Measuring frailty in vascular surgery patients undergoing open and catheter-based interventions

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Submitted: October 2016

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of a Master's Degree in Epidemiology, Biostatistics, and Occupational Health

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English Abstract

Background: Frailty is a multi-dimensional syndrome that reflects a state of decreased physiologic reserves. Our objective was to explore the role of frailty in patients with vascular disease, and determine the prognostic value of frailty on predicted mortality in vascular patients undergoing open and catheter-based interventions.

Methods: After performing a literature review of frailty in vascular surgery, two retrospective studies were performed. The first study was a post-hoc analysis of the multi-institutional FRAILTY-AVR study evaluating the prognostic impact of physical frailty (as measured by the short physical performance battery) as well as access site on 12-month mortality in patients undergoing transcatheter aortic valve repair (TAVR). The second study evaluated the prognostic impact of psoas muscle area (PMA) (as measured from a pre-operative CT scan), as a surrogate for total body muscle mass, in patients undergoing open and endovascular aneurysm repairs at a single vascular center.

Results: Based on 10 previous studies, the prevalence of frailty was found to be as high as 60%. Our first cohort of 638 patients underwent TAVR. Forty-nine percent of the cohort with peripheral arterial disease (PAD) underwent non-femoral TAVR compared to only 17% without PAD. Non-femoral access (adjusted OR 1.90, 95% CI 1.10 to 3.27) and physical frailty (adjusted OR 3.57, 95% CI 1.82 to 7.69) were found to associated with increased 12-month mortality, without evidence of interaction between these variables. Our second cohort of patients undergoing open and endovascular aneurysm repairs consisted of 149 patients. PMA was independently associated with all-cause mortality with a hazard ratio of 0.86 per cm^2 (95% CI 0.79 to 0.93). Addition of PMA to the model with the clinical covariates resulted in an improvement in C-statistic from 0.57 to 0.67 and BIC from 307 to 301.

Conclusions: Physical frailty and non-femoral TAVR access were shown to have a higher 12-month mortality. Risk factors such as physical frailty in conjunction with PAD status will play an increasingly important role in identifying high-risk individuals and will play a role in selecting the ideal access site for patients undergoing TAVR. Furthermore, an alternate facet to frailty that incorporates PMA, as a surrogate for total body muscle mass, may be added to traditional risk assessments and may help identify a subset of vulnerable patients who may have an incrementally higher risk of mortality after aortic aneurysm surgeries.

French Abstract

Introduction: La fragilité est un syndrome complexe qui reflète l'état diminué des réserves physiologiques. Notre objectif était d'explorer la valeur pronostique de la fragilité chez les patients atteints d'une maladie vasculaire périphérique permettant ainsi de prédire la mortalité chez ceux qui subiront des interventions vasculaires ouvertes ou endovasculaires.

Méthodes: Après avoir effectué une revue de la littérature sur la fragilité en chirurgie vasculaire, deux études rétrospectives ont été effectuées. La première était une analyse secondaire de l'étude multicentrique FRAILTY-AVR qui a évalué l'impact pronostique de la fragilité physique et du site d'accès sur la mortalité à 12 mois chez les patients subissant un remplacement de la valve aortique par voie transcathéter (RVAT). La seconde étude avait pour objectif d'évaluer l'impact pronostique de l'aire du muscle psoas (AMP) chez les patients subissant une réparation ouverte ou endovasculaire d'un anévrisme de l'aorte abdominale (RAAA). L'AMP est un indicateur de la sarcopénie et est reconnue comme une technique valide permettant d'estimer la masse musculaire du patient. L'AMP a été mesurée par coupe axiale sur le CT scan par l'entremise d'un logiciel semi-automatisé retrouvé sur le site web Coreslicer.com.

Résultats: Sur la base de 10 études, la prévalence de la fragilité était aussi élevée que de 60%. Notre première cohorte était composée de 638 patients ayant subi un RVAT. Quarante et neuf pour-cent de la cohorte atteinte d'une maladie artérielle périphérique (MVAS) a subi un RVAT par un accès autre que fémoral par rapport à seulement 17% de ceux sans MVAS. Chez les patients physiquement frêles, l'accès non-fémoral (OR 1.90, IC à 95% 1.10 to 3.27) et la fragilité physique (OR 3.57, IC à 95% 1.82 to 7.69) étaient associés à une mortalité accrue à 12 mois, sans évidence d'interaction. La deuxième cohorte était composée de 149 patients subissant une RAAA. Il y avait une association entre l'AMP et la mortalité avec un hasard ratio de 0.86 par

cm^2 (IC à 95% 0.79 à 0.93). L'ajout de l'AMP au modèle comprenant les covariables cliniques a donné lieu à une amélioration de la C-statistique de 0.57 à 0.67 et BIC de 307 à 301.

Conclusions: Les patients physiquement frêles, atteints d'une MVAS, et subissant un accès par approche non-fémorale pour un RVAT avaient un taux de mortalité à 12 mois plus élevé. Les facteurs de risque tels que la fragilité physique combinée à la MVAS joueront un rôle plus important dans l'identification des personnes à risque élevé et pourront également aider dans la sélection du site d'accès optimal pour ces patients subissant un RVAT. Également, une autre facette à la fragilité incorpore l'AMP comme marqueur de la sarcopénie. Elle pourrait être ajoutée à l'évaluation des risques traditionnels pour ainsi aider à identifier un sous-ensemble de patients vulnérables étant considérablement à risque plus élevé de mortalité après une RAAA.

Acknowledgements

I would like to thank my thesis supervisors for their guidance and support throughout my academic endeavors to pursue a MSc in Epidemiology. Dr. Jonathan Afilalo has shared with me his enthusiasm for research, the tools needed to pursue academic vascular surgery, and most importantly he has been a pillar in the way he manages his time in being a clinician-scientist. The thesis and the included manuscripts would not have been possible without his constant support and availability. I would like to thank my collaborators in the Division of Vascular Surgery: Drs. Oren K. Steinmetz and Daniel I. Obrand for their constant availability and enthusiasm throughout this entire process despite their busy clinical practices. They were always available in providing feedback on study design, methodology as well as critical review of the included manuscripts. I would like to thank Dr. Philippe Charbonneau who assisted in the French translation of my abstract. I would like to thank the entire Frailty Research Group consisting of a team of research coordinators and research assistants who without their perpetual work and support, none of this would be possible. I would like to thank Matthew Ades, a medical student, who has always given his enthusiasm and availability to achieve the variety of projects we are collaborating on together. He has given me the strength and motivation to continue pushing the frontiers of academic vascular surgery. The Frailty Research Group did not receive any additional remuneration for their involvement in this project and often invested significant time and effort beyond the regular working hours in their respective schedules.

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Thesis candidate. Initiation of concept and design of literature review and the two cohort studies. Wrote the protocol. Prepared and submitted application for research ethics approval. Trained research assistants to aid in data collection as well as using Coreslicer software to measure psoas muscle area. Created an online database to collect and organize data. Developed initial statistical approach and performed statistical analyses under the supervision of principal supervisor. Wrote the thesis document and two manuscripts.

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Chapter 1: Thesis Introduction

Assessing frailty in surgical patients is relatively a new area of investigation. There has been an explosion in this area of research over the past 10 years. Pre-operative surgical risk prediction is central to decision making in surgery. However, current surgical risk prediction models under-perform in older patients as they only capture a snapshot of the patient's condition and do not reflect the patient's physiologic reserves that will be called upon at a time of major stress, such as surgery. Integration of frailty assessment has thus been advocated to improve operative risk prediction.

Frailty is a multi-dimensional syndrome that reflects inactivity, low muscle mass, and reduced energy. There are a variety of frailty definitions in the literature (1) and there has been an exponential growth of instruments to diagnose frailty in older patients with heterogeneous sensitivities and specificities (2). The lack of a single unifying frailty definition and instrument poses a great challenge with ongoing research in the area of frailty. Nonetheless, across the varying definitions and instruments used to assess frailty, it has been well documented across a variety of surgical specialties that frail patients have a greater risk of perioperative adverse outcomes, including morbidity, major adverse cardiovascular events, and mortality (3, 4).

The consideration of frailty in vascular surgery patients is a growing interest particularly in a patient population consisting primarily of an expanding aging population with extensive comorbidities undergoing a variety of major endovascular and open interventions. Therefore, integrating frailty alongside clinical risk factors may further improve pre-operative risk stratification in patients undergoing vascular surgery. In doing so, frailty assessment may aid in the allocation of surgical resources, and may decrease costs by preventing patients from receiving costly and potentially unnecessary procedures. Consideration of frailty may also serve

as a tool to improve patient counselling on operative risk, and thereby ensure that patients benefit from more personalized treatment plans that will maximize their likelihood of a positive patient-centered outcome. Finally, frailty may be used as a potential therapeutic target in the pre-operative management of surgical patients in order to change a patient's risk profile through a variety of interventions (5), and subsequently lead to improved post-operative outcomes.

Thus, the objective of this thesis was to perform a review of the literature to delineate the role of frailty and the current tools used to assess frailty in patients undergoing vascular surgery procedures; and subsequently, to perform two retrospective studies using two tools (physical frailty and psoas muscle area) to demonstrate how these instruments may be used as prognostic indicators for adverse peri-operative outcomes, such as morbidity and mortality, in older vascular patients. In Chapter 2, definitions of frailty and what is known about the pathophysiology of frailty are reviewed. Next, the role for pre-operative risk prediction in surgery is explained along with current tools used in clinical practice. The pitfalls for current tools used in pre-operative risk prediction are identified and the need for frailty measures are elucidated. Finally, measurement tools that assess frailty in vascular surgery are outlined and described in detail. Chapter 3 is the first manuscript entitled, "**The effect of access site and physical frailty in older adults undergoing transcatheter aortic valve replacement"**, which explores the interaction between transcatheter aortic valve replacement access site and physical frailty in predicting all-cause 12-month mortality. Chapter 4 is a transitioning chapter and covers the limitations of physical frailty measurements in a vascular surgery population, and proposes more objective measurements for frailty, such as muscle mass. Chapter 5 is the second manuscript entitled, **"Psoas Muscle Area Predicts All-Cause Mortality After Endovascular and Open Aortic Aneurysm Repair",** which investigates the association between psoas muscle area, as a validated surrogate marker

for total body muscle mass, and post-operative mortality after endovascular or open aortic aneurysm repair. Chapter 6 summarizes the main findings of this thesis, the main epidemiological concerns for this thesis, and future research underway. Finally, Appendices A, B, C, D, E, F, and G delineate the frailty measures discussed in this thesis in greater detail.

Chapter 2: Literature Review - What is known about frailty?

2.1 Defining Frailty

Frailty is a multi-dimensional syndrome that reflects a state of decreased physiologic reserves and vulnerability to stressors (6). The clinical frailty phenotype may be characterized by core domains, including slowness, weakness, weight loss, low physical activity, exhaustion, cognitive impairment, and mood disturbance that may be measured using frailty screening tools (Table 1) (1, 7). Slowness is measured by a short-distance gait speed test, weakness by a handgrip strength test, and other domains by questionnaire. However, frailty may also be characterized by an accumulation of deficits that can encompass diverse signs, symptoms, comorbidities, as well as disabilities (8-10) (Figure 1). Advanced age, socio-economic environment, malnutrition, and numerous comorbidities may lead to low muscle mass, resulting in decreased strength and power, leading to reduced energy and culminating to inactivity. Functional dependency may be perceived as an advanced symptom of frailty, which is further associated with post-operative morbidity and mortality (11). Furthermore, strong associations are also seen between frailty and cognitive impairment, both of which are predominantly seen in a geriatric population. The coexistence frailty and cognitive impairment has been shown to be associated with increased susceptibly to adverse health outcomes and a longer length of stay in hospital (12).

Frailty Domain	Measurement
Weakness	Grip strength
Slowness	Gait speed
Low physical activity	Kcal per week
Exhaustion	Self-reported
Weight loss	>10 lbs over 12 months

Table 1: Clinical frailty phenotype (1)

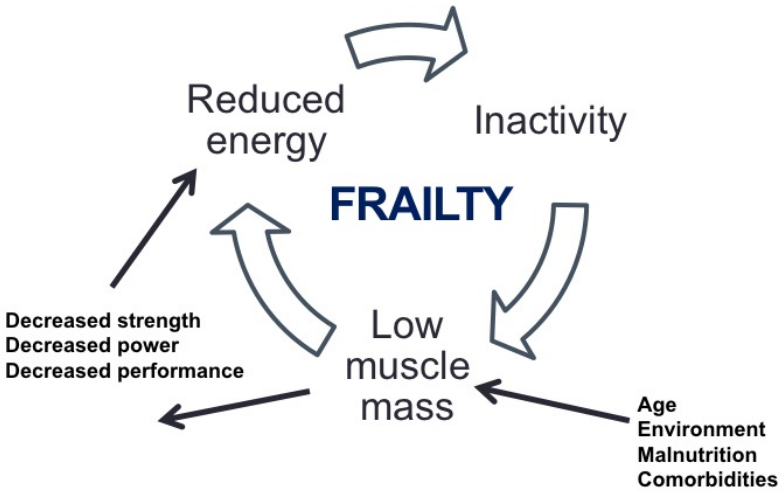

Figure 1: Conceptual diagram describing the frailty syndrome

2.2 Pathophysiology of Frailty

The pathophysiology of frailty is believed to be a result of predisposing molecular and disease-related triggers, which in turn lead to multiple physiologic impairments, that result in the clinical frailty phenotype. The impaired physiologic systems are centered around the dysregulation of the immune, hormonal, and endocrine systems, resulting in an upregulation of inflammatory cytokines, including interleukin-6 (IL-6) and C-reactive protein (CRP), decreased testosterone levels, and insulin resistance (13, 14). This dysregulation leads to a catabolic milieu with a subsequent net loss of muscle mass, which consequently results in a progressive decline in muscle mass and strength known as sarcopenia (15).

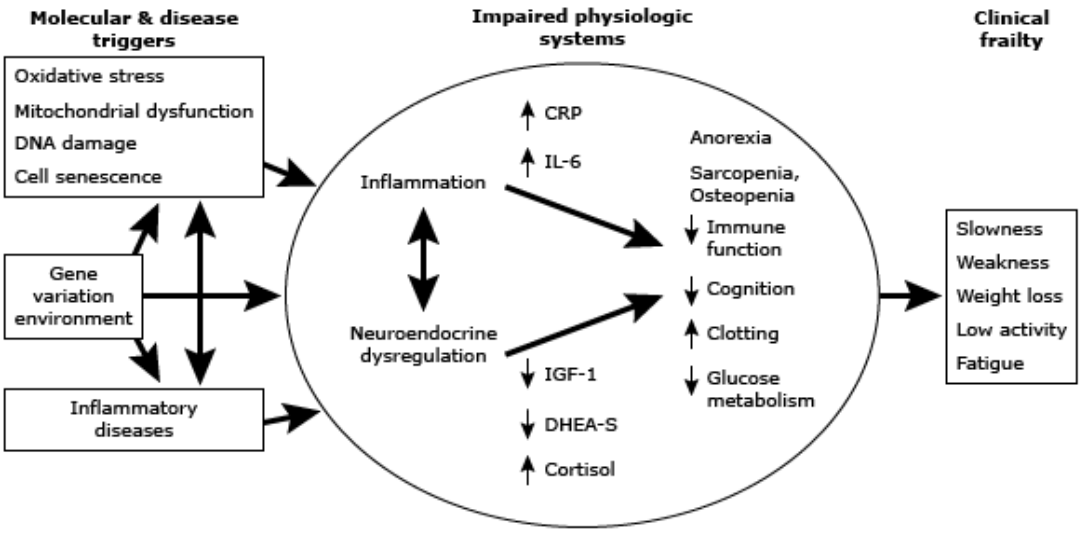

Figure 2: Conceptual diagram describing the pathophysiology of frailty (16)

Skeletal muscle is the principal reservoir for amino acids (17). Therefore, a decline in muscle mass or low mass muscle impedes the body's capability to mobilize amino acids that are needed for protein synthesis (18). Moreover, during stress, there is a need for increased protein synthesis that is required for immune function, wound healing, and acute phase reactants, such that amino acid requirements are four-fold greater than what is required under steady-state conditions (19). Taken together, the frailty-associated catabolic state with its progressive decline in muscle mass is further compounded by acute and chronic physiologic stressors, which can be further exacerbated by other catabolic stimuli, such as inactivity and malnutrition. It is with no surprise that pre-operative frailty, operative stressors, as well as perioperative inactivity and malnutrition results in a perpetual catabolic cycle that results in deconditioning, prolonged recovery, perioperative morbidity, and mortality (20).

2.3 Pre-Operative Risk Prediction: The Role of Frailty

Pre-operative risk prediction is an essential tool relied upon by clinicians and surgeons to counsel and guide patients towards the appropriate therapy and to help plan patients' perioperative needs. When predicting pre-operative risk, an attempt is made to quantify the probability of a peri-operative adverse outcome. This is accomplished by integrating age, sex, comorbidities, illness severity, and type of procedure. Various vascular surgery risk scores have been developed to facilitate and objectively evaluate this risk.

2.3.1 Vascular Surgery Pre-Operative Risk Scores

Pre-operative risk scores serve at least 3 important purposes (21):

1. Guiding medical and surgical decisions

   The peri-operative predicted risk is used by the end-user to better ascertain the risk-benefit ratio and ultimately guide patients towards open repair, endovascular repair, hybrid repair, or medical management. Additionally, patients identified as having a high predicted risk may benefit from more intensive pre- and peri-operative optimization (i.e. medical optimization, pre-operative rehabilitation). Furthermore, the predicted peri-operative risk may be shared with the patient to inform them of their personalized risk through the informed consent process.

2. Comparing provider performance

   The predicted peri-operative risk is used to calculate a risk-adjusted mortality for a given surgeon or hospital. This may be needed for public reporting of outcomes and quality improvement programs, such as the Vascular Quality Initiative (VQI) or the National Surgical Quality Improvement Program (NSQIP).

3. Academic research

The peri-operative predicted risk is used by the researcher to describe the study population and to adjust for confounding. Moreover, a minimum peri-operative predicted risk of mortality may be used as an inclusion criterion for participation in a clinical trial.

Several pre-operative surgical risk scores exist with the Revised Cardiac Risk Index (RCRI), or Revised Lee's criteria, being widely adopted in the medical community for the perioperative evaluation of vascular patients at our institution (22). The RCRI is a risk score system ranging from 0-6 points, which is based largely on a patient's comorbidities, including history of coronary artery disease (CAD), congestive heart failure (CHF), insulin-dependent diabetes mellitus, creatinine > 2g/dL and high risk surgery (Table 2) (22). However, the RCRI has not been validated in the vascular surgery population; therefore, the RCRI score underestimates post-operative adverse outcomes in this population (Table 2). This led to the development of a vascular surgery-specific risk prediction score, the Vascular Surgery Group of New England Cardiac Risk Index (VSG-CRI), with a score ranging from 0 to 15 points (23). The VSG-CRI also comprises of risk factors that are largely based on a patient's comorbidities, including age, CAD, CHF, chronic obstructive pulmonary disease (COPD), creatinine > 1.8 g/dL, history of smoking, insulin dependent diabetes mellitus, and long-term beta-blockade (23).

Number of Points	Predicted RCRI Predicted Risk (%)	VSG-CRI Predicted Risk (%)
0	0.4	2.6
1	0.9	6.7
2	6.6	11.6
≥3	11.0	18.4

Table 2: RCRI Underestimates the Risk of In-Hospital Adverse Cardiac Events in Vascular Surgery Patients (22, 23)

2.3.2 The Need for Frailty Risk Scores in Vascular Surgery

The standard assessment of pre-operative risk with currently available risk scores captures a snapshot of a patient's health status at the time of the pre-operative evaluation, which is heavily focused on comorbidities (22, 23). Current pre-operative assessment does not capture a patient's physiologic reserves, which will be called upon at the time stress, such as a vascular intervention. Current pre-operative risk scores only capture certain known impairments but fail to capture the multitude of subclinical impairments that progressively accumulate with age that ultimately determine a patient's physiologic reserves, that will be called upon at the time of major stress (24). These subclinical impairments may be responsible for the heterogeneity that is seen in older patients prior to surgery, for instance, why two patients with comparable age, illness severity, comorbidity burden, and predicted pre-operative risk score (either using RCRI or VSG-CRI) often have vastly different responses to the stress of surgery, such that of a vascular intervention.

2.4 Tools to Assess Frailty

2.4.1 Frailty Assessment Tools Reliant on Comorbidities and Physical Performance Parameters

Physical frailty may be captured with a variety of tools, including the Fried frailty scale, modified Fried frailty scale, the short physical performance battery, 5-meter gait speed, and handgrip strength (Table 3).

The Fried frailty scale (25) encompasses slowness, weakness, weight loss, low physical activity, and exhaustion with greater than 3 out of 5 criteria required for a diagnosis of frailty (Appendix A). This is the most frequently cited frailty tool, shown to predict mortality and disability in a large cohort of community-dwelling elders and cardiovascular patients (26). The expanded Fried frailty scale (6) adds cognitive impairment and mood with greater than 3 out of 7 criteria required for a diagnosis of frailty (Appendix B).

The short physical performance battery (SPPB) (27) encompasses slowness, weakness, and balance. This is measured by a series of 3 timed physical performance tests (gait speed, chair rises, and tandem balance) where each is scored 1-4 and a total score ≤5/12 is required for a diagnosis of frailty (Appendix C). The SPPB was shown to predict outcomes in community-dwelling elders (28), as well as in patients' with peripheral arterial disease (29) and heart failure (30).

The 5-meter gait speed and handgrip strength have been advocated as single measures of frailty that often outperform more elaborate tools. The gait speed test has been shown to be an excellent tool for measuring frailty (31) in community dwellers. Slow gait speed predicts 5-year survival (32) and cardiac-related mortalities (33). Similar results have been shown with handgrip strength in elderly community dwellers (34).

Physical Frailty Assessment Tool	Description	Cut-off for Frailty
Fried scale	5-item scale: (1) Slow gait speed, (2) Weak handgrip strength, (3) Weight loss, (4) Low physical activity, (5) Exhaustion	≥3 criteria
Modified Fried scale	7-item scale: (1-5) Fried scale items, (6) Cognitive impairment, (7) Depressed mood	≥3 criteria
Short Physical Performance Battery	3-item scale: (1) Gait speed, (2) Tandem balance, (3) Repeated chair stands	Total score ≤5 (each item scored 1-4)
5-meter gait speed	Time taken to walk 5 meters at a comfortable pace	>6 seconds
Handgrip strength	Kilograms of force exerted squeezing a handgrip dynamometer at the maximal strength	≤30 kg ♂ ≤20 kg ♀

Table 3: Frailty assessment tools reliant on physical performance

The Canadian Study of Health and Aging (CSHA) originally developed the Clinical Frailty Scale (CFS) (35) as a 7-point scale, where 1 is characterized as "Very Fit" and 7 is characterized as "Severely Frail". The CFS encompasses comorbidity, cognitive impairment, and disability. The CFS was later revised to a 9-point scale in 2011 (Appendix D) (36).

The modified frailty index (mFI) was created from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database (37), and comprises 11-items, which all reflect a patient's comorbidities (Appendix E). The score ranges from 0-11, where 0 represents an absence of frailty and 11 represents the highest degree of frailty.

The Edmonton Frail Scale (EFS) (38) is a 17-point scale that encompasses cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and physical frailty performance using a 3-meter gait speed (Appendix F). A score of 0 represents an absence of frailty, whereas a score of 17 represents the highest degree of frailty.

The Groningen Frailty Indicator (GFI) (39) encompasses 8 domains, including mobility, vision, hearing, nutrition, comorbidity, cognition, psychosocial, and physical fitness with a score of 4 or more indicative of a higher risk for frailty (Appendix G). This score has been validated in specialties, which include oncology, pulmonology, and traumatology. However, the GFI was not found to be statistically significant in predicting post-operative delirium or length of stay in vascular surgery patients.

2.4.2 Muscle mass as a measure of frailty

There are several limitations to physical frailty assessment tools. First, physical frailty assessments, such as the 5-meter gait speed has a high sensitivity (99%) but low specificity (64%) to diagnose frailty (2); therefore, this results in several false positives and may not be an ideal tool to accurately diagnose frailty alone. Furthermore, accuracy is further reduced in the acute care setting (40) where frailty may be influenced by several other factors such as acute or chronic illness-related deficits in physical function. Third, physical frailty assessments may not be feasible in 10-45% of patients due to illness or mobility-related impairments, with these figures being higher in a vascular surgery population with peripheral arterial disease. These patients pose the greatest challenge to clinicians since their functional capacity and frailty are difficult to gauge as these patients may be limited by their disease and not necessarily by their inherent frailty. Fourth, physical frailty scales use self-reported weight loss and may be subject to inaccuracies; therefore, physical frailty tools do not objectively account for low muscle mass or malnutrition.

Muscle mass is an appealing measure of frailty because it is objective and independent of patient compliance and symptoms. Shen *et al*. first reported that muscle area in a single cross-

sectional slice at the level of the L4 vertebrae was highly correlated with total body muscle volume (41). It was further shown that reporting the area of the psoas muscle alone at the level of the L4 vertebrae was an excellent predictor of postoperative survival after non-cardiac surgery (42, 43). The thoracic muscles were also quantified in this model, including the pectoralis major, serratus anterior, lattisimus dorsi, trapezius, erector spinae, and transversospinalis (44). However, the pre-operative evaluation of thoracic skeletal muscle using CT has not been extensively explored and the measurement of all the above mentioned thoracic muscles is quite labor-intensive.

Existing frailty tools fall short in that they focus on low muscle strength and associated physical frailty (measured by handgrip strength, gait speed, and chair rises) with little attention to low muscle mass. Low muscle mass may be captured with subjective or objective measures of weight loss; however, weight loss is a flawed measure of muscle mass because excess adiposity may often conceal low muscle mass (45). Excess adiposity with low muscle mass is an entity called "sarcopenic obesity" and it is especially prevalent in older patients (46). Therefore, an objective measure of low muscle mass may be a more stable marker that is less likely to fluctuate, and may be highly suitable for the assessment of frailty.

Low muscle mass and frailty have been associated with adverse post-operative outcomes in various medical and surgical populations (47-51). Since patients referred for open or endovascular aneurysm repair routinely get a CT scan to assess vascular anatomy, psoas muscle area is a very promising marker which can be measured in a short period of time as the clinician is reviewing a patient's CT scan. Our Frailty Research Group developed a free, online, and semi-automated software (Coreslicer) that can measure psoas muscle area in less than 1 minute, and has been validated in a cohort of patients undergoing transcatheter aortic valve replacement

(TAVR). This study demonstrated that low psoas muscle area is a marker of frailty and was associated with midterm survival in women who undergo TAVR (52).

2.4.2 Frailty Assessment in Vascular Surgery

Ten studies, all published in the past 5 years, addressed the prevalence or prognostic impact of frailty (Table 4). Notably, there are 7 different frailty assessments in this review, which highlights the lack of consensus among researchers and clinicians.

Study	N	Setting	Frailty Assessment Tool	Frail	Outcome
Arya (53), 2016	15,843	Arterial vascular surgery procedures	Modified Frailty Index	37.3%	Non-home discharge: OR 1.6 (95% CI: 1.4 – 1.8)
Brahmbhatt (54), 2016	24.645	Infra-inguinal vascular procedures	Modified Frailty Index	59.8%	30-day mortality: OR 1.74 (95%CI: 1.37 – 2.20) 30-day morbidity: OR 1.26 (95%CI: 1.18 – 1.35)
O'Neill (55), 2016	392	Arterial vascular surgery procedures	Clinical impression	30.6%	All-cause Mortality: HR 2.14 (95% CI: 1.51 – 3.05)
Thiede (56), 2016	17	Peripheral arterial disease	Fried Frailty Scale	53%	A 25-step gait test was associated with pre-frailty
Arya (57), 2015	23, 207	Elective aneurysm repair	Modified Frailty Index	23%	30-day mortality: EVAR OR 1.9 (95% CI 1.2 – 3.0) OAR OR 2.3 (95% CI 1.5 – 2.1)
Partridge (58), 2015	125	Arterial vascular surgery procedures	Edmonton Frailty Scale	52%	Preop care: OR 7.77 (95% CI:2.55 – 23.68) Polypharmacy: OR 3.50 (95%CI: 1.14 – 10.75) Cognitive impairment: OR 10.18 (95%CI: 2.77 – 37.41)
Scarborough (11), 2015	174,143	Complex general or vascular procedures	Pre-operative functional dependence	N/A	30-day Mortality: OR 1.75 (95% CI: 1.54-1.98) Major morbidity: OR 1.51 (95%CI: 1.41 – 1.62)
Karam (59), 2013	67,308	Vascular surgery procedures	Modified Frailty Index	N/A	30-day mortality: OR 2.06
Lee (43), 2011	262	Abdominal aortic aneurysm surgery	Cross-sectional area of psoas muscles	N/A	90-day mortality: HR 0.98 per 1 cm^2 decline in muscle area
Pol (39), 2011	142	Vascular surgery procedures	Groningen Frailty Indicator ≥4	35%	Post-operative delirium: Nonsignificant Length of stay: Nonsignificant

Table 4: Assessment of frailty in a vascular surgery population

Arya *et al*. (53) had a clearly defined research question with an appropriately designed retrospective study. The study captured 15,843 vascular surgery patients from the NSQIP database. The study showed that frailty (as measured by the modified frailty index[mFI]) was associated with non-home discharge (OR 1.6, 95% CI 1.4 to 1.8). The population of study was a heterogeneous group of vascular surgery patients. On multivariable logistic regression, only open procedures were adjusted for, and not the specific type of vascular surgery. In as such, the status of frailty may differ across these different subgroups of vascular surgery patients.

Brahmbhatt *et al*. (54) had a clearly defined research question with an appropriately designed retrospective study using the NSQIP database. The study investigated the interaction between gender and frailty (using the mFI) on outcomes among 24,645 patients undergoing infra-inguinal vascular surgery. On multivariable logistic regression, the interaction between female gender and increased mFI scores were associated with 30-day mortality (OR 2.05, 95% CI 1.48 to 2.84) and 30-day morbidity (OR 1.67, 95% CI 1.51 to 1.84). Despite the robust sample size and appropriate analytic techniques investigating interaction between gender and frailty, the primary outcomes of 30-day morbidity and 30-day mortality are arguably not an adequate period of follow-up for patients undergoing high-risk surgeries (60). Alternative outcomes that may have been used are 60-day or 90-day morbidity and mortality.

O'Neill *et al*. (55) had a clearly defined research question with an appropriately designed retrospective study. The study investigated if a physician's clinical impression of frailty was associated with all-cause mortality in 392 patients undergoing vascular surgery. On Cox regression, once adjusting for appropriate clinical covariates including RCRI, the clinical impression of frailty was associated with all-cause mortality (HR 2.14, 95% CI 1.51 to 3.05). A major limitation of the study was the definition for the clinical impression of frailty. In this

study, a clinical impression of frailty accounted for the patient's health status and pre-operative risk, using the RCRI. This raises concerns in that there may be collinearity seen between clinical impression and RCRI, and thus both should not be adjusted for in the model.

Thiede *et al*. (56) had a clearly defined research question. The study captured only 17 patients with peripheral arterial disease (PAD) and evaluated the association between physical performance impairments and frailty. The study showed that a 25-step sensor-based in-clinic gait test identified pre-frailty (based on the Fried scale) in regression models, after adjusting for age, sex, and BMI. Although effect sizes (ORs) were given for each component of the gait performance, there were no reported 95% confidence intervals; therefore, statistical significance was based on the reporting of a p-value. Furthermore, the p-value does not provide a good measure of evidence regarding a model or hypothesis and should be refrained from being used (61).

Arya *et al*. (57) had a clearly defined research question with an appropriately designed retrospective study. The study captured 23, 207 vascular surgery patients and showed that frailty (as per the modified frailty index) was associated with 30-day mortality in the endovascular aneurysm repair group (EVAR) (OR 1.9, 95% CI 1.2 to 3.0) and the open aortic aneurysm group (OAR) (OR 2.3, 95% CI 1.5 to 2.1). Frailty was also associated with severe complications after EVAR (OR 1.7, 95% CI 1.3 to 2.1) and OAR (OR 1.8, 95% CI 1.5 to 2.1). Despite the robust sample size, as well as the magnitude and precision of the effect estimates, some limitations should be noted. First, the primary outcome was 30-day mortality, which is arguably not an adequate period of follow-up for patients undergoing high-risk surgeries (60). Alternative outcomes that may have been used include 60-day or 90-day mortality. Second, the analytic techniques in the multivariable logistic regression model adjusted for the American Society of

Anesthesiology (ASA) score as a measure of pre-operative risk, which has been previously shown to be a very poor predictor of risk (62).

Partridge *et al*. (58) did not have a clearly defined research question, in that the authors did not specify the specific adverse post-operative outcomes, which were being studied in the study population. The prospective study captured 125 patients undergoing both elective and emergency vascular procedures; however, walking based tests were not feasible in 45% of the patients in the study. The study showed that adverse post-operative outcomes in the most frail of patients (as per the Edmonton Frail Scale) was associated with cognitive impairment (OR 10.18, 95% CI 2.77 to 37.41), receiving pre-operative care (OR 7.77, 95% CI 2.55 to 23.68), and the use of 6 or more medications (OR 3.55, 95% CI 1.14 to 10.75). The above confidence intervals are notably wide resulting in less precision of the parameter. Thus, the results and conclusions should have been formulated given this imprecision.

Scarborough *et al*. (11) had a clearly defined research question with an appropriately designed propensity-matched retrospective study using the NSQIP database. The study investigated the association between functional status and early post-operative outcomes in patients undergoing both major general or vascular surgery procedures. The study captured 174,143 patients and showed that functional dependence was associated with 30-day mortality (OR 1.74, 95% CI 1.54 to 1.98) and 30-day major morbidity (OR 1.51, 95% CI 1.41 to 1.62). Some limitations should be noted. First, the definition for dependence and independence arose from coding within the NSQIP database, and does not follow validated definitions using the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) definitions for functional dependence. Second, the propensity-matched cohort was not matched for important factors that may influence functional dependence or post-operative adverse outcomes,

such as cognitive dysfunction or pre-operative risk scores. Third, given the heterogeneity of the cohort, which includes both general surgery and vascular surgery procedures, it would be difficult to extrapolate these findings to a vascular surgery population given these results were not stratified by the type of procedure.

Karam *et al*. (59) did not have a clearly defined research question, in that the authors did not specify the specific adverse post-operative outcomes, which were being studied in this retrospective study using the NSQIP database. The study captured 67,308 vascular surgery patients and evaluated the association between frailty (as per the modified frailty index) and post-operative 30-day mortality. The study showed that high frailty index scores were associated with 30-day mortality (OR 2.06, P<0.001). The study did not report 95% confidence intervals; therefore, statistical significance was based on the reporting of a p-value. Furthermore, the p-value does not provide a good measure of precision or evidence regarding a model or hypothesis and should be refrained from being used (61). Finally, the outcome measure of 30-day mortality is not an adequate period of follow-up for patients undergoing high-risk surgeries (60). Alternative outcomes that may have been used include 60-day or 90-day mortality.

Lee *et al*. (43) had a clearly defined research question with an appropriately designed retrospective study. The study evaluated the association between psoas muscle area and 90-day mortality in patients undergoing elective open aortic aneurysm repairs. The study showed that psoas muscle area at the L4 level was associated with 90-day post-operative mortality (HR 0.33 per 1000 mm^2 increase in PMA [95% CI 0.16 to 0.68], which equates to a HR of 0.98 per 1 cm^2 increase in PMA) in patients undergoing open abdominal aortic aneurysm repairs. Some limitations should be noted. First, their patient population included only those undergoing open aneurysm repair, which comprises of a vascular surgery population that is typically younger and

with a decreased burden of comorbid conditions and frailty. Second, although the follow-up duration was adequate (mean follow-up of 3 months); the study was not designed to capture late or long-term mortality. Third, their analytic techniques in the Cox regression model only adjusts for stroke and diabetes as comorbid conditions. Although these are important covariates, adjusting for pre-operative risk (using one of a number of pre-operative risk scores) may have been more appropriate to capture comorbid conditions and pre-operative health status.

Pol *et al*. (39) had a clearly defined research question with an appropriately designed prospective study. The study enrolled 142 vascular surgery patients and evaluated the association between the Groningen Frailty Indicator (GFI) and the incidence of post-operative delirium (POD) as a primary outcome. The more appropriate term that should have been used in this study was in-hospital delirium, because this study did not capture re-admissions secondary to delirium. Furthermore, the population of study was a heterogeneous group of vascular surgery patients undergoing percutaneous and open interventions for aortic and peripheral disease, as well as lower extremity amputations. The status of frailty may certainly differ across these different subgroups, and it does not appear that the type of surgery was adjusted for in their multivariable model. Also, on multivariable regression, frailty was not associated with the outcome of POD (OR 1.9, 95% CI 0.9 to 3.7). Despite this, the authors conclude that GFI can be helpful in the early detection of POD, which is not supported by the results of the study.

Given what is known about frailty within a cardiovascular population, the objective of this thesis was to explore the role of physical frailty using one of the largest prospective studies evaluating frailty in elderly cardiovascular patients (FRAILTY-AVR) undergoing transcatheter aortic valve replacement (TAVR). We sought to investigate the possible interaction between physical frailty and TAVR access site, determine the prognostic value of this interaction as a

predictor of mortality, and to descriptively explore the association with atherosclerotic risk factors, like PAD, that may impart additional risk in individuals undergoing TAVR. Furthermore, given the limitations of physical frailty assessment tools, we also sought to explore the role of psoas muscle area, as a surrogate for total body muscle mass, as a predictor for all-cause mortality in patients undergoing open and endovascular aortic aneurysm repair.

CHAPTER 3: Retrospective cohort study

Submitted manuscript: “The effect of access site and physical frailty in older adults undergoing transcatheter aortic valve replacement”

This manuscript is submitted to the Journal of American College of Cardiology (JACC) Interventions.

The effect of access site and physical frailty in older adults undergoing transcatheter aortic valve replacement

Running title: TAVR Access and Physical Frailty

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This study was presented at the Interactive Poster Session of the 2016 Vascular Annual Meeting in National Harbor, MD on June 9th, 2016.

ABSTRACT

Objective: We sought to explore, as a pilot study, the interaction between access site and physical frailty in predicting all-cause mortality in patients undergoing transcatheter aortic valve replacement (TAVR).

Methods: This study is a post hoc analysis of the FRAILTY-AVR prospective cohort study, including a total of 14 participating centers in the United States, Canada, and France. Consecutive older adult patients who underwent TAVR between July 1, 2012 and March 31, 2015 were identified and subsequently stratified according to trans-femoral and non-femoral access site. The pre-procedural frailty assessment included a multi-item questionnaire, the expanded Fried frailty scale, and short physical performance battery (SPPB). Multivariable regression models were adjusted for relevant covariates and investigated the association between non-femoral TAVR access, physical frailty, and an interaction between these two variables. The primary endpoint was 12-month all-cause mortality.

Results: Among 638 older adults with a mean age of 83.7 (SD = 5.6 years), the prevalence of physical frailty was 76%. The access site was trans-femoral in 492 (77%) and non-femoral in 146 (23%) patients. Patients with non-femoral access were more likely to have CAD, PAD, and greater 12-month mortality. Among patients without documented PAD, 431 (83%) underwent a trans-femoral access and 88 (17%) underwent a non-femoral access. Among patients with documented PAD, 61 (51%) underwent a trans-femoral access and 58 (49%) underwent non-femoral access. Multivariable logistic regression revealed that non-femoral TAVR access (adjusted OR 1.90, 95% CI 1.10 to 3.27) and physical frailty (adjusted OR 3.57, 95% CI 1.82 to 7.69) were associated with 12-month mortality, without evidence of interaction between these variables.

Conclusions: Non-femoral TAVR access and physical frailty imparts a greater risk of 12-month mortality. Therefore, risk factors such as physical frailty may play an increasingly important role in identifying high-risk individuals undergoing TAVR.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is increasingly being used to treat frail elderly patients who may not be candidates for surgical aortic valve replacement (SAVR). TAVR is most commonly performed through a trans-femoral approach and thus necessitates evaluation of the peripheral vasculature, including common femoral artery diameter, arterial tortuosity and ileo-femoral calcification using imaging technologies, such as angiography or CT (63). Candidates who do not meet the anatomical requirements for a trans-femoral vascular access may undergo alternative non-femoral vascular access using subclavian, trans-aortic, or trans-apical sites. It has been shown that non-femoral TAVR procedures, once adjusting for relevant covariates, have a greater risk for major bleeding, conversion to open surgery, as well as greater 30-day and two-year mortality as compared to trans-femoral procedures (64, 65).

Frailty is a multi-dimensional syndrome that reflects a state of decreased physiologic reserves and vulnerability to stressors (6). When exposed to invasive procedures, frail patients may be less likely to tolerate these procedures and have a heightened risk of mortality and morbidity (66-68). Due to its less invasive nature, TAVR is increasingly being used in frail patients as an alternative to SAVR. However, TAVR has a spectrum of access site options with certain benefits and pitfalls of each technique (69). Non-femoral TAVR procedures are more invasive than trans-femoral, and hence expose frail patients to additional operative stress and risk. Thus, these patients may be more vulnerable to suffering post-procedural adverse outcomes. It is unclear whether the combination of TAVR access site and physical frailty imparts higher risk in patients undergoing TAVR. Accordingly, this pilot study sought to explore the interaction between TAVR access site and physical frailty in predicting all-cause 12-month mortality.

METHODS

Study Design

This study is a post hoc analysis of the FRAILTY-AVR (NCT01845207) prospective cohort study, which was designed to compare the value of different frailty scales to predict mortality after TAVR or SAVR (70). A total of 14 centers participated in the United States, Canada, and France. For the purposes of this study, consecutive older adult patients who underwent TAVR between July 1, 2012 and March 31, 2015 were identified and subsequently stratified according to trans-femoral and non-femoral access site. This study was approved by the ethics committee at the participating centers and patients were required to sign an informed consent before being enrolled.

Population

The FRAILTY-AVR study included patients who were greater than 70 years old with symptomatic aortic stenosis who were referred for TAVR or SAVR with or without concomitant cardiac revascularization. Exclusion criteria were emergency surgery, replacement of more than one valve, aortic surgery, clinical instability, severe neuropsychiatric impairment, and non-English or non-French speaking.

TAVR Access

Trans-femoral access was defined as delivery of the aortic valve device through percutaneous or open access of the left or right common femoral artery (71). Non-femoral access was defined as delivery of the aortic valve device through open access of the subclavian artery, carotid artery, ascending aorta (via a right mini-sternotomy) or left ventricular apex (via a left mini-

thoracotomy) (71). Peripheral arterial disease (PAD) status was ascertained by a combination of a patient questionnaire and electronic health records.

Frailty Variables

Pre-procedural frailty was ascertained by the expanded Fried frailty scale and the short physical performance battery (SPPB). The expanded Fried frailty scale encompasses slowness, weakness, weight loss, low physical activity, exhaustion, cognitive impairment, and mood with greater than 3 out of 7 criteria required for a diagnosis of frailty (6). SPPB encompasses slowness, weakness, and balance. SPPB is measured by a series of 3 timed physical performance tests (gait speed, chair rises, and tandem balance) where each is scored 0-4, and a total score of >8 is normal, 6-8 is mildly frail, and 0-5 is significantly frail (27).

Endpoints

The primary endpoint was 12-month all-cause mortality ascertained by contacting the patients or their family members by telephone and verifying the hospital-level electronic health records. There were no patients lost to follow-up at this time point. Post-procedural major adverse cardiovascular complications were defined according to the Valve Academic Research Consortium (VARC) 2 consensus criteria (72).

Statistics

Continuous variables were summarized with the sample mean and standard deviation, and categorical variables were summarized with frequency tables. Multivariable logistic regression was used to estimate the association between 12-month all-cause mortality adjusting

for age, sex, BMI, atrial fibrillation, lung disease, coronary artery disease (CAD), PAD, pre-operative glomerular filtration rate (GFR), pre-operative hemoglobin, left ventricular ejection fraction (LVEF), aortic valve mean gradient, and pulmonary artery systolic pressure (PASP). We performed 3 other regression models with the first including non-femoral access site, the second including non-femoral access site and physical frailty, and the third including an interaction variable between access site and physical frailty. Survival curves were generated with the Kaplan-Meier method. Statistical analyses were performed with the RStudio software package (Version 0.99.491, Boston, MA) and STATA software package (version 14.1, College Station, Texas).

RESULTS

Our cohort consisted of 638 patients who underwent TAVR with a mean age of 83.7 (SD=5.6) years and 54.2% males. The access site was trans-femoral in 492 (77.1%) and non-femoral in 146 (22.8%) patients, including 74 apical (11.6%), 58 direct aortic (9.1%), 10 axillary or subclavian (1.6%), and 4 carotid (0.6%) accesses. The prevalence of frailty in the cohort was 76.0%, including 213 patients (33.4%) who were mildly frail and 272 patients (42.6%) who were significantly frail.

Patients with non-femoral access were more likely to have CAD (proportional difference 0.13, 95% CI 0.05 to 0.22), PAD (proportional difference 0.27, 95% CI 0.19 to 0.36), and less likely to have atrial fibrillation (proportional difference -0.13, 95% CI -0.22 to -0.05). Other comorbid conditions as well as physical frailty scores were balanced between the trans-femoral and non-femoral groups (Table 5). Among patients without documented PAD, 431 (83%) underwent a trans-femoral access and 88 (17%) underwent a non-femoral access. Among

patients with documented PAD, 61 (51%) underwent a trans-femoral access and 58 (49%) underwent non-femoral access (Table 6).

At 12 months, 83 deaths (17%) were observed in the trans-femoral group and 35 deaths (24%) were observed in the non-femoral group. On univariate analysis, the association between non-femoral access and 12-month mortality was not conclusive (unadjusted OR 1.55, 95% CI 0.99 to 2.42). However, there was a significant association between physical frailty using a SPPB cut off of 5 and 8 points and 12- month mortality (unadjusted OR 4.10, 95% CI 2.18 to 8.56) and (unadjusted OR 2.02, 95% CI 1.35 to 3.04), respectively. Survival curves estimated the greatest mortality in patients who were frail and underwent TAVR via a non-femoral access (Figure 3). Three multivariable logistic regression models were performed to estimate 12-month mortality adjusting for relevant clinical covariates with the first model including non-femoral TAVR access, the second including non-femoral TAVR access and physical frailty, and the third including non-femoral TAVR access, physical frailty, and an interaction term for these two variables (Table 7). The first model demonstrated that predictors for 12-month mortality were non-femoral TAVR access (adjusted OR 2.02, 95% CI 1.17 to 3.43), atrial fibrillation, pre-operative GFR and pre-operative hemoglobin values. The second model demonstrated that predictors of 12-month mortality were non-femoral TAVR access (adjusted OR 1.90, 95% CI 1.10 to 3.27), physical frailty (adjusted OR 3.57, 95% CI 1.82 to 7.69), as well as BMI, atrial fibrillation pre-operative GFR and pre-operative hemoglobin values. The third model, on the other hand, demonstrated that predictors of 12-month mortality were physical frailty (adjusted OR 3.28, 95% CI 1.56 to 7.79), BMI, atrial fibrillation pre-operative GFR and pre-operative hemoglobin values. The third model did not show conclusive associations between non-femoral TAVR access or the interaction between non-femoral TAVR and physical frailty (Table 7).

Sensitivity analysis was performed using the expanded Fried frailty scale, and this showed consistent results. The univariate analysis demonstrated an association between Fried frailty scale and 12-month mortality (unadjusted OR 2.73, 95% CI 1.68 to 4.62). Once adjusting for relevant covariates, non-femoral TAVR access (adjusted OR 2.04, 95% CI 1.18 to 3.48) and Fried frailty scale (adjusted OR 2.17, 95% CI 1.29 to 3.79) retained statistical significance for its association with 12-month mortality.

DISCUSSION

While outcomes are generally less favorable in non-femoral as compared with trans-femoral TAVR procedures, our study is the first to investigate that two processes may predict an association with 12-month all-cause mortality: non-femoral TAVR access site and physical frailty status. There is no conclusive evidence that there may be an interaction between non-femoral TAVR access and physical frailty status; however, the sample was too small in this pilot study to say anything conclusive in either direction of that effect. TAVR access routes are determined by the patient's vascular anatomy and may be indicative of their physical frailty status and comorbidity (73). Frailty status was prospectively determined by the SPPB and by the expanded Fried frailty scale, and while non-femoral patients had a greater burden of comorbid conditions at baseline, these findings persisted after adjustment in multivariable regression models.

Our study builds on previous work demonstrating the importance of TAVR access site as a prognostic indicator of post-procedural outcomes (74). Ruparelia *et al.,* in a single center cohort study of 829 patients from Milan, demonstrated that non-femoral access was strongly associated with cardiac mortality (HR 2.96, 95% CI 1.65 to 5.30) as well as 2-year mortality (HR

2.56, 95% CI 1.59 to 4.11 (75). The SOURCE XT registry of 2688 patients demonstrated that non-femoral access was associated, albeit less strongly, with 1-year mortality (HR 1.84, 95% CI 1.51 to 2.25) (76). The FRANCE-2 registry of 3195 patients demonstrated that patients with CAD or PAD were more likely to undergo a trans-apical approach (P<0.001), and that a trans-apical approach was modestly associated with 1-year mortality (HR 1.45, 95% CI 1.09 to 1.92) (77) and 30-day mortality (HR 2.02, 95% CI 1.47 to 2.78) (78). Recently, Edwards *et al*. developed predictive models using the data of 13,718 patients undergoing TAVR in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) Registry, and the study identified that non-femoral access site was a predictor of in-hospital mortality (HR 1.98, 95% CI 1.65 to 2.33) (74).

However, several studies have failed to report an independent effect of access site on short- or long-term mortality. The U.K. TAVI Registry suggested that the effect of non-femoral access on 1-year mortality was not apparent after adjusting for patient characteristics and comorbidities in multivariable analysis (65). Several other studies (79, 80), including an analysis of the CoreValve US Pivotal Trial (81), have not found access site to be an independent predictor of outcomes. A recent meta-analysis synthesized 28 TAVR studies and concluded that non-femoral access was associated with a modestly increased risk of 30-day (OR 1.79, 95% CI 1.56 to 2.04) and 1-year mortality (OR 1.47, 95% CI 1.33 to 1.67) compared to trans-femoral access but cautioned that further research was needed to evaluate whether this increased risk was consistently observed across intermediate-risk, high-risk, and prohibitive-risk subgroups (82).

The results of this study address this knowledge gap by evaluating the risk of non-femoral access in frail patients; however, more robust studies are needed to address these effects and the possibility of interaction between these variables. There are at least two hypothesized

reasons to explain the inter-related effect of non-femoral access and physical frailty. The first reason pertains to the more invasive nature of the non-femoral procedure, which imparts a greater physiological stress to the patient and consequently places them at a greater risk for morbidity and mortality, which can manifest in the short-term owing to procedural complications or in the medium-term owing to deconditioning and progressive functional decline. The second reason pertains to the higher prevalence of PAD in patients undergoing the non-femoral procedure, which was found to be 49% in our population, as compared to 17% of patients without PAD.

PAD represents a state of heightened systemic vascular inflammation (83) associated with an elevated risk of cardiovascular events and mortality (84, 85). Endothelial dysfunction is believed to be a key contributing mechanism to the progression of atherosclerosis (86), and patients with PAD demonstrate local (87) and systemic (88) endothelial dysfunction. Taken together, pre-operative physical frailty, operative physiologic stressors, and PAD synergistically contribute to the inflammatory milieu that may promote sarcopenia, deconditioning, and adverse outcomes (20). The complex interplay between the pathophysiological mechanisms between frailty, stressors associated with non-femoral TAVR access, and PAD have yet to be explored. There is limited and debatable evidence concerning the prognostic impact of PAD in TAVR. Consideration of PAD is advocated in the SURgical replacement and Transcatheter Aortic Valve Implantation trial (SURTAVI) risk score (89, 90), and PAD was shown to be predictive of 30-day mortality (HR 1.8, 95% CI 1.2 to 2.7) in a cohort study (91). Some investigators recommend formal assessment of PAD as a component of the pre-procedural assessment before TAVR regardless of access site (91).

Limitations of our study include that this post-hoc analysis of the FRAILTY-AVR study was not designed to capture the multi-factorial rationale for access site decisions made by treating clinicians. PAD ascertainment was largely performed through patient self-reports and electronic health records, which may be subject to inaccuracies and does not capture severity of disease. It is unclear whether physical frailty scores are predictive in patients with concomitant PAD as they may reflect underlying PAD rather than frailty status; however, death at 12-months does not appear to be modified by PAD status in patients who are frail in this cohort. Furthermore, despite the association seen between frailty and non-femoral TAVR access, we did not show a statistically significant interaction between these variables in our regression model as it relates to 12-month mortality. Interaction variables are limited by the large sample size needed to show a statistically significant interaction effect, and we may not be powered for this analysis.

Despite these limitations, we have shown that non-femoral TAVR access and physical frailty is associated with greater 12-month mortality. These considerations may be integrated into the pre-procedural risk assessment and decision making before TAVR in order to tailor the procedural approach. While the vascular access approach is largely dictated by anatomical features, and may not be modifiable on the basis of frailty, it does remain pertinent to predict adverse events and counsel patients. Significant physical frailty should not be equated with non-operability, but rather, the utility of physical frailty alongside clinical risk factors, such as PAD, and operative approaches should be used to identify a high-risk subset of TAVR patients.

CONCLUSION

The role of TAVR continues to evolve and expand at a rapid pace, especially among frail and older patients who may not be candidates for open surgical aortic valve replacement. Non-

femoral TAVR access and physical frailty imparts a greater risk of 12-month mortality. Therefore, risk factors such as physical frailty in conjunction with PAD status will play an increasingly important role in identifying high-risk individuals undergoing TAVR. Integrating physical frailty alongside individual clinical risk factors is likely to further improve risk stratification and result in individualized care for TAVR patients.

TABLES

Table 5: Baseline characteristics of cohort of patients undergoing TAVR stratified by access site

Characteristics	Total N=638	Trans-Femoral TAVR access N=492	Non-Femoral TAVR Access N=146
Demographics			
Age (years)	83.7±5.6	84.2±5.6	82.0±5.5
Female sex (%)	293 (46%)	227 (46%)	65 (44%)
Height (m)	1.6±0.1	1.6 ± 0.1	1.7 ± 0.1
Weight (kg)	72.7±17.2	73.0±16.9	71.9±18.2
BMI (kg/m^2)	26.7±5.5	26.8 ± 5.5	26.3 ± 5.7
Patient characteristics			
Aortic valve mean gradient (cm/s)	46.0±16.0	46.0±16.5	46.1±14.0
Pulmonary artery systolic pressure (mmHg)	42.7±15.8	42.9±15.7	42.0±16.4
Left ventricular ejection fraction (%)	54.7±13.0	54.4±13.1	55.9±12.5
Atrial fibrillation (%)	255 (40%)	211 (43%)	43 (30%)
Hypertension (%)	517 (81%)	391 (79%)	127 (87%)
Dyslipidemia (%)	440 (69%)	330 (67%)	110 (75%)
Coronary artery disease (%)	376 (59%)	277 (56%)	101 (69%)
Cerebrovascular disease (%)	128 (20%)	96 (20%)	32 (22%)
Peripheral arterial disease (%)	119 (19%)	61 (12%)	58 (40%)
Diabetes mellitus (%)	167 (26%)	124 (25%)	43 (29%)
COPD (%)	132 (21%)	95 (19%)	37 (25%)
Chronic Kidney Disease (%)	134 (21%)	101 (21%)	33 (23%)
Pre-operative GFR (mL/min)	53.4±17.0	53.9±16.2	51.5±19.4
Pre-operative Hemoglobin	119.5±16.7	118.7±16.4	121.9±17.8
Frailty Domains and Assessments			
Cognitive impairment, MMSE<24	144 (23%)	109 (22%)	35 (24%)
Depression Screening	219 (34%)	165(34%)	54 (37%)
Fried score, points	3.3±1.7	3.3±1.7	3.2±1.7
Fried ≥5	424 (66%)	329 (67%)	95 (65%)
Short Physical Performance Battery(SPPB)	5.9±3.2	5.9±3.3	5.7±3.2
SPPB ≤5	272 (43%)	206 (42%)	66 (45%)
SPPB ≤8	485 (76%)	371 (75%)	114 (78%)
Endpoints			
MACE	47 (7%)	31 (6%)	16 (11%)
12-month mortality (%)	118 (18%)	83 (17%)	35 (24%)

Table 6: Characteristics of TAVR access among patients with PAD

Characteristics	PAD N= 119	No PAD N=519
TAVR access		
Trans-femoral access	61 (51%)	431 (83%)
Non-femoral access	58 (49%)	88 (17%)
Apical access	33 (27.7%)	41 (8.0%)
Direct aortic access	22 (18.5%)	36 (6.9%)
Axillary or subclavian access	2 (1.7%)	8 (1.5%)
Carotid access	1 (0.10%)	3 (0.01%)

Table 7: Univariate and multivariable logistics regression investigating factors predictive of 12-month mortality

	Univariate Analysis	Model 1	Model 2	Model 3
Non-femoral TAVR Access	1.55 (0.99 to 2.42)	**2.02 (1.17 to 3.43)**	**1.90 (1.10 to 3.27)**	1.35 (0.19 to 6.19)
Frailty (SPPB<8 points)	**4.10 (2.18 to 8.56)**	n/a	**3.57 (1.82 to 7.69)**	**3.28 (1.56 to 7.79)**
Interaction: Access*Frailty	N/A	n/a	n/a	1.46 (0.30 to 10.89)
Peripheral arterial disease	1.22 (0.73 to 1.97)	0.94 (0.52 to 1.65)	0.88 (0.48 to 1.56)	0.88 (0.48 to 1.55)
Age, per year	**1.05 (1.01 to 1.09)**	1.04 (0.99 to 1.08)	1.02 (0.98 to 1.07)	1.02 (0.98 to 1.07)
Female	1.04 (0.70 to 1.56)	0.99 (0.63 to 1.56)	0.89 (0.56 to 1.41)	0.89 (0.56 to 1.41)
Body Mass Index, per kg/m^2	**0.94 (0.90 to 0.98)**	0.96 (0.92 to 1.00)	**0.95 (0.91 to 0.99)**	**0.95 (0.91 to 0.99)**
COPD	1.10 (0.67 to 1.77)	1.05 (0.60 to 1.78)	1.05 (0.59 to 1.80)	1.05 (0.59 to 1.80)
CAD	1.09 (0.73 to 1.66)	0.89 (0.56 to 1.41)	0.89 (0.56 to 1.42)	0.89 (0.56 to 1.42
Atrial Fibrillation	1.97 (1.32 to 2.96)	**1.98 (1.27 to 3.10)**	**1.87 (1.19 to 2.94)**	**1.86 (1.19 to 2.93)**
Pre-operative GFR, per mL/min	**0.97 (0.96 to 0.98)**	**0.98 (0.97 to 0.99)**	**0.98 (0.97 to 0.99)**	**0.98 (0.97 to 0.99)**
Pre-operative Hgb, per g/L	**0.96 (0.95 to 0.98)**	**0.97 (0.96 to 0.98)**	**0.97 (0.96 to 0.99)**	**0.97 (0.96 to 0.98)**
LVEF, per %	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.02)	1.01 (0.99 to 1.02)	1.01 (0.99 to 1.02)
Mean Gradient, per cm/s	0.99 (0.97 to 1.00)	0.99 (0.98 to 1.02)	0.99 (0.97 to 1.00)	0.99 (0.97 to 1.00)
PASP, ≥60 mmHg	**1.88 (1.05 to 3.25)**	1.65 (0.88 to 3.01)	1.66 (0.88 to 3.04)	1.66 (0.88 to 3.04)

Legend - TAVR: Transcatheter aortic valve replacement; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; GFR: Glomerular filtration rate; Hgb: Hemoglobin LVEF: Left ventricular ejection fraction; PASP: Pulmonary artery systolic pressure.

FIGURES

Figure 3: Kaplan-Meier survival curve on the effect of frailty and TAVR Access on All-Cause Mortality

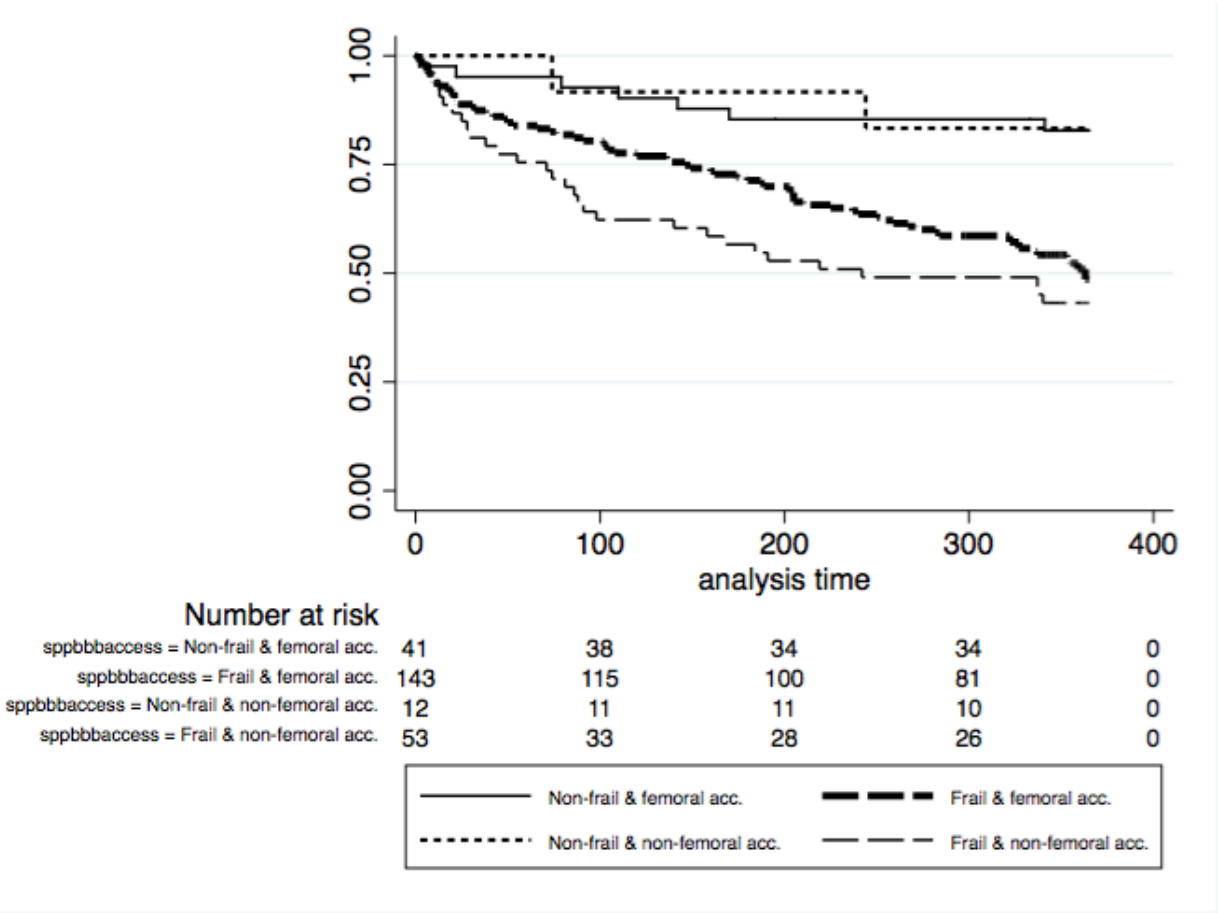

Figure 3

Legend: At 12 months, 83 deaths (17%) were observed in the trans-femoral group and 35 deaths (24%) were observed in the non-femoral group. When stratified by frailty (SPPB≤8), the greatest mortality in patients were seen in those frail and who underwent TAVR via a non-femoral access.

CHAPTER 4: Transitioning from physical frailty to muscle mass

Physical frailty assessments may not be appropriate in patients with illness or mobility-related impairments, as these tools are not capturing a patient's intrinsic frailty. Up to 45% of patients with PAD may not be able to perform physical frailty tests (58). Given the limitations of physical frailty assessment tools, frailty measures that are not reliant on physical performance have been investigated. In as such, low muscle mass is an appealing measure of frailty because it is objective and independent of patient compliance and symptoms. The psoas muscle area (PMA) is a validated surrogate for total body muscle mass (41). Low PMA has been associated with post-operative morbidity and mortality in various medical and surgical specialties (92-98).

Our Frailty Research Group developed a free, online, and semi-automated software (Coreslicer) that can measure PMA in less than 1 minute, and it has been validated in a cohort of patients undergoing transcatheter aortic valve replacement (TAVR). Since patients referred for open or endovascular aneurysm repair routinely get a CT scan to assess vascular anatomy, PMA is a very promising marker for adverse post-operative outcomes, which can be measured in a short period of time as the clinician is reviewing a patient's CT scan. We therefore sought to explore the role of PMA as a predictor for all-cause mortality in patients undergoing open and endovascular aortic aneurysm repair.

Chapter 5: Retrospective cohort study

Published manuscript: “Psoas Muscle Area Predicts All-Cause Mortality After Endovascular and Open Aortic Aneurysm Repair”

This manuscript is published in the European Journal of Vascular and Endovascular Surgery in the October 2016 issue.

Psoas Muscle Area Predicts All-Cause Mortality After Endovascular and Open Aortic Aneurysm Repair

Running title: Psoas Muscle Area in Aortic Aneurysm Repair

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This study was presented in the Vascular Medicine Poster Session at the 2016 American College of Cardiology, Chicago, IL, April 3rd, 2016.

ABSTRACT

Objective: Psoas muscle area (PMA) is a validated surrogate for muscle mass than can be easily measured from a clinical CT scan. We sought to determine whether PMA was associated with post-operative mortality after endovascular or open aortic aneurysm repair.

Methods: A retrospective review was undertaken of patients who underwent elective endovascular or open aortic aneurysm repair between 2010-2015 at a tertiary vascular center in Montreal, Quebec, Canada. Pre-operative CT scan images were analyzed with the CoreSlicer.com software tool to measure PMA at the axial level of the L4 vertebrae. Measurements were made by two independent observers blinded to clinical data. The primary endpoint was all-cause mortality.

Results: The cohort consisted of 149 patients with a mean age of 75.6 (SD = 8.8 years). The mean PMA was 24.0 (SD = 5.8) cm^2 in males, and 14.3 (SD = 3.1) cm^2 in females. There were 31 deaths over a mean follow-up of 682 days. After adjusting for age, sex, revised cardiac risk index, and surgical approach, Cox regression estimated an association between PMA and all-cause mortality with a hazard ratio of 0.86 per cm^2 (95% CI 0.79 to 0.93). Addition of PMA to the model with the clinical covariates resulted in an improvement in the C-statistic from 0.57 to 0.67 and BIC from 307 to 301 (with lower BIC values preferred).

Conclusions: PMA is independently associated with all-cause mortality after elective endovascular and open aortic aneurysm repair, and may be integrated in the pre-operative risk assessment to optimize care in high-risk frail patients.

Keywords: Psoas muscle area, Frailty, Aneurysm, Aortic surgery, Endovascular surgery

INTRODUCTION

The incidence of aortic aneurysms rises sharply in individuals over 60 years of age, many of which have multiple chronic conditions and a high risk of operative morbidity (99). It was recently shown in a systematic review that 5-year survival in patients undergoing elective infra-renal aneurysm repair was only 69% despite advances in medical and surgical therapies (100). When surgical risk is judged to be high, endovascular repair should be considered as a less invasive alternative (101-103). Surgical risk prediction is therefore central to both decision making and patient counselling on the ideal approach to aortic aneurysm repair (21, 102). Current surgical risk prediction models under-perform in the elderly as they only capture a snapshot of the patient's condition and do not reflect the patient's physiologic resiliency to the stress of surgery (104, 105). Integration of frailty assessment has thus been advocated to improve operative risk prediction (106-111).

Frailty is a multi-factorial syndrome that reflects an age-related decline in muscle mass and strength known as sarcopenia (112). Psoas muscle area (PMA) is a simple measure of muscle mass that can be measured from a single axial slice on a clinical CT scan. Low PMA has been associated with post-operative morbidity and mortality in various specialties, including: hepatobiliary (92-94), colorectal surgery (95), general surgery (20), gynecology (96), orthopedic surgery (97), and vascular surgery with open infra-renal AAA repair (98). However, PMA has yet to be examined in patients undergoing open and endovascular infra-renal AAA repair as well as thoracoabdominal aneurysm repair, a population that has significantly greater risk of frailty.

Accordingly, we sought to determine whether PMA was associated with post-operative mortality after endovascular or open aortic aneurysm repair, and whether PMA added incremental value above existing risk prediction models.

MATERIALS AND METHODS

Study Design

This study was approved by the ethics committee at the Jewish General Hospital in Montreal, Quebec. Consecutive adult patients who underwent endovascular or open aortic aneurysm repair between January 2010 and July 2015 at a single university-affiliated center (Jewish General Hospital, McGill University) were identified from a clinical database and operative records. Inclusion criteria were: age 50 years or older, asymptomatic or symptomatic infra-renal or thoracoabdominal aneurysms (Crawford Extent I-V) undergoing an infra-renal endovascular aneurysm repair (EVAR), complex aneurysm repair, or open aneurysm repair. Infused CT scans were routinely performed before all procedures for clinical purposes and no scans were requested for research purposes. Exclusion criteria were: emergency surgery for ruptured aneurysm and DICOM CT scan data not available, corrupt, or incomplete.

Clinical Data Collection

Covariates of interest were extracted from electronic medical records, including: age, sex, height, weight, body mass index (BMI), cardiovascular and non-cardiovascular comorbid conditions, smoking status, pre-operative aneurysm size, predicted risk of operative mortality using the Revised Cardiac Risk Index (RCRI; range 0-6), and American Society of Anesthesiologists *(ASA; range 1-5)* physical status classification. Patients were followed from the time of their index surgery for all-cause mortality, which was the primary endpoint of this study. Vital status was ascertained through regular follow-up visits with the operating surgeons and hospital records. For patients that did not return for follow-up visits, vital status was ascertained by contacting patients or their family members. Deaths and complications were

reported using the Society for Vascular Surgery (SVS) reporting guidelines (113, 114).

Psoas 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), which has been previously validated in over 200 patients undergoing transcatheter aortic valve repairs (52), and 82 patients undergoing open cardiac surgery (Zuckerman *et al*, in press*)*, in which the mean inter-observer difference of total PMA was found to be -0.5 cm^2 (95% CI -0.9 to 1.8 cm^2) and the mean intra-observer difference was 0.4 cm^2 (95% CI -1.7 to 2.4 cm^2). 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 vertebral endplate). This slice level has been shown to optimally correlate with psoas muscle volume and frailty. A semi-automatic contour detection algorithm was used to define the cross-sectional area of the left and right psoas muscles in the axial plane (summed to calculate the PMA), and secondarily, a threshold detection filter was applied between -30 to +150 Hounsfield units to only include the pixels containing muscle tissue and exclude intramuscular adipose tissue (summed to calculate lean PMA). PMA and lean PMA were represented as a continuous variable and sex-stratified tertiles. Measurements were performed by two independent observers blinded to clinical data.

Statistics

Continuous variables were summarized with the sample mean, standard deviation, and depicted graphically with histograms and boxplots. Pearson's correlation was used to assess

linear correlation between two variables. Categorical variables were summarized with frequency tables and linear regression was used to compare the prevalence across PMA tertiles. Cox regression was used to estimate PMA's association with all-cause mortality adjusting for age, sex, BMI, surgical approach (open vs. endovascular), and RCRI predicted risk of mortality. Data was complete for these covariates with the exception of 20 patients who were missing BMI values. These values were imputed using multiple imputation with nearest neighbour algorithms. Additional covariates were entered in the model (e.g. cancer) as sensitivity analyses. Harrell's C statistic and the Bayesian information criterion (BIC) were used to assess the incremental value of adding PMA to the model containing the RCRI. Survival curves were generated by the Kaplan-Meier method. Statistical analyses were performed with the STATA software package (version 14.1, College Station, Texas).

RESULTS

Our cohort consisted of 238 patients; however, 89 patients (37%) were excluded because of inadequate or missing pre-operative CTs. This left us with 149 patients that entered the analysis with a mean age at surgery of 75.6 (SD = 8.8) years. The majority were endovascular procedures (85%) performed in males (84%). Mean PMA was 24.0±5.8 cm^2 in males and 14.3 (SD = 3.1) cm^2 in females. When grouped in sex-stratified tertiles, the lowest tertile was ≤21.7 cm^2 in males and ≤13.5 cm^2 in females, whereas the highest tertile was ≥26.2 cm^2 in males and ≥15.5 cm^2 in females.

PMA was negatively correlated with age (R = -0.35, 95% CI -0.19 to -0.48) and positively correlated with weight (R=0.40, 95% CI 0.22 to 0.56) and BMI (R=0.35, 95% CI 0.17 to 0.52). Patients with low PMA were more likely to have a pre-operative diagnosis of cancer

and to undergo endovascular procedures, most notably complex endovascular procedures; other comorbid conditions were not different across tertiles of PMA (Table 8).

There were 6 deaths that occurred at 30-days; with the crude mortalities for open repair, infra-renal EVAR, and complex EVAR being 1.3%, 1.3%, and 2% respectively. A total of 31 deaths occurred during the period of observation, which consisted of a mean follow-up of 22.4 months and 307 person-years; with the crude mortalities for open repair, EVAR and complex EVAR being 4.0%, 11.4%, and 9.4%. The causes of early and late death are detailed in Table 9. Seventeen deaths (35%) were observed in the low PMA tertile as compared to 9 (18%) in the mid PMA tertile and 5 (10%) in the high PMA tertile, with a proportional difference between low PMA and high PMA of 0.25 (95% CI 0.09 to 0.40). After adjusting for age, sex, BMI, surgical approach, and RCRI predicted risk of operative mortality, Cox regression estimated an association between PMA and all-cause mortality with a hazard ratio of 0.86 per cm^2 increase in PMA (95% CI 0.79 to 0.93) (Table 10; Figure 4). Addition of PMA to the model with the clinical covariates resulted in an improvement in C-statistic from 0.57 to 0.67 and BIC from 307 to 301 (with lower BIC values being preferred). A difference of 6 suggests strong evidence in favor of the model (115).

As expected, lean PMA was slightly smaller than PMA (since pixels containing adipose tissue were subtracted), such that mean lean PMA was 22.7±5.6 cm^2 in males and 13.1±3.3 cm^2 in females. When lean PMA was entered in the multivariable Cox regression model instead of PMA, there was a modest improvement in C-statistic to 0.69 and BIC to 299.

When the pre-operative diagnosis of cancer was added to the regression model as a sensitivity analysis (HR 0.82, 95% CI 0.34 to 2.00), there was no evidence of residual confounding. When models were run stratified by sex, there was no indication of effect-

modification by sex (HR 0.88 per cm^2 in males [95% CI .81 to .97] in males vs. 0.86 per cm^2 in females [95% CI .63 to 1.17]), although the absolute number of females was small and thus the analysis was inconclusive. Furthermore, there was no evidence of interaction between age and PMA in this sample.

DISCUSSION

Our study has shown that low PMA is independently associated with post-operative all-cause mortality in a broad cohort of elderly adults undergoing endovascular and open aortic aneurysm repairs. The magnitude of this effect is estimated to be a 14% reduction in mortality for every 1 cm^2 increase in PMA. Addition of PMA resulted in a net improvement in model performance, which is incremental to established risk predictors used in clinical practice. Furthermore, lean PMA, a variant of PMA that accounts for muscle mass as well as intramuscular adiposity, provided further improvement in model performance.

This study builds on the concept of low muscle mass as a core component of frailty (48-51, 112) and the emerging body of literature supporting PMA as a prognostic indicator of operative risk. In a previous cohort of patients undergoing open repair of infra-renal AAA, Lee *et al*. showed that PMA at the L4 level was associated with 90-day post-operative mortality (HR 0.33 per 1000 mm^2 increase in PMA, which equates to a HR of 0.98 per 1 cm^2 increase in PMA). The magnitude of the effect is consistent with that reported in this study, although differences should be noted. First, our patient population was weighted towards those undergoing endovascular repair with only a small minority undergoing open surgical repair; therefore, our patients were substantially older (mean age 75.6 vs. 69.5 years) and had a greater burden of comorbid conditions. Second, our follow-up duration was substantially longer (mean follow-up

22 months vs. 3 months) and allowed us to capture late mortality. Third, our analytical approach was focused on demonstrating the incremental value of PMA and lean PMA in improving prediction above established risk scores. Most importantly, we used a new open-source tool, developed by members in our Frailty Research Program, that provides a faster and semi-automated measurement of PMA, that may be easily integrated into clinical practice.

In another cohort of 574 patients undergoing open surgical replacement of the proximal thoracic aorta, Ganapathi *et al*. retrospectively showed that six clinical markers of frailty were predictive of outcomes. Their markers for frailty were: advanced age, anemia, history of stroke, hypoalbuminemia, low body mass index, and low total psoas muscle volume. Frailty, defined as 2 or more of these criteria, was associated with 5-fold increase in odds of 30-day and 1-year mortality (116). The patient population and psoas measurement technique was different in this study, with their technique involving 8 separate measurements of psoas muscle area summed with specialized software to calculate a volume. Our technique involves 1 single measurement of psoas muscle area made with the semi-automatic web-based CoreSlicer software that is readily accessible, and therefore has the advantage of being less time-consuming and more pragmatic for clinical application.

Our group has shown in the Montreal-Munich Study that this approach for measuring PMA adds incremental value in patients undergoing transcatheter aortic valve repair (TAVR) (52). PMA was measured in an identical fashion in 208 TAVR patients and was associated with all-cause mortality in women after adjusting for Society for Thoracic Surgery (STS) predicted risk of mortality (HR 0.88 per cm^2 increase in PMA, 95% CI 0.78 to 0.99). The 12% reduction in mortality per 1 cm^2 of PMA in the cohort undergoing TAVR is highly consistent with the 14% reduction observed in this cohort undergoing endovascular and open aortic aneurysm repair.

Integrating frailty alongside clinical risk factors and additional geriatric domain is likely to further improve risk stratification. Srinivasan *et al*. integrated measures of comorbidity and disability (Charlston score, Katz score, vision impairment, hearing impairment, and polypharmacy) and applied this scale to a select group of 184 patients undergoing ruptured aneurysm repair. This integrated model achieved a high index of discrimination to predict 1-year mortality (C-statistic 0.84) (117). Despite the differing definitions of frailty in the literature, the components of a geriatric assessment should ideally reflect muscle mass, physical performance, nutrition, cognitive function, mood, social support, and disability.

Limitations of our study include that it was a single-institution retrospective cohort, although results should be generalizable based on their consistency with the results observed in external cohorts. Also, despite the association seen between age and PMA, we did not show a statistically significant interaction between these variables in our regression model as it relates to all-cause mortality. Interaction variables are limited by the large sample size needed to show a statistically significant interaction effect, and we may not be powered for this analysis. There may have been a non-differential selection bias as we excluded patients for whom we could not retrieve a pre-operative CT scan in digital DICOM format; these patients were more likely to be complex cases referred from community-based hospitals. However, we did capture a sizeable number of complex endovascular procedures and adjusted for surgical approach. Furthermore, complex endovascular aortic repairs included juxta-renal fenestrated repairs as well as more complex supra-renal branched aortic repairs reflecting aortic aneurysm extent, which also carries distinctive mortalities and post-operative risks, which was not accounted for in this study. Finally, our study includes one component of the frailty syndrome, low muscle mass, and we

were not able to capture other components of the frailty syndrome due to availability of the collected data.

Despite these limitations, we have shown that low PMA is associated with all-cause mortality, which may be integrated into pre-operative risk assessments in patients undergoing endovascular and open aortic aneurysm repairs in order to counsel patients and tailor the operative approach. Low PMA should be not equated with non-operability, but rather, the utility of PMA should be as a therapeutic target to identify a high-risk subset of patients that could benefit from pre- or post-operative interventions aimed at improving muscle mass and strength. Interventions shown to be effective include moderate-intensity exercise programs and protein supplementation.

CONCLUSION

PMA is independently associated with all-cause mortality after elective endovascular and open aortic aneurysm repair. PMA may be integrated in the pre-operative risk assessment of vascular patients to identify and optimize high-risk frail patients and direct them towards less invasive interventions. In doing so, the allocation of surgical and endovascular procedures may be improved, decreasing costs by preventing patients from receiving costly and potentially unnecessary procedures. Consideration of frailty may also serve as a tool to improve patient counselling on operative risk, and thereby ensure that patients benefit from more personalized treatment plans that will maximize their likelihood of a positive patient-centered outcome.

Funding Sources:

The present work was supported by grants from the Canadian Institutes of Health Research (CIHR)-Canada Graduate Scholarships, and Fonds de recherche du Québec – Santé (FRQS) Master's Grant.

TABLES

Table 8: Baseline characteristics of patients stratified by low, mid and high PMA tertiles

Characteristics	Low PMA Tertile M: ≤21.7 cm^2 F: ≤13.5 cm^2	Mid PMA Tertile M: 21.8-26 cm^2 F:13.6-15.4 cm^2	High PMA Tertile M:≥26.2 cm^2 F:≥15.5 cm^2
Demographics			
Age (years)	80.4±6.2	76.0±8.2	70.6±9.1
Male sex (%)	41 (84%)	42 (84%)	42 (84%)
Height (m)	1.7±0.1	1.7±0.1	1.7±0.1
Weight (kg)	68.7±12.7	75.4±16.1	83.9±13.2
BMI (kg/m^2)	25.2±3.4	26.1±4.5	28.6±3.7
BSA (m^2)	1.8±0.2	1.9±0.2	2.0±0.2
Past Medical History			
Initial AAA size (cm)	6.1±1.2	6.0±1.2	6.2±1.2
Pack year smoking history	43.7±25.9	43.8±17.4	47.7±28.1
Hypertension (%)	42 (86%)	45 (90%)	40 (80%)
Dyslipidemia (%)	33 (67%)	37 (74%)	37 (74%)
Coronary artery disease (%)	19 (39%)	21 (42%)	24 (48%)
Peripheral arterial disease (%)	8 (16%)	8 (16%)	3 (6%)
Cerebrovascular disease (%)	7 (14%)	9 (18%)	6 (12%)
Diabetes Mellitus (%)	7 (14%)	12 (24%)	10 (20%)
Cancer (%)	15 (31%)	14 (28%)	4 (8%)
Procedural Variables			
ASA (range: 1-5)	3.0±0.21	3.0±0.61	3.0±0.20
RCRI (range: 0-6)	1.8±0.72	1.78±0.91	1.74±0.78
Endovascular repair (%)	46 (94%)	43 (86%)	37 (74%)
Infra-renal EVAR (%)	31 (63%)	36 (72%)	30 (60%)
Complex EVAR (%)	15 (31%)	7 (14%)	7 (14%)
Open repair, infra-renal (%)	3 (6%)	7 (14%)	13 (26%)
Endpoints			
30-day mortality (%)	4 (8%)	1 (2%)	1 (2%)
All-cause death (%)	17 (35%)	9 (18%)	5 (10%)

AAA: Abdominal aortic aneurysm, ASA: American Society of Anesthesiologists, BMI: Body mass index, BSA: Body surface area, EVAR: Endovascular aneurysm repair, F: Female, M: Male, RCRI: Revised cardiac risk index.

Table 9: Causes of early and late deaths

Cause of death	Number (%)
Deaths less than 30 days	**7 (4.7%)**
Procedure-related	3 (2.0%)
Systemic complications	3 (2.0%)
Cardiac	1 (1.3%)
Cerebrovascular	1 (0.7%)
Pulmonary	1 (0.7%)
Indeterminate	1 (0.7%)
Late deaths (≥ 30 days)	**24 (16.9%)**
Aneurysm-related	1 (0.7%)
Systemic complications	10 (7.0%)
Cardiac	4 (2.8%)
Pulmonary	4 (2.8%)
Cerebrovascular	1 (0.7%)
Pulmonary embolism	1 (0.7%)
Cancer	3 (2.1%)
Indeterminate	10 (7.0%)

Table 10: Cox regression for all-cause death after aortic aneurysm repair.

Risk factor	Hazard Ratio	95% Confidence Interval
Age, per year	1.01	0.96 to 1.06
Female	0.45	0.15 to 1.33
Body Mass Index, per kg/m^2	1.03	0.93 to 1.13
Revised Cardiac Risk Index, per point	1.09	0.71 to 1.68
Endovascular Approach	0.83	0.26 to 2.60
Psoas Muscle Area, per cm^2	0.86	0.79 to 0.93

FIGURE LEGENDS

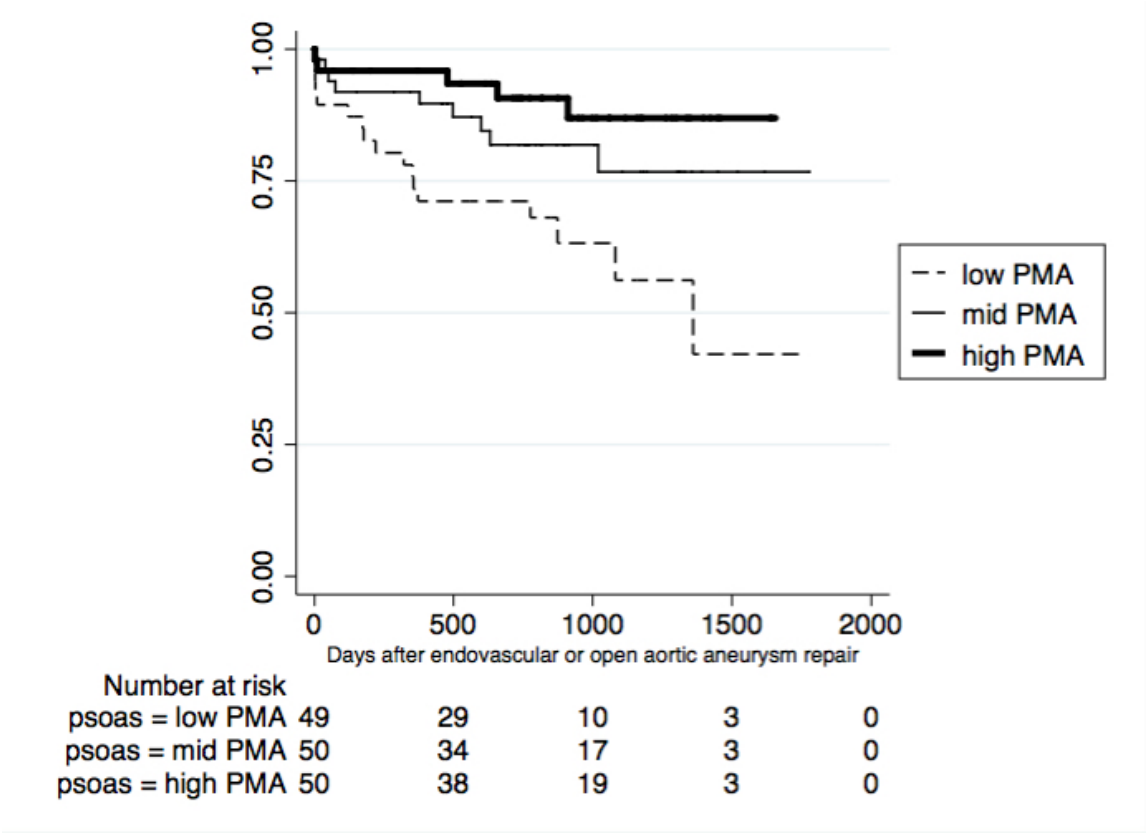


Figure 4

Title: Kaplan-Meier Survival Curves for PMA Tertiles

Legend: Thirty-one deaths occurred during 307 person-years: 5 in the open repair group, 17 in the infra-renal EVAR group, and 9 in the complex EVAR group. The standard deviation exceeds 10% (SD=14.3%) for the low PMA at 1360 days.

Chapter 6: Thesis Conclusion

The concept of frailty as it pertains to vascular surgery patients has been explored in this thesis. Frailty and vascular disease may be inter-related on a pathophysiologic level, with frail older adults demonstrating worse outcomes post-operatively, particularly as it pertains to mortality. Frailty can be as high as 60% in a vascular surgery population; therefore, clinicians and surgeons should be sensitized to the importance of addressing frailty pre-operatively.

A literature review identified the high prevalence of frailty and the heterogeneous tools used to assess frailty. Physical frailty tools are the most commonly used tools to assess frailty. The first manuscript entitled, "**The effect of access site and physical frailty in older adults undergoing transcatheter aortic valve replacement**" explores the interaction between TAVR access site and physical frailty in predicting all-cause 12-month mortality as a pilot study. Among 638 older adults, the prevalence of physical frailty was 76%. Patients with non-femoral access were more likely to have CAD and PAD. Furthermore, among patients without documented PAD, 431 (83%) underwent a trans-femoral access and 88 (17%) underwent a non-femoral access. Among patients with documented PAD, 61 (51%) underwent a trans-femoral access and 58 (49%) underwent non-femoral access. Multivariable logistic regression revealed that non-femoral TAVR access (adjusted OR 1.90, 95% CI 1.10 to 3.27) and physical frailty (adjusted OR 3.57, 95% CI 1.82 to 7.69) were associated with 12-month mortality, without evidence for interaction between these variables. This study has shown that frail older patients undergoing TAVR who undergo non-femoral access site have the worst post-operative outcomes, which may be partially explained by a susceptible population, namely patients with PAD. However, physical frailty tools may not be appropriate with patients limited by their comorbidities or disease status, as these tools are not capturing a patient's inherent frailty.

Therefore, as frailty tools develop, frailty measures that are not reliant on physical performance may be more appropriate for a vascular surgery population. We address this gap in our study investigating the prognostic impact of psoas muscle area in patients undergoing aortic aneurysm repair.

The second manuscript entitled, "**Psoas Muscle Area Predicts All-Cause Mortality After Endovascular and Open Aortic Aneurysm Repair**"**,** explores the association between psoas muscle area (PMA), as a validated surrogate marker for total body muscle mass, and post-operative all-cause mortality after endovascular or open aortic aneurysm repair. Among 149 patients, the mean PMA was 24.0 (SD = 5.8) cm^2 in males, and 14.3 (SD = 3.1) cm^2 in females. There were 31 deaths over a mean follow-up of 682 days. After adjusting for age, sex, revised cardiac risk index, and surgical approach, Cox regression estimated an association between PMA and all-cause mortality with a hazard ratio of 0.86 per cm^2 (95% CI 0.79 to 0.93). Furthermore, addition of PMA to the model with the clinical covariates resulted in an improvement in C-statistic from 0.57 to 0.67 and BIC from 307 to 301 (with lower BIC values preferred). Therefore, this study has shown that PMA was independently associated with all-cause mortality in this cohort, and may be easily integrated in the pre-operative risk assessment of vascular patients to identify and optimize high-risk patients.

The main epidemiological concerns of the first manuscript include a small sample size that may have led to inconclusive results when investigating the interaction between non-femoral access and physical frailty. Interaction variables are limited by the large sample size needed to show a statistically significant interaction effect, and we may not be powered for this analysis. Second, this post-hoc analysis of the FRAILTY-AVR study was not designed to capture the decision making process made by treating clinicians for site of access for TAVR patients. Third,

a non-differential misclassification bias may have resulted with PAD status. PAD ascertainment was largely through patient self-reports and electronic health records, which may be subject to inaccuracies and does not capture severity of disease.

The main epidemiological concerns of the second manuscript include the heterogeneity of the vascular surgery population undergoing aortic aneurysm repair. Our study included simple and complex endovascular aortic repairs, which included juxta-renal fenestrated repairs as well as more complex supra-renal branched aortic repairs. These complex procedures reflect aortic aneurysm extent and carry distinctive mortalities and post-operative risks, which were not accounted for in the study. Second, despite the association seen between age and PMA, we did not show a statistically significant interaction between these variables in our regression model as it relates to all-cause mortality. Interaction variables are limited by a large sample size needed to show a statistically significant interaction effect, and we may not be powered for this analysis. Third, there may have been a non-differential selection bias as we excluded patients for whom we could not retrieve a pre-operative CT scan in digital DICOM format; these patients were more likely to be complex cases referred from community-based hospitals. However, we did capture a sizeable number of complex endovascular procedures and adjusted for surgical approach. Finally, our study includes only one component of the frailty syndrome, low muscle mass, and we were not able to capture other frailty components due to the availability of the collected data.

With this review and experience, our Frailty Research Group is performing a prospective study in patients with PAD: FRailty Assessment in Lower Extremity arterial Disease (FRAILED). We hope to identify the best tool to assess frailty in vascular surgery patients with PAD and predict who will suffer major morbidity and mortality after endovascular and open

surgical interventions. We also hope to identify if low muscle mass (measured on a pre-operative CT) compared to frailty scores is more predictive of post-operative morbidity and mortality in these patients. We also hope to translate this model to patients undergoing aortic aneurysm repair. This study will equip clinicians with the best tool to accurately and efficiently assess frailty and identify the best tool that predicts morbidity and mortality. Our group is also piloting a prospective study to evaluate if an interventional strategy in high-risk patients (as measured with frailty scores and muscle mass) may modify a patient's risk profile. Our study entitled "**Prehabilitation to Enhance Functional Recovery after Endovascular Abdominal Aortic Aneurysm Repair: A prospective study**" will incorporate a multidimensional strategy including a supervised exercise program, nutritional counseling, and smoking cessation. The results of these ongoing studies will enable clinicians to identify high-risk patients and guide their vascular patients towards a more personalized treatment plan that will maximize their likelihood of a positive outcome. High-risk patients may benefit from pre-operative optimization aimed at improving muscle mass and strength, which may modify a patient's risk profile and improve clinical and patient-centered outcomes. This new paradigm in risk stratification may enable the optimal allocation of surgical and endovascular procedures, and may decrease costs by preventing patients from receiving costly but un-useful procedures. Furthermore, by integrating frailty into risk scores, policymakers and researchers will have more accurate predictions of risk in performance analysis and in the conduct of clinical trials.

Chapter 7: Appendices

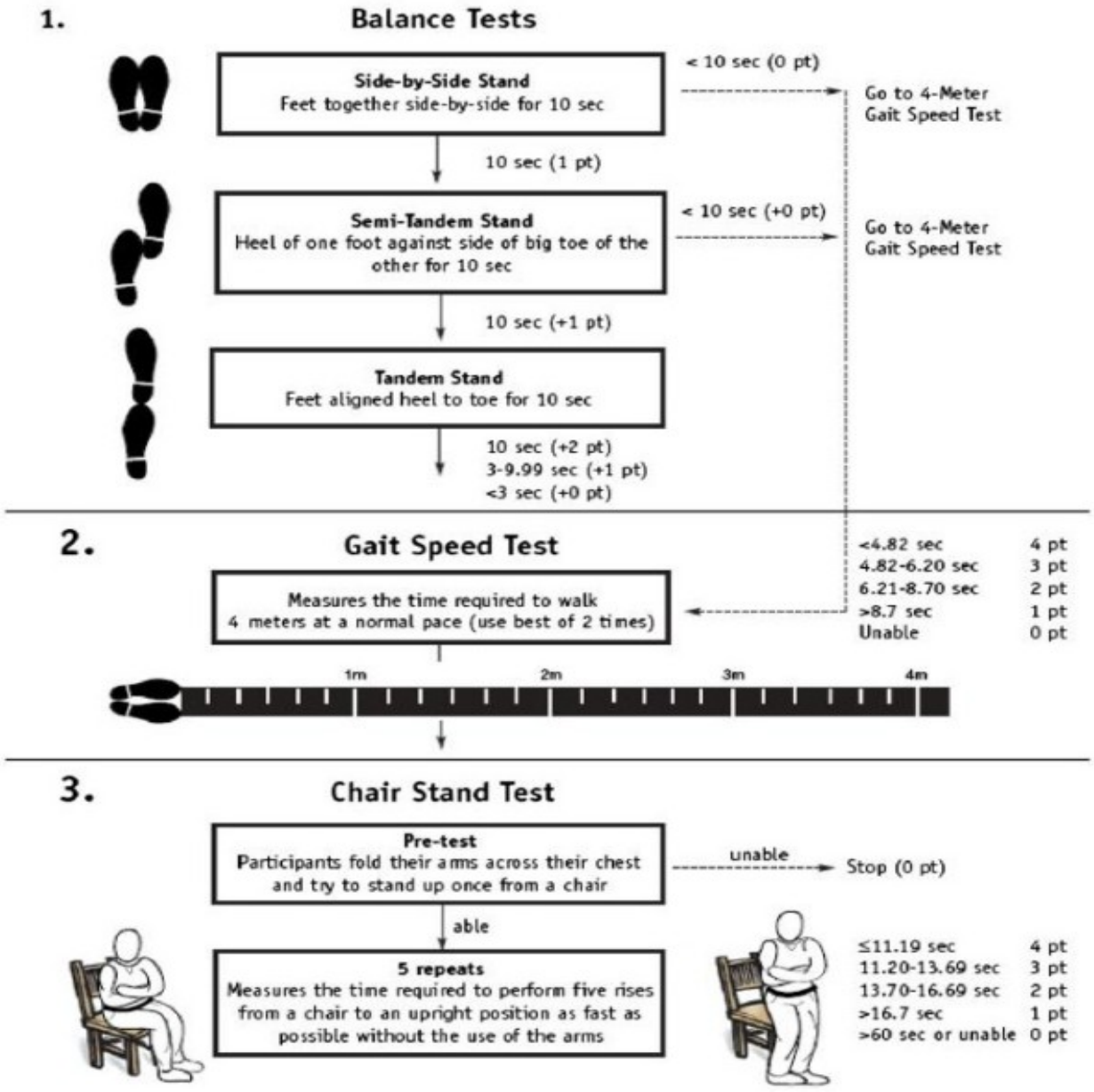
Appendix A: Fried Frailty Scale

	Frailty Domain	Method of Measurement	Cutoffs for Measurement
1	Slowness	5-meter gait speed *Patient is asked to walk at a comfortable pace from a 0-meter start line to past a 5-meter finish line, the cue to start and stop the stopwatch is the first footfall after the start line and first footfall after the finish line, this is repeated 3 times and the average time is recorded*	<u>Sex- and height-based cutoff</u> ♂ ≤173 cm: **≤0.65 m/s** >173 cm: **≤0.76 m/s** ♀ ≤159 cm: **≤0.65 m/s** >159 cm: **≤0.76 m/s** <u>Simplified cutoff (preferred)</u> ♂/♀: **≤0.83 m/s**
2	Weakness	Handgrip strength *Patient is asked to squeeze a handgrip dynamometer as hard as possible, this is repeated 3 times (with each hand and then with the strongest hand) and the maximum value is recorded*	<u>Sex- and BSA-based cutoff</u> ♂ ≤24 kg/m^2: **≤29 kg** 24.1-28 kg/m^2: **≤30 kg** >28 kg/m^2: **≤32 kg** ♀ ≤26 kg/m^2: **≤17 kg** 26.1-29 kg/m^2: **≤18 kg** >29 kg/m^2: **≤21 kg** <u>Simplified cutoff (preferred)</u> ♂: **≤30 kg** ♀: **≤20 kg**
3	Low physical activity	Paffenbarger Physical Activity Questionnaire(118)	♂: **<383 kcal/week** ♀: **<270 kcal/week**
4	Weight loss	Self-reported	**>10 lbs or >5% in past year**
5	Exhaustion	2 questions: How often do you feel like "Everything I did was an effort" ""I could not get going"	If answered either question **Most of the time or** **Moderate amount of the time**

Appendix B: Modified Fried Frailty Scale

	Frailty Domain	Method of Measurement	Cutoffs for Measurement
1	Slowness	5-meter gait speed *Patient is asked to walk at a comfortable pace from a 0-meter start line to past a 5-meter finish line, the cue to start and stop the stopwatch is the first footfall after the start line and first footfall after the finish line, this is repeated 3 times and the average time is recorded*	<u>Sex- and height-based cutoff</u> ♂ ≤173 cm: **≤0.65 m/s** >173 cm: **≤0.76 m/s** ♀ ≤159 cm: **≤0.65 m/s** >159 cm: **≤0.76 m/s** <u>Simplified cutoff (preferred)</u> ♂/♀: **≤0.83 m/s**
2	Weakness	Handgrip strength *Patient is asked to squeeze a handgrip dynamometer as hard as possible, this is repeated 3 times (with each hand and then with the strongest hand) and the maximum value is recorded*	<u>Sex- and BSA-based cutoff</u> ♂ ≤24 kg/m^2: **≤29 kg** 24.1-28 kg/m^2:**≤30 kg** >28 kg/m^2: **≤32 kg** ♀ ≤26 kg/m^2: **≤17 kg** 26.1-29 kg/m^2:**≤18 kg** >29 kg/m^2: **≤21 kg** <u>Simplified cutoff (preferred)</u> ♂: **≤30 kg** ♀: **≤20 kg**
3	Low physical activity	Paffenbarger Physical Activity Questionnaire(118)	♂: **<383 kcal/week** ♀: **<270 kcal/week**
4	Weight loss	Self-reported	**>10 lbs or >5% in past year**
5	Exhaustion	2 questions: How often do you feel like "Everything I did was an effort" ""I could not get going"	y if answered either question **Most of the time or** **Moderate amount of the time**
6	Cognitive impairment	Mini-mental status examination	**Score <27/30**
7	Depressed mood	Geriatric depression scale (5-item)	**Score ≥2/5**

Appendix C: Short Physical Performance Battery (27)



Appendix D: Clinical Frailty Scale (35)

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care,** from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

Appendix E: Modified Frailty Index (mFI) (37)

Items of the modified frailty index	Points
History of diabetes mellitus	1
History of congestive heart failure	1
History of hypertension requiring medication	1
History of transient ischemic attack or cerebrovascular accident (CVA)	1
History of CVA with neurologic deficit	1
Functional status (not independent)	1
History of myocardial infarction	1
History of prior percutaneous coronary intervention or angina	1
History of peripheral vascular disease	1
History of either COPD or pneumonia	1
History of impaired sensorium	1

Appendix F: Edmonton Frail Scale (EFS) (38)

Frailty Domain	Item	0 point	1 point	2 points
Cognition	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of "ten after eleven"	No errors	Minor spacing errors	Other errors
Health	In the past year, how many times have you been admitted to the hospital? In general, how would you describe your health?	0 "Excellent/Good"	1-2 "Fair"	≥2 "Poor"
Functional status	With how many of the following activities do you require help? (meal prep, shopping, transport, telephone, housekeeping, laundry, managing money, taking medications)	0-1	2-4	5-8
Social support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication use	Do you use five or more different prescription medications on a regular basis? At times, do you forget to take your medications?	No No	Yes Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel depressed or sad?	No	Yes	
Continence	Do you have a problem with losing control of urine or when you don't want to?	No	Yes	
Functional performance	I would like you to sit in this chair with your back and arms resting. Then, when I say "GO", please stand up and walk a safe and comfortable pace to mark on the floor (3m away), and return to the chair to sit down.	0-10 s	11-20s	≥20s or patient unwilling or requires assistance

Appendix G: Groningen Frailty Indicator (GFI) (39)

Item	Sometimes	Yes	No
Mobility: Can the patient perform this task without any help? (using tools like walking sticks, wheelchairs or walker is regarded as independent)			
1. Go shopping	-	0	1
2. Walk around outside (around the house or to neighbours)	-	0	1
3. Dressing and undressing	-	0	1
4. Toilet visit	-	0	1
Vision			
5. Does the patient experience problems in daily life with poor vision?	-	1	0
Hearing			
6. Does the patient experience problems in daily life by poor hearing?	-	1	0
Nutrition			
7. Has the patient involuntarily lost weight (>6kg) in the past 6 months (or >3 kgs in one month)	-	1	0
Comorbidity			
8. Does the patient currently use four or more difference types of medication?	-	1	0
Cognition			
9. Does the patient currently have complaints about his memory (or has a history of dementia)?	0	1	0
Psychosocial			
10. Does the patient sometimes experience emptiness around him?	1	1	0
11. Does the patient sometimes miss people around him?	1	1	0
12. Does the patient sometimes feel abandoned?	1	1	0
13. Has the patient recently felt sad or depressed?	1	1	0
14. Has the patient recently felt nervous or anxious?	1	1	0
Physical Fitness			
15. Which grade would the patient give its physical fitness (0-10, ranging from very bad to good) 0-6=1 and 7-10=0		1	0
Total Score GFI A score of 4 or more indicates a higher risk for frailty and possibly delirium			

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