exercise and

resistance training are beneficial in the prevention and treatment of sarcopenia (68) and that decreased physical activity hastens the sarcopenia process (69). However, given the complex interplay of mechanisms involved, exercise alone is insufficient to completely prevent age-related loss of muscle mass and function. Similarly, nutritional supplementation has been studied and has included: protein, essential amino acids, creatine, ß-hydroxy-ß-methylbutyrate (HMB), vitamin D, and others (70). In studies that evaluate the role of both exercise and nutritional supplementation, it appears that most of the benefit comes from the exercise component, but that various nutritional supplements may act synergistically in the treatment of sarcopenia (67, 70). In recent years, a host of inflammatory cytokines and endocrine disturbances have been implicated in the pathophysiology of sarcopenia (56, 62). Consequently, there are several ongoing trials investigating the role of well-established pharmaceutical agents such as metformin or angiotensin-receptor blockers which act along these pathways. Similarly, novel agents such as bimagrumab which is a monoclonal antibody that induces skeletal muscle hypertrophy by blocking the activin type-II receptor thus inhibiting myostatin and GDF-11 signalling, are currently being studied in Phase I-III clinical trials (71, 72). However, the benefit of intervention seems to be limited to those who are actually sarcopenic, highlighting the importance of measuring and identifying sarcopenia to determine those who may benefit (73, 74).

1.5 – Measuring Sarcopenia

Measuring muscle mass is the critical difference between the assessment of sarcopenia compared to frailty. Measuring muscle mass is desirable as it is an objective measure that can be obtained in older adults regardless of their functional status. In the clinical setting, “shrinking” or loss of muscle mass is measured by weight loss which is commonly self-reported. However, weight is not a good predictor of muscle mass because ageing is often associated with weight

stability and a muscle-to-fat mass ratio decline, resulting in what has been termed as “sarcopenic obesity”, masking the underlying reduction in muscle (75). Other anthropomorphic measures have been evaluated given their obvious practicality but remain less precise than measuring muscle mass (76). As such, the assessment of muscle mass requires more accurate tools.

1.5.1 – Tools for Measuring Sarcopenia

In addition to a measure of muscle function, the two-dimensional definition of sarcopenia requires a measure of muscle mass. Techniques used for this measure are aimed at balancing precision and convenience (77). Traditionally, muscle mass has been measured using a variety of imaging options, including dual energy X-ray absorptiometry (DXA), computed tomography (CT) and magnetic resonance imaging (MRI) which remains the gold-standard (57). Although MRI is the most precise, DXA remains the most commonly used technique as it is inexpensive, available in clinical and research settings, overall well tolerated by older adults, and measures appendicular muscle mass which was the focus of the original sarcopenia definition (77). As measured by DXA, the cutoff values of appendicular muscle mass for sarcopenia are 7.26kg/m2 in men and 5.45 kg/m2 in woman (78). One of the limitations of DXA is its inability to differentiate between water and some lean tissue, overestimating muscle mass in older adults (54). MRI provides both higher resolution and accuracy, but has limitations in its applicability; MRI is time-consuming and expensive with more limited availability and cannot be used in certain conditions such as metallic joint prostheses. CT-scan provides similar estimates to MRI, but delivers significantly more radiation than DXA.

Bioelectrical impedance is gaining popularity given that it is inexpensive, simple to use, and does not expose the patient to radiation. However, it is not a direct measure of muscle mass,

measuring resistance differences in the tissues and as such is vulnerable to inaccuracies, particularly in patients with fluid retention (77).

Recently, Malmstrom et al. developed a simple questionnaire to screen for sarcopenia; the SARC-F contains 5 questions regarding strength and performance. Despite the questionnaire remaining open to subjectivity, it has been validated and has demonstrated the ability to identify older adults with impaired physical function (79) and at higher risk of disability (80). Again, this tool does not measure muscle mass directly. Therefore, there remained a need to find a direct measure of muscle mass that could be simply measured in both research and clinical settings.

1.5.2 - CT-scan Skeletal Muscle Cross-sectional Area

Many older adults have CT scans for clinical reasons. The peri-operative period is a common setting in which many patients undergo CT imaging to diagnose the primary pathology or plan the surgical procedure. In both scenarios, there has been a growing interest to leverage the clinical CT-scans to evaluate muscle mass. As DXA and MRI are less readily accessible, clinical CT scans provided an opportunity to investigate the prognostic value of sarcopenia in patients undergoing surgery. However, in the clinical setting CT of the whole body is rarely done, and usually does not include appendicular muscle. Therefore, there was a need for a surrogate measure of total muscle mass that could utilize the available images, usually of the abdomen-pelvis or thorax, as an alternative to measuring total body muscle mass. In 2004, Shen et al. showed that there was a strong correlation between total body skeletal muscle and a single abdominal cross-sectional image on CT-scan, in healthy adults (81). In 2008, Mourtzakis et al. further elucidated this correlation in a cancer patient population (82). Later, Prado et al. went on to established cut-off values in a similar patient population and showed that low muscle mass as

measured by skeletal muscle index (cross-sectional area/height^2) at the L3 level was an independent predictor of poor functional status and mortality (83).

1.5.3 – CT-scan Psoas Muscle Cross-sectional Area (PMA)

In 2010, the Michigan Morphomics Analysis Group published a pilot study in patients undergoing liver transplantation where they measured the psoas muscle cross-sectional area (PMA) as a novel surrogate marker of muscle mass (84). The psoas muscle is a core postural muscle of the trunk and is responsible primarily for hip flexion. It plays an integral role in basic daily functions such as sitting and ambulating. Because the psoas muscle is used regularly throughout the day, it remains resistant to acute stressors during which appendicular muscle mass atrophies quickly. The changes in the psoas muscle and other core muscles of the trunk happen more slowly, and as such reflect the state of overall health or chronic illness (84). Within a short period of time, several studies utilizing a similar technique for measuring PMA on peri-operative CT scans were published in patients undergoing a host of different surgeries, such as abdominal aortic aneurysm repair (85), resection of liver metastases (86), radical cystectomy (87), resection of primary neoplasms (88, 89), and others.

1.5.4 – CT-scan Cross-sectional Muscle Measurement in the Peri-operative Setting

To review the evidence for CT-based muscle area as a prognostic marker in the peri-operative setting, I queried PubMed using the advanced search builder tool. I scanned the titles of the 389 results and then a narrowed group of abstracts in order to look for original studies that measured muscle mass on CT-scan in a surgical patient population. Overall there were 58 original studies between August 2010 and March 2017 that met these criteria, of which 26 (45%) pertained to the resection of solid neoplasms, 15 (26%) to liver transplant or hepatectomy, and

17 (29%) relating to surgery for other non-malignant pathologies. The list of these studies can be found in appendix 2.

Overall, the patients in these studies were younger than those undergoing TAVR, required significantly more invasive surgical interventions than transcatheter intervention and better fit the profile of cachexia than that of sarcopenia. While sarcopenia and cachexia overlap, the two conditions remain distinct, as described earlier (90). As such, we sought to determine if measuring muscle mass using the CT surrogate of PMA could predict post-procedural outcomes in an older, less inflammatory population with AS undergoing TAVR, a less invasive intervention.

1.5.5 – CT-scan Cross-sectional Muscle Measurement in TAVR assessment

Our group was among the first to explore these methods in patients with AS, with several others following suit shortly thereafter. Table 1 describes the methodological aspects of all 8 studies to date (including our unpublished cohort) that have utilized CT measures of muscle mass to predict procedural outcomes in patients undergoing TAVR. The outcomes out these studies are described in Table 2 which can be found later in Chapter 3.

Table 1: Methodology of studies including CT-measures of muscle mass in patients undergoing TAVR

Study	Measure	Measurement tool	Segmentation Software	Muscle Area (mean)
Dahya V et al. (Dec. 2016)	SMI: L3 skeletal muscle cross-sectional area indexed to height squared (cm2/m2)	density threshold brush (−29 to 150 HU)	Slice-O-Matic software, version 5.0, (Tomovision, Montreal, Quebec, Canada)	Male: SMA - 139 ± 25 cm2, SMI - 45 ± 9 cm2/m2 Female: SMA - 100 ± 22 cm2, SMI - 39 ± 8 cm2/m2
Garg L et al. (Feb. 2017)	PMI: L3 psoas muscle cross-sectional area indexed to BSA (cm2/m2)	perimeter polygon tracing (area interpolation)	Aquarius (version 4.4.11; TeraRecon, Foster City, California).	Male: SMI - 4.15 cm2/m2 Female: SMI - 3.47 cm2/m2
Mamane S et al. (Feb. 2016)	PMA: L4 psoas muscle cross-sectional area	density threshold brush (−30 to 150 HU)	CoreSlicer.com web-based software package (version 1.0.0; Montreal, Quebec, Canada)	Male: PMA - 21.9 ± 4.4 cm2 Female: PMA - 14.1 ± 3.5 cm2

Mamane S et al. (unpublished)	PMA: L4 psoas muscle cross-sectional area	density threshold brush (−30 to 150 HU)	CoreSlicer.com web-based software package (version 1.0.0; Montreal, Quebec, Canada)	Male: PMA - 21.2 ± 4.4cm2 Female: PMA - 14.9 ± 3.7cm2
Mok M et al. (Mar. 2016)	SMI: L3 skeletal muscle cross-sectional area indexed to height squared (cm2/m2)	density threshold brush (−29 to 150 HU)	SliceOmatic, version 4.3 (TomoVision, Magog, Quebec, Canada)	Male: SMA - 136.9 ± 25.8 cm2, SMI - 71.5 ± 11.7cm2/m2 Female: SMA - 100.9 ± 25.9 cm2, SMI - 60.6 ±12.9 cm2/m2
Nemec U et al. (Mar. 2017)	SMI: T7, T12, L3 skeletal muscle cross-sectional area indexed to height squared (cm2/m2)	density threshold brush (−29 to 150 HU)	Osirix (v8.0.1; Pixmeo SARL, Bernex, Switzerland).	Male: SMA - 154.4 ± 28.3 cm2, SMI - 51.7 ± 9.8 cm2/m2 Female: SMA - 123.3 ± 26.7 cm2, SMI - 49.8 ± 11.4 cm2/m2
Paknikar R (Mar. 2016)	PMA: L4 psoas muscle cross-sectional area	semi-automated algorithm	MATLAB version 13.0 (MathWorks, Natick, Mass)	Male: PMA - 2659 ± 711 mm2 Female: PMA - 1666 ± 490 mm2
Saji M et al. (Jul. 2016)	PMI: L4 psoas muscle cross-sectional area indexed to BSA (cm2/m2)	perimeter polygon tracing (area interpolation)	Carestream Vue Picture Archiving and Communication System radiology software program (version 11.3, Carestream Health, Rochester, New York)	PMI: 1016 ± 229 mm2/m2
HU: Hounsfield unit, PMA: psoas muscle area, PMI: psoas muscle index, SAVR: surgical aortic valve replacement, SMI: skeletal muscle index, TAVR: transcatheter aortic valve replacement				

In these studies, the two favoured measures are cross-sectional area of skeletal muscle at the level of L3 (82) and cross-sectional area of the psoas muscle at the level of L4 (84). There is no consensus regarding indexation of these measures; some studies index to BSA, some to height squared, and others use the unadjusted measurement value. Unlike whole body muscle mass (78), muscle cross-sectional area at on a single slice appears to be less predictably affected by height or body size (91). However, sex significantly affects single slice cross-sectional area and should be considered when adjusting or stratifying measures (92, 93). Given the heterogeneity in measurement techniques and indexation, the prevalence of sarcopenia in this patient population is also very variable, as there are no well defined cut-off points for each CT-scan measure. Currently, some studies use cut-offs proposed by Prado et al. (83, 94). However, these cut-off values were ascertained from a cancer patient population and likely overestimates the prevalence of sarcopenia in non-cancer populations. Likewise, these cut-offs pertain only to complete

skeletal muscle cross-sectional area at L3 and do not identify any cut-offs for any specific muscles, such as the psoas muscle.

1.5.6 – Feasibility and Reliability of Measuring Psoas Muscle Area

Prior to conducting our retrospective study in older adults undergoing TAVR, we wanted to elaborate on the methodology for measuring PMA. Mainly, we wanted to 1) determine if the straight axial cross-sectional area was similar to the axial cross-sectional area aligned perpendicular to the psoas muscle, as the psoas muscle does not lie vertically, 2) confirm that L4 was the best level at which to measure PMA, and 3) to know if PMA was a feasible and reliable measure in patients undergoing TAVR, as this information was not readily available in the published literature. From our potential cohort, we selected a random subset of 50 CT scans to perform these analyses. The cross-sectional area of the psoas muscles was manually planimetered on multiplanar reconstructed images at 9 pre-defined levels from L3 to L5 in both the straight axial plane and axial plane aligned perpendicular to the psoas muscle. We then measured the three-dimensional psoas muscle volume (PMV) between the L1-L5 levels using the Materialise Mimics imaging suite (Leuven, Belgium). PMA at the superior aspect of the L4 level on straight axial image was the more closely correlated to three-dimensional psoas muscle volume ($r=0.91$; $p<0.001$) than PMA at the other levels tested. Independent observers performed triplicate measurements in a subset of 30 cases to assess inter-observer reliability. Bland Altman analysis showed 95% limits of agreement of -3.14 to 2.67 cm2 with a mean difference of -0.23 cm2 between observer 1 and observer 2; and 95% limits of agreement of -3.33 to 2.27 with a mean difference of -0.53 between observer 1 and observer 3. I presented these findings at the 2015 International Conference on Frailty and Sarcopenia (91). Further details of our methodology are elucidated in our manuscript found in chapter 2.

With these findings, we were well equipped to perform a retrospective cohort study to determine the prognostic role of psoas muscle area as a surrogate for muscle mass in patients undergoing TAVR. The Montreal-Munich study is presented in manuscript form in chapter 2. For this study, I assembled the cohort and reviewed the electronic health records to create a database of TAVR patients from McGill. I then obtained and merged a matching database from the Munich site. I collected the previously performed CT scans in digital format and performed all muscle measurements. I participated in the data analysis with my supervisor. Finally, I authored and presented the abstract and manuscript as first author.

Chapter 2: Prognostic Role of Psoas Muscle Area – A Retrospective Cohort Study

Published manuscript: "Psoas Muscle Area and All-Cause Mortality After Transcatheter Aortic Valve Replacement: The Montreal-Munich Study".

The retrospective cohort study investigating the prognostic role of psoas muscle area in patients undergoing transcatheter aortic valve replacement is presented in manuscript format below. This manuscript was initially published in the Canadian Journal of Cardiology on February 1st 2016, in volume 32, issue 2, pages 177-182.

Psoas Muscle Area and All-Cause Mortality After Transcatheter Aortic Valve Replacement: The Montreal-Munich Study

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No portion of the text has been copied from other material in the literature (unless in quotation marks, with citation).

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ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine
HR	Hazard ratio
OR	Odds ratio
PMA	Psoas muscle area
STS	Society of Thoracic Surgeons
TAVR	Transcatheter aortic valve replacement
VARC	Valve Academic Research Consortium

STRUCTURED ABSTRACT

Background: Psoas muscle area (PMA) is a novel measure of frailty that can be efficiently measured from CT images and help predict risk in older adults referred for transcatheter aortic valve replacement (TAVR). The objective of this study was to determine if PMA would be incrementally predictive of mortality and morbidity after TAVR.

Methods: The pre-TAVR CT scans of 208 consecutive patients at two hospitals in Montreal and Munich were analyzed to measure the cross-sectional area of the left and right psoas muscles on a single axial slice at the level of L4. The primary outcome was all-cause mortality assessed by sex-stratified Cox regression models adjusted for the STS predicted risk of mortality.

Results: The mean age was 80.7±6.8 years with 55% females and a total of 57 deaths over a mean follow-up of 504 days. PMA was lower in non-survivors compared to survivors among women (12.9 vs. 14.5 cm^2, p=0.047) but not men (21.7 vs. 22.4 cm^2, p=0.50). The association between PMA and all-cause mortality in women persisted after adjusting for STS risk (HR 0.88 per cm^2, 95% CI 0.78 to 0.99). An association between PMA and bleeding complications was seen in men (OR 0.78, 95% CI 0.62 to 0.97). Sensitivity analyses normalizing PMA to body mass index yielded similar results.

Conclusion: This study demonstrates that PMA is a marker of frailty associated with midterm survival in women undergoing TAVR. Further research is warranted to pursue PMA as a prognostic marker and therapeutic target in this vulnerable population.

Keywords: frailty, sarcopenia, psoas muscle, computed tomography, transcatheter aortic valve replacement

Brief summary: Psoas muscle area, a novel measure of frailty and sarcopenia, was measured by semi-automatically tracing the border of the left and right psoas muscles on a single axial CT image acquired before transcatheter aortic valve replacement. Two-hundred-eight patients were retrospectively included at two hospitals in Montreal and Munich. In women, low psoas muscle area was found to be associated with all-cause mortality (12% hazard difference per cm^2) independent of STS risk score.

INTRODUCTION

Frailty is a geriatric syndrome of decreased reserve and resiliency to stressors that has been associated with adverse health outcomes in older adults with cardiovascular disease.[1] In the setting of transcatheter aortic valve replacement (TAVR), frail patients face a 2-3 fold higher risk of functional decline and mortality at 6-12 months.[2,3] Clinicians have embraced the concept of frailty to refine estimates of procedural risk in complex elderly patients referred for TAVR. However, existing tools to assess frailty rely heavily on physical performance tests, which are less feasible in very frail or acutely ill patients; approximately 1 in 5 patients referred for TAVR cannot complete the most basic of frailty assessments – the 5-meter gait speed test.[4] Existing tools are also limited by the fact that they use weight loss as a blunt surrogate for muscle mass, which has been shown to be inaccurate in many patients, especially those with low muscle mass masked by excess adiposity ("sarcopenic obesity").[5]

Low muscle mass is a core component of frailty that has the advantage of being objectively quantifiable regardless of mobility, disability, or illness acuity. Traditionally, specialized and difficultly accessible equipment was required to measure muscle mass and thus limited its applicability in clinical care.[6] Over the past years, the simple measure of cross-sectional psoas muscle area (PMA) has been validated as a prognostic surrogate for muscle mass that can be measured with high reproducibility on axial abdominal CT scan images.[7,8] PMA has been shown to predict adverse postoperative outcomes in non-cardiac surgery, but has yet to be evaluated in patients undergoing TAVR. Since CT scans are routinely performed prior to TAVR in order to assess vascular anatomy, these images are readily available without the need for additional testing. Therefore, we sought to leverage the available CT scan images to measure PMA and determine its association with long-term mortality after TAVR.

METHODS

Study Design. Consecutive adult patients who underwent TAVR at two university-affiliated centers were identified from each center's local TAVR registry. The participating centers were: McGill University

Health Center (Montreal, Quebec; December 2007 to July 2013) and Munich Heart Institute (Munich, Germany; September 2010 to July 2011). Inclusion criteria were TAVR performed and pre-procedural abdomino-pelvic CT scan retrieved in digital DICOM format. Infused CT scans were routinely performed before TAVR for clinical purposes; no scans were requested for research purposes. The sole exclusion criterion was CT scan data not available, corrupt, or incomplete.

Clinical Data Collection. Patient characteristics were extracted from the centers' local TAVR registries supplemented by additional chart review when necessary. Covariates included: age, sex, height, weight, body surface area, body mass index (BMI), comorbid conditions, and Society of Thoracic Surgeons (STS) predicted risk of mortality.[9] Outcome measures were extracted from the TAVR registries, which are updated on a regular basis as patients are followed on an annual or bi-annual basis in the longitudinal TAVR clinics at both sites. The primary outcome was all-cause mortality and the secondary outcomes were procedural major or minor vascular and bleeding complications based on the VARC II consensus document.[10]

Psoas Muscle Measurements. PMA was measured on the pre-procedural CT scan images using the CoreSlicer.com web-based software package (version 1.0.0, Montreal, Quebec) as shown in Figure 1. The axial series of images was opened in a multiplanar reconstruction view to identify the desired slice at the top of the L4 vertebrae in the sagittal plane (standardized as the slice just below the anterior-superior aspect of the bright vertebral endplate). This slice level has been shown to optimally correlate with psoas muscle volume and frailty.[11] The threshold brush tool was used to define the cross-sectional area of the left and right psoas muscles in the axial plane using a muscle inclusion threshold of -30 to +150 Hounsfield units.[12] PMA was calculated as the sum of the left and right psoas areas and represented as a continuous variable in non-indexed and BMI-indexed format (based on the recommendation of the Foundation for the National Institutes of Health[13]), as well as sex-stratified tertiles.

Statistical Analyses. All analyses were stratified by sex. Descriptive statistics and distributional histograms were examined. Cuzick's test was used to compare the prevalent characteristics and

comorbidities across tertiles of PMA. Student's t-test was used to compare the risk of our primary and secondary outcomes according to PMA. Cox and logistic regression models were used to determine PMA's association with mortality and procedural complications, respectively. Models were adjusted for the STS predicted risk of mortality. Survival curves were generated by the Kaplan-Meier method. For the primary outcome, Harrell's C statistic was used to assess the incremental value of adding PMA to a model containing the STS predicted risk of mortality. Statistical analyses were performed with the STATA software package (version 14, College Station, Texas).

RESULTS

Descriptive characteristics of the study cohort (n=208) are shown in Table 1. The mean age at the time of TAVR was 80.7 ± 6.8 years and the proportion of females was 55%. The mean STS predicted risk of mortality was 6.0 ± 3.9 % with an observed risk of 7% at 30 days and 25% at 1 year. Over a mean follow-up period of 504 ± 476 days, a total of 57 all-cause deaths were observed. During the in-hospital period, 41% of patients experienced a VARC composite early safety event, of which 18% experienced a bleeding complication and 17% a vascular complication (major or minor).

PMA was normally distributed as shown in Figure 2. The mean PMA was 21.9 ± 4.4 cm^2 in males and 14.1 ± 3.5 cm^2 in females. Baseline characteristics stratified by sex-stratified PMA tertiles are shown in Table 1. Patients with low PMA were slightly older, with lower BMI, a higher prevalence of diabetes mellitus and a lower prevalence of chronic lung disease. There was no significant difference in STS predicted risk of mortality between the lowest and highest tertiles of PMA. When PMA was indexed to BMI, the mean PMA/BMI was 0.83 ± 0.18 in males and 0.56 ± 0.16 in females.

PMA was significantly lower in non-survivors as compared to survivors in the female group (mean PMA 12.9 cm^2 vs. 14.5 cm^2, p=0.047) whereas this association was not seen in the male group (mean PMA 21.7 cm^2 vs. 22.4 cm^2, p=0.50). There was a trend towards PMA being lower among males suffering a bleeding complication (mean PMA 19.8 cm^2 vs. 22.3 cm^2, p=0.06) although PMA was not otherwise

associated with the occurrence of post-procedural complications. The majority of the death were attributed to cardiac causes (71%) and occurred >30 days after the index TAVR (74%).

After adjusting for STS predicted risk, the association between PMA and all-cause mortality persisted in the female group (HR 0.88 per 1 cm^2 increase in PMA, 95% CI 0.78 to 0.99). Addition of PMA to the Cox regression model containing STS predicted risk resulted in an improvement in Harrell's C statistic from 0.62 to 0.67. PMA was not significantly associated with mortality in the male group (HR 1.01 per 1 cm^2 increase in PMA, 95% CI 0.93 to 1.10). Kaplan-Meier survival estimates by tertile of PMA for males and females are shown in Figure 3 and 4, respectively.

Adjusted logistic regression analysis revealed an association between PMA and bleeding complications in the male group (OR 0.78, 95% CI 0.62 to 0.97). PMA was not significantly associated with bleeding complications in the female group (OR 1.03, 95% CI 0.90 to 1.17) or with vascular complications in either the male or female group (OR 0.90, 95% CI 0.71 to 1.14 and OR 0.92, 95% CI 0.78 to 1.10 respectively).

Sensitivity analysis incorporating psoas muscle density (defined as mean Hounsfield unit value of the left and right psoas muscles) did not reveal a significant incremental association. The Cox regression analysis amalgamating males and females did not show a significant overall association for PMA although it did confirm an interaction between PMA and female sex (P=0.06). When the Cox regression analysis was repeated using indexed PMA/BMI instead of non-indexed PMA, the observed association with all-cause mortality in the female group was slightly strengthened (HR 0.03 per 1 cm^2/BMI increase, 95% CI 0.002 to 0.72, p=0.03).

DISCUSSION

This study is the first to demonstrate the proof-of-concept that low PMA – a biological marker for sarcopenia and frailty – is associated with increased mortality after TAVR, particularly in women. The magnitude of this association was clinically important and independent of the STS predicted risk, conferring

a 12% hazard for every 1 cm^2 increment in PMA. Indexing PMA measurements to BMI further strengthened the observed association. The effect of PMA on post-procedural complications was less compelling, with a possible association detected between low PMA and bleeding complications in males. Of note, PMA measurements were readily feasible within 5 minutes or less using publicly available software and routine clinical CT scan images.

Our results are consistent with prior studies that have examined the prognostic value of PMA in non-cardiac surgery. In this emerging body of evidence, low PMA has been associated with post-operative mortality and morbidity after proximal aortic surgery,[14] open abdominal aortic surgery,[15] endometrial cancer surgery,[16] colorectal cancer surgery,[17] liver cancer surgery,[18] and liver transplantation.[19] Furthermore, our observed effect in women undergoing TAVR was similar in magnitude and direction to our recently completed study in 149 patients undergoing endovascular or open abdominal aneurysm repair, in which there was a 14% hazard of all-cause mortality for every 1 cm^2 increment in PMA (unpublished data, 2015).

The mechanism linking PMA and post-TAVR mortality is thought to be related to the central role of skeletal muscle in the frailty syndrome, acting as the main reservoir for amino acids in the body, which when depleted, impairs several vital functions necessary for recovery.[20] Frail patients with low muscle mass have impaired muscle protein synthesis and a high risk of deconditioning after an invasive procedure; this is compounded by the vicious cycle of inadequate nutrition and decreased physical activity.[21] Thus, in addition to its role as a prognostic marker, PMA may be considered as a screening tool to identify vulnerable patients that may benefit from protein supplementation and physical rehabilitation to optimize their frailty status before and after the TAVR procedure.[22]

The interaction between PMA and sex persisted despite indexing for body size, such that PMA was predictive of mortality in females but not in males. A possible explanation for this intriguing result is that the effect of sarcopenia on mortality may only become important at very low values of PMA; the lowest tertile was 6.0-12.4 cm^2 in females, no male had a PMA below this threshold (the lowest tertile was 13.6-

19.4 cm^2 in males). If PMA influences risk below a very low absolute threshold, there may not have been enough males with sufficiently low PMA to observe harm. Another possible explanation is that the effect of sarcopenia on mortality is diluted in males because their risk of mortality is mainly driven by a higher burden of comorbid cardiovascular disease (in this cohort the prevalence of myocardial infarction was 31% in males vs. 19% in females).[23]

Using clinical scales to measure frailty, our group and others have previously reported a similar interaction between frailty and female sex. In the Longitudinal Aging Study Amsterdam, frailty was predictive of mortality to a greater extend in community-dwelling females than in males independent of comorbidity and disability.[23] In the Frailty ABC'S study, females with slow gait speed had an adjusted odds ratio of 8.62 for mortality or major morbidity after cardiac surgery, whereas males with slow gait speed had an adjusted odds ratio of 1.65.[24] Therefore, the current results reaffirm that the impact of frailty, whether measured by clinical scales or PMA, is more pronounced in females after an invasive cardiac procedure.

In secondary analyses, low PMA appeared to be associated with increased bleeding complications in men undergoing TAVR. This association persisted after adjusting for access (trans-femoral vs. trans-apical or direct aortic) and was consistent with a prior study by Green that showed an odds ratio of 2.2 for clinical frailty and post-TAVR major bleeding complications.[4] The lack of a significant effect in women may reflect the play of chance or differences in the etiologic factors responsible for bleeding in this group of patients. Further studies are warranted to understand the influence of low muscle mass on procedural bleeding risk in older men and women. Moreover, similar to our observation, the study by Green found that most of the frailty-related adverse events occurred after the initial 30-day post-TAVR period.

Interpretation of these results should be considered in light of the following limitations. First, clinical frailty markers were not captured in the local TAVR registries such that the complementary or incremental effect of PMA when used alongside gait speed and handgrip strength could not be ascertained in this study. Given that sarcopenia is defined as the combination of low muscle mass and low muscle strength or performance, integration of these parameters is promising. Second, although our sample size

compares favorably with other studies of frailty in TAVR (N=100-300 in most studies), a larger sample size would be beneficial to produce robust confidence intervals for the various strata. Third, whereas all-cause mortality was chosen as our primary outcome, future studies should consider the relationship between PMA and patient-centered outcomes such as functional recovery, disability, and quality of life. Lastly, use of the STS risk score to predict all-cause mortality in TAVR patients is an extrapolation since this risk score was derived and validated to predict short-term outcomes in surgical patients.

CONCLUSION

PMA is a biological marker for frailty that has now been shown to be associated with midterm survival in women undergoing TAVR. Addition of PMA to the STS predicted risk model resulted in improved model performance to discriminate survivors from non-survivors. This novel marker has the advantage of being readily measurable from clinical CT scan images that are routinely ordered before TAVR. Beyond its demonstrated role as a prognostic risk factor, PMA has the potential to serve as a screening tool to identify frail patients that could benefit from targeted strategies to optimize muscle mass and strength before a cardiac intervention.

** The following reference list applies only to chapter 2*

REFERENCES

1. Afilalo J, Alexander KP, Mack MJ, et al. Frailty Assessment in the Cardiovascular Care of Older Adults. *J Am Coll Cardiol*. 2014;63(8):747-762. doi:10.1016/j.jacc.2013.09.070.

2. Green P, Arnold SV, Cohen DJ, et al. Relation of Frailty to Outcomes After Transcatheter Aortic Valve Replacement (from the PARTNER Trial). *Am J Cardiol*. 2015;116(2):264-269. doi:10.1016/j.amjcard.2015.03.061.

3. Schoenenberger AW, Stortecky S, Neumann S, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). *Eur Heart J*. September 2012. doi:10.1093/eurheartj/ehs304.

4. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. *JACC Cardiovasc Interv*. 2012;5(9):974-981. doi:10.1016/j.jcin.2012.06.011.

5. Kim TN, Choi KM. The implications of sarcopenia and sarcopenic obesity on cardiometabolic disease. *J Cell Biochem*. 2015;116(7):1171-1178. doi:10.1002/jcb.25077.

6. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. In: Vol 39. 2010:412-423. doi:10.1093/ageing/afq034.

7. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: Current Concepts and Imaging Implications. *American Journal of Roentgenology*. 2015;205(3):W255-W266. doi:10.2214/AJR.15.14635.

8. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and

precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab*. 2008;33(5):997-1006. doi:10.1139/H08-075.

9. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. *Ann Thorac Surg*. 2009;88(1 Suppl):S23-S42. doi:10.1016/j.athoracsur.2009.05.056.

10. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60(15):1438-1454. doi:10.1016/j.jacc.2012.09.001.

11. Mamane S, Piazza N, Nelson K, et al. Feasibility and Reliability of Psoas Muscle Area As A Novel Measure for Sarcopenia and Frailty in Patients Undergoing Transcatheter Aortic Valve Implantation. *Journal of Frailty Aging*.

12. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol*. 1998;85(1):115-122.

13. Cawthon PM, Peters KW, Shardell MD, 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):567-575. doi:10.1093/gerona/glu023.

14. Ganapathi AM, Englum BR, Hanna JM, et al. Frailty and risk in proximal aortic surgery. *J Thorac Cardiovasc Surg*. 2014;147(1):186–191.e1. doi:10.1016/j.jtcvs.2013.09.011.

15. Lee JS-J, He K, Harbaugh CM, et al. Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair. *J Vasc Surg*. 2011;53(4):912-917.

doi:10.1016/j.jvs.2010.10.111.

16. Kuroki LM, Mangano M, Allsworth JE, et al. Pre-operative assessment of muscle mass to predict surgical complications and prognosis in patients with endometrial cancer. *Ann Surg Oncol*. 2015;22(3):972-979. doi:10.1245/s10434-014-4040-8.

17. Jones KI, Doleman B, Scott S, Lund JN, Williams JP. Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. *Colorectal Dis*. 2015;17(1):O20-O26. doi:10.1111/codi.12805.

18. Valero V, Amini N, Spolverato G, et al. Sarcopenia adversely impacts postoperative complications following resection or transplantation in patients with primary liver tumors. *J Gastrointest Surg*. 2015;19(2):272-281. doi:10.1007/s11605-014-2680-4.

19. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg*. 2010;211(2):271-278. doi:10.1016/j.jamcollsurg.2010.03.039.

20. Wolfe RR. Regulation of muscle protein by amino acids. *J Nutr*. 2002;132(10):3219S–24S.

21. Ferrucci L, Maggio M, Ceda GP, Beghi C, Valenti G, De Cicco G. Acute postoperative frailty. *ACS*. 2006;203(1):134-135. doi:10.1016/j.jamcollsurg.2006.03.005.

22. 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):134-143. doi:10.1016/j.pcad.2014.07.004.

23. O'Connor SA, Morice M-C, Gilard M, et al. Revisiting Sex Equality With Transcatheter Aortic Valve Replacement Outcomes: A Collaborative, Patient-Level Meta-Analysis of 11,310 Patients. *J Am Coll Cardiol*. 2015;66(3):221-228. doi:10.1016/j.jacc.2015.05.024.

24. Afilalo J, Eisenberg MJ, Morin J-F, 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):1668-1676. doi:10.1016/j.jacc.2010.06.039.

Table 1. Baseline Characteristics Stratified by PMA Tertiles

	PMA High Tertile	PMA Mid Tertile	PMA Low Tertile	P-value
Age	79.6 ± 7.0	79.7 ± 6.9	83.1 ± 5.9	0.001
Female	56%	55%	55%	0.97
Height, m	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	0.04
Weight, kg	78.1 ± 15.7	72.6 ± 14.1	64.6 ± 13.5	<0.001
BMI, m/kg^2	28.3 ± 5.6	26.5 ± 4.4	24.2 ± 4.3	<0.001
BSA, m^2	1.9 ± 0.2	1.8 ± 0.2	1.7 ± 0.2	<0.001
Diabetes	31%	31%	52%	0.11
Hypertension	81%	81%	96%	0.10
Myocardial infarction	19%	31%	26%	0.58
Cerebrovascular disease	15%	19%	11%	0.66
Peripheral arterial disease	23%	19%	33%	0.39
Chronic lung disease	27%	33%	15%	0.14
Creatinine, umol/L	112.9 ± 42.5	104.7 ± 73.3	101.7 ± 46.0	0.03
Left ventricular ejection fraction, %	58.5 ± 17.7	57.0 ± 18.0	55.1 ± 20.6	0.53
NYHA class III-IV	79%	75%	70%	0.08
STS predicted risk of mortality, %	6.0 ± 4.1	5.2 ± 3.0	6.4 ± 4.3	0.39
Valve size, mm	27.2 ± 1.8	26.5 ± 2.4	27.1 ± 2.1	0.78
Femoral approach	62%	52%	54%	0.29

Abbreviations: BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association; PMA, psoas muscle area; STS, Society of Thoracic Surgeons.

FIGURE LEGENDS

Figure 1: Measurement of PMA with the CoreSlicer.com Software

Measurement of psoas muscle area with the CoreSlicer.com Software. After uploading the computed tomography scan, the image corresponding to the top of the L4 vertebrae is identified, and the area of the left and right psoas muscles is semi-automatically measured at this level.

Figure 2: Distribution of PMA Stratified by Sex

Distribution of psoas muscle area stratified according to sex.

Figure 3: Effect of PMA Tertiles on All-Cause Mortality After TAVR in Males

Kaplan-Meier survival estimates: effect of psoas muscle area (PMA) tertiles on all-cause mortality after transcatheter aortic valve replacement in males.

Figure 4: Effect of PMA Tertiles om All-Cause Mortality After TAVR in Females

Kaplan-Meier survival estimates: effect of psoas muscle area (PMA) tertiles on all-cause mortality after transcatheter aortic valve replacement in females.

Figure 1: Measurement of PMA with the CoreSlicer.com Software

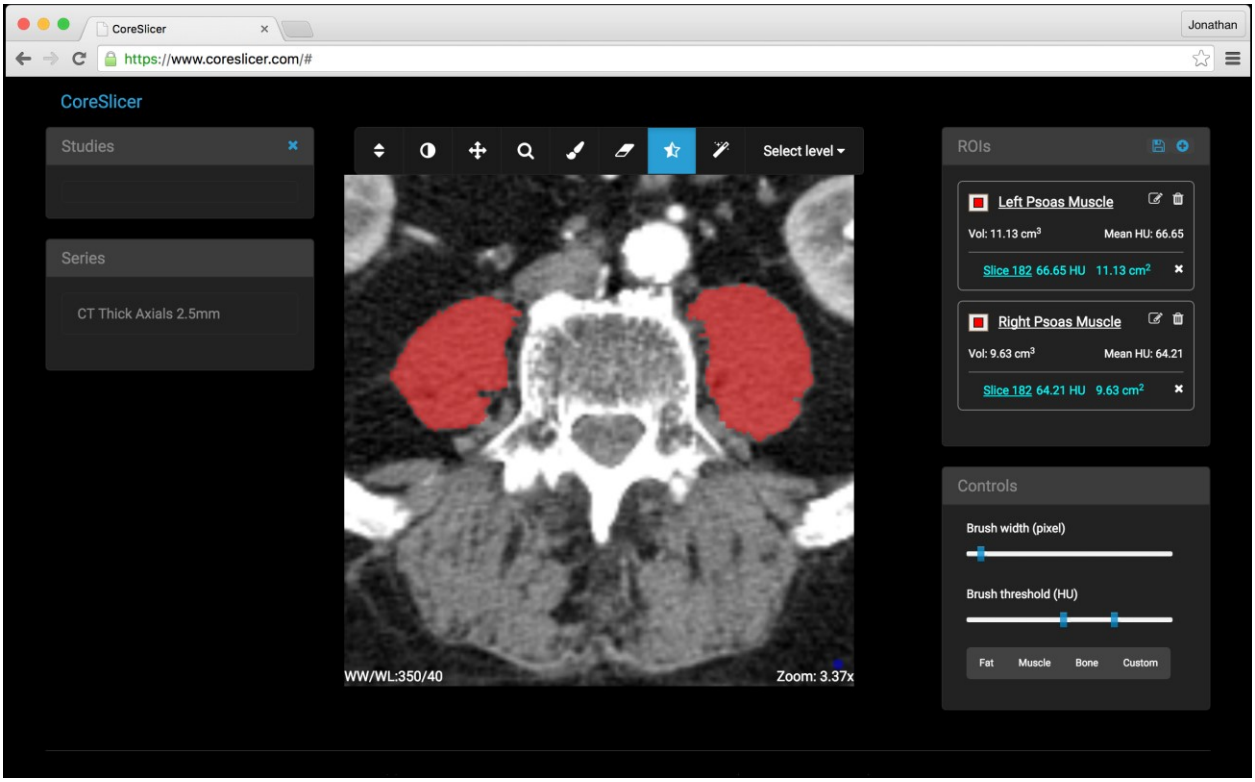


Figure 2: Distribution of PMA Stratified by Sex

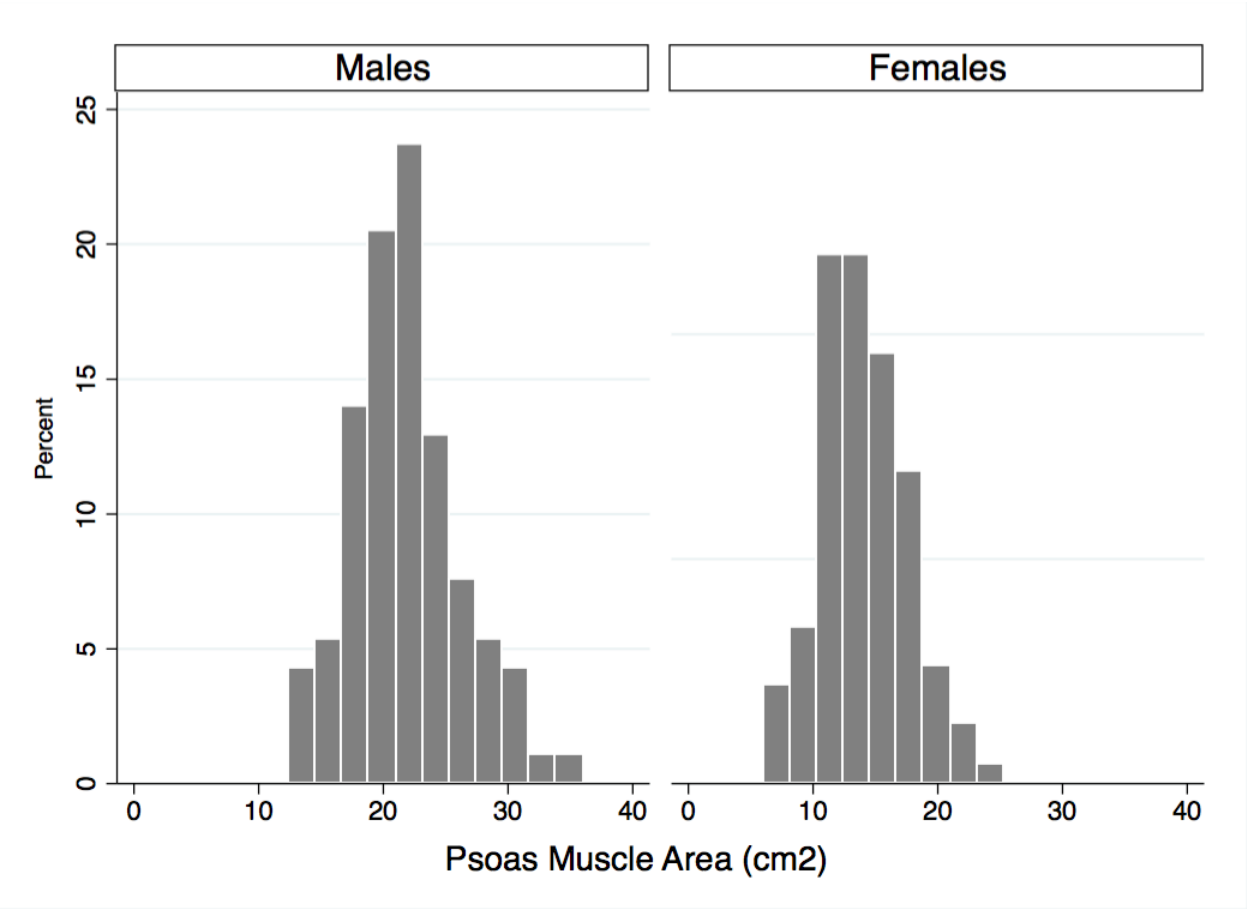


Figure 3: Effect of PMA Tertiles on All-Cause Mortality After TAVR in Males

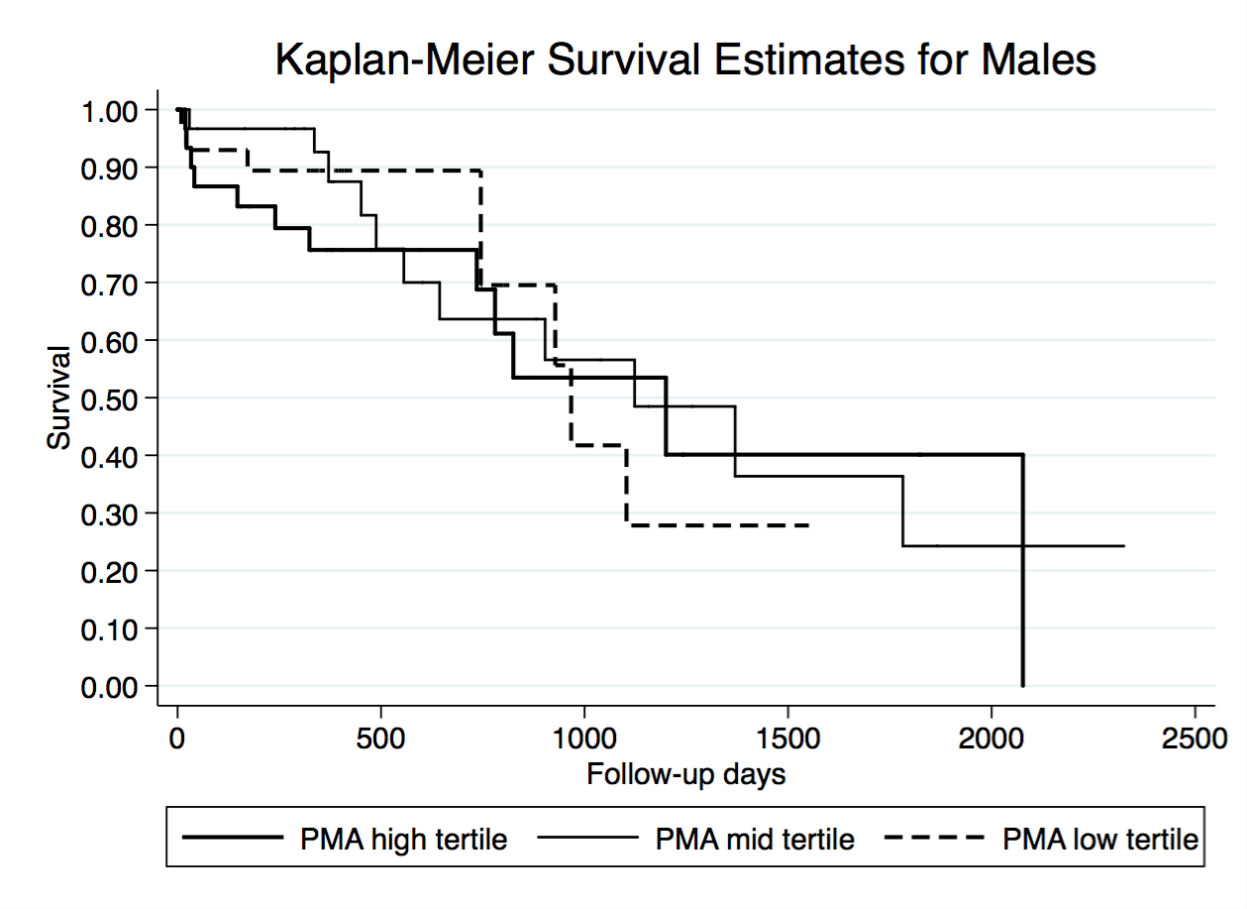
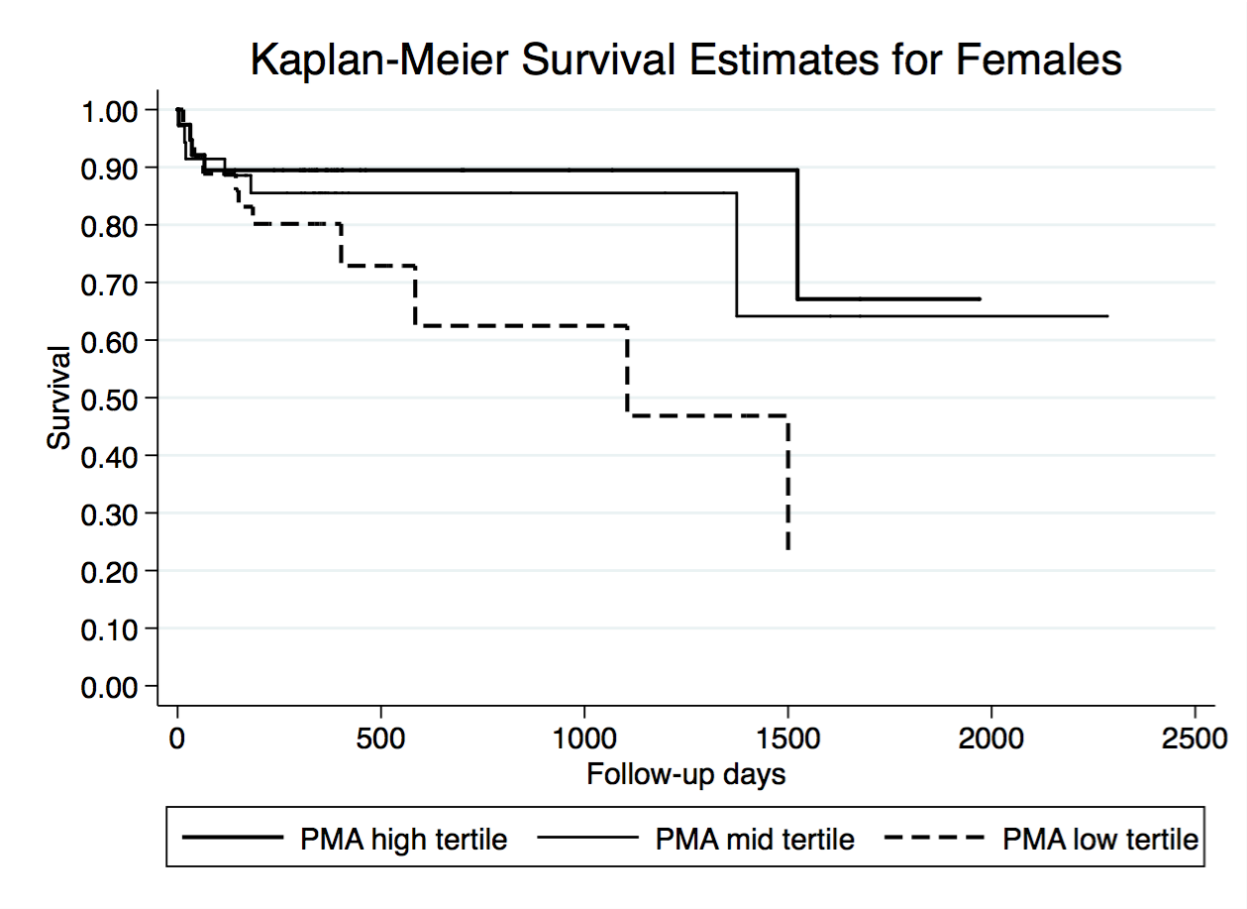


Figure 4: Effect of PMA Tertiles om All-Cause Mortality After TAVR in Females



Chapter 3 - Transition from the Evaluation of Muscle Mass in a Retrospective Cohort to Sarcopenia in a Prospective Cohort

After the Montreal-Munich cohort study, an additional 6 retrospective studies were published, investigating the role of CT measures of muscle mass as a prognostic indicator in patients undergoing TAVR. Their methodologies were previously summarized in Table 1. Table 2 summarizes the various outcomes of these studies.

Table 2: Studies including CT-measures of muscle mass in patients undergoing TAVR

Study	Study design	Population (n)	Mean age (years)	STS-PROM (%)	Outcome	Effect size
Dahya V et al. (Dec. 2016)	retrospective single centre	104	81	not reported	length of stay	ß -0.07 (SE 0.03, p=0.03)
Garg L et al. (Feb. 2017)	retrospective single centre	152	83.3 ± 6.5	6.9 ± 3.4	1) early poor outcome (30 day composite outcome) 2) 1-year mortality 3) high resource utilization (PLOS, discharge to rehab, readmission)	1) OR 3.18 (CI 1.29 to 7.83; p=0.012) 2) non-significant 3) OR 2.65 (CI 1.32 to 5.31; p=0.006)
Mamane S et al. (Feb. 2016)	retrospective multi-centre	208	80.7 ± 6.8	6.0 ± 3.9	cumulative all-cause mortality	1) female: HR 0.88 (CI, 0.78-0.99) 2) male: HR 1.01 (CI, 0.93-1.10)
Mok M et al. (Mar. 2016)	retrospective multi-centre	460	81 ± 8	6.9 ± 3.9	1) 30-day mortality 2) cumulative mortality	1) SMI: non-signifiant 2) SMI: HR 1.55 (CI 1.02 to 2.36, p=0.04)
Nemec U et al. (Mar. 2017)	retrospective single centre	157	82 ± 10	7.1 ± 5.3	1) length of stay 2) 30-day mortality 3) 1-year mortality	1) OR 0.95 (0.90–0.99, p=0.013) 2) OR 0.97 (0.89–1.06, p=0.563) 3) OR 0.95 (0.90–1.00, p=0.061)
Paknikar R (Mar. 2016)	retrospective single centre	156 (SAVR) 139 (TAVR)	70.4 ± 13.8 (SAVR) 79 ± 8.2 (TAVR)	3.04 ± 3.28 (SAVR) 6.48 ± 4.52 (TAVR)	1) late mortality 2) high resource utilization (ICU >7d, LOS >14d, readmission)	1) PMA: HR, 0.52 (p=0.016) 2) PMA: OR, 0.56 (p=0.001)
Saji M et al. (Jul. 2016)	retrospective single centre	236	80.1 ± 8.7	8.5 ± 4.6	1) 30-day mortality 2) 6-month mortality 3) early combined safety endpoint (VARC-II)	1) not reported 2) HR 1.53, (CI 1.06 to 2.21) 3) not reported

PMA: psoas muscle area, SAVR: surgical aortic valve replacement, SMI: skeletal muscle index, STS-PROM: Society of Thoracic Surgeons predicted risk of mortality, TAVR: transcatheter aortic valve replacement

When the term ‘sarcopenia’ was initially coined by Irwin Rosenberg in 1988, the primary focus was on muscle mass and body composition (95). This definition was later championed by Baumgartner (78) and others, until researchers began to realize the important role of muscle

function in the assessment of sarcopenia. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) recommended that the working definition of sarcopenia contain both a measure of muscle mass and of muscle function (52).

In a recent meta-analysis by Beaudart et al., only 17 prospective studies were found to have assessed outcomes associated with sarcopenia according to the EWGSOP definition. In their analysis, there was a clear association between sarcopenia and mortality (OR 3.6, CI 2.96 to 4.37) and functional disability (OR 3.03, CI 1.8 to 5.12) (96). Of the studies described in Chapter 1 evaluating the prognostic role of sarcopenia in patients undergoing surgical procedures and those specific to patients undergoing TAVR, I could not identify any that reported measuring muscle function in addition to muscle mass. In keeping with the widely-accepted definition, there was a need for a prospective study investigating the role of sarcopenia, as defined by a measure of both muscle mass and muscle function in patients undergoing TAVR in order to address this knowledge gap.

Given that the effect size was modest in our retrospective study and that low PMA was only associated with mortality in women primarily in the lowest PMA tertile, we hypothesized that the missing link was muscle function. As such, we designed a planned analysis of the prospective multicenter FRAILTY-AVR cohort study to investigate the effects of sarcopenia on various outcomes in older adults undergoing TAVR. We also sought to derive a sarcopenia score as the only currently available sarcopenia score (SARC-F) remains a questionnaire and does not include measurements of muscle mass or function (97). Consequently, we conducted a prospective cohort study evaluating the prognostic role of sarcopenia in older adults undergoing TAVR, and it is presented in manuscript format in Chapter 5. For this study, I prospectively collected CT scans in digital format for patients undergoing TAVR from each participating site

and I performed all muscle measurements. I participated in the data analysis with my supervisor. Finally, I authored and presented the abstract and manuscript as first author.

Chapter 4: Prognostic Role of Sarcopenia - Prospective Cohort Study

Manuscript to be submitted: "Incremental Prognostic Value of Sarcopenia in Older Adults Undergoing Transcatheter Aortic Valve Replacement"

The prospective cohort study investigating the prognostic role of sarcopenia in patients undergoing transcatheter aortic valve replacement is presented in manuscript format below. This manuscript is not yet submitted for publication.

Incremental Prognostic Value of Sarcopenia in Older Adults Undergoing Transcatheter Aortic Valve Replacement

The FRAILTY-AVR Study

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Jonathan Afilalo and Louis Mullie developed the CoreSlicer software but do not hold any financial incentives or patents related to its use.

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ABSTRACT

Background: Sarcopenia is a "biologic substrate of frailty". Low muscle mass has recently emerged as a predictor of outcomes in older adults undergoing transcatheter aortic valve replacement (TAVR). While previous studies focus on the prognostic role of muscle mass in isolation, our study evaluates complementary measures of muscle mass and function.

Objectives: To determine the incremental prognostic value of psoas muscle area (PMA) in older adults undergoing TAVR. To derive a sarcopenia score incorporating both muscle mass and muscle function, and determine its incremental predictive value on post-procedural outcomes in older adults undergoing TAVR.

Methods: A multicenter international prospective cohort study of older adults ≥70 years of age undergoing TAVR was assembled to measure PMA on routine pre-procedural CT scans. Patients underwent a comprehensive frailty evaluation, which included a short performance physical battery (SPPB). End-points of interest were all-cause mortality, length of stay (LOS) and disability.

Results: The cohort consisted of 386 TAVR patients that had available CT scans with a mean age of 83.5 ± 5.8 years. The mean PMA was 21.2 ± 4.4cm^2 in males and 14.9 ± 3.7cm^2 in females. Lower PMA was associated with longer LOS (+0.32 days per cm^2, 95% CI 0.08 to 0.56) but not mortality at 1 year. The combination of low PMA and slow chair rises, reflecting sarcopenia was associated with longer LOS (+4.8 days, 95% CI 1.97 to 7.68) and increased mortality at 1 year (OR 5.61, 95% CI 1.58 to 19.91).

Conclusion: Sarcopenia, defined by a practical score combining muscle mass on pre-TAVR CT scans and physical performance tests, is a potent predictor of LOS during index hospitalization and all-cause mortality during the ensuing year.

KEYWORDS

Sarcopenia, Frailty, Muscle mass, Transcatheter aortic valve replacement

ABBREVIATIONS

ADL, IADL	Activities of Daily Living, Instrumental Activities of Daily Living
AIC	Akaike Information Criterion
AS	Aortic Stenosis
DICOM	Digital Imaging and Communications in Medicine
EFT	Essential Frailty Toolset
PMA	Psoas Muscle Area
OARS	Older Americans Resources and Services
SMA	Skeletal Muscle Area
SPPB	Short Physical Performance Battery
STS-PLOS	Society of Thoracic Surgeons Predicted Length of Stay
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
TAVR	Transcatheter Aortic Valve Replacement

INTRODUCTION

Aortic Stenosis is among the leading causes of valvular heart diseases in the developed world (1, 2), and transcatheter aortic valve replacement (TAVR) has become a proven treatment option for older adults who were previously considered to be at high or intermediate risk for surgical AVR (3-5). Despite a clear reduction in mortality, poor functional recovery and quality of life (QOL) remain an issue in older adults (6, 7). Given the advanced age and multiple chronic conditions in this patient population, frail patients face an increased risk of disability and mortality after TAVR in comparison to their less frail counterparts (8, 9). Therefore, the evaluation of frailty, which is a geriatric syndrome of decreased resilience to stressors (10), is a critical task for risk prediction and patient selection in older adults undergoing TAVR (7, 11, 12). Sarcopenia is the "biological substrate of frailty" and is defined as age-related decline in skeletal muscle mass and function (13-15). Sarcopenia has emerged as a powerful predictor of mortality and physical functioning in older adults (16, 17). Measuring sarcopenia pre-procedurally is an attractive risk stratification tool as muscle mass can be objectively measured (18, 19), provides insight into a patient's physiologic reserves (20), and can potentially be treated (21).

However, existing tools to measure muscle mass are highly specialized and often not easily accessible (19), or rely on inaccurate surrogates such as self-reported weight loss, limiting its clinical use. Currently, sarcopenia scores are limited to subjective questionnaires and do not include direct measurements of muscle mass or function (22-24). In recent years, surrogate imaging markers such as cross-sectional psoas muscle area (PMA) and skeletal muscle area (SMA) on clinically indicated CT-scans have been shown to predict operative mortality and functional disability in patients undergoing numerous types of surgery (25-29). Practically, these measures have been shown to be reproducible in patients undergoing cardiac surgery and TAVR

(30-33). More specifically in patients undergoing TAVR, pre-procedural PMA and SMA have been shown to predict adverse outcomes including mortality (34-36) and high resource utilisation (37, 38), although initial studies were retrospective in nature and had important limitations. These studies evaluated the predictive value of CT muscle mass surrogates independently as they did not include any functional measures such as gait speed or chair rises. Accordingly, we sought to prospectively determine the prognostic value of low muscle mass as measured by PMA, and to determine whether this was incremental to lower-extremity muscle performance as measured by the short physical performance battery (SPPB) (39, 40) which has been shown to predict 1-year mortality or worsening disability after TAVR (41). Likewise, we derived a sarcopenia score that included both a measure of muscle mass (PMA) and muscle function (chair rises), to identify if this score adds incremental value above existing risk prediction models (42).

METHODS

Study Design

FRAILTY-AVR was a prospective international multicentre cohort study that sought to evaluate the prognostic role of frailty in older adults undergoing aortic valve replacement at 14 academic hospitals across Canada, the United States and France. Patient characteristics, frailty measures, CT scans, and outcomes were prospectively collected by trained observers at each of the participating hospitals. The CT scans were subsequently analyzed by our centralized core lab team at the Jewish General Hospital Centre for Clinical Epidemiology (Montreal, QC). Ethics approval was obtained from hospitals' review boards, and patients provided informed consent to participate in the study. We conducted a pre-planned analysis of this study to determine the incremental value of PMA on routine pre-TAVR CT scans.

Patient Population

Consecutive patients with severe AS were screened and approached to participate between January 2012 and December 2015. Patients ≥70 years old who underwent TAVR and who had a retrievable abdomino-pelvic CT scan in DICOM format were included in our analysis. Infused CT scans were routinely performed before TAVR for clinical purposes; no scans were requested for research purposes. All CT-scans were done within 3 months prior to TAVR, and most were done within 1 month. We excluded patients who had CT scan data that was not in the appropriate format or incomplete for the purpose of measuring PMA. Patients with at least 6 months of follow-up data were included in the analysis. Other inclusion and exclusion criteria were the same as in the primary study (41).

PMA Measurements

Using Osirix MD software (version 7.0, Switzerland), the axial pre-procedural CT scan series of images were opened in a multiplanar reconstruction view to localize the slice at the top of the L4 vertebrae in the sagittal plane, standardized as the slice just below the anterior-superior aspect of the bright vertebral end plate (figure 1a). Our data suggest that this slice level is optimally correlated with psoas muscle volume (33) and is the most common level reported in similar research. The selected axial slice was opened in the coreslicer.com web-based software package (version 1.0, Canada), where PMA was measured using the density threshold brush tool, using a skeletal muscle inclusion threshold of -30 to 150 Hounsfield units (figure 1b). PMA was calculated as the sum of the left and right psoas areas and represented as a continuous variable in nonindexed format. In order to test inter-observer reliability, a subset of 100 CT scans were independently analyzed by a second observer. The Pearson's inter-observer correlation was

r=0.96. We also performed a Bland-Altman analysis that showed 95% limits of agreement -3.17 to 2.87 cm2, with a mean difference of -0.15 (CI, -0.45 to 0.15).

Sarcopenia Score

We developed a sarcopenia score that includes chair rises as a measure of lower extremity muscle performance and PMA as a measure of muscle mass, with a maximum score of 2. 1 point was assigned for chair rises >15 seconds (time to stand 5 times from a seated position without using arms) (43, 44), and/or 1 point for PMA in the lowest tertile. The sex-specific lowest tertile cut-offs were nearly identical to our previous retrospective cohort (30). Patients with 0 points were categorized as having no sarcopenia, with 1 point as pre-sarcopenia and with 2 points as sarcopenia. In deriving the score, we tested each component of SPPB and a measure of upper-extremity performance in the model. Chair-rise was the most predictive of outcomes, and remains a simple test. Grip strength did not improve the model and increased testing complexity. This is consistent with previous risk-score validation studies in patients undergoing TAVR (12).

Covariates

Measurements of frailty, cognition and disability were obtained during pre-procedure evaluation. Medical records were used to detail patient comorbidities, pre- and post-procedure laboratory results and information on disposition at hospital discharge. Specifically, lower-extremity muscle performance was measured by the SPPB; the SPPB consists of 5-meter gait speed, timed chair rises, and timed standing balance, with each scored 0-4 for a composite score of 0-12.

The Society of Thoracic Surgeons (STS) risk model was used to calculate the predicted risk of mortality (PROM) and prolonged length of stay (PLOS) for each patient (42). Data was

collected by trained observers at each participating site and subsequently reviewed centrally for quality assurance.

Outcomes

For this analysis, the outcome measures were all-cause mortality at 6 and 12 months, post-procedural length of stay (LOS) defined as number of days from index procedure to hospital discharge and new disability defined as ≥2 new deficits in activities of daily living (ADL) and instrumental activities of daily living (IADL) as measured by the Older Americans Resources and Services (OARS) questionnaire.

Statistical Analyses

Descriptive statistics and distributional histograms were examined. Continuous variables were summarized as means with standard deviation (SD). As PMA was normally distributed, parametric statistics were used. Univariate analyses were performed using Cuzick's test for trend to compare patient characteristics across sex-specific tertiles of PMA and to identify associations between PMA and the defined outcomes. Multivariable regression analysis was used to determine the effect of PMA on outcome measures after adjusting for covariates of interest which were selected based on a review of validated risk models and univariate analyses. Specifically, we adjusted for SPPB in all analyses, STS-PROM in mortality analyses, and STS-PLOS in analyses of LOS. We used Akaike's information criterion (AIC) to determine if the addition of PMA improved the quality of previous models. For $\Delta AIC = AIC_{priormodel} - AIC_{newmodel}$, more positive values imply improved outcome prediction, where values 0-2 suggest slight improvement, 4-7 considerable improvement and >10 substantial improvement

(45). Survival curves were generated using the Kaplan-Meier method. Analyses were performed using the STATA software package (version 14, USA).

RESULTS

Of the 669 patients that underwent TAVR in the FRAILTY-AVR cohort, 543 patients had available CT scans for analysis. Our study cohort consisted of 386 patients after excluding patients due to CT datasets that were in the incorrect format, that truncated or excluded the L4 region, or that had insufficient resolution for analysis. The flow diagram for enrollment is shown in figure 2.

Descriptive characteristics of the study cohort stratified by PMA are shown in table 1. The mean age at the time of TAVR was 83.5 ± 5.8 years, with 89% of patients ≥80 years old. The proportion of females was 44%. The mean STS-PROM was 6.5 ± 4.4% with an observed risk of mortality of 4% at 30 days, 11% at 6 months and 16% at 1 year. The mean post-procedural LOS was 7.6 ± 9.3 days, with 30% of patients being discharged to a skilled-care facility. The mean baseline SPPB score was 5.9 ± 3.2. The mean baseline disability (ADL/IADL deficit) was 2 ± 2.5. Descriptive characteristics stratified by sarcopenia score are shown in supplemental table 1. Patients without PMA CT scan measurements were similar to the study cohort (supplemental table 2).

A distributional histogram of sex-stratified PMA is shown in figure 3. The mean PMA was 21.2 ± 4.4cm^2 in males and 14.9 ± 3.7cm^2 in females. As PMA was significantly larger in males than females, all analyses were done according to sex-specific tertiles. The lowest tertile cut-off was 19.15cm^2 in men and 12.95cm^2 in females (figure 3).

Baseline characteristics according to sex-specific PMA tertile are shown in table 1. Patients with smaller PMA were older ($p<0.001$), had lower BSA ($p<0.001$), lower grip strength ($p<0.001$), higher STS-PROM ($p=0.003$), and higher STS-PLOS ($p=0.01$). Univariate analyses revealed that PMA was not associated with frailty scales: Fried ($p=0.28$), SPPB ($p=0.15$), and EFT ($p=0.06$).

In multivariable analyses, Lower PMA was associated with longer LOS (+0.32 days per cm^2, 95% CI 0.08 to 0.56), an effect that was independent of SPPB and incremental to STS-PLOS and SPPB (ΔAIC 5.1). Patients in the lowest PMA tertile stayed on average 3.3 days longer than the highest (95% CI 1.14 to 5.46). Lower PMA was also associated with more disability at 6 months (+0.14 activities per cm2, 95% CI 0.01 to 0.26), but added limited incremental predictive value when added to a model already including SPPB (ΔAIC 2.5). The lowest PMA tertile was not independently associated with mortality at 6 months (OR 1.72, 95% CI 0.77 to 3.84) or 1 year (OR 1.48, 95% CI 0.74 to 2.96). These findings are detailed in supplemental table 3.

Overall, 107 patients (27.7%) were considered to have sarcopenia. At 1 year, the incidence of death was 3.7% (2/54) in non-sarcopenic patients, 15.2% (34/224) in pre-sarcopenic patients and 24.3% (26/107) in sarcopenic patients (figure 4). Sarcopenia was associated with increased mortality at 6 months (OR 11.6, 95% CI 1.49 to 90.16) and 1 year (OR 5.61, 95% CI 1.58 to 19.91). This predictive value was independent of SPPB and incremental to STS-PROM and SPPB (ΔAIC 6.8 at 6 months, ΔAIC 6.2, at 1 year). Kaplan-Meier survival estimates according to sarcopenia score are shown in figure 5.

Sarcopenia was associated with longer LOS (4.8 days, 95% CI 1.97 to 7.68), an effect that was incremental to STS-PLOS (ΔAIC 11.6). Sarcopenia was also associated with increased

disability defined as a reduction in number of ADL/IADLs at 6 months (3.3, 95% CI 1.74 to 4.85), that was independent and incremental to baseline function (ΔAIC 16.2). These findings are summarized in table 2. We performed multiple sensitivity analyses with different PMA cut-offs, PMA indexed for BSA, and separate sex-stratified analyses, all yielding comparable results.

DISCUSSION

To our knowledge, this is the first study to prospectively investigate the predictive role of sarcopenia in patients undergoing TAVR. In this study, we demonstrate that low muscle mass as measured by PMA is associated with longer length of stay and adds incremental benefit above the standard risk model STS-PLOS and functional tool SPPB. Measuring PMA was feasible in 93% of patients with CT scans that included the L4 region and were in DICOM format, could be readily completed within 5 minutes and was reproducible. PMA has the added benefit of being easily and rapidly acquired pre-procedurally, regardless of a patient's acute or chronic physical limitations, both of which are limitations of performance-based frailty testing, restricting their use to patients that can actively participate. Our findings build on an emerging literature demonstrating that CT-measured muscle mass surrogates such as PMA are important predictors of outcomes (30, 34-37), particularly LOS after TAVR (37, 38). Our predictive cut-offs for low PMA of 19.15cm^2 in men and 12.95cm^2 in females were very similar to the cut-off values from our previous TAVR cohort (30) and aortic aneurysm repair cohort (31). Further external validation is required before implementation of these cut-offs.

Despite this growing literature, there are no previous studies that evaluate the complementary role of muscle mass and function, with most studies listing this as an important limitation. We address this knowledge gap by deriving a practical sarcopenia score that

incorporates a measure of lower-extremity muscle function (chair rises) and muscle mass (PMA), demonstrating its ability to incrementally predict mortality, LOS and disability after TAVR, in older adults. We chose chair rises as a measure of lower-extremity performance as it has the advantage of being a simple and reproducible test (46) with well defined prognostic cut-off values (43, 44) that are independent of sex, and can be done without specialized equipment (video demonstration available at www.vimeo.com/118356014). Moreover, it is the only performance test included in the recently validated essential frailty toolset stemming from the FRAILTY-AVR cohort (41). In our model, we did not find added benefit from grip strength, a measure of upper-extremity muscle function. These findings highlight the important incremental gain of including both a measure of muscle mass and muscle function during the pre-procedural evaluation of sarcopenia.

This is also the first prospective study to investigate the predictive value of sarcopenia on patient-centred functional outcomes in older adults undergoing TAVR, demonstrating that lower PMA and sarcopenia are predictive of worsening disability. Skeletal muscle is an important reservoir of amino acids and a marker of nutritional status (47). Surgery leads to state of hypermetabolism and catabolism causing muscle wasting (48, 49). We hypothesize that pre-procedurally, sarcopenic patients start with insufficient muscle protein reserves, lacking the substrate to withstand the catabolic nature of the perioperative period, in turn limiting recovery and leading to disability and death over the following year.

Complementarily, patients who were not sarcopenic (0/2 points) were protected by their reserves, with only 2 patients (3.7%) dying after 1 year in comparison to 63 patients (16%) in the overall cohort. This finding supports the hypothesis that patients should be sufficiently

physically robust prior to undergoing surgery in order to be able to withstand the physiologic stress.

In terms of disability, non-sarcopenic patients remained stable, while sarcopenic patients became more disabled in comparison to their preprocedural status. These findings highlight the important role of targeting sarcopenic patients for prehabilitation and aggressive early rehabilitation post-procedurally in order to minimize functional loses, improve recovery and reduce mortality. Graded exercise and nutritional interventions such as protein supplementation have been shown to improve muscle mass and performance in older adults (21, 50). However, further studies are warranted in patient with AS to know if such interventions are feasible in the relatively short time between diagnosis and TAVR, and to test if curtailing sarcopenia pre-procedurally translates into improved outcomes.

Our results must be considered in the context of certain limitations. Firstly, unavailability of CT scans limited analysis to 58% of patients included in the larger TAVR cohort. However, there were no major differences when comparing the comorbidities and frailty indices of these two groups (supplemental table 1). A larger sample size as initially anticipated would have lead to narrower confidence intervals for our outcome measures. Secondly, the intervention was not randomized and frailer patients may have been directed toward TAVR over SAVR. Conceivably, the measured effect of sarcopenia on outcomes could be diluted if applied to a less frail population. However, in our cohort, the STS-PROM was only 6.5% which is low in comparison to previous randomized control trials of high risk patients undergoing TAVR that reported STS-PROM ranging from 7.4% to 11.8% (51). Thirdly, SAVR patients did not receive pre-procedural CT-scans and as such a measure of muscle mass could not be obtained. This limits the generalizability of our findings. Fourthly, the STS-PROM predicts 30 day or in-hospital

mortality, but not long-term mortality. In our model for 6 month and 1 year mortality, we adjusted for STS-PROM as risk prediction models for long-term outcomes are only recently externally validated and not yet well incorporated into clinical practice (12). Fifthly, not all details of pre- and post-operative care are available, and if unbalanced could conceivably influence the results. However, amongst the 19% of patients that were discharged to rehabilitation, there was no meaningful difference in the rate of rehabilitation between PMA tertiles. Lastly, in defining a sarcopenia score, we selected the lowest PMA tertile as our cut-off for low PMA, as there are not well-established standardized cut-off points. We did a sensitivity analysis using mean PMA as the cut-off (37) which yielded similar results. There remains a need to formally describe normal PMA values in a healthy population, and validate PMA cut-offs in defining sarcopenia.

CONCLUSIONS

While previous studies have suggested an association between PMA and morbidity after TAVR, our study is the first to do so prospectively and to be able to adjust for critical confounders such as SPPB. Low PMA was independently and incrementally predictive of longer LOS and disability, and sarcopenia was incrementally predictive of mortality, LOS, and disability after TAVR. Our findings suggest that the pre-TAVR evaluation of sarcopenia should dually include complementary measures of muscle mass and function, and that sarcopenia may be a therapeutic target to optimize outcomes in older adults undergoing TAVR.

CLINICAL PERSPECTIVES

Competency in Medical Knowledge:

Sarcopenia is the "biological substrate" of frailty and a significant predictor of mortality, length of stay and disability in older adults undergoing transcatheter aortic valve implantation. A pre-procedural sarcopenia score used for risk prediction should include complementary measures of muscle mass and function.

Transitional Outlooks:

1) Psoas muscle area cut-off values are needed to define low muscle mass in order to externally validate our sarcopenia score and integrate its routine use into pre-TAVR risk assessment.
2) Clinical trials targeting the treatment of sarcopenia are needed and should focus on exercise and nutritional supplementation.

** The following reference list applies only to chapter 4*

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.
2. Iung B, Baron G, Tornos P, Gohlke-Barwolf C, Butchart EG, Vahanian A. Valvular heart disease in the community: a European experience. Curr Probl Cardiol. 2007;32(11):609-61.
3. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597-607.
4. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-98.
5. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374(17):1609-20.
6. Lindman BR, Alexander KP, O'Gara PT, Afilalo J. Futility, benefit, and transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2014;7(7):707-16.
7. Puri R, Iung B, Cohen DJ, Rodes-Cabau J. TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. Eur Heart J. 2016;37(28):2217-25.
8. Green P, Arnold SV, Cohen DJ, Kirtane AJ, Kodali SK, Brown DL, et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER trial). Am J Cardiol. 2015;116(2):264-9.
9. Schoenenberger AW, Stortecky S, Neumann S, Moser A, Juni P, Carrel T, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). Eur Heart J. 2013;34(9):684-92.
10. 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.
11. Kim DH, Kim CA, Placide S, Lipsitz LA, Marcantonio ER. Preoperative Frailty Assessment and Outcomes at 6 Months or Later in Older Adults Undergoing Cardiac Surgical Procedures: A Systematic Review. Ann Intern Med. 2016;165(9):650-60.
12. Arnold SV, Afilalo J, Spertus JA, Tang Y, Baron SJ, Jones PG, et al. Prediction of Poor Outcome After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016;68(17):1868-77.

13. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.
14. Abellan van Kan G, Andre E, Bischoff Ferrari HA, Boirie Y, Onder G, Pahor M, et al. Carla Task Force on Sarcopenia: propositions for clinical trials. J Nutr Health Aging. 2009;13(8):700-7.
15. Visser M. Towards a definition of sarcopenia--results from epidemiologic studies. J Nutr Health Aging. 2009;13(8):713-6.
16. Keevil VL, Romero-Ortuno R. Ageing well: a review of sarcopenia and frailty. Proc Nutr Soc. 2015;74(4):337-47.
17. Kim TN, Choi KM. The implications of sarcopenia and sarcopenic obesity on cardiometabolic disease. J Cell Biochem. 2015;116(7):1171-8.
18. Pahor M, Manini T, Cesari M. Sarcopenia: clinical evaluation, biological markers and other evaluation tools. J Nutr Health Aging. 2009;13(8):724-8.
19. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: Current Concepts and Imaging Implications. AJR Am J Roentgenol. 2015;205(3):W255-66.
20. Cesari M, Leeuwenburgh C, Lauretani F, Onder G, Bandinelli S, Maraldi C, et al. Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. Am J Clin Nutr. 2006;83(5):1142-8.
21. 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.
22. Tanaka S, Kamiya K, Hamazaki N, Matsuzawa R, Nozaki K, Maekawa E, et al. Utility of SARC-F for Assessing Physical Function in Elderly Patients With Cardiovascular Disease. J Am Med Dir Assoc. 2017;18(2):176-81.
23. 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.
24. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013;14(8):531-2.
25. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010;211(2):271-8.

26. Lee JS, He K, Harbaugh CM, Schaubel DE, Sonnenday CJ, Wang SC, et al. Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair. J Vasc Surg. 2011;53(4):912-7.
27. Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg. 2012;16(8):1478-86.
28. Smith AB, Deal AM, Yu H, Boyd B, Matthews J, Wallen EM, et al. Sarcopenia as a predictor of complications and survival following radical cystectomy. J Urol. 2014;191(6):1714-20.
29. Miller AL, Min LC, Diehl KM, Cron DC, Chan CL, Sheetz KH, et al. Analytic morphomics corresponds to functional status in older patients. J Surg Res. 2014;192(1):19-26.
30. 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.
31. Drudi LM, Phung K, Ades M, Zuckerman J, Mullie L, Steinmetz OK, et al. Psoas Muscle Area Predicts All-Cause Mortality After Endovascular and Open Aortic Aneurysm Repair. Eur J Vasc Endovasc Surg. 2016;52(6):764-9.
32. 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. 2016.
33. Mamane S PN, Nelson K, et. al. Feasibility and reliability of psoas muscle area as a novel measure for sarcopenia and frailty in patients undergoing transcatheter aortic valve implantation. Journal of Frailty and Ageing. 2015;4((supplement 1)):19-108.
34. Mok M, Allende R, Leipsic J, Altisent OA, Del Trigo M, Campelo-Parada F, et al. Prognostic Value of Fat Mass and Skeletal Muscle Mass Determined by Computed Tomography in Patients Who Underwent Transcatheter Aortic Valve Implantation. Am J Cardiol. 2016;117(5):828-33.
35. Paknikar R, Friedman J, Cron D, Deeb GM, Chetcuti S, Grossman PM, et al. Psoas muscle size as a frailty measure for open and transcatheter aortic valve replacement. J Thorac Cardiovasc Surg. 2016;151(3):745-50.
36. 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.

37. Garg L, Agrawal S, Pew T, Hanzel GS, Abbas AE, Gallagher MJ, et al. Psoas Muscle Area as a Predictor of Outcomes in Transcatheter Aortic Valve Implantation. Am J Cardiol. 2017;119(3):457-60.
38. Dahya V, Xiao J, Prado CM, Burroughs P, McGee D, Silva AC, et al. Computed tomography-derived skeletal muscle index: A novel predictor of frailty and hospital length of stay after transcatheter aortic valve replacement. Am Heart J. 2016;182:21-7.
39. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M85-94.
40. Volpato S, Cavalieri M, Sioulis F, Guerra G, Maraldi C, Zuliani G, et al. Predictive value of the Short Physical Performance Battery following hospitalization in older patients. J Gerontol A Biol Sci Med Sci. 2011;66(1):89-96.
41. Afilalo J, Lauck s, Kim DH, Lefevre T, Piazza N, Lachapelle K, et al. The Frailty-AVR Study. J Am Coll Cardiol. 2016 Apr;67(13):8.
42. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. Ann Thorac Surg. 2009;88(1 Suppl):S23-42.
43. Bohannon RW. Reference values for the five-repetition sit-to-stand test: a descriptive meta-analysis of data from elders. Percept Mot Skills. 2006;103(1):215-22.
44. Buatois S, Miljkovic D, Manckoundia P, Gueguen R, Miget P, Vancon G, et al. Five times sit to stand test is a predictor of recurrent falls in healthy community-living subjects aged 65 and older. J Am Geriatr Soc. 2008;56(8):1575-7.
45. Burnham K AD. Model Selection and Multimodel Inference. 2nd ed. New York: Springer; 2002. 515 p.
46. Medina-Mirapeix F, Bernabeu-Mora R, Llamazares-Herran E, Sanchez-Martinez MP, Garcia-Vidal JA, Escolar-Reina P. Interobserver Reliability of Peripheral Muscle Strength Tests and Short Physical Performance Battery in Patients With Chronic Obstructive Pulmonary Disease: A Prospective Observational Study. Arch Phys Med Rehabil. 2016;97(11):2002-5.
47. Wolfe RR. Regulation of muscle protein by amino acids. J Nutr. 2002;132(10):3219S-24S.
48. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. JPEN J Parenter Enteral Nutr. 2013;37(5 Suppl):21S-9S.

49. Gore DC, Jahoor F, Wolfe RR, Herndon DN. Acute response of human muscle protein to catabolic hormones. Ann Surg. 1993;218(5):679-84.
50. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int. 2017.
51. Talbot-Hamon C, Afilalo J. Transcatheter Aortic Valve Replacement in the Care of Older Persons with Aortic Stenosis. J Am Geriatr Soc. 2017.

FIGURE LEGENDS

Figure 1: Psoas Muscle Area Measurement

1a) Localizing the top of the L4 axial slice. The axial CT scan series of images is opened in a multiplanar reconstruction view. The sagittal plane is used to localize the top of L4, standardized as the slice just below the anterior-superior aspect of the bright vertebral end plate.

1b) Measuring Psoas Muscle Area. The axial slice is opened in the CoreSlicer.com software where PMA is measured using the density threshold brush tool, using a skeletal muscle inclusion threshold of -30 to 150 Hounsfield units.

Figure 2: Flow Diagram

A total of 669 older adults underwent TAVR. We were unable to obtain a CT scan dataset in 126 patients. The reasons included: no preprocedural CT scan, site-specific logistics of image acquisition and data storage. 157 patients had CT scans that were uninterpretable because they were in the incorrect format, did not include the L4 region of interest, or were of insufficient quality to make accurate measurements.

Abbreviations: CT, Computed Tomography; ROI, Region of Interest; TAVR, Transcatheter Aortic Valve Replacement.

Figure 3: Psoas Muscle Area Distribution

Distribution of psoas muscle area as stratified by sex, including sex-specific means and lowest tertile cut-off values.

Abbreviation: PMA, Psoas Muscle Area

Figure 4: Sarcopenia Score and Mortality

Each histogram bar represents the percentage of deaths for each sarcopenia score. 0 = No Sarcopenia, deaths – 2/54 patients; 1 = Pre-Sarcopenia, deaths – 34/224 patients; 2 = Sarcopenia, deaths – 26/107.

Figure 5: Kaplan-Meier Curve for Survival

Kaplan-Meier survival estimates of the effect of sarcopenia score on mortality in older adults undergoing TAVR.

Abbreviation: TAVR, transcatheter aortic valve replacement

TABLES

Table 1 – Baseline Characteristics Stratified by Sex-Stratified Psoas Tertile

	Total	Low Psoas	Mid Psoas	High Psoas	p-value
Age	83.5 ± 5.8	84.9 ± 4.9	83.7 ± 6	81.9 ± 5.9	<0.001
Female	172 (44%)	57 (45%)	57 (45%)	58 (44%)	1.00
BSA (m^2)	1.8 ± 0.2	1.7 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	<0.001
Hypertension	317 (82%)	109 (85%)	106 (83%)	102 (78%)	0.30
Diabetes	95 (25%)	30 (23%)	31 (24%)	34 (26%)	0.89
CAD	240 (62%)	83 (65%)	83 (65%)	74 (56%)	0.28
NYHA class	2.7 ± 0.7	2.7 ± 0.7	2.8 ± 0.6	2.7 ± 0.6	0.72
PAD	75 (19%)	28 (22%)	23 (18%)	24 (18%)	0.68
CVA	36 (9%)	13 (10%)	14 (11%)	9 (7%)	0.49
COPD	93 (24%)	26 (20%)	38 (30%)	29 (22%)	0.18
CKD	183 (47%)	54 (42%)	69 (54%)	60 (46%)	0.16
GI disease	82 (21%)	29 (23%)	24 (19%)	29 (22%)	0.71
CTD	21 (5%)	9 (7%)	8 (6%)	4 (3%)	0.32
Arthritis	172 (44%)	57 (45%)	58 (45%)	57 (44%)	0.96
Osteoporosis	76 (20%)	30 (23%)	26 (20%)	20 (15%)	0.25
Dementia	13 (3%)	7 (5%)	3 (2%)	3 (2%)	0.27
Depression	42 (11%)	8 (6%)	18 (14%)	16 (12%)	0.11
Falls	91 (24%)	31 (24%)	33 (26%)	27 (21%)	0.60
Walking aid	109 (28%)	39 (30%)	37 (29%)	33 (25%)	0.62
Living assistance	39 (10%)	19 (15%)	10 (8%)	10 (8%)	0.09
Albumin (g/L)	38.8 ± 4.6	38.3 ± 5.1	38.8 ± 4.5	39.5 ± 4.3	0.06
Hemoglobin (g/L)	117.9 ± 16.3	116.2 ± 15.9	118.1 ± 16	119.5 ± 16.8	0.09
SPPB	5.9 ± 3.2	5.8 ± 3.2	5.7 ± 3	6.3 ± 3.4	0.15
Fried scale	2.4 ± 1.4	2.4 ± 1.3	2.5 ± 1.3	2.3 ± 1.5	0.28
EFT	2.2 ± 1.2	2.3 ± 1.2	2.3 ± 1.2	2 ± 1.1	0.06
ADL/IADL deficit	242 (63%)	87 (68%)	80 (63%)	75 (57%)	0.20
Grip strength (kg)	23.4 ± 9.9	21.2 ± 9.8	23.1 ± 8.5	25.9 ± 10.8	<0.001
Gait speed (m/s)	0.71 ± 0.27	0.68 ± 0.25	0.69 ± 0.27	0.75 ± 0.29	0.07
Chair rise (s)	18.9 ± 7.9	19.5 ± 8.7	20.4 ± 8.6	16.9 ± 6	0.07
Chair rise >15s	301 (78%)	100 (78%)	107 (84%)	94 (72%)	0.07
Balance	2.3 ± 1.5	2.3 ± 1.5	2.3 ± 1.5	2.4 ± 1.5	0.37
STS-PROM (%)	6.5 ± 4.4	7.1 ± 5	6.9 ± 4.3	5.5 ± 3.5	0.003
STS-PLOS (%)	13.3 ± 7.1	013.9 ± 7.6	14.2 ± 7	11.7 ± 6.4	0.01

Cuzick's test for trend was used to compare patient characteristics across sex-specific tertiles of PMA. Abbreviations: ADL/IADL, Activities of Daily Living / Instrumental Activities of Daily

Living; BSA, Body Surface Area; CAD, Coronary Artery Disease; COPD, Chronic Obstructive Pulmonary Disease; CTD, Connective Tissue Disease; CVA, Cerebrovascular Accident; CKD, Chronic Kidney Disease; EFT, Essential Frailty Toolset; GI, Gastro-Intestinal; NYHA, New York Heart Association; PAD, Peripheral Arterial Disease; SPPB, Short Physical Performance Battery, STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; STS-PLOS, Society of Thoracic Surgeons Prolonged Length of Stay; TAVR, Transcatheter Aortic Valve Replacement.

Table 2: Incremental value of the Sarcopenia Score

Outcome	Adjusted Odds Ratio (95% CI)*	ΔAIC
Mortality - 6 months	11.6 (1.49, 90.16)	6.8
Mortality - 12 months	5.61 (1.58, 19.91)	6.2
Outcome	**Adjusted ß coefficient (95% CI)****	**ΔAIC**
LOS (days)	4.8 (1.97 to 7.68)	11.6
Disability (ADL/IADL deficit)	3.3 (1.74 to 4.85)	16.2

Multivariable logistic regression models were adjusted for the STS-PROM and SPPB. Multivariate linear regression models for the outcomes length of stay and disability were adjusted for STS-PLOS and baseline ADL/IADL, respectively. ADL/IADL deficit was calculated by subtracting baseline deficits from total deficits at 6 months. For AIC, a positive value indicates improved discrimination, where values 0-2 suggest slight improvement, 4-7 considerable improvement and >10 substantial improvement.

Abbreviations: ADL/IADL, Activities of Daily Living / Instrumental Activities of Daily Living, AIC, Akaike Information Criterion; LOS, Length of Stay; SPPB, Short Physical Performance Battery, STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; STS-PLOS, Society of Thoracic Surgeons Prolonged Length of Stay

SUPPLEMENTAL TABLES

Supplemental Table 1 – Cohort Comparison by CT Interpretability

	CT uninterpretable (n=283)	CT interpretable (n=386)	p-value
Age	83.6 ± 5.6	83.5 ± 5.7	0.76
Female	132 (47%)	171 (44%)	0.51
BSA (m^2)	1.8 ± 0.3	1.8 ± 0.2	0.55
Hypertension	222 (78%)	316 (82%)	0.23
Diabetes	85 (30%)	95 (25%)	0.24
CAD	161 (57%)	239 (62%)	0.14
NYHA class	2.7 ± 0.7	2.8 ± 0.7	0.65
PAD	49 (17%)	75 (19%)	0.52
CVA	25 (9%)	36 (9%)	0.92
COPD	46 (16%)	93 (24%)	0.01
CKD	142 (50%)	182 (47%)	0.26
GI disease	48 (17%)	98 (25%)	0.005
CTD	10 (4%)	21 (5%)	0.28
Arthritis	82 (29%)	172 (45%)	<0.001
Osteoporosis	26 (9%)	75 (19%)	<0.001
Dementia	4 (1%)	13 (3%)	0.13
Depression	14 (5%)	42 (11%)	0.008
Falls	63 (22%)	91 (24%)	0.84
Walking aid	61 (22%)	109 (28%)	0.03
Living assistance	28 (10%)	39 (10%)	0.98
Albumin (g/L)	37 ± 4.9	38.8 ± 4.7	<0.001
Hemoglobin (g/L)	122.1 ± 16.9	118 ± 16.3	0.002
SPPB, /12	6.2 ± 3.3	5.9 ± 3.2	0.45
Fried scale, 5	2.3 ± 1.3	2.4 ± 1.4	0.6
EFT, /5	2.3 ± 1.2	2.2 ± 1.2	0.26
ADL/IADL deficit	2.3 ± 2.8	2 ± 2.5	0.15
Grip strength (kg)	25.1 ± 9.6	23.9 ± 9.5	0.21
Gait speed (m/s)	0.7 ± 0.2	0.7 ± 0.3	0.64
Chair rise (s)	1.3 ± 1.3	1.2 ± 1.2	0.32
Chair rise >15s	219 (77%)	300 (78%)	0.9
Balance, /4	2.5 ± 1.5	2.3 ± 1.5	0.23
STS-PROM (%)	6.1 ± 3.9	6.5 ± 4.4	0.37
STS-PLOS (%)	12.7 ± 6.6	13.3 ± 7	0.46

Abbreviations: ADL/IADL, Activities of Daily Living / Instrumental Activities of Daily Living; BSA, Body Surface Area; CAD, Coronary Artery Disease; COPD, Chronic Obstructive Pulmonary Disease; CTD, Connective Tissue Disease; CVA, Cerebrovascular Accident; CKD, Chronic Kidney Disease; EFT, Essential Frailty Toolset; GI, Gastro-Intestinal; NYHA, New York Heart Association; PAD, Peripheral Arterial Disease; SPPB, Short Physical Performance Battery, STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; STS-PLOS, Society of Thoracic Surgeons Prolonged Length of Stay; TAVR, Transcatheter Aortic Valve Replacement.

Supplemental Table 2 – Baseline Characteristics Stratified by Sarcopenia Classification

	Total	No Sarcopenia	Pre-Sarcopenia	Sarcopenia	p-value
Age	83.6 ± 5.7	82.3 ± 6.2	83.1 ± 5.8	85.4 ± 4.7	<0.001
Female	171 (45%)	15 (26%)	108 (48%)	48 (48%)	0.01
BSA (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.7 ± 0.2	<0.001
Hypertension	316 (82%)	42 (74%)	186 (82%)	88 (88%)	0.08
Diabetes	95 (25%)	11 (19%)	61 (27%)	23 (23%)	0.44
CAD	239 (62%)	37 (65%)	135 (59%)	67 (67%)	0.39
NYHA class	2.7 ± 0.6	2.6 ± 0.6	2.8 ± 0.6	2.8 ± 0.8	0.13
PAD	75 (20%)	12 (21%)	43 (19%)	20 (20%)	0.93
CVA	36 (9%)	1 (2%)	23 (10%)	12 (12%)	0.09
COPD	93 (24%)	17 (30%)	58 (26%)	18 (18%)	0.19
CKD	225 (59%)	29 (51%)	144 (63%)	52 (52%)	0.07
GI disease	82 (21%)	9 (16%)	50 (22%)	23 (23%)	0.53
CTD	21 (5%)	2 (4%)	11 (5%)	8 (8%)	0.4
Arthritis	172 (45%)	15 (26%)	110 (48%)	47 (47%)	0.01
Osteoporosis	75 (20%)	4 (7%)	45 (20%)	26 (26%)	0.02
Dementia	84 (22%)	7 (12%)	46 (20%)	31 (31%)	0.02
Depression	124 (32%)	9 (16%)	88 (39%)	27 (27%)	0.002
Falls	91 (24%)	6 (11%)	57 (25%)	28 (28%)	0.03
Walking aid	108 (28%)	11 (19%)	64 (28%)	33 (33%)	0.19
Living assistance	39 (10%)	2 (4%)	20 (9%)	17 (17%)	0.02
Albumin (g/L)	38.8 ± 4.7	39.4 ± 4.9	39.2 ± 4.5	37.6 ± 4.8	0.02
Hemoglobin (g/L)	117.9 ± 16.2	124 ± 13.6	117.6 ± 17	114.9 ± 14.8	<0.001
SPPB, /12	5.9 ± 3.2	9.4 ± 2	5.6 ± 3.1	4.8 ± 2.7	<0.001
Fried scale, 5	2.4 ± 1.4	1.6 ± 1.2	2.5 ± 1.4	2.7 ± 1.2	<0.001
EFT, /5	2.1 ± 1.2	0.8 ± 0.8	2.2 ± 1.1	2.7 ± 1	<0.001
ADL/IADL deficit	242 (63%)	19 (33%)	150 (66%)	73 (73%)	<0.001
Grip strength (kg)	23.8 ± 9.5	30.6 ± 10.7	23.3 ± 8.7	20.9 ± 8.8	<0.001
Gait speed (m/s)	0.7 ± 0.27	0.88 ± 0.29	0.69 ± 0.26	0.62 ± 0.23	<0.001
Chair rise (s)	18.8 ± 7.9	12 ± 1.9	19.9 ± 7.4	23.6 ± 8.3	<0.001
Chair rise >15s	299 (78%)	0 (0%)	199 (88%)	100 (100%)	<0.001
Balance, /4	2.3 ± 1.5	3.0 ± 1.2	2.3 ± 1.5	2.1 ± 1.5	<0.001
STS-PROM (%)	6.6 ± 4.4	5.9 ± 4.1	6.4 ± 4.2	7.4 ± 5.1	0.02
STS-PLOS (%)	13.4 ± 7.1	12.1 ± 7.3	13.4 ± 7.0	14.3 ± 7.2	0.02

Cuzick's test for trend was used to compare patient characteristics across sex-specific tertiles of PMA. Abbreviations: ADL/IADL, Activities of Daily Living / Instrumental Activities of Daily

Living; BSA, Body Surface Area; CAD, Coronary Artery Disease; COPD, Chronic Obstructive Pulmonary Disease; CTD, Connective Tissue Disease; CVA, Cerebrovascular Accident; CKD, Chronic Kidney Disease; EFT, Essential Frailty Toolset; GI, Gastro-Intestinal; NYHA, New York Heart Association; PAD, Peripheral Arterial Disease; SPPB, Short Physical Performance Battery, STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; STS-PLOS, Society of Thoracic Surgeons Prolonged Length of Stay; TAVR, Transcatheter Aortic Valve Replacement.

Supplemental Table 3: Incremental Value of Psoas Muscle Area

a) Mortality – 6 months

Variable	Adjusted Odds Ratio (95% CI)	ΔAIC
PMA (per cm^2)	1.72 (0.77, 3.84)	-0.4
SPPB	0.89 (0.8, 0.99)	
STS-PROM	32000.3 (67.52, 1.52x10^7)	

b) Mortality – 12 months

Variable	Adjusted Odds Ratio (95% CI)	ΔAIC
PMA (per cm^2)	1.48 (0.74, 2.96)	-1
SPPB	0.92 (0.84, 1.01)	
STS-PROM	192704.7 (639.86, 5.8x10^7)	

c) Length of Stay (days)

Variable	Adjusted ß coefficient (95% CI)	ΔAIC
PMA (per cm^2)	-0.32 (-0.56, -0.08)	5.1
Age	-0.1 (-.028, 0.07)	
Female sex	-1.71 (-3.87, 0.46)	
BSA (kg/m^2)	-1.89 (-6.75, 2.98)	
SPPB	-0.46 (-0.76, -0.17)	
STS-PLOS	21.14 (7.42, 34.85)	

d) Disability (ADL/IADL deficit)

Variable	Adjusted ß coefficient (95% CI)	ΔAIC
PMA (per cm^2)	-0.14 (-0.26, -0.01)	2.5
Age	-0.07 (-0.02, 0.16)	
Female sex	-2.02 (-3.28, -0.76)	
BSA (kg/m^2)	-1.23 (-3.94, 1.48)	
SPPB	-0.29 (-0.46, -0.11)	

For AIC, a positive value indicates improved discrimination, where values 0-2 suggest slight improvement, 4-7 considerable improvement and >10 substantial improvement.

Abbreviations: ADL/IADL, Activities of Daily Living / Instrumental Activities of Daily Living, AIC, Akaike Information Criterion; BSA, Body Surface Area; LOS, Length of Stay, PMA, Psoas Muscle Area; SPPB, Short Physical Performance Battery, STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; STS-PLOS, Society of Thoracic Surgeons Prolonged Length of Stay

FIGURES

Figure 1: Psoas Muscle Area Measurement

figure 1a

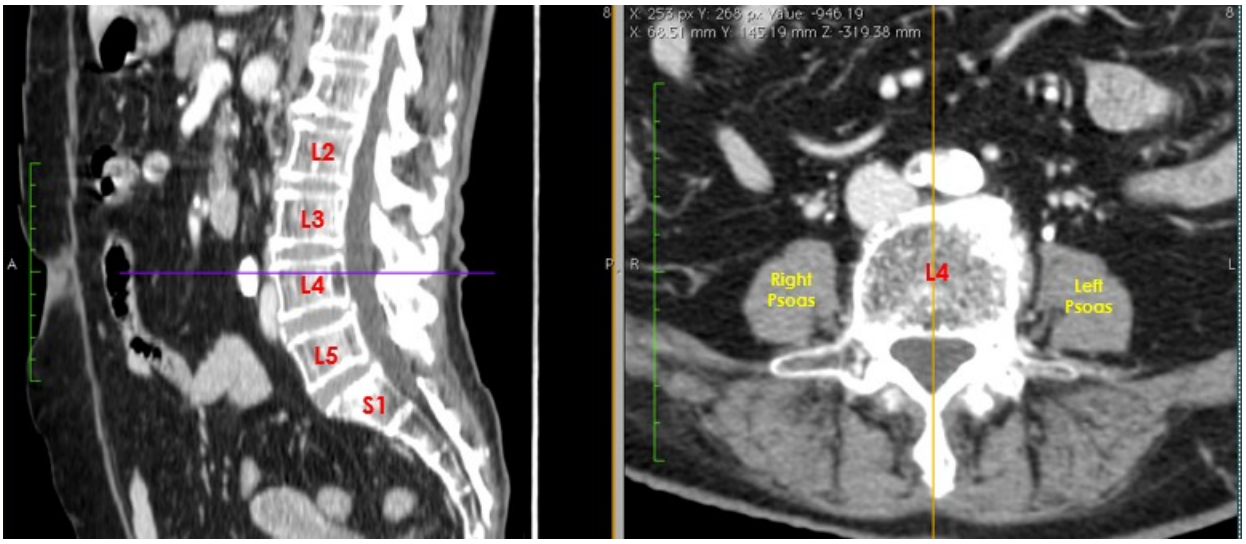


figure 1b

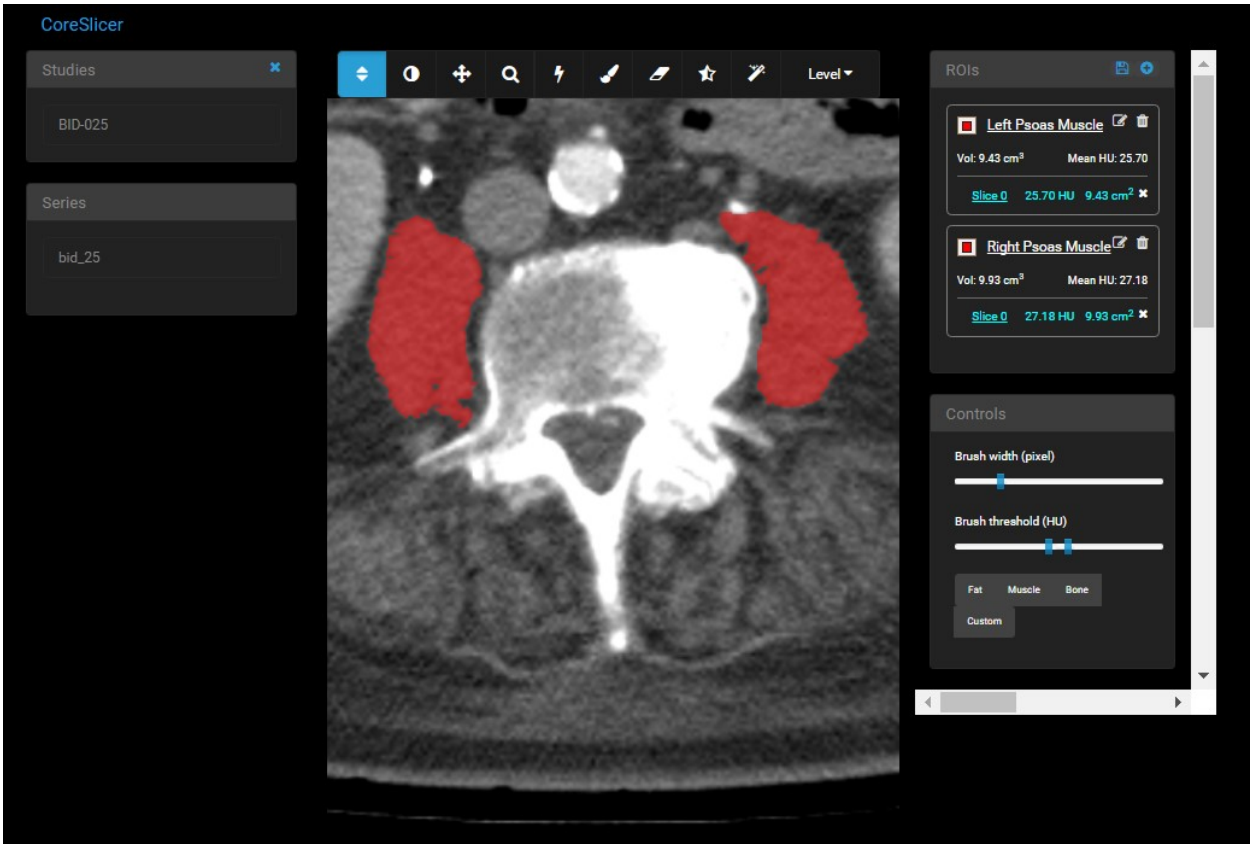


Figure 2: Flow Diagram

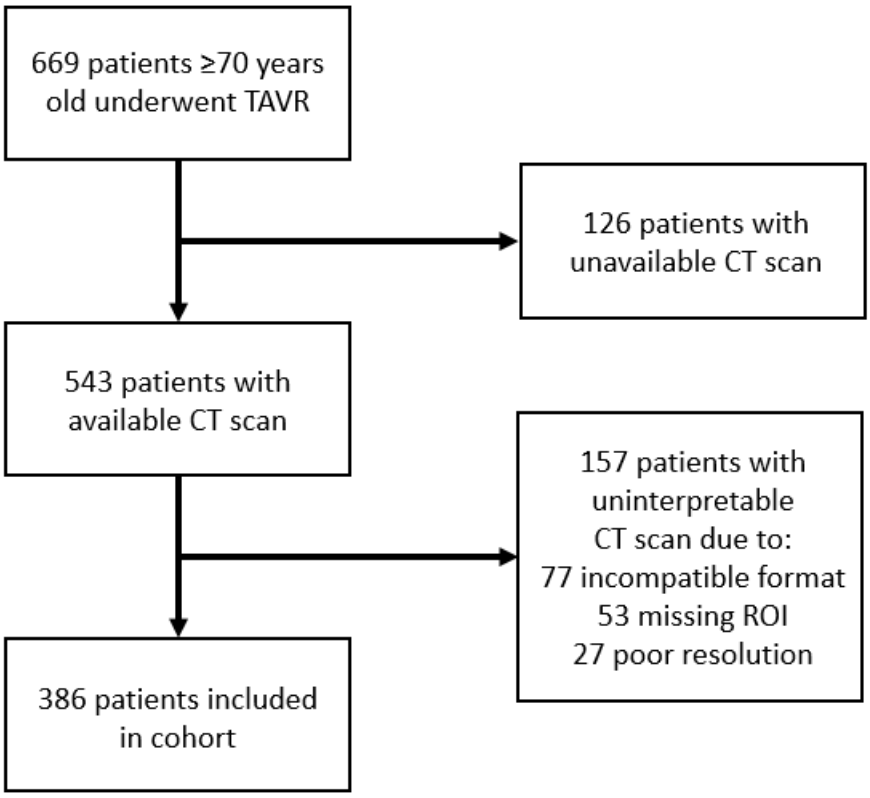


Figure 3: Psoas Muscle Area Distribution

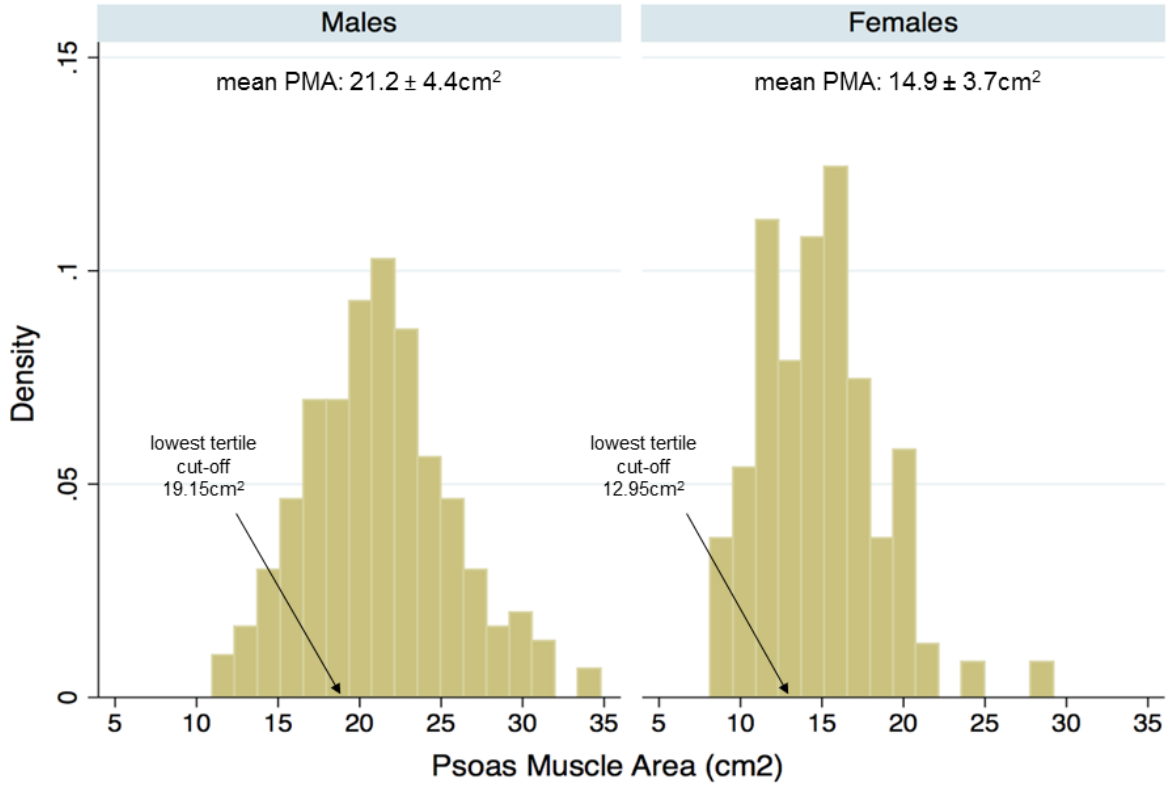


Figure 4: Sarcopenia Score and Mortality

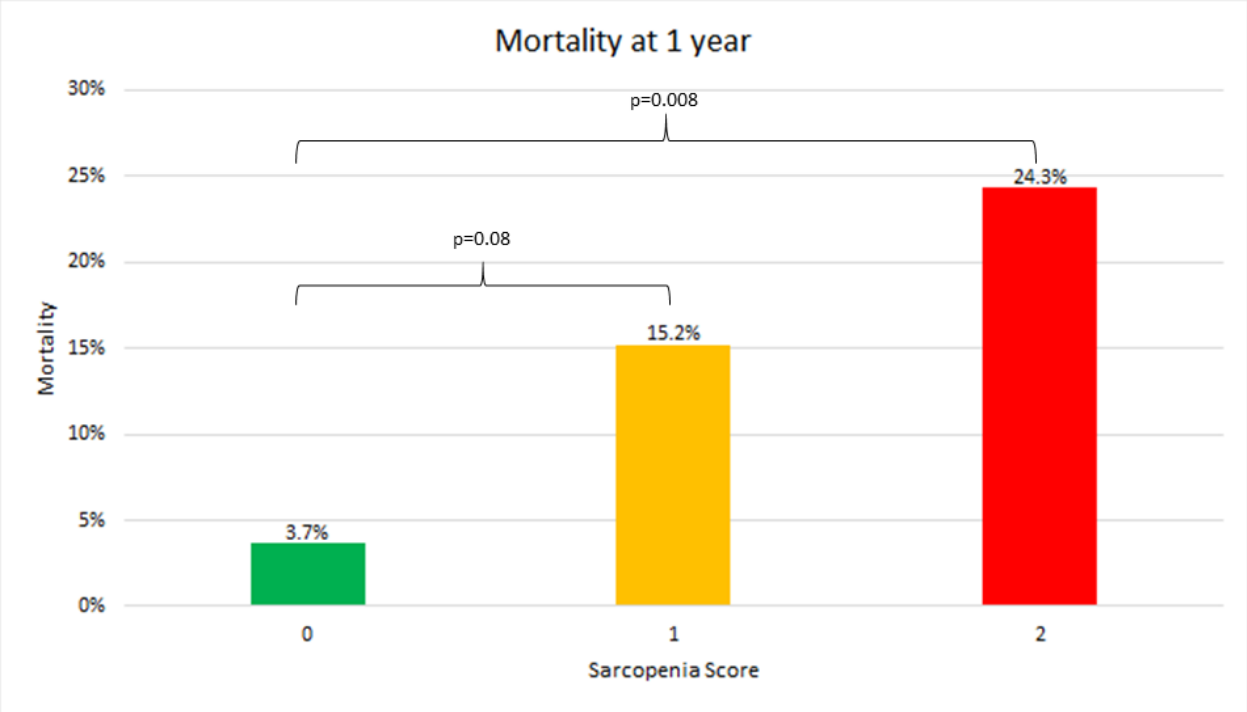
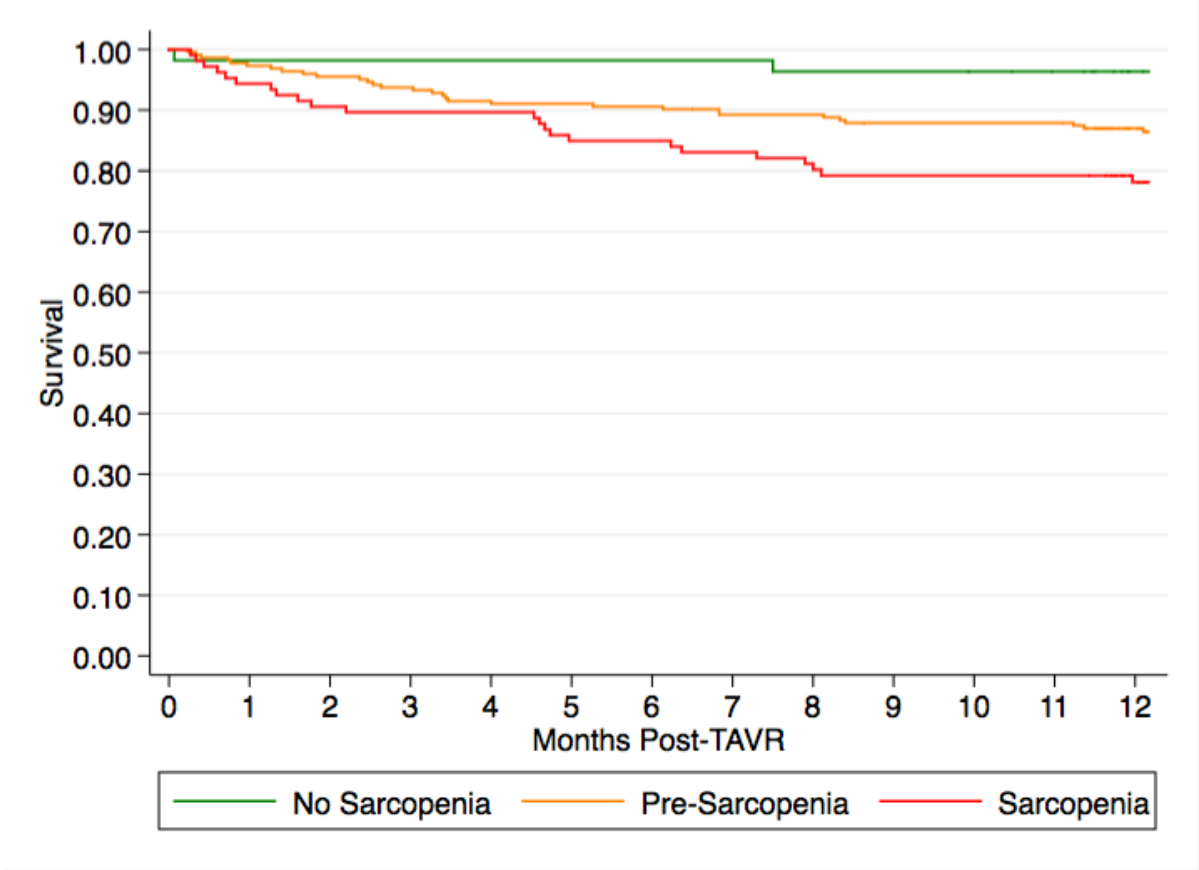


Figure 5: Kaplan-Meier Curve for Survival



Chapter 5: Conclusion

Sarcopenia, a core component of frailty, plays a significant role in determining the elderly patient's ability to withstand the physiologic stressors of surgery. In this thesis, the prognostic role of low muscle mass and sarcopenia as measured by CT-scan cross-sectional area have been explored in older adults undergoing TAVR. The prevalence of sarcopenia in this population is not well defined owing to the lack of accepted cut-offs for muscle mass as measured by CT-scan cross-sectional area. Nevertheless, our findings show that non-indexed total PMA $<19.2cm^2$ in men, and $<13.0cm^2$ in women are predictive of adverse outcomes, although these values remain to be externally validated. We found that measuring PMA at the L4 level optimally correlated with psoas muscle volume and physical performance measures. We developed a software tool and methodology for accurately measuring PMA, and made this tool freely available for clinicians and researchers to use (www.coreslicer.com). We showed that PMA could be reliably measured from clinical CT scans and that inter-observer variability was within acceptable limits.

Fewer than 30% of studies evaluating the role of CT-measured muscle mass in the peri-operative setting included patients with non-malignant pathologies, and all studies were conducted retrospectively. Only 8 studies evaluated patients undergoing TAVR, with each study utilizing a different measure of muscle mass; including PMA, PMI and SMI. Most studies reported an association between low muscle mass and mid-term mortality, but the effect was modest in comparison to the studies that included cancer patients or cirrhotic patients undergoing resection or transplant, respectively. This is likely due to the prominent cachexia occurring in these other patient populations undergoing more invasive surgeries with prolonged recovery times. Cachexia is a highly inflammatory state in which catabolism occurs more rapidly than in

age-related muscle loss (69). In cachectic patients, it stands to reason that the acuity and rapidity of muscle wasting makes recovery from the catabolic state of major surgery more difficult, and as such PMA is a stronger predicter of poor outcomes in this patient population. In comparison, patients undergoing TAVR are unlikely to be cachectic and the lesser catabolic stress of a minimally invasive surgery may translate into a smaller predictive value of PMA.

In our retrospective cohort study of 208 patients undergoing TAVR, we found that in women, low PMA was associated with a 12% increased risk of cumulative mortality (mean follow-up 504 days) per cm^2 of PMA, but not with short-term procedural mortality. These findings were consistent with other studies evaluating the role of frailty in patients undergoing TAVR, in as much as the frailty phenotype more consistently predicted mid-term outcomes rather than short-term outcomes (21, 50). The likely explanation for this is two-fold. Firstly, 30-day mortality is between 3-7%, even in higher risk populations (11, 12, 92). Therefore, the effect of PMA may be masked in smaller cohorts that lack the statistical power to show a differential effect in the context of a low event rate. Secondly, the minimally invasive nature of TAVR may be insufficient to elicit poor early recovery in patients with low PMA. We hypothesize that the catabolic nature of surgery has a devastating effect on muscle mass and function, particularly when starting with insufficient reserves, preventing patients from effectively recovering, and leading to a cascade of progressive disability and death in the mid-to-long term.

Regarding sex-differences, several studies have found that frailty may play a more important role in women than in men (98, 99). Generally, women have lower muscle mass than do men. We hypothesize that low muscle mass may affect outcomes in an absolute, rather than relative manner, implying a threshold below which patients have marked difficulty resisting the stresses of surgery. An alternative hypothesis in this mostly octogenarian population stems from

the male-female health-survival paradox (100), in which the men that are selected to survive into older age are more fit in comparison to their female counterparts who begin with a longer life-expectancy at baseline. We did not find a similar interaction between female sex and PMA in our prospective cohort. There are a couple of possible explanations for this difference. Firstly, the outcome measure of sarcopenia in the FRAILTY-AVR study included a measure of muscle function. It is plausible that even though muscle mass is overall lower in women, muscle function may play a greater role, masking any sex-differences seen when measuring muscle mass alone. Secondly, in the FRAILTY-AVR study, we did not find an association between low PMA and mortality. Given that the effect size of PMA on mortality in women was modest in the Montreal-Munich study, and that none of the other 8 studies investigating the role of PMA in patients undergoing TAVR reported any sex-difference, this could have been the play of chance or unmeasurable differences in the cohort.

To our knowledge, FRAILTY-AVR is the first prospective study to evaluate the role of muscle mass in older adults undergoing TAVR. Likewise, it is the first study to propose a sarcopenia score that includes muscle mass and muscle function. In this multi-center cohort of 386 older adults undergoing TAVR, low PMA alone was not predictive of mortality. However, when added to the measure of slow chair rise, the combination was strongly predictive of mortality at both 6 and 12 months. A patient with sarcopenia was greater than 5 times more likely to die after 1 year than their non-sarcopenic counterparts. Low PMA and sarcopenia were also associated with prolonged length of stay and disability at 6 months. These findings reaffirm the prognostic value of measuring muscle mass prior to TAVR, but suggest that a measure of muscle function should be dually included in the peri-procedural evaluation of sarcopenia. Sarcopenia was a stronger predictor of all measured outcomes than muscle mass alone, and adds

incremental prognostic values above standard STS risk prediction model and SPPB. It is important to emphasize that while sarcopenia is a predictor of poor outcomes, being physically robust is a predictor of longevity. Notably, only 2 patients (3.7%) with normal muscle mass and function died within 1 year post-TAVR, highlighting the importance of these parameters prior to surgery.

While several trials have demonstrated the benefit of nutrition and exercise in frail older adults (66), there is a paucity of published studies investigating therapeutic strategies targeting frailty and sarcopenia in the peri-procedural setting. However, there are currently several ongoing trials investigating the therapeutic role of exercise in the peri-TAVR setting. TAVR-Prehab (101), STEP (102), and TAVR-FRAILTY (103) are each investigating the role of different pre-procedural exercise programs on frailty status and patient-centred outcomes such as physical activity and quality of life. Similarly, REHAB-TAVR (104) and PTOTtAVR (105) are studying the role of post-procedural rehabilitation on resource utilization and disability.

Moving forward, we will shift our focus toward therapeutic interventions as the FRAILTY-AVR study has directly informed the conduct of a forthcoming randomized controlled trial, PERFORM-TAVR that was recently funded by a CIHR Project Grant to test the effect of a home-based exercise and protein supplementation intervention on patient-centred outcomes in sarcopenic patients following TAVR.

References

** The following reference list applies only to chapters 1,3, and 5*

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.
2. Iung B, Baron G, Tornos P, Gohlke-Barwolf C, Butchart EG, Vahanian A. Valvular heart disease in the community: a European experience. Curr Probl Cardiol. 2007;32(11):609-61.
3. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. J Am Coll Cardiol. 1997;29(3):630-4.
4. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013;62(11):1002-12.
5. Lindman BR, Patel JN. Multimorbidity in Older Adults with Aortic Stenosis. Clin Geriatr Med. 2016;32(2):305-14.
6. Braunwald E. On the natural history of severe aortic stenosis. Journal of the American College of Cardiology. 1990;15(5):1018-20.
7. Bouma BJ, van Den Brink RB, van Der Meulen JH, Verheul HA, Cheriex EC, Hamer HP, et al. To operate or not on elderly patients with aortic stenosis: the decision and its consequences. Heart. 1999;82(2):143-8.
8. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. Eur Heart J. 1988;9 Suppl E:57-64.
9. Marquis-Gravel G, Redfors B, Leon MB, Genereux P. Medical Treatment of Aortic Stenosis. Circulation. 2016;134(22):1766-84.
10. Wenaweser P, Pilgrim T, Kadner A, Huber C, Stortecky S, Buellesfeld L, et al. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. J Am Coll Cardiol. 2011;58(21):2151-62.
11. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597-607.

12. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-98.
13. Grube E, Sinning JM, Vahanian A. The Year in Cardiology 2013: valvular heart disease (focus on catheter-based interventions). Eur Heart J. 2014;35(8):490-5.
14. Reardon MJ, Reynolds MR. Cost-effectiveness of TAVR in the non-surgical population. J Med Econ. 2013;16(4):575-9.
15. Reynolds MR, Lei Y, Wang K, Chinnakondepalli K, Vilain KA, Magnuson EA, et al. Cost-Effectiveness of Transcatheter Aortic Valve Replacement With a Self-Expanding Prosthesis Versus Surgical Aortic Valve Replacement. J Am Coll Cardiol. 2016;67(1):29-38.
16. Osnabrugge RL, Kappetein AP, Reynolds MR, Cohen DJ. Cost-effectiveness of transcatheter valvular interventions: economic challenges. EuroIntervention. 2013;9 Suppl:S48-54.
17. Lindman BR, Alexander KP, O'Gara PT, Afilalo J. Futility, benefit, and transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2014;7(7):707-16.
18. Talbot-Hamon C, Afilalo J. Transcatheter Aortic Valve Replacement in the Care of Older Persons with Aortic Stenosis. J Am Geriatr Soc. 2017.
19. Arnold SV, Spertus JA, Vemulapalli S, Li Z, Matsouaka RA, Baron SJ, et al. Quality-of-Life Outcomes After Transcatheter Aortic Valve Replacement in an Unselected Population: A Report From the STS/ACC Transcatheter Valve Therapy Registry. JAMA Cardiol. 2017.
20. Lange R, Beckmann A, Neumann T, Krane M, Deutsch MA, Landwehr S, et al. Quality of Life After Transcatheter Aortic Valve Replacement: Prospective Data From GARY (German Aortic Valve Registry). JACC Cardiovasc Interv. 2016;9(24):2541-54.
21. Green P, Woglom AE, Genereux P, Daneault B, Paradis JM, Schnell S, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovasc Interv. 2012;5(9):974-81.
22. O'Brien SM, Shahian DM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. Ann Thorac Surg. 2009;88(1 Suppl):S23-42.
23. Wendt D, Osswald BR, Kayser K, Thielmann M, Tossios P, Massoudy P, et al. Society of Thoracic Surgeons score is superior to the EuroSCORE determining mortality in high risk patients undergoing isolated aortic valve replacement. Ann Thorac Surg. 2009;88(2):468-74; discussion 74-5.

24. Arnold SV, Spertus JA, Vemulapalli S, Dai D, O'Brien SM, Baron SJ, et al. Association of Patient-Reported Health Status With Long-Term Mortality After Transcatheter Aortic Valve Replacement: Report From the STS/ACC TVT Registry. Circ Cardiovasc Interv. 2015;8(12):e002875.
25. Osnabrugge RL, Arnold SV, Reynolds MR, Magnuson EA, Wang K, Gaudiani VA, et al. Health status after transcatheter aortic valve replacement in patients at extreme surgical risk: results from the CoreValve U.S. trial. JACC Cardiovasc Interv. 2015;8(2):315-23.
26. Mack MJ, Holper EM. TAVR Risk Assessment: Does the Eyeball Test Have 20/20 Vision, or Can We Do Better? J Am Coll Cardiol. 2016;68(4):353-5.
27. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. Am J Cardiol. 2009;103(11):1616-21.
28. 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.
29. Cesari M, Leeuwenburgh C, Lauretani F, Onder G, Bandinelli S, Maraldi C, et al. Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. Am J Clin Nutr. 2006;83(5):1142-8.
30. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
31. Drey M, Pfeifer K, Sieber CC, Bauer JM. The Fried frailty criteria as inclusion criteria for a randomized controlled trial: personal experience and literature review. Gerontology. 2011;57(1):11-8.
32. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc. 2010;58(4):681-7.
33. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M85-94.
34. Paffenbarger RS, Jr., Lee IM. Physical activity and fitness for health and longevity. Res Q Exerc Sport. 1996;67(3 Suppl):S11-28.
35. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.
36. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-95.

37. Shimura T, Yamamoto M, Kano S, Kagase A, Kodama A, Koyama Y, et al. Impact of the Clinical Frailty Scale on Outcomes After Transcatheter Aortic Valve Replacement. Circulation. 2017.
38. Afilalo J. The Clinical Frailty Scale: Upgrade Your Eyeball Test. Circulation. 2017.
39. Ahlund K, Ekerstad N, Oberg B, Back M. Physical Performance Impairments and Limitations Among Hospitalized Frail Older Adults. J Geriatr Phys Ther. 2017.
40. Wou F, Gladman JR, Bradshaw L, Franklin M, Edmans J, Conroy SP. The predictive properties of frailty-rating scales in the acute medical unit. Age Ageing. 2013;42(6):776-81.
41. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. CMAJ. 2014;186(2):E95-102.
42. Kojima G. Frailty as a Predictor of Future Falls Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. J Am Med Dir Assoc. 2015;16(12):1027-33.
43. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210(6):901-8.
44. Kulmala J, Nykanen I, Hartikainen S. Frailty as a predictor of all-cause mortality in older men and women. Geriatr Gerontol Int. 2014;14(4):899-905.
45. Shamliyan T, Talley KM, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. Ageing Res Rev. 2013;12(2):719-36.
46. Schoenenberger AW, Stortecky S, Neumann S, Moser A, Juni P, Carrel T, et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). Eur Heart J. 2013;34(9):684-92.
47. Stortecky S, Schoenenberger AW, Moser A, Kalesan B, Juni P, Carrel T, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. JACC Cardiovasc Interv. 2012;5(5):489-96.
48. Green P, Arnold SV, Cohen DJ, Kirtane AJ, Kodali SK, Brown DL, et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER trial). Am J Cardiol. 2015;116(2):264-9.
49. Afilalo J, Mottillo S, Eisenberg MJ, Alexander KP, Noiseux N, Perrault LP, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. Circ Cardiovasc Qual Outcomes. 2012;5(2):222-8.
50. Arnold SV, Afilalo J, Spertus JA, Tang Y, Baron SJ, Jones PG, et al. Prediction of Poor Outcome After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016;68(17):1868-77.

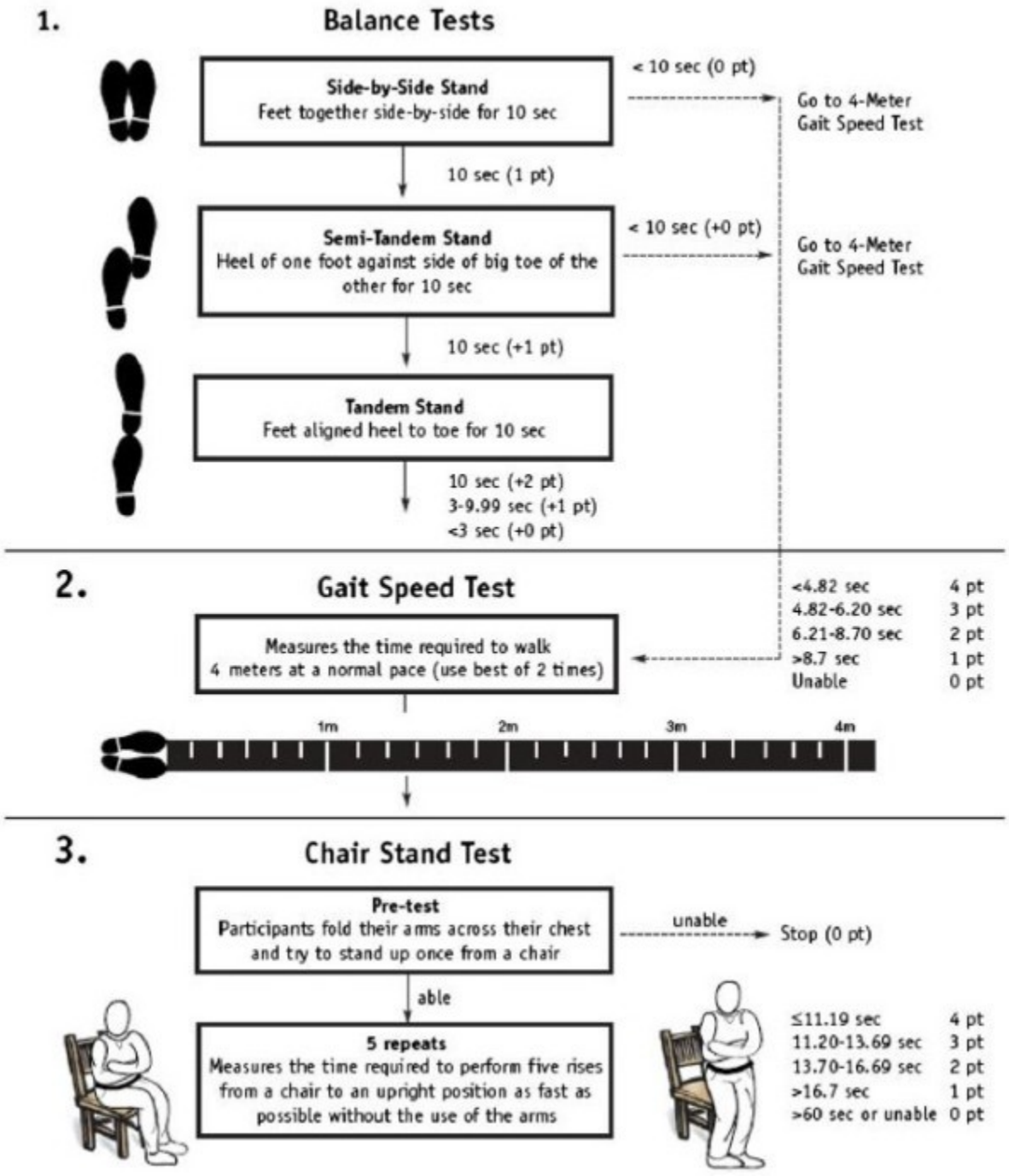
51. Chikwe J, Adams DH. Frailty: the missing element in predicting operative mortality. Semin Thorac Cardiovasc Surg. 2010;22(2):109-10.
52. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.
53. Laviano A. Young blood. N Engl J Med. 2014;371(6):573-5.
54. Pahor M, Manini T, Cesari M. Sarcopenia: clinical evaluation, biological markers and other evaluation tools. J Nutr Health Aging. 2009;13(8):724-8.
55. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. J Cachexia Sarcopenia Muscle. 2014;5(4):253-9.
56. Walrand S, Guillet C, Salles J, Cano N, Boirie Y. Physiopathological mechanism of sarcopenia. Clin Geriatr Med. 2011;27(3):365-85.
57. Abellan van Kan G, Andre E, Bischoff Ferrari HA, Boirie Y, Onder G, Pahor M, et al. Carla Task Force on Sarcopenia: propositions for clinical trials. J Nutr Health Aging. 2009;13(8):700-7.
58. "sarcopenia". Merriam Webster. 2017.
59. Laviano A, Gori C, Rianda S. Sarcopenia and nutrition. Adv Food Nutr Res. 2014;71:101-36.
60. Argiles JM, Anker SD, Evans WJ, Morley JE, Fearon KC, Strasser F, et al. Consensus on cachexia definitions. J Am Med Dir Assoc. 2010;11(4):229-30.
61. Keevil VL, Romero-Ortuno R. Ageing well: a review of sarcopenia and frailty. Proc Nutr Soc. 2015;74(4):337-47.
62. Bano G, Trevisan C, Carraro S, Solmi M, Luchini C, Stubbs B, et al. Inflammation and sarcopenia: A systematic review and meta-analysis. Maturitas. 2017;96:10-5.
63. Kim TN, Choi KM. The implications of sarcopenia and sarcopenic obesity on cardiometabolic disease. J Cell Biochem. 2015;116(7):1171-8.
64. Nilwik R, Snijders T, Leenders M, Groen BB, van Kranenburg J, Verdijk LB, et al. The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. Exp Gerontol. 2013;48(5):492-8.
65. Deschenes MR. Effects of aging on muscle fibre type and size. Sports Med. 2004;34(12):809-24.
66. 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.
67. Martone AM, Marzetti E, Calvani R, Picca A, Tosato M, Santoro L, et al. Exercise and Protein Intake: A Synergistic Approach against Sarcopenia. Biomed Res Int. 2017;2017:2672435.

68. Porter MM. The effects of strength training on sarcopenia. Can J Appl Physiol. 2001;26(1):123-41.
69. Evans WJ. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. Am J Clin Nutr. 2010;91(4):1123S-7S.
70. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int. 2017.
71. Molfino A, Amabile MI, Rossi Fanelli F, Muscaritoli M. Novel therapeutic options for cachexia and sarcopenia. Expert Opin Biol Ther. 2016;16(10):1239-44.
72. Rooks D, Praestgaard J, Hariry S, Laurent D, Petricoul O, Perry RG, et al. Treatment of Sarcopenia with Bimagrumab: Results from a Phase II, Randomized, Controlled, Proof-of-Concept Study. J Am Geriatr Soc. 2017.
73. Yu SC, Khow KS, Jadczak AD, Visvanathan R. Clinical Screening Tools for Sarcopenia and Its Management. Curr Gerontol Geriatr Res. 2016;2016:5978523.
74. 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.
75. Gallagher D, Ruts E, Visser M, Heshka S, Baumgartner RN, Wang J, et al. Weight stability masks sarcopenia in elderly men and women. Am J Physiol Endocrinol Metab. 2000;279(2):E366-75.
76. Visser M. Towards a definition of sarcopenia--results from epidemiologic studies. J Nutr Health Aging. 2009;13(8):713-6.
77. Cesari M, Fielding RA, Pahor M, Goodpaster B, Hellerstein M, van Kan GA, et al. Biomarkers of sarcopenia in clinical trials-recommendations from the International Working Group on Sarcopenia. J Cachexia Sarcopenia Muscle. 2012;3(3):181-90.
78. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8):755-63.
79. Tanaka S, Kamiya K, Hamazaki N, Matsuzawa R, Nozaki K, Maekawa E, et al. Utility of SARC-F for Assessing Physical Function in Elderly Patients With Cardiovascular Disease. J Am Med Dir Assoc. 2017;18(2):176-81.
80. 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.

81. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004;97(6):2333-8.
82. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.
83. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-35.
84. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010;211(2):271-8.
85. Lee JS, He K, Harbaugh CM, Schaubel DE, Sonnenday CJ, Wang SC, et al. Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair. J Vasc Surg. 2011;53(4):912-7.
86. Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. HPB (Oxford). 2011;13(7):439-46.
87. Smith AB, Deal AM, Yu H, Boyd B, Matthews J, Wallen EM, et al. Sarcopenia as a predictor of complications and survival following radical cystectomy. J Urol. 2014;191(6):1714-20.
88. Sheetz KH, Zhao L, Holcombe SA, Wang SC, Reddy RM, Lin J, et al. Decreased core muscle size is associated with worse patient survival following esophagectomy for cancer. Dis Esophagus. 2013;26(7):716-22.
89. Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg. 2012;16(8):1478-86.
90. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011;12(4):249-56.
91. Mamane S, Nelson K, et. al. Feasibility and reliability of psoas muscle area as a novel measure for sarcopenia and frailty in patients undergoing transcatheter aortic valve implantation. Journal of Frailty and Ageing. 2015;4((supplement 1)):19-108.

92. 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.
93. 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.
94. Prado CM, Birdsell LA, Baracos VE. The emerging role of computerized tomography in assessing cancer cachexia. Curr Opin Support Palliat Care. 2009;3(4):269-75.
95. Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr. 1997;127(5 Suppl):990S-1S.
96. Beaudart C, Zaaria M, Pasleau F, Reginster JY, Bruyere O. Health Outcomes of Sarcopenia: A Systematic Review and Meta-Analysis. PLoS One. 2017;12(1):e0169548.
97. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013;14(8):531-2.
98. 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.
99. Puts MT, Lips P, Deeg DJ. Sex differences in the risk of frailty for mortality independent of disability and chronic diseases. J Am Geriatr Soc. 2005;53(1):40-7.
100. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE. Sex differences in frailty: A systematic review and meta-analysis. Exp Gerontol. 2017;89:30-40.
101. Prehabilitation for Patients Undergoing Transcatheter Aortic Valve Replacement. https://ClinicalTrials.gov/show/NCT03107897.
102. A STEP for Patients Prior to Undergoing TAVR: A Pilot Study. https://ClinicalTrials.gov/show/NCT02766075.
103. Prehabilitation to Improve Functional and Clinical Outcomes in Patients With Aortic Stenosis. https://ClinicalTrials.gov/show/NCT02597985.
104. Home-Based Exercise Program For Recovery After Transcatheter Aortic Valve Replacement. https://ClinicalTrials.gov/show/NCT02805309.
105. Physical Therapy and Occupational Therapy After Transcatheter Aortic Valve Replacement. https://ClinicalTrials.gov/show/NCT03117296.

Appendix 1: Short Physical Performance Battery (SPPB)



Appendix 2: List of studies evaluating the prognostic role of CT-scan cross-sectional muscle measurement in the peri-operative setting (in descending chronological order)

Author	Title	Journal	Date
Wada Y et al.	Pre-operative volume rather than area of skeletal muscle is a better predictor for post-operative risks for respiratory complications in living-donor liver transplantation.	Br J Radiol.	April 2017
Rutten IJ et al.	The influence of sarcopenia on survival and surgical complications in ovarian cancer patients undergoing primary debulking surgery.	Eur J Surg Oncol	April 2017
Boutin RD et al.	CT of Patients With Hip Fracture: Muscle Size and Attenuation Help Predict Mortality.	Am J Roentgenol.	March 2017
Ninomiya G et al.	Clinical impact of sarcopenia on prognosis in pancreatic ductal adenocarcinoma: A retrospective cohort study.	Int J Surg.	March 2017
Deren ME et al.	Increased Mortality in Elderly Patients with Sarcopenia and Acetabular Fractures.	J Bone Joint Surg Am.	February 2017
Ishihara H et al.	Sarcopenia predicts survival outcomes among patients with urothelial carcinoma of the upper urinary tract undergoing radical nephroureterectomy: a retrospective multi-institution study.	Int J Clin Oncol.	February 2017
Dirks RC et al.	Sarcopenia in emergency abdominal surgery.	J Surg Res.	January 2017
Hervochon R et al.	Body Mass Index and Total Psoas Area Affect Outcomes in Patients Undergoing Pneumonectomy for Cancer.	Ann Thorac Surg.	January 2017
Jaap K et al.	Morphometric Predictors of Morbidity after Pancreatectomy.	J. Am Surg.	December 2016
Drudi LM et al.	Psoas Muscle Area Predicts All-Cause Mortality After Endovascular and Open Aortic Aneurysm Repair.	Eur J Vasc Endovasc Surg.	December 2016
Zuckerman J et al.	Psoas Muscle Area and Length of Stay in Older Adults Undergoing Cardiac Operations.	Ann Thorac Surg.	November 2016
Grotenhuis BA et al	Sarcopenia/Muscle Mass is not a Prognostic Factor for Short- and Long-Term Outcome After Esophagectomy for Cancer.	World J Surg.	November 2016
Bokshan SL et al.	Effect of Sarcopenia on Postoperative Morbidity and Mortality After Thoracolumbar Spine Surgery.	Orthopedics	November 2016
Sandini M et al.	A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer.	Nutrition	November 2016
Carrara G et al.	Preoperative sarcopenia determinants in pancreatic cancer patients.	Clin Nutr.	October 2016
Itoh S et al.	Effect of Sarcopenic Obesity on Outcomes of Living-Donor Liver Transplantation for Hepatocellular Carcinoma.	Anticancer Res.	June 2016

Yabusaki N et al.	Adverse impact of low skeletal muscle index on the prognosis of hepatocellular carcinoma after hepatic resection.	Int J Surg.	June 2016
Boer BC et al.	Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer.	Int J Colorectal Dis.	June 2016
Hale AL et al	Impact of sarcopenia on long-term mortality following endovascular aneurysm repair.	Vasc Med.	June 2016
Nishigori T et al.	Sarcopenia as a predictor of pulmonary complications after esophagectomy for thoracic esophageal cancer.	J Surg Oncol.	May 2016
Tamandl D et al.	Markers of sarcopenia quantified by computed tomography predict adverse long-term outcome in patients with resected oesophageal or gastro-oesophageal junction cancer.	Eur Radiol.	May 2016
Higashi T et al.	Sarcopenia, but not visceral fat amount, is a risk factor of postoperative complications after major hepatectomy.	Int J Clin Oncol.	April 2016
Zhuang CL et al.	Sarcopenia is an Independent Predictor of Severe Postoperative Complications and Long-Term Survival After Radical Gastrectomy for Gastric Cancer: Analysis from a Large-Scale Cohort.	Medicine (Baltimore)	March 2016
Paknikar R et al.	Psoas muscle size as a frailty measure for open and transcatheter aortic valve replacement.	J Thorac Cardiovasc Surg.	March 2016
Pecorelli N et al.	Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery.	Br J Surg.	March 2016
Mok M et al.	Prognostic Value of Fat Mass and Skeletal Muscle Mass Determined by Computed Tomography in Patients Who Underwent Transcatheter Aortic Valve Implantation.	Am J Cardiol.	March 2016
Terjimanian M et al.	Abdominal adiposity, body composition and survival after liver transplantation.	Clin Transplant.	March 2016
Okumura S et al.	Impact of the preoperative quantity and quality of skeletal muscle on outcomes after resection of extrahepatic biliary malignancies.	S. Surgery.	March 2016
Mamane S et al.	Psoas Muscle Area and All-Cause Mortality After Transcatheter Aortic Valve Replacement: The Montreal-Munich Study.	Can J Cardiol.	February 2016
Psutka SP et al.	Decreased Skeletal Muscle Mass is Associated with an Increased Risk of Mortality after Radical Nephrectomy for Localized Renal Cell Cancer.	J Urol.	February 2016
Kobayashi A et al.	Impact of postoperative changes in sarcopenic factors on outcomes after hepatectomy for hepatocellular carcinoma.	Pancreat Sci.	January 2016
Sur MD et al.	Radiographic Sarcopenia and Self-reported Exhaustion Independently Predict NSQIP Serious Complications After Pancreaticoduodenectomy in Older Adults.	Ann Surg Oncol.	November 2015

Huang DD et al.	Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer.	Colorectal Dis.	November 2015
van Vugt JL et al.	Skeletal Muscle Depletion is Associated with Severe Postoperative Complications in Patients Undergoing Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis of Colorectal Cancer.	Ann Surg Oncol.	October 2015
Sharma P et al.	Sarcopenia as a predictor of complications in penile cancer patients undergoing inguinal lymph node dissection.	World J Urol.	October 2015
Tegels JJ et al.	Sarcopenia is highly prevalent in patients undergoing surgery for gastric cancer but not associated with worse outcomes.	J Surg Oncol.	September 2015
Amini N et al.	Impact Total Psoas Volume on Short- and Long-Term Outcomes in Patients Undergoing Curative Resection for Pancreatic Adenocarcinoma: a New Tool to Assess Sarcopenia.	J Gastrointest Surg.	September 2015
Levolger S et al.	Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma.	J Surg Oncol.	August 2015
Okumura S et al.	Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer.	Surgery	June 2015
Voron T et al.	Sarcopenia Impacts on Short- and Long-term Results of Hepatectomy for Hepatocellular Carcinoma.	Ann Surg.	June 2015
Joglekar S et al.	Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma.	J Surg Oncol.	May 2015
Kuroki LM et al.	Pre-operative assessment of muscle mass to predict surgical complications and prognosis in patients with endometrial cancer.	Ann Surg Oncol.	March 2015
Jones KI et al.	Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications.	Colorectal Dis.	January 2015
Du Y et al.	Sarcopenia is a predictor of outcomes in very elderly patients undergoing emergency surgery.	Surgery	September 2014
Zarinsefat A et al.	Perioperative changes in trunk musculature and postoperative outcomes.	J Surg Res	September 2014
Itoh S et al.	Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma.	Ann Surg Oncol.	September 2014
Montano-Loza AJ et al.	Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation.	Liver Transpl.	June 2014
Smith AB et al.	Sarcopenia as a predictor of complications and survival following radical cystectomy.	J Urol.	June 2014
Masuda T et al	Sarcopenia is a prognostic factor in living donor liver transplantation.	Liver Transpl.	April 2014

Hasselager R et al.	Core muscle size assessed by perioperative abdominal CT scan is related to mortality, postoperative complications, and hospitalization after major abdominal surgery: a systematic review.	Arch Surg.	March 2014
Krell RW et al.	Association between sarcopenia and the risk of serious infection among adults undergoing liver transplantation.	Liver Transpl.	December 2013
Harimoto N et al.	Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma.	Br J Surg.	October 2013
Sheetz KH et al.	Decreased core muscle size is associated with worse patient survival following esophagectomy for cancer.	Dis Esophagus.	September 2013
Dello SA et al.	Sarcopenia negatively affects preoperative total functional liver volume in patients undergoing liver resection.	HPB (Oxford)	March 2013
Lieffers JR et al.	Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery.	Br J Cancer.	September 2012
Englesbe MJ et al.	Analytic morphomics, core muscle size, and surgical outcomes.	Ann Surg.	August 2012
Lee JS et al.	Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair.	J Vasc Surg.	April 2011
Englesbe MJ et al.	Sarcopenia and mortality after liver transplantation.	J Am Coll Surg.	August 2010