Impact of Nutrition in Frail Older Adults Undergoing Invasive Cardiac Procedures

Thesis candidate:

Michael Goldfarb, MD

MSc Thesis

Department of Experimental Medicine, McGill University, Montreal, Canada

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English Abstract

Background: The majority of people undergoing cardiac surgery and transcatheter aortic valve replacement (TAVR) are older adults and about half of these older adults are considered frail. Frailty is associated with increased morbidity and mortality in patients undergoing invasive cardiac procedures. Frail older adults undergoing invasive cardiac procedures are at increased risk of being malnourished, an independent risk factor for poor outcomes, yet there are minimal data on nutritional screening and actual protein intake in this setting. In addition, whether frailty status incrementally increases hospitalization costs and healthcare use has yet to be established.

Methods: A literature search was performed to explore the role of protein and muscle metabolism, as well as to define malnutrition and the role of protein supplementation in older adults undergoing invasive cardiac procedures. Data from the Frailty-AVR study, a prospective, international, multi-centre cohort study of older adults undergoing frailty screening prior to aortic valve replacement, was used to assess the relationship of preoperative serum albumin and nutritional status with 1-year mortality in patients undergoing transcatheter and surgical aortic valve replacement. The costs of index hospitalization following cardiac surgery were obtained from two centres participating in the Frailty-AVR cohort.

Results: Hypoalbuminemia was a strong, independent predictor of mortality following TAVR in older adults. Older adults identified as malnourished had an almost 3-fold increase in 1-year mortality following cardiac surgery and TAVR. Frailty status in older adults is also associated with increased hospital costs following index hospitalization for cardiac surgery.

Conclusion: Serum hypoalbuminemia and malnutrition are independent predictors of mortality in older adults undergoing invasive cardiac procedures. Actual protein intake in the postprocedural period appears to be insufficient. Further research is needed to assess whether nutritional intervention in the perioperative period will improve clinical outcomes in older adults undergoing invasive cardiac procedures. The cost implication of invasive cardiac approaches in the management of frail older adults needs to be explored as well.

French Abstract

Contexte: La majorité des personnes subissant une chirurgie cardiaque et un remplacement de la valve aortique transcathéter (RVAT) sont des adultes plus âgés et environ la moitié de ces adultes âgés sont considérés fragiles. La fragilité est associée à une augmentation de la morbidité et de la mortalité chez les patients subissant des procédures cardiaques invasives. Les personnes âgées fragiles qui subissent des interventions cardiaques invasives sont plus à risque de souffrir de malnutrition, un facteur de risque indépendant ayant de mauvais résultats, mais il existe peu de données sur le dépistage nutritionnel et l'apport réel de protéines dans ce contexte. En outre, cela doit encore être établie si le statut de fragilité augmente progressivement les coûts d'hospitalisation et l'utilisation des soins de santé.

Méthodes: Une recherche documentaire a été réalisée pour explorer le rôle du métabolisme protéique et musculaire, ainsi que pour définir la malnutrition et le rôle de la supplémentation en protéines chez les adultes plus âgés subissant des procédures cardiaques invasives. Les données de l'étude Frailty-AVR, une étude de cohorte multicentrique prospective et internationale sur des personnes âgées subissant un dépistage de fragilité avant le remplacement valvulaire aortique, ont été utilisées pour évaluer la relation entre la sérumalbumine préopératoire et l'état nutritionnel avec la mortalité à 1 an chez les patients subissant un remplacement de la valve aortique transcathéter et chirurgicale. Les coûts de l'hospitalisation indicielle après chirurgie cardiaque ont été obtenus auprès de deux centres participant à la cohorte Frailty-AVR.

Résultats: L'hypoalbuminémie était un prédicteur fort et indépendant de la mortalité à la suite du RVAC chez les adultes plus âgés. Les personnes âgées identifiées comme souffrant de malnutrition ont presque triplé leur mortalité à 1 an après une chirurgie cardiaque et un RVAC. Le statut de fragilité chez les personnes âgées est également associé à une augmentation des coûts hospitaliers après l'hospitalisation en chirurgie cardiaque.

Conclusion: L'hypoalbuminémie et la malnutrition sériques sont des prédicteurs indépendants de la mortalité chez les personnes âgées subissant des interventions cardiaques invasives. La consommation réelle de protéines au cours de la période postprocédurale semble être

insuffisante. Des recherches supplémentaires sont nécessaires pour évaluer si l'intervention nutritionnelle dans la période périopératoire permettra d'améliorer les résultats cliniques chez les adultes âgés subissant des procédures cardiaques invasives. L'implication des coûts des approches cardiaques invasives dans la prise en charge des personnes âgées fragiles doit également être explorée.

Contribution of authors

Michael Goldfarb, MD

Thesis candidate. Performed literature review. Wrote research proposals. Wrote informed consent documents, initial nutritional questionnaire, and other study related documents. Submitted documentation to the institutional research ethics board. Co-developed study design and methodology for included studies. Assisted with data analysis. Wrote initial and revised manuscripts for the albumin, nutritional screening, and cost of care studies. Attended research team meetings. Presented initial research findings to the Masters Thesis Committee. Performed literature review. Wrote thesis document.

Jonathan Afilalo, MD, MSc

Thesis supervisor. Guidance and support for all aspects of manuscripts and thesis. Co-developed study design and methodology for albumin, nutritional screening, and cost of care studies. Involved with data analysis. Chaired research team meetings. In-depth revision of manuscripts and thesis document.

Jose Morais, MD

Member of the thesis committee. Reviewed and contributed to the albumin manuscript.

Louis Perrault, MD PhD

Member of the thesis committee. Reviewed and contributed to the albumin manuscript.

The following authors reviewed and contributed to the cost of care manuscript:
Lawrence Rudski, MD, Jean-Francois Morin, MD, Yves Langlois, MD, Felix Ma, MD, James Brophy, MD PhD, Melissa Bendayan, Jonathon Afilalo, MD MSc

The following authors reviewed and contributed to the albumin manuscript:
Sandra Lauck, PhD, John Webb, MD, Dae Kim, MD MPH, Jeffrey Popma, MD, Nicolo Piazza, MD, Giuseppe Martucci, MD, Marino Labinaz, MD, Andre Lamy, MD, Mark Peterson, MD,

Nicolas Noiseux, MD, Andrew Rassi, MD, Brian Lindman, MD, Phillipe Genereux, MD, Rakesh Aurora, MD, Anita Asgar, MD, Jonathon Afilalo, MD MSc

The following authors reviewed and contributed to the malnutrition and mortality manuscript: Sandra Lauck, PhD, John G. Webb, MD, Anita W. Asgar, MD MSc, Louis P. Perrault, MD PhD, Nicolo Piazza, MD PhD, Giuseppe Martucci, MD, Kevin Lachapelle, MD, Nicolas Noiseux, MD MSc, Dae H. Kim, MD ScD, Jeffrey J. Popma, MD, Thierry Lefèvre, MD, Marino Labinaz, MD, Andre Lamy, MD, Mark D. Peterson, MD PhD, Rakesh C. Arora, MD, PHD, Philippe Généreux, MD, José A. Morais, MD, Jean-Francois Morin, MD, Lawrence Rudski, MD, Jonathan Afilalo, MD MSc

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Chapter 1: Introduction

A. Overview and Rationale

Older adults comprise the majority of individuals undergoing cardiac surgery and transcatheter aortic valve replacement (TAVR).[1, 2] While age is an independent predictor of morbidity and mortality in the periprocedural period, there is considerable evidence of good quality of life and long-term mortality results in carefully selected cohorts of older adults.[3-6]

About half of older adults undergoing cardiac surgery and TAVR are frail.[7] Frailty is a strong predictor beyond the chronological age of increased morbidity, mortality, and institutionalization in patients undergoing cardiac surgery and TAVR.[8-12] Frailty is a complex geriatric syndrome characterized by sarcopenia, subclinical multi-organ dysfunction, and a reduced capability of handling physiological stress. Sarcopenia is the age-related alteration in protein metabolism, decline in muscle mass, strength, and functional capacity. In frail older adults, the sarcopenic process in the skeletal muscle is accelerated due to increased catabolism and impaired ability to use amino acids for anabolic processes.[13, 14] The underlying mechanism of sarcopenia in frail older adults is multifactorial and includes inadequate physical activity, alteration of endocrine function, chronic disease, inflammation, oxidative stress, and nutritional deficiencies, such as insufficient protein intake.[15, 16] About 15% of sarcopenic patients have "sarcopenic obesity", a process in which adipose tissue replaces skeletal muscle mass, resulting in obesity co-existing with decreased strength from sarcopenia.[17] Sarcopenic obesity in frail older adults is also associated with an increase in adverse events following cardiac surgery.[18]

Due to the clinical significance of frailty in cardiac surgery and TAVR, as well as the pathophysiological link between inadequate nutrition and frailty, the objective of this thesis was to explore the use of a commonly used nutritional screening biomarker, serum albumin concentration, and a nutritional screening tool, the Mini-Nutritional Assessment-Short Form (MNA-SF), to predict poor outcomes in older adults undergoing cardiac surgery or TAVR. In addition, due to the potential implications for healthcare resource management, the cost of index hospitalization by frailty status in older adults will be explored.

B. Protein and Muscle Metabolism in Frail Older Adults

Nutrition is an integral part of perioperative care in older adults undergoing invasive cardiac procedures, particularly cardiac surgery. Maintaining an adequate nutritional status with both macronutrients (i.e. fat, protein, carbohydrates) and micronutrients (ie. vitamins and minerals) is essential for the optimal function of cells and organs, wound healing, and maintenance of muscle strength. An adequate supply of protein is essential in combatting the protein-energy deficit, which is even more pronounced in the sarcopenic patient. The objective of nutritional intervention in the sarcopenic older adult during the perioperative period is to preserve muscle mass and strength, improve postoperative recovery, maintain functional capabilities on discharge, and decrease both short and longer term mortality.

A brief primer on the basic principles of protein and muscle metabolism is necessary to understand the role of protein metabolism in frail older adults. Amino acids are the principal nutrients responsible for muscle protein synthesis stimulation.[19] The free amino acid pool in the body is composed of ingested proteins, degraded tissue proteins, and internally synthesized amino acids. Free amino acids are used for protein synthesis, cellular pathways or removed as urea. Amino acids can be classified as “non-essential”, meaning that the body can produce them from other molecular building blocks, or “essential”, meaning that they need to be ingested in the diet. Muscle metabolism is a balance between signals favouring anabolism versus catabolism.

There are a number of important changes to protein and muscle metabolism that occur with aging. In older adults, there is both a blunting of stimulation of protein synthesis by amino acids[20] and inhibition of protein breakdown by insulin.[21] Essential amino acids are primarily responsible for muscle anabolism in older adults,[22] while non-essential amino acids do not seem to be required to stimulate net muscle protein synthesis.[23] However, the signal by essential amino acids to favour anabolism is not sensed or converted into muscle synthesis as well by the muscle in older adults resulting in decreased muscle synthesis for the same dose of protein stimulation. Acute and chronic disease occurring with aging also result in inflammation and catabolism.[24] These age-related changes are mediated by multifactorial etiologies including endocrine, oxidative stress, decreased use, and chronic disease.[15, 16] Frailty further increases the age-related changes in protein and muscle metabolism by increasing the rate of protein catabolism and reducing muscle mass.[14] There is increasing evidence that the pathophysiology of frailty is in part mediated by chronic inflammation.[25]

C. Protein Supplementation in the Frail Older Adult: Rationale and Literature Review

I. Clinical Evidence

Increased protein ingestion may able to counteract sarcopenia in frail older adults since the anabolic response to a large amount of protein ingestion remains intact in older adults,[26-28] although the resulting degree of muscle anabolism is lower than in younger individuals.[29] Frail older adults have shown the capacity to respond to protein supplementation with increased post-absorptive protein synthesis rates and an increase in lean body mass, particularly when malnourished.[30, 31] Moreover, the anabolic effect of perioperative nutrition is associated with increased age and the patient's preoperative catabolic state.[32] One study showed that supplementation with the essential acid amino acid L-arginine in older adults for five days prior to undergoing cardiac surgery resulted in decreased postoperative markers of inflammation.[33] Dietary protein supplementation improves physical performance including measures of leg strength, short performance physical battery (SPPB) scores, and disability scores, such as activities of daily living.[34] In older hospitalized patients, protein supplementation has been demonstrated to improve functional status on discharge and decrease in-hospital mortality; these findings were more pronounced in older adults who were more malnourished at baseline.[35] In critically ill patients, higher protein intake is associated with improvements in ventilator-free days, Sequential Organ Failure Assessment scores, and 60-day mortality.[36-38]

II. Quantity

Protein requirements increase with increasing age as anabolic resistance and catabolic stimuli occur.[39] To overcome the anabolic resistance and increased muscle catabolism, frail older adults require more protein (1.2 – 2 g/kg/d) than younger individuals (0.8 g/kg/d).[24, 40] However, these protein goals are based on data from community living older adults and may be insufficient for the needs of critically ill frail older adults in the immediate postoperative period, as well as in the longer term recovery and convalescent period. Adequate amounts of protein intake are required in frail older adults to maintain a neutral tissue protein balance in order to attenuate the catabolic response, to preserve muscle mass, and, ultimately, to maintain physical function. A recent systematic review of protein requirement in the critically ill suggested that a daily protein intake of 2.0-2.5 g/kg/d is safe and may be an appropriate target.[41] While the optimal dose of

protein in frail older adults in the perioperative period is uncertain, protein requirements are likely considerably higher than current recommendations.[42, 43]

In addition, there is evidence that older adults consume inadequate amounts of dietary protein. In community-dwelling older adults, only about one-quarter of individuals meet the recommended protein targets with dietary intake.[44] In a cohort of mostly surgical patients, 21% of older adults had a nutrient intake less than half of the recommended intake.[16]

III. Type of Protein

The type of protein ingested also impacts muscle metabolism. In older adults, whey protein is superior to other types of protein at increasing muscle protein synthesis.[45] Whey protein is composed primarily of essential amino acids, especially branched-chain amino acids (valine, isoleucine and leucine). The branched-chain amino acids are rapidly metabolized during stress by skeletal muscle to stimulate muscle protein synthesis.[46] The ability of whey protein to stimulate muscle protein synthesis is above and beyond the effect of the constituent essential amino acids.[47] Other potential beneficial properties of whey protein in frail older adults include rapid absorption and high digestibility in the small intestine when bowel transit and absorption may be prolonged,[48] anti-inflammatory properties,[49] and being rich in cysteine, a required substrate for the synthesis of a glutathione, a key anti-oxidant.[50]

The branched-chain amino acid leucine is the most potent stimulator of muscle protein synthesis and inhibitor of muscle catabolism in skeletal muscle.[51, 52] Leucine acts by activating the rapamycin mammalian target of rapamycin, the signaling pathway which regulates protein synthesis in skeletal muscle.[53] While leucine by itself does not appear to drive muscle synthesis,[54] adding leucine to a protein meal in older adults, particularly a whey protein meal, leads to increased post-prandial muscle protein synthesis.[55-59] A meta-analysis of nearly 1000 older adults showed that leucine supplementation resulted in an increased gain in lean body mass compared to the respective control groups, particularly in those with considerable sarcopenia.[60] Leucine supplementation also decreased the muscle wasting associated with age and bedrest.[51] Supplementation with β-hydroxy-β-methylbutyrate (HMB), a leucine metabolite, has been shown to preserve muscle mass during prolonged bedrest.[61] Even when consuming a hypocaloric diet, supplementation with high whey protein and leucine can preserve appendicular muscle mass in obese older adults.[62]

The optimal leucine dose for the promotion of muscle protein synthesis is an important consideration due to the decreased response of leucine stimulation, as well as the anabolic resistance that occurs with age.[63] Higher amounts of leucine, such as 2 or more grams at one time, can overcome the impaired responsiveness of muscle protein synthesis in older muscle.[20, 55, 64] A high leucine content in an overall low protein supplement was found to be almost as successful at muscle protein synthesis as a high protein supplement.[65] There is also evidence that leucine-rich essential amino acid mixtures have anabolic properties in catabolic states.[66] Intermittent dosing (ie. with meals) can also help overcome the anabolic resistance in frail older adults.[67] There may be no practical maximum dose of protein intake to promote anabolism in the context of a meal.

IV. Timing for Protein Supplementation

Each stage of perioperative process provides an opportunity for nutritional assessment and intervention. The cardiac surgical process involves preoperative assessment and preparation, the surgery itself, postoperative monitoring and care in an intensive care unit, care in a less involved unit, hospital discharge, and follow-up care. Each of these phases of care represent potential opportunities for protein supplementation interventions in the frail, malnourished older adult.

IVa. Preoperative

Nutritional screening in the preoperative period allows for identification of older adults who are malnourished or at-risk for malnourishment. Once identified, referral to a dietician for further nutritional assessment and potential intervention can be considered. Salvino et al. outlined three main criteria of whether preoperative nutrition support is indicated: (1) severely malnourished patient, (2) elective surgery that can be safely postponed for one week or more and (3) nutritional support has been shown to improve outcomes.[68] Thus, in certain cases, it may be beneficial to slightly delay an elective procedure in order to address and attempt to correct nutritional issues prior to the procedure. Alternatively, more intensive intraoperative or postoperative nutritional support may be considered in patients who have been flagged as undernourished or at-risk.

In the immediate preoperative period, patients are often subjected to a period of fasting, which can further impair the recovery of patients from the surgical trauma.[69] Longer preoperative fasting times are associated with postoperative complications and prolonged length of hospital stay.[70] A preoperative intravenous glucose and essential amino acid infusion has been shown to decrease the catabolic effects of the preoperative fasting state, such as skeletal muscle breakdown, and improve postoperative whole body protein balance.[71]

IVb. Intraoperative

Improvements in anesthesia and surgical technique over the past few decades have minimized the catabolic stress of the surgery, yet cardiac surgery in frail older adults, particularly in the setting of cardio-pulmonary bypass, remains a profound iatrogenic stressor resulting in an acute inflammatory response and insulin resistance on top of an existing chronic inflammatory state, impaired endocrine function, and sarcopenia.[72-74] Muscle protein catabolism increases during the surgery and in the postoperative period to meet tissue demands, a necessary physiological response. However, if the catabolic response is too great, particularly in an already sarcopenic, malnourished older adult, organ function and survival may be compromised.[75, 76]

Essential amino acids, particularly BCAAs, but not non-essential amino acid concentrations, decrease dramatically during cardiac surgery.[77] This suggests a potential role for perioperative or postoperative amino acid supplementation to maintain the serum levels of amino acids. Perioperative amino acid infusions may decrease the inflammatory response and improve recovery from surgical stress.[78] Perioperative amino acid supplementation has been shown to decrease markers of inflammation,[33] reduce myocardial enzyme release, improve post-operative hemodynamic performance,[79] shorten recovery time from neuromuscular blockade,[80] and decrease duration of hospitalization following abdominal surgery.[81] In patients undergoing off-pump coronary bypass graft surgery, perioperative amino acid infusions have been shown to reduce the duration of postoperative mechanical ventilation, decrease the length of intensive care unit stay, and time until fit for hospital discharge.[78] Amino acid infusions may also reduce the incidence of postoperative atrial fibrillation, a complication that can prolong hospitalization following cardiac surgery.[78]

IVc. Postoperative

There is extensive catabolism in the first week following cardiac surgery due to breakdown of skeletal muscle for use in gluconeogenesis, acute phase protein synthesis, and adenosine triphosphate in rapidly turning over visceral tissues (ie. liver, bone marrow).[82-84] Prolonged bedrest in the postoperative period results in further loss of skeletal muscle mass, as well as decreased protein synthesis and muscle strength. Under experimental conditions, 10 days of bedrest results in a 2 kilogram loss of muscle mass.[85] Even a small amount of reduction in muscle mass postoperatively in older adults can prolong hospitalization, decrease muscle protein synthesis, lead to long-term effects on muscle strength, increase the risk of falls, worsen quality of life, and lead to a loss of independence following discharge.[86, 87]

Increased protein intake in the postoperative period, particularly of essential amino acids, has been shown to decrease protein catabolism[88-90] and there is evidence that early and adequate nutrition in postsurgical patients decreases the length of hospital stay.[91] Yet there are a number of barriers to adequate caloric and protein intake in the postoperative period. Patients report being frequently interrupted at mealtime, not being served food when a meal was missed, finding the food unappetizing, having changes in taste sensitivity, and feeling too unwell to eat.[92, 93] Malnourished patients and patients who consumed less than half of the served meal more commonly reported several of these barriers to food intake. Even by the second postoperative week about one-third of patients still report poor appetite, nausea, and impaired taste.[94] Even when hospitalized patients are offered adequate protein and calorie intake, they do not consume enough.[95]

V. Safety of Protein Supplementation

The safety profile of protein supplementation has been established.[51] Consuming a reasonable amount more than the recommended daily allowance of protein does not appear to be harmful.[96] The primary mechanism by which protein may be toxic is by overwhelming the urea cycle's capacity resulting in generation of ammonia. In normal adults, the rate of urea synthesis was 3.8 g protein/kg into urea per day.[97] The urea synthetic rate varies considerably based on age, liver, renal, and disease status. In critical illness, such as in the immediate postoperative cardiac surgery period, the rate of urea synthesis is increased.[98] The rate of urea synthesis also increases with increased protein intake in an autoregulatory feedback loop. There is no evidence

that a hyperammonia state results in adverse effects. Fluid intake from protein supplementation may lead to fluid overload and high doses of protein may result in gastrointestinal upset.[99] Based on the available evidence, protein intake much higher than the currently recommended range appears to be safe, particularly in the absence of severe liver disease, renal disease, refractory hypotension, and severe sepsis.[41]

D. Identifying Malnutrition in Older Adults

Identifying malnutrition in older adults undergoing invasive cardiac procedures is important since poor nutritional status is associated with an impaired immune response, decreased cardio-respiratory function, slower wound healing, early deconditioning of the diaphragmatic and skeletal muscles, prolonged hospital stay, increased mortality, and higher hospital costs following major surgery.[100-107] However, the assessment of nutritional status in the frail older adult prior to cardiac surgery and TAVR is challenging and the optimal method of screening has not been established. Identifying malnutrition is further complicated by the lack of a universally agreed upon definition of malnutrition in older adults.[108, 109] Preoperative weight loss has been used as a marker of malnutrition risk in older adults prior to major surgery since preoperative weight loss is a predictor of adverse postoperative complications.[110] A weight loss of ≥5% of total body weight in the prior month and/or a weight loss of ≥10% in the prior 6 months and/or a body mass index (BMI) of 21.0 k/m^2 are considered significant cutoffs for preoperative weight loss.[106, 111] Using these cutoff values, 10-25% of older adults undergoing cardiac surgery are considered undernourished.[105, 112, 113]

A number of nutritional status screening tools have been developed for the assessment of nutrition status and identification of patients at risk for malnutrition and those already malnourished.[114] In general, these questionnaires are composed of several of the following domains: recent weight loss, BMI, recent decreased appetite or poor food intake, acute disease, eating difficulties, mobility, and neuropsychological problems. The Subjective Global Assessment (SGA) is considered the gold standard of nutritional assessment and involves a comprehensive nutritional evaluation that correlates well with objective assessments of nutritional status and has a high interobserver agreement. However, the SGA is too cumbersome and impractical for routine nutritional screening.[115] The Mini-Nutritional Assessment – Short Form (MNA-SF) was developed for malnutrition screening in older adults and it has the highest

validity and reliability relative to other screening tools in community living older adults.[116-118] In older inpatients, the MNA-SF has excellent sensitivity (89-100%), but poor specificity (38-49%) for detecting malnutrition.[119-121] Lomivorotov et al. compared a number of nutritional screening tools in a population of older adults undergoing cardiac surgery and found that the MNA-SF had both a sensitivity and specificity of more than 80%, when using the SGA as the reference, for the detection of malnourished or at-risk patients.[122] The MNA-SF was also found to be independently predictive of length of hospital stay and postoperative complications.[123, 124] However, while the MNA-SF had a good negative predictive value for malnutrition or being at-risk for malnutrition (98.6%) in this study, the positive predictive value of a positive MNA-SF was only 20%. The low positive predictive value was likely due to low prevalence of malnutrition in older adults (1%) and at-risk patients (22%) in the study population. Kaiser et al. found that in a predominantly female cohort (75.2%) of more than 4000 people with a mean age greater than 80, the MNA was found to classify approximately two-thirds as malnourished or at-risk for malnourishment.[125] Notably, there was a considerable discrepancy in the prevalence of malnutrition between various settings of adults with malnutrition rates of 5.8% in the community, 38.7% in the hospital, and 50.5% in rehabilitation centres. Thus, the MNA-SF may be an effective screening tool for malnutrition in older adults undergoing cardiac surgery and TAVR due to the high prevalence of frailty in these settings.

Due to the increased risk of malnutrition in older adults undergoing cardiac surgery and TAVR, as well as the known risk of malnutrition for morbidity and mortality in the postoperative period, the “Malnutrition and Mortality Risk in Older Adults Undergoing Aortic Valve Replacement” study was designed to determine the association of the preprocedural nutritional status and mortality.

Chapter 2: Malnutrition and Mortality Risk in Older Adults Undergoing Aortic Valve Replacement

Our pre-planned analysis of a prospective cohort study of nutritional screening in older adults is presented as a manuscript.

The manuscript has been submitted for publication.

Malnutrition and Mortality in Older Adults Undergoing Aortic Valve Replacement

Michael Goldfarb, MD,[1] Sandra Lauck, PhD,[2] John G. Webb, MD,[2] Anita W. Asgar, MD, MSc,[3] Louis P. Perrault, MD, PhD,[4] Nicolo Piazza, MD, PHD,[5] Giuseppe Martucci, MD,[5] Kevin Lachapelle, MD,[6] Nicolas Noiseux, MD, MSc,[7] Dae H. Kim, MD, ScD,[8] Jeffrey J. Popma, MD,[9] Thierry Lefèvre, MD,[10] Marino Labinaz, MD,[11] Andre Lamy, MD,[12] Mark D. Peterson, MD, PhD,[13] Rakesh C. Arora, MD, PhD, [14] José A. Morais, MD,[15] Jean-Francois Morin, MD,[16] Lawrence Rudski, MD,[1] Jonathan Afilalo, MD, MSC,[1,17] on behalf of the FRAILTY-AVR Investigators

[1]Division of Cardiology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; [2]Centre for Heart Valve Innovation, St. Paul's Hospital, University of Vancouver, Vancouver, British Columbia, Canada; [3]Division of Cardiology, Institut de Cardiologie de Montréal, Université de Montréal, Montreal, Quebec, Canada; [4]Division of Cardiac Surgery, Institut de Cardiologie de Montréal, Université de Montréal, Montreal, Quebec, Canada; [5]Division of Cardiology, McGill University Health Centre, Montreal, Quebec, Canada; [6]Division of Cardiac Surgery, McGill University Health Centre, Montreal, Quebec, Canada; [7]Division of Cardiac Surgery, Centre Hospitalier de l'Université de Montréal, Centre de Recherche du CHUM, Montreal, Quebec, Canada; [8]Division of Gerontology, Beth Israel Deaconess Medical Center, Harvard University, Boston, Massachusetts; [9]Division of Cardiology, Beth Israel Deaconess Medical Center, Harvard University, Boston, Massachusetts; [10]Division of Cardiology, Institut Cardiovasculaire Paris Sud, Hôpital Privé Jacques Cartier, Massy, France; [11]Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; [12]Division of Cardiac Surgery, Hamilton Health Sciences, Population Health Research Institute,

McMaster University, Hamilton, Ontario, Canada; [13]Division of Cardiac Surgery, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [14]Section of Cardiac Surgery, Max Rady College of Medicine, Rady Faculty of Health Scienece, University of Manitoba, Winnipeg, Manitoba, Canada; [15]Division of Geriatric Medicine, McGill University Health Centre, Montreal, Quebec, Canada; [16]Division of Cardiac Surgery, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; [17]Centre for Clinical Epidemiology, Jewish General Hospital, Lady Davis Institute for Medical Research, Montreal, Quebec, Canada.

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Address for correspondence:

Jonathan Afilalo, MD, MSc, FACC, FRCPC

3755 Cote Ste Catherine Rd, E-222, Montreal, QC H3T 1E2

Phone: (514) 340-8232 / Fax: (514) 221-3785

Email: jonathan.afilalo@mcgill.ca

STRUCTURED ABSTRACT

Background: Older adults undergoing aortic valve replacement are at increased risk of preprocedural malnutrition. The association of preprocedural nutritional status and longer-term mortality has yet to be determined.

Methods: We searched the Frailty-AVR cohort, a prospective multi-center international study, between 2012-2016 for patients ≥ age 70 years who had a preprocedural Mini-Nutritional Assessment-Short Form (MNA-SF) score and underwent transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) with or without coronary artery bypass grafting. The MNA-SF (range 0-14; a score of ≤7 is considered malnourished and 8-11 is at-risk for malnutrition) is a validated and highly sensitive tool for the diagnosis of malnutrition in older adults. The primary outcome was 1-year all-cause mortality.

Results: There were 1,158 patients included in the analysis (mean age 81.3 years, 481 females [42%], 727 TAVR, 431 SAVR, mean Society of Thoracic Surgeons-predicted risk of mortality score 5.1% [STS-PROM]). Overall, 8.7% of patients were malnourished and 32.8% were at-risk for malnutrition. Malnourished older adults had a nearly 3-fold increased risk of 1-year mortality compared to those with normal nutritional status (28% vs 10%, P<0.001). There was no significant difference between nutritional status groups in the Valve Academic Research Consortium-2 (VARC-2) composite safety endpoint at 30 days (all-cause mortality, reoperation, acute kidney injury, major bleed, or major vascular complication). After adjustment for frailty status, STS-PROM, and procedure type, the preprocedural nutritional status was a significant predictor of both 1-year mortality (OR = 0.92 per MNA-SF point, 95% CI 0.86-0.99) and the 30-day VARC-2 safety composite endpoint (OR = 0.94 per MNA-SF point, 95% CI 0.89-0.99).

Conclusion: Preprocedural nutritional status is a strong predictor of 1-year mortality in older adults following aortic valve replacement. Further studies are needed to explore whether pre- and post-procedural nutritional interventions can improve clinical outcomes in these patients.

INTRODUCTION

Malnutrition is common in older adults with a pooled prevalence of 23% and a hospital-based prevalence of 39%.[1] Malnutrition is a major risk factor leading to the development of frailty, disability, and death.[2, 3] The impact of malnutrition among patients undergoing cardiac surgery or transcatheter aortic valve replacement (TAVR) is limited.[4-6] However, among patients undergoing general surgery, malnutrition is associated with delayed wound healing, postoperative complications, prolonged hospital length of stay (LOS), hospital readmission, and death.[7]

The evaluation of nutritional status is challenging in older adults, in part because body weight and traditional markers of malnutrition are not reliable indicators and. as a result, malnutrition is often overlooked. Amongst four nutritional screening tools compared in older adults undergoing cardiac surgery, the Mini-Nutritional Assessment-Short Form (MNA-SF) had the highest sensitivity for detecting malnutrition (85%) and was independently predictive of postoperative complications and LOS.[8, 9] The MNA-SF was developed with a geriatric focus, has been validated in various settings, and its six questions are easier to administer than other more comprehensive nutritional screening tools.[10, 11]

In addition to the prognostic value of identifying malnutrition, there is actionable therapeutic value for implementing nutritional interventions that have been shown to be effective in preventing morbidity and mortality.[12] While nutritional guidelines recommend screening for nutrition risk in all hospitalized older adults, they acknowledge that this is based on weak levels of evidence stemming from small uncontrolled studies.[13] Likewise, an international consensus statement on nutrition in cardiac surgery concluded that "valid and reliable data are urgently needed to improve the so-far non-standardized clinical practice of nutrition screening."[14] Thus,

our objective was to assess the prevalence and prognostic impact of malnutrition screening with the MNA-SF on outcomes in a large multicentre cohort of older adults undergoing surgical or transcatheter aortic valve replacement.

METHODS

Study Population

FRAILTY-AVR is a prospective cohort study conducted at 14 centers in Canada, the United States, and France, between 2012-2017. Patients ≥70 years of age who underwent TAVR or SAVR with or without coronary artery bypass grafting were enrolled. A comprehensive assessment of frailty and geriatric domains, including the MNA-SF, was performed before the procedure. Patients were followed for vital status and functional outcomes at 6 and 12 months after the procedure. Exclusion criteria were language barriers and moderate-to-severe neuropsychiatric impairments precluding informed consent, emergent surgery, unstable vital signs, and multi-valve surgery or replacement of the aorta.

Nutritional Screening

Prior to the procedure, a trained clinical research assistant administered the MNA-SF according to its standardized protocol. The six MNA-SF domains encompass questions relating to (1) food intake, (2) weight loss, (3) basic mobility, and (4) disease acuity, as well as measurements relating to (5) body mass index and (6) cognitive or mood impairment. The MNA-SF has been validated in frail multimorbid elders and shown to have similar accuracy to the longer-version.[15] Rather than relying on self-report, cognitive function was assessed using the Mini-Mental Status Examination, and mood was assessed using the Geriatric Depression Scale Short Form.[16, 17] Patients were grouped based on their composite MNA-SF score: normal

nutritional status (scores 12-14), at-risk of malnutrition (scores 8-11), and malnutrition (scores 0-7).[18]

Measurements

Prior to the procedure, frailty was assessed using the Short Physical Performance Battery (SPPB) and the Fried scale.[19, 20] Clinical operative risk was represented using the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) that captures patient age, sex, comorbidities, and cardiac status.[21] Following the procedure, the electronic medical record was reviewed for demographic, comorbid, procedural, and postprocedural data, including complications, disposition, and last known vital status. If patients could not be reached to determine their vital status, relative were contacted and health records linked with administrative data were queried; no patient was lost to follow-up for the 1-year mortality endpoint.

Outcomes

The primary outcome was 1-year all-cause mortality. The secondary outcome was 30-day mortality or major morbidity defined according to the Valve Academic Research Consortium-2 (VARC-2) composite safety endpoint (all-cause mortality, reoperation, acute kidney injury, major bleed, or major vascular complication).[22] Individual components of the composite safety endpoint and postprocedural resource use were also evaluated.

Statistical Analysis

Continuous data are presented as means ± standard deviations. Categorical data are presented as counts and percentages. The Cuzick test was used to detect significant univariate differences across MNA-SF groups. For the multivariable analysis, logistic regression was used to determine the association between MNA-SF and 1-year mortality after adjusting for the clinical operative risk, physical frailty, and type of procedure performed. Survival analysis was

calculated using the Kaplan–Meier method. A sensitivity analysis was performed to adjust for individual covariates associated with MNA-SF (age, sex, stroke, chronic kidney disease, chronic lung disease, anemia, pulmonary hypertension, mean aortic gradient, left ventricular ejection fraction, SPPB, and procedure type). Analyses were performed using Stata version 12 (StataCorp, College Station, TX, USA). A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 1,158 patients (727 TAVR, 431 SAVR) were included with a mean age of 81.3 ± 6.1 years and 481 (41.5%) females. The mean MNA-SF score was 11.5 ± 2.5 points out of 14, with 101 (8.7%) patients being malnourished, 380 (32.8%) being at-risk for malnutrition, and 677 (58.5%) having normal nutritional status, as shown in Figure 1. Baseline characteristics by MNA-SF group are shown in Table 1, and further sub-stratified by procedure type in Supplemental Table 1. Patients in the malnourished group were older, more likely to be female, more likely to undergo TAVR than SAVR, more likely to have prior stroke, chronic kidney disease, chronic lung disease, anemia, lower left ventricular ejection fraction, and higher STS-PROM. Serum albumin, which is not included in the MNA-SF but is a nonspecific biomarker of nutritional status, was significantly reduced in higher-risk MNA-SF categories.

Geriatric Domains

Lower MNA-SF scores, suggestive of malnutrition, were associated with increasing levels of frailty as measured by the SPPB scale shown in Figure 2, and a threefold increase in

frailty as measured by the Fried scale (74% in malnourished group vs. 25% in normal group, P<0.001). Both upper and lower extremity indices of physical weakness were significantly reduced in the malnourished group, who were more likely to report falls (26% vs. 15%, P<0.001) and disabilities for basic and instrumental activities of daily living (77% vs. 42%, P<0.001). These geriatric characteristics stratified by MNA-SF group are shown in Table 1.

Unadjusted Analysis of Postoperative Outcomes

The primary outcome of 1-year all-cause mortality occurred in 28 (27.7%) patients in the malnourished group, 62 (16.3%) in the at-risk group, and 66 (9.7%) in the normal group (P<0.001), as shown in Table 2 and further sub-stratified by procedure type in Supplemental Table 2. Kaplan-Meier curves are displayed in Figure 3. The secondary outcome of 30-day composite safety events occurred in 25 (24.8%) patients in the malnourished group, 110 (28.9%) in the at-risk group, and 150 (22.2%) in the normal group (P=0.08). Malnourished patients had a longer LOS in the intensive care unit (P=0.03) and were more likely to require discharge to rehabilitation or convalescence facilities (P=0.002).

Adjusted Analysis of Postoperative Outcomes

In the multivariable model adjusting for STS-PROM, SPPB, and procedure type, every 1-point decrease in MNA-SF was associated with an 8% increase in adjusted 1-year mortality (OR 1.08, 95% CI 1.01 to 1.16) and a 6% increase in adjusted 30-day composite safety events (OR 1.06, 95% CI 1.001 to 1.12). The effect of MNA on mortality was similar (OR 1.10, 95% CI 1.02 to 1.18) in a sensitivity analysis adjusting for individual covariates associated with MNA (Supplemental Table 3). When MNA was analyzed as a categorical variable, patients in the

malnourished group had a higher risk of adjusted mortality (OR 1.76, 95% CI 1.02 to 3.07) but not patients in the at-risk group (OR 1.26, 95% CI 0.85 to 1.87) as compared to those in normal group (OR 1.00, referent).

DISCUSSION

To our knowledge, this is the first study to systematically screen for malnutrition and demonstrate that it could predicts poor outcomes following TAVR and SAVR. The findings of this study can be summarized as follows: 1) Patients can be easily screened for the presence or absence of malnutrition; 2) Malnutrition is a risk factor for mid-term mortality and to a lesser extent, short-term mortality, and major morbidity following aortic valve intervention; 3) This risk associated with malnutrition persists even after adjusting for frailty and other potential confounders. In addition, those that screened positive for malnutrition were more likely to require specialized services at healthcare facilities (rehabilitation, convalescence) post-procedure. Lastly, signs of malnutrition were closely correlated with the phenotype of frailty and the presence of disability for activities of daily living, reaffirming the overlap between these geriatric syndromes in these patients.

Poor nutritional status has been shown to be risk factor for mortality in older adults living in the community,[23] living in nursing homes,[15] undergoing hip surgery,[24, 25] and hospitalized for acute decompensated heart failure.[26-28] In patients undergoing TAVR, there have been no previous studies focusing on nutritional status. In patients undergoing open cardiac surgery, Lomivorotov et al. observed a prevalence of 1% for malnutrition and 19% for at risk MNA-SF, while Chermesh et al. observed a prevalence of 18% for high-risk and 2% for moderate-risk

malnutrition scores.[8, 9, 29, 30] Cumulatively, these studies suggested that 20% of open cardiac surgery patients were either positive or at risk for malnutrition.

The lower rate of malnutrition in the aforementioned studies compared to ours can be explained by the markedly younger age (mean 60-65 vs. 81 years) and lower-risk nature of their patients. Notwithstanding this difference, their studies and ours similarly showed that malnutrition was associated with a higher rate of postoperative 30-day mortality and major morbidity, although their multivariable models only adjusted for the EuroSCORE and did not account for other confounders such as frailty. This study has added value in that it carefully considered the presence of concomitant frailty and demonstrated an independent effect of malnutrition on both 30-day and 1-year outcomes, and it included a larger sample size of older higher-risk patients such as those undergoing TAVR whose nutritional risk had not previously been investigated despite manifesting a very high burden of frailty.

Malnutrition and frailty are closely connected at the epidemiological and pathophysiological levels, since sarcopenia is a core element in the phenotype of frailty.[31] Malnourished patients are more likely to be frail at baseline, and to develop progressive worsening frailty; whereas patients that consume a balanced diet rich in protein and antioxidants are less likely to exhibit shrinking muscle mass and decreasing muscle strength over time.[2] In the community, 68% of malnourished older adults were found to be frail – fourfold higher than normally nourished – but only 8% of frail older adults were found to be malnourished; speaking to the multiple mechanisms by which frailty may arise in an individual.[32] In this study, 74% of malnourished patients were found to be frail by Fried's scale – threefold higher than normally nourished – but only 17% of frail patients were found to be malnourished.

Frailty may be an intermediate step in the pathway between malnutrition and mortality. Malnutrition leads to an impaired host immune response and a pro-inflammatory state, which are key mechanisms in the pathogenesis of physical frailty.[33] Reduced handgrip strength, a marker of physical frailty, predicts poor nutritional status.[34, 35] Anemia, elevated C-reactive protein, inadequate food intake, and reduced mobility are prevalent in both malnourished and frail older adults.[36]

Given that malnourished or at risk older adults undergoing cardiac surgery or TAVR constitute a group at higher risk for 1-year mortality, this study raises the question of whether pre- and postoperative interventions should be considered in this population to improve postoperative outcomes. Malnutrition is likely a modifiable target. Malnourished older adults have shown the capacity to respond to protein supplementation with increased post-absorptive protein synthesis rates and an increase in lean body mass.[37, 38] Moreover, the anabolic effect of perioperative nutrition is associated with increased age and the patient's preoperative catabolic state.[39] In one study, malnourished, hospitalized older adults with reduced handgrip strength had marked improvement in both nutritional status and handgrip strength after only two weeks of enhanced nutritional support. Thus, preoperative nutrition support may be considered in the severely malnourished patient when elective surgery can be safely postponed for one week or more.[40] In addition, there may be a role for more intensive intraoperative or postoperative nutritional support in malnourished or at risk patients. However, there is currently limited evidence whether pre- and postoperative nutritional support improves longer-term outcomes. There is an ongoing prospective trial investigating whether a multidisciplinary strategy involving nutritional support for preprocedural optimization ("prehab") in older adults prior to elective cardiac surgery improves outcomes.[41] Further studies are needed to determine if nutritional

interventions improve clinical outcomes in malnourished and at risk older adults undergoing invasive cardiac procedures.

There are limitations to our study. First, systematic confirmatory testing with a formal nutritional evaluation was not performed in this study, possibly leading to misclassification of nutritional status. However, the MNA-SF is a well-validated and highly-sensitive instrument to screen for malnutrition in older adult and cardiac surgical populations. Second, MNA-SF was administered by different research assistants at each study site and was subject to recall bias from patients. However, this approach is consistent with a real world application of this nutritional screening tool.

CONCLUSIONS

Malnourished older adults, identified using MNA-SF, had a nearly 3-fold increase in 1-year mortality following aortic valve replacement. However, when physical frailty was included in the analysis, the mortality risk due to malnutrition was attenuated, yet remained significant. Whether nutritional intervention in the pre- and postoperative period improves longer-term mortality in malnourished or at risk older adults undergoing surgical or transcatheter aortic valve replacement needs to be further elucidated.

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Figure 1. Mini-Nutritional Assessment Subdomains

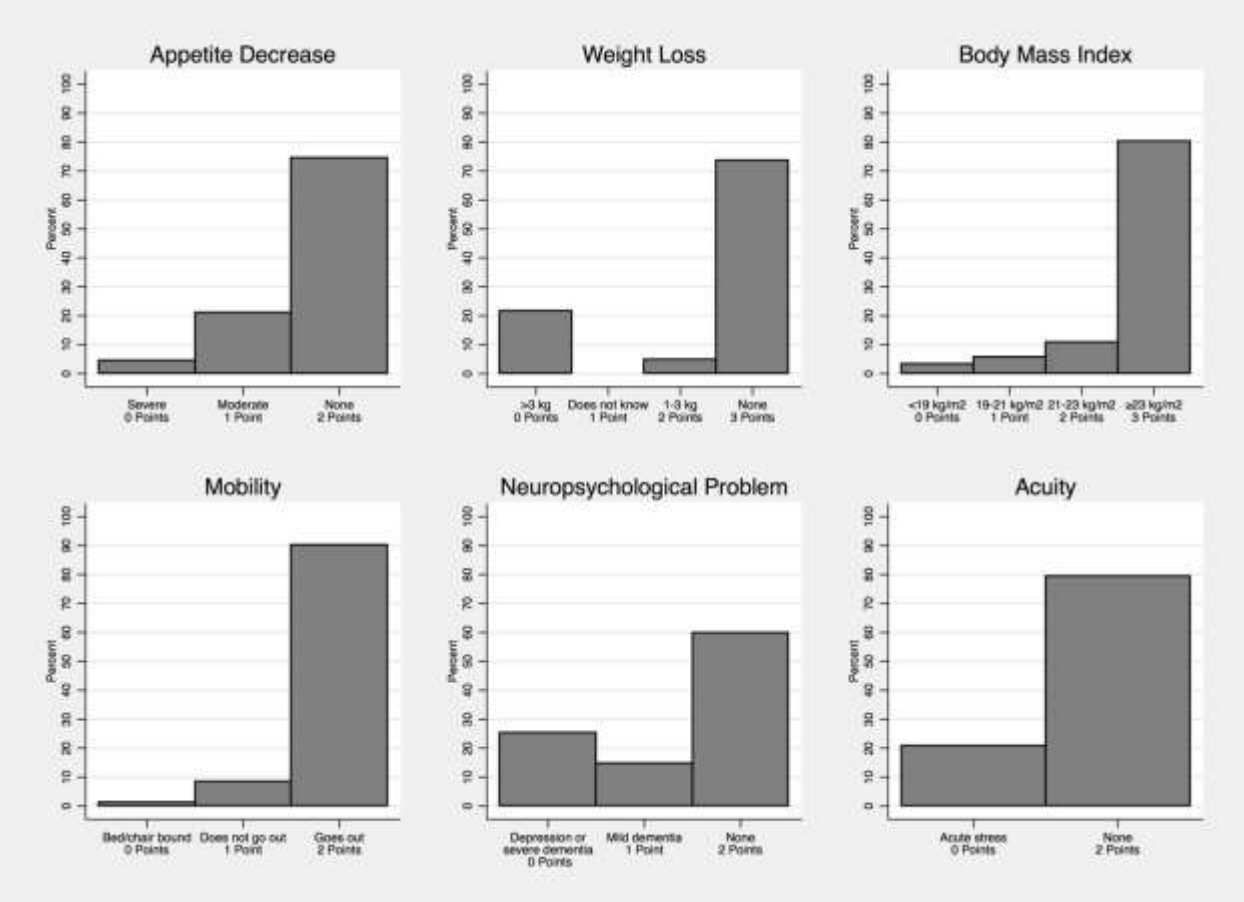


Figure 2. Relationship between Nutrition and Physical Frailty

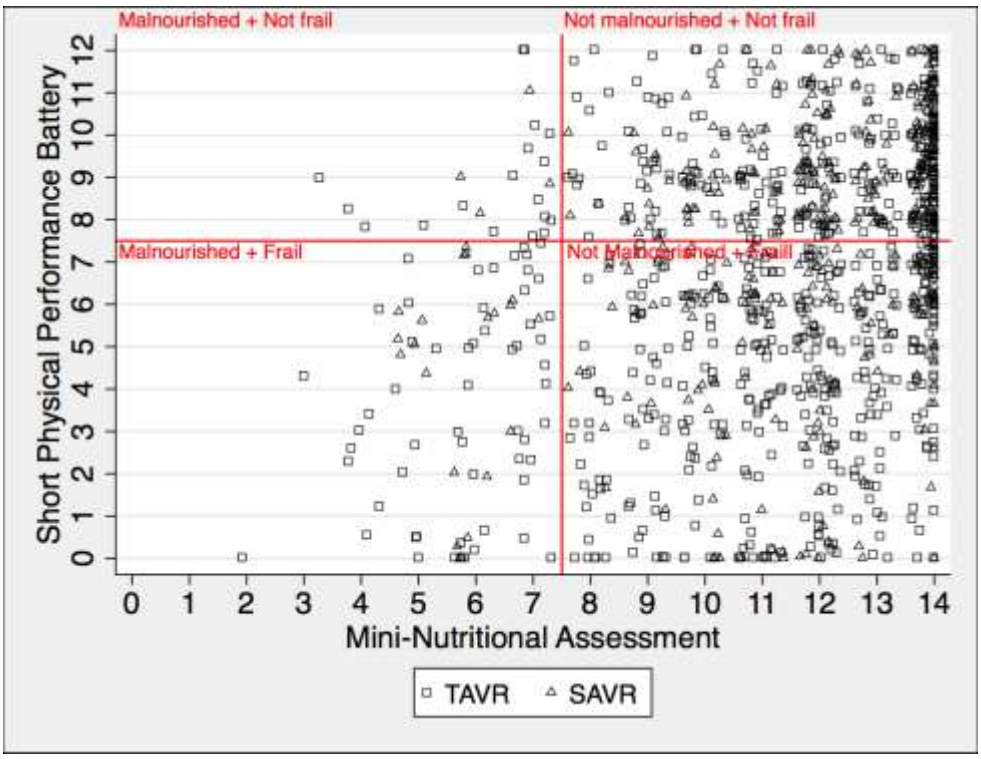
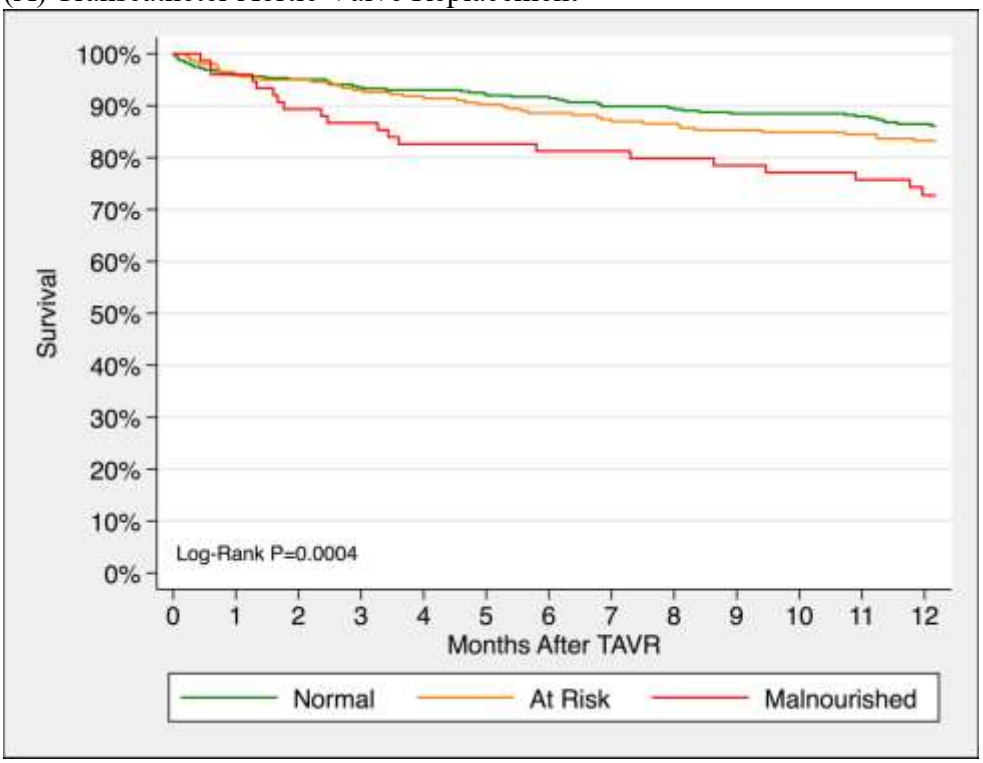


Figure 3. Kaplan-Meier Curves for All-Cause Mortality by Nutritional Status

(A) Transcatheter Aortic Valve Replacement



(B) Surgical Aortic Valve Replacement

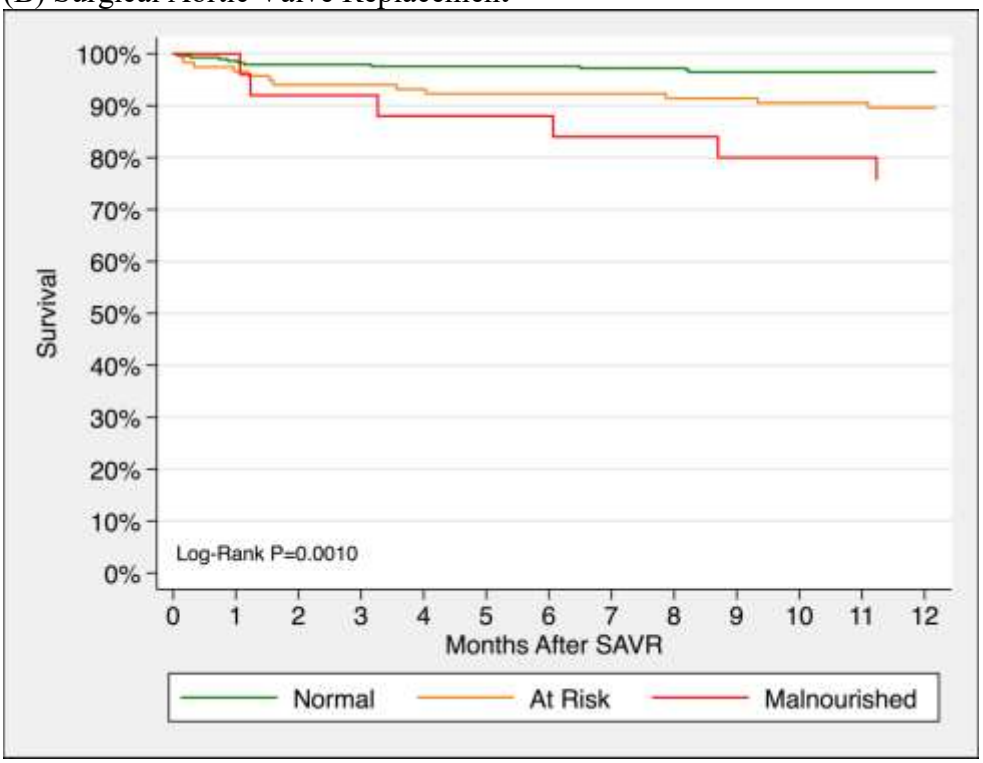


Table 1. Baseline Characteristics by Nutritional Status

	Normal **MNA 12-14** **N=677**	**At-risk** **MNA 8-11** **N=380**	**Malnutrition** **MNA 0-7** **N=101**	**P-value**
Age	80.7 ± 6.2	81.6 ± 5.8	83.4 ± 5.9	<0.001
Female	250 (37%)	178 (47%)	53 (52%)	<0.001
Body mass index, kg/m2	28.5 ± 5	26.8 ± 5.9	23.7 ± 5.4	<0.001
Weight, kg	79.0 ± 16.3	73.2 ± 17.7	65.1 ± 16.5	<0.001
Weight loss over past year, kg	0.1 ± 0.4	3.7 ± 5.3	8.7 ± 5.9	<0.001
Diabetes	184 (27%)	113 (30%)	24 (24%)	0.97
Coronary artery disease	415 (61%)	231 (61%)	63 (62%)	0.95
Prior stroke	41 (6%)	33 (9%)	12 (12%)	0.02
Peripheral arterial disease	93 (14%)	61 (16%)	15 (15%)	0.44
Chronic kidney disease	328 (48%)	205 (54%)	67 (66%)	<0.001
Chronic lung disease	97 (14%)	76 (20%)	22 (22%)	0.008
Gastrointestinal disease	132 (19%)	84 (22%)	27 (27%)	0.08
Cancer	99 (15%)	61 (16%)	15 (15%)	0.70
Left ventricular ejection fraction, %	57.9 ± 11.4	54.9 ± 12.7	49.7 ± 15.3	<0.001
Mean aortic gradient, mmHg	47.2 ± 15.8	44.1 ± 15.8	44.9 ± 15.3	0.004
Pulmonary artery pressure, mmHg	40.2 ± 14	41.1 ± 15.4	45.2 ± 14.5	0.009
Hemoglobin, g/L	125.7 ± 17	120.1 ± 16.7	114.6 ± 17.5	<0.001

Serum albumin, g/L	39.6 ± 4.9	38.2 ± 4.8	36.3 ± 4.8	<0.001
STS-PROM, %	4.4 ± 3.2	5.8 ± 3.9	7.9 ± 5.4	<0.001
TAVR	388 (57%)	263 (69%)	76 (75%)	<0.001
SAVR	289 (43%)	117 (31%)	25 (25%)	<0.001
Geriatric Domains				
SPPB, out of 12	7.4 ± 3.0	6.1 ± 3.3	4.9 ± 3.1	<0.001
Fried frailty scale	172 (25%)	188 (49%)	73 (74%)	<0.001
Falls	104 (15%)	91 (24%)	26 (26%)	<0.001
Gait speed, m/sec	0.8 ± 0.3	0.6 ± 0.3	0.5 ± 0.4	<0.001
Grip strength, kg	27.5 ± 10.4	24.0 ± 10.4	20.9 ± 9.9	<0.001
Cognitive impairment	90 (13%)	75 (20%)	29 (29%)	<0.001
Depressed mood	115 (17%)	166 (44%)	69 (68%)	<0.001
ADL/IADL disabilities, out of 14	1 ± 1.7	2 ± 2.6	3.5 ± 3.3	<0.001

Abbreviations: ADL/IADL, basic and instrumental activities of daily living; MNA, mini nutritional assessment; SAVR, surgical aortic valve replacement; SPPB, short physical performance battery; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; TAVR, transcatheter aortic valve replacement.

Table 2. Outcomes by Nutritional Status

	Normal MNA 12-14 N=677	**At-risk MNA 8-11 N=380**	**Malnutrition MNA 0-7 N=101**	**P-value**
1-year mortality	66 (10%)	62 (17%)	28 (29%)	<0.001
30-day mortality	23 (3%)	23 (6%)	6 (6%)	0.05
30-day composite endpoint	150 (22%)	110 (29%)	25 (25%)	0.08
Reoperation	55 (8%)	46 (12%)	11 (11%)	0.07
Stroke	15 (2%)	7 (2%)	5 (5%)	0.31
Acute kidney injury	46 (7%)	43 (11%)	7 (7%)	0.15
Major bleeding complication	81 (12%)	56 (15%)	8 (8%)	0.91
Major vascular complication	23 (3%)	23 (6%)	3 (3%)	0.33
ICU length of stay, hours	72.6 ± 91.6	81.6 ± 108.9	91.3 ± 135.4	0.03
Hospital length of stay, days	8.5 ± 8.9	9.1 ± 11.8	10.5 ± 12.1	0.25
Discharge to facility	196 (29%)	134 (35%)	43 (43%)	0.002

Abbreviations: ICU, intensive care unit; MNA, mini nutritional assessment. * Composite endpoint refers to VARC composite safety endpoint: all-cause death, stroke, acute kidney injury, reoperation, major bleeding or vascular complication.

Table 3. Multivariable Logistic Regression Analysis

	1-year mortality *Odds Ratio (95% CI)*	**30-day composite endpoint** *Odds Ratio (95% CI)*
Malnutrition, per 1-point ↓ MNA	1.08 (1.01, 1.16)	1.06 (1.001, 1.12)
Frailty, per 1-point ↓ SPPB	1.14 (1.07, 1.20)	1.03 (0.98, 1.07)
STS-PROM, per %	1.10 (1.05, 1.15)	1.02 (0.99, 1.06)
Procedure, TAVR (vs. SAVR)	1.63 (1.04, 2.57)	0.81 (0.60, 1.09)

Abbreviations: CI, confidence interval; MNA, mini nutritional assessment; SAVR, surgical aortic valve replacement; SPPB, short physical performance battery; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; TAVR, transcatheter aortic valve replacement.

Supplemental Table 1A. Baseline Characteristics by Nutritional Status in TAVR Patients

	Normal **MNA 12-14** **N=388**	**At-risk** **MNA 8-11** **N=263**	**Malnutrition** **MNA 0-7** **N=76**	**P-value**
Age	83.4 ± 5.6	83.1 ± 5.6	84.8 ± 5.5	0.40
Female	164 (42%)	127 (48%)	40 (53%)	0.05
BMI, kg/m2	27.9 ± 5.1	26.2 ± 5.5	23 ± 4.9	<0.001
Weight, kg	76.3 ± 16.5	71.3 ± 17	62.7 ± 14.5	<0.001
Weight loss over past year, kg	0.1 ± 0.4	3.8 ± 5.4	8.9 ± 6	<0.001
Diabetes	103 (27%)	69 (26%)	17 (22%)	0.54
Coronary artery disease	229 (59%)	152 (58%)	49 (64%)	0.61
Prior stroke	26 (7%)	27 (10%)	11 (14%)	0.02
Peripheral arterial disease	68 (18%)	49 (19%)	11 (14%)	0.77
Chronic kidney disease	218 (56%)	147 (56%)	56 (74%)	0.04
Chronic lung disease	68 (18%)	58 (22%)	18 (24%)	0.10
Gastrointestinal disease	75 (19%)	56 (21%)	19 (25%)	0.26
Cancer	63 (16%)	44 (17%)	14 (18%)	0.67
Left ventricular ejection fraction, %	57.1 ± 11.7	54.8 ± 12.5	48.4 ± 15.1	<0.001
Mean aortic gradient, mmHg	48.5 ± 16.5	45.1 ± 16.1	44.8 ± 14.2	0.01
Pulmonary artery pressure, mmHg	42.6 ± 15.2	41.9 ± 15.6	47.4 ± 14.6	0.07
Hemoglobin, g/L	122.5 ± 16.1	118.3 ± 16.6	112.4 ± 16.8	<0.001
Serum albumin, g/L	39 ± 4.6	38.2 ± 4.7	36.1 ± 4.9	<0.001
STS-PROM, %	5.4 ± 3.5	6.5 ± 4.2	9.0 ± 5.6	<0.001

Non-femoral access	89 (23%)	64 (24%)	14 (18%)	0.64
Geriatric Domains				
SPPB, out of 12	6.8 ± 3	5.8 ± 3.4	4.8 ± 3.2	<0.001
Fried frailty scale	127 (33%)	141 (54%)	60 (79%)	<0.001
Falls	68 (18%)	64 (24%)	22 (29%)	0.007
Gait speed, m/sec	0.7 ± 0.3	0.6 ± 0.3	0.4 ± 0.4	<0.001
Grip strength, kg	25 ± 9.6	23 ± 10.4	20.1 ± 9.9	<0.001
Cognitive impairment	68 (18%)	61 (23%)	24 (32%)	0.003
Depressed mood	74 (19%)	109 (42%)	50 (66%)	<0.001
ADL/IADL disabilities, out of 14	1.4 ± 1.9	2.4 ± 2.9	4.0 ± 3.4	<0.001

Abbreviations: ADL/IADL, basic and instrumental activities of daily living; BMI, body mass index; SPPB, short performance physical battery; STS-PROM, Society of Thoracic Surgery predicted risk of mortality.

Supplemental Table 1B. Baseline Characteristics by Nutritional Status in SAVR Patients

	Normal MNA 12-14 N=289	**At-risk MNA 8-11 N=117**	**Malnutrition MNA 0-7 N=25**	**P-value**
Age	77.1 ± 4.9	78.4 ± 4.7	79.2 ± 5.1	0.003
Female	86 (30%)	51 (44%)	13 (52%)	0.001
BMI, kg/m2	29.2 ± 4.8	28.1 ± 6.4	25.8 ± 6.3	<0.001
Weight, kg	82.7 ± 15.3	77.5 ± 18.6	72.3 ± 20.5	<0.001
Weight loss over past year, kg	0.1 ± 0.5	3.5 ± 5	8.1 ± 5.6	<0.001
Diabetes	81 (28%)	44 (38%)	7 (28%)	0.23
Coronary artery disease	186 (64%)	79 (68%)	14 (56%)	0.85
Prior stroke	15 (5%)	6 (5%)	1 (4%)	0.85
Peripheral arterial disease	25 (9%)	12 (10%)	4 (16%)	0.26
Chronic kidney disease	110 (38%)	58 (50%)	11 (44%)	0.08
Chronic lung disease	29 (10%)	18 (15%)	4 (16%)	0.12
Gastrointestinal disease	57 (20%)	28 (24%)	8 (32%)	0.12
Cancer	36 (12%)	17 (15%)	1 (4%)	0.64
Left ventricular ejection fraction, %	59 ± 10.8	55 ± 13.3	53.6 ± 15.4	0.002
Mean aortic gradient, mmHg	45.5 ± 14.8	41.7 ± 14.9	45.3 ± 18.5	0.05
Pulmonary artery pressure, mmHg	36.1 ± 10.3	38.4 ± 14.5	38.4 ± 12	0.53
Hemoglobin, g/L	130.1 ± 17.1	124 ± 16.4	121.3 ± 18.2	<0.001
Serum albumin, g/L	40.3 ± 5.2	38.2 ± 5.1	36.9 ± 4.5	<0.001
STS-PROM, %	3 ± 1.8	4.1 ± 2.2	4.4 ± 2.5	<0.001

Concomitant CABG	158 (55%)	64 (55%)	8 (32%)	0.14
Geriatric Domains				
SPPB, out of 12	8.3 ± 2.6	6.7 ± 3.1	5.3 ± 2.9	<0.001
Fried frailty scale	45 (16%)	47 (40%)	14 (56%)	<0.001
Falls	36 (12%)	27 (23%)	4 (16%)	0.04
Gait speed, m/sec	0.9 ± 0.3	0.7 ± 0.3	0.6 ± 0.3	<0.001
Grip strength, kg	30.9 ± 10.6	26.4 ± 10	23.4 ± 9.5	<0.001
Cognitive impairment	22 (8%)	14 (12%)	5 (20%)	0.03
Depressed mood	41 (14%)	57 (49%)	19 (76%)	<0.001
ADL/IADL disabilities, out of 14	0.5 ± 1	1.1 ± 1.6	2.1 ± 2.8	<0.001

Abbreviations: ADL/IADL, basic and instrumental activities of daily living; BMI, body mass index; CABG, coronary artery bypass graft; SPPB, short performance physical battery; STS-PROM, Society of Thoracic Surgery predicted risk of mortality

Supplemental Table 2A. Outcomes by Nutritional Status in TAVR Patients

	Normal MNA 12-14 N=388	**At-risk MNA 8-11 N=263**	**Malnutrition MNA 0-7 N=76**	**P-value**
1-year mortality	54 (15%)	50 (20%)	22 (30%)	0.002
30-day mortality	17 (4%)	18 (7%)	4 (5%)	0.36
30-day composite endpoint	83 (21%)	74 (28%)	19 (25%)	0.14
Reoperation	32 (8%)	34 (13%)	8 (11%)	0.16
Stroke	5 (1%)	6 (2%)	5 (7%)	0.01
Acute kidney injury	31 (8%)	29 (11%)	5 (7%)	0.71
Major bleed	36 (9%)	26 (10%)	5 (7%)	0.67
Major vascular complication	18 (5%)	23 (9%)	2 (3%)	0.57
ICU length of stay, hours	83.8 ± 97.6	86.2 ± 117.1	98.4 ± 147.7	0.88
Hospital length of stay, days	7.1 ± 7.7	7.6 ± 9.8	9.3 ± 10.7	0.07
Discharge to facility	104 (27%)	87 (33%)	33 (43%)	0.003

Abbreviations: ICU, intensive care unit; MNA, mini nutritional assessment; TAVR, transcatheter aortic valve replacement. * Composite endpoint refers to VARC composite safety endpoint: all-cause death, stroke, acute kidney injury, reoperation, major bleeding or vascular complication.

Supplemental Table 2B. Outcomes by Nutritional Status in SAVR Patients

	Normal MNA 12-14 N=289	**At-risk MNA 8-11 N=117**	**Malnutrition MNA 0-7 N=25**	**P-value**
1-year mortality	12 (4%)	12 (11%)	6 (25%)	<0.001
30-day mortality	6 (2%)	5 (4%)	2 (8%)	0.06
30-day composite endpoint	67 (23%)	36 (31%)	6 (24%)	0.28
Reoperation	23 (8%)	12 (10%)	3 (12%)	0.35
Stroke	10 (3%)	1 (1%)	0 (0%)	0.09
Acute kidney injury	15 (5%)	14 (12%)	2 (8%)	0.06
Major bleeding complication	45 (16%)	30 (26%)	3 (12%)	0.22
Major vascular complication	5 (2%)	0 (0%)	1 (4%)	0.82
ICU length of stay, hours	58.7 ± 81.5	72.6 ± 90.1	73.9 ± 99.5	0.02
Hospital length of stay, days	10.4 ± 10	12.6 ± 14.8	14 ± 15.2	0.02
Discharge to facility	92 (32%)	47 (40%)	10 (40%)	0.11

Abbreviations: ICU, intensive care unit; MNA, mini nutritional assessment; SAVR, surgical aortic valve replacement. * Composite endpoint refers to VARC composite safety endpoint: all-cause death, stroke, acute kidney injury, reoperation, major bleeding or vascular complication.

Supplemental Table 3. Multivariable Logistic Regression Sensitivity Analysis

	1-year mortality *Odds Ratio (95% CI)*
Malnutrition, per 1-point ↓ MNA	1.10 (1.18, 1.02)
Frailty, per 1-point ↓ SPPB	1.13 (1.20, 1.06)
Age, per year	1.05 (1.01, 1.09)
Female sex	1.03 (0.55, 1.94)
Prior stroke	0.99 (0.66, 1.48)
Chronic kidney disease	1.27 (0.86, 1.88)
Chronic lung disease	1.13 (0.71, 1.81)
Anemia	2.05 (1.21, 3.47)
Pulmonary hypertension >60 mmHg	2.25 (1.48, 3.41)
Mean aortic gradient, per mmHg	0.98 (0.97, 1.00)
LVEF, per %	1.00 (0.99, 1.02)
Concomitant CABG	2.64 (1.20, 5.81)
Procedure, TAVR (vs. SAVR)	2.88 (1.38, 5.99)

Abbreviations: CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; MNA, mini nutritional assessment; SAVR, surgical aortic valve replacement; SPPB, short

performance physical battery; STS-PROM, Society of Thoracic Surgery predicted risk of mortality; TAVR, transcatheter aortic valve replacement.

Chapter 3: Preprocedural Nutritional Screening and Risk Prediction

The overall prevalence of malnutrition in our cohort was 8.7% and 1 in 3 older adults were at-risk for malnutrition. Our study showed that malnourishment in older adults was associated with an almost a 3-fold increased likelihood of 1-year mortality compared to those with normal nutritional status. In addition, older adults at-risk for malnutrition had an increased risk of 1-year mortality as well. These findings suggest that the nutritional status assessment with the MNA-SF is a useful prognostic tool for longer-term mortality in older adults undergoing transcatheter and surgical aortic valve replacement.

Our study raises the clinically important question of whether perioperative interventions could improve postoperative outcomes in malnourished or at-risk older adults. Nutritional supplementation, particularly protein-rich meals, has been shown to improve protein synthesis and increase lean muscle in malnourished older adults.[30, 31] Intraoperative, postoperative, and postdischarge protein supplementation may also mitigate the catabolic effects of the operation and hasten anabolic growth and improved physical functioning. Thus, preoperative identification of older adults who are malnourished or at-risk provides a window of opportunity for clinicians to implement strategies prior to invasive cardiac procedures, such as protein supplementation, which may improve outcomes in this higher risk group.

Nutritional biomarkers have also been investigated for their role as preoperative prognostic determinants. Serum albumin is a widely available and frequently used biomarker to indicate nutritional status in the preoperative period. In malnutrition states, inadequate protein intake results in impaired hepatic synthesis of albumin and reduced serum albumin levels. However, the serum albumin level also reflects other physiological processes besides nutritional status. Serum albumin levels are affected by disorders of hepatic synthesis, inflammation, chronic disease, fluid compartmental shifts, and from acute stressors such as surgery and acute illness.[126] Thus, serum albumin levels are not solely an indicator of nutritional status, but also reflect overall illness severity, both acute and chronic.

Lower serum albumin levels are predictive of adverse postoperative outcomes, such as mortality, in cardiac surgical populations,[104, 107, 127] but there is limited evidence on the use of serum albumin as a preoperative prognostic marker in TAVR.[128, 129] Thus, we investigated whether serum albumin levels were predictive of mortality in a cohort of older adults undergoing TAVR.

Chapter 4:

Published manuscript: "Serum Albumin as an Incremental Predictor of Mortality in Older Adults Undergoing Transcatheter Aortic Valve Replacement: Results from the Multicentre Frailty-AVR Study"

Our planned analysis of a prospective cohort study of serum albumin as a mortality predictor in older adults undergoing TAVR is presented as a manuscript.

The abstract was presented as a poster presentation at the American College of Cardiology Scientific Sessions in Washington D.C. in March 2017.

The manuscript will be submitted for publication.

Serum Albumin as an Incremental Predictor of Mortality in Older Adults Undergoing Transcatheter Aortic Valve Replacement: Results from the Multicentre Frailty-AVR Study

Michael Goldfarb MD[a], Sandra Lauck PhD[b], John Webb MD[b], Dae Kim MD MPH[c], Jeffrey Popma MD[d], Nicolo Piazza MD[e], Giuseppe Martucci MD[e], Marino Labinaz MD[f], Andre Lamy MD[g], Mark Peterson MD[h], Nicolas Noiseux MD[i], Andrew Rassi MD[j], Brian Lindman MD[k], Phillipe Genereux MD[l], Rakesh Aurora MD[m], Jose Morais MD[n], Anita Asgar MD[o], Louis Perrault MD[o], Jonathan Afilalo MD MSc[a,p,q]

[a] Division of Experimental Medicine, Faculty of Medicine, McGill University, Montreal, QC;
[b] Centre for Heart Valve Innovation, St. Paul's Hospital, Vancouver, BC, Canada;
[c] Division of Gerontology, Beth Israel Deaconess Medical Center, Boston, MA, United States;
[d] Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, MA, United States;
[e] Division of Cardiology, McGill University Health Centre, Montreal, QC, Canada;
[f] Division of Cardiology, Ottawa Heart Institute, Ottawa, ON, Canada;
[g] Department of Surgery, Hamilton General Hospital, Hamilton, ON, Canada;
[h] Division of Cardiac Surgery, St. Michael's Hospital, Toronto, ON, Canada;
[i] Division of Cardiac Surgery, Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada;
[j] Division of Cardiology, Massachusetts General Hospital, Boston, MA, United States;
[k] Division of Cardiology, Washington University, St. Louis, MO, United States;
[l] Division of Cardiology, Hôpital du Sacré-Coeur de Montréal, Montreal, QC, Canada;
[m] Division of Cardiac Surgery, St-Boniface, Winnipeg, MB, Canada;
[n] Division of Cardiology, Institut de Cardiologie de Montreal, Montreal, QC, Canada;
[o] Division of Cardiac Surgery, Institut de Cardiologie de Montreal, Montreal, QC, Canada;
[p] Centre for Clinical Epidemiology, Lady Davis Institute, McGill University, Montreal, QC.
[q] Division of Cardiology, Jewish General Hospital, McGill University, Montreal, QC;

First author surname and short title: Goldfarb – Albumin and Post-TAVR Mortality

Address for correspondence:

Jonathan Afilalo, MD, MSc, FACC, FRCPC

3755 Cote Ste Catherine Rd, E-222, Montreal, QC H3T 1E2

Phone: (514) 340-8232 / Fax: (514) 221-3785

Email: jonathan.afilalo@mcgill.ca

Abstract

Background: Hypoalbuminemia is a biomarker for malnutrition and chronic inflammation that has been implicated in the pathobiology of frailty, and been shown to be a risk factor for mortality and morbidity in general medical and surgical cohorts. Data from single-centre retrospective series suggests that hypoalbuminemia may be a risk factor in older adults undergoing transcatheter aortic valve replacement (TAVR) but its incremental value has yet to be confirmed in a prospective study that collected and adjusted for clinical frailty parameters.

Methods and Results: We conducted a pre-planned analysis of the prospective Frailty-AVR cohort study enrolling older adults ≥70 years from 14 centres in 3 countries (2012-2015). After excluding one centre that did not measure serum albumin, 399 out of 489 patients had a documented pre-TAVR serum albumin that was recorded as a continuous variable. The primary endpoint was 1-year all-cause mortality. We used multivariable logistic regression and adjusted for age, sex, body mass index, glomerular filtration rate, comorbid conditions including cirrhosis, ejection fraction, disability, and frailty according to Fried's scale. Compared to patients in the highest albumin tertile (≥40 g/L), those in the lowest tertile (<35 g/L) had more marked weight loss, anemia, inactivity, disability, and frailty, and a higher risk of mortality at 30 days (7.9% vs. 1.9%) and 1 year (21.3% vs. 7.9%). Following adjustment, serum albumin was the strongest independent predictor of 1-year mortality (OR 0.53 for every 10 g/L or 1 g/dL, 95% CI 0.34 to 0.82, P=0.005), resulting in an integrated discrimination improvement of 0.02 and an increase in model c-statistic from 0.69 to 0.72. The optimal cutoff favoring specificity was serum albumin <30 g/L (OR 2.73, 95% CI 1.34 to 5.99; sensitivity 28%, specificity 89%).

Conclusions: Hypoalbuminemia is a powerful predictor of post-TAVR mortality, which adds incremental value above existing risk models and clinical frailty scales. Further research is warranted testing the effect of nutritional interventions targeted to frail older adults with low serum albumin.

Key words: Albumin, transcatheter aortic valve replacement, frailty, risk prediction

Introduction

Transcatheter aortic valve replacement (TAVR) has been established as an effective procedure in high-risk elderly with severe aortic stenosis with improvement in quality of life indices and 1 and 5-year mortality rates similar to conventional surgical aortic valve replacement.[1-3] The number of TAVR procedures performed annually and the number of TAVR-eligible elderly are increasing substantially.[4, 5] Guiding organizations, such as the Valve-Associated Research Consortium, have emphasized the importance of preprocedural risk stratification to assist with appropriate patient selection but have yet to adopt formal "TAVR-specific" criteria.[6]

Measurement of serum albumin levels is recommended in older adults as a marker of nutritional status and muscle wasting.[7, 8] Yet serum albumin is a complex marker which reflects a number of non-nutritional factors, such as hepatic synthetic dysfunction, kidney disease, infection, dilution, and inflammation. Indeed, in individuals with chronic inflammation and/or disability, such as in the frailty syndrome, serum albumin levels correlate poorly with nutritional parameters.[9, 10] Serum albumin levels are inversely associated with post-TAVR mortality and add incremental prognostic value in addition to other frailty markers.[11, 12] As a result, serum albumin is being incorporated into pre-TAVR risk assessment tools.[8]

However, the optimal preprocedural serum albumin level for prediction of post-TAVR mortality in older adults has yet to be determined. Previous studies have proposed various dichotomous cutoff levels for serum albumin, ranging from 35 grams/liter (g/L) to 40g/L, based on the spread of albumin values and not by sensitivity and specificity.[11-13] In addition, available data are limited by small, single-centre studies and/or a lack of frailty markers. As a result, guiding authorities provide various cutoff levels for albumin in the definition of frailty (≤33g/L)[7]

and as a risk factor for poor outcomes post-TAVR (<35g/L).[6] Our objective was to evaluate the relationship between preprocedural serum albumin level and all-cause mortality in older adults undergoing TAVR and to propose appropriate cutoff levels of serum albumin based on sensitivity and specificity which can be incorporated into TAVR risk prediction scores.

Methods:

Study population

We retrospectively reviewed the Frailty-AVR registry for patients who underwent TAVR between 2012-2015. The Frailty-AVR study is an ongoing prospective cohort of more than 800 elderly patients across 13 centres in Canada, USA and France undergoing aortic valve replacement. Inclusion criteria to the study are age ≥70 years, aortic stenosis undergoing aortic valve replacement and/or CAD undergoing revascularization and signed informed consent. Exclusion criteria included emergency surgery, clinical instability, severe neuropsychiatric impairment, not English or French speaking and replacement of >1 valve or aortic segment.

Data collection and Measurement

Patients enrolled in the registry had a comprehensive preprocedural frailty assessment including demographic, clinical data, laboratory data (including serum albumin level), comorbidities, self-reported and measured functional capabilities, muscle strength, the short performance physical battery (composed of gait speed, chair rises and tandem balance), disability, mood, neurocognitive status, height, weight and nutritional status prior to TAVR by a trained health care professional.

Post-hospitalization, a research assistant recorded procedural data and postprocedural complications including in-hospital mortality. A follow-up phone call was completed at 6 months and 12 months post-hospitalization assessing vital status and functional status. We abstracted demographics, comorbidities, preprocedural albumin level, resource use and outcomes from the database (JA, MG).

Study Endpoints

The co-primary outcomes of the study were (1) preprocedural serum albumin and all-cause post-TAVR mortality at 30-days, 6 months and 12 months and (2) determining the sensitivity and specificity of preprocedural albumin levels in predicting all-cause post-TAVR mortality.

Statistical Analysis

Continuous data are presented as mean ± standard deviation. Categorical data are presented as frequencies and percentages. The Cuzick trend test was used to detect trends between groups. We used logistic and multivariate Cox proportional hazard models to examine the association of serum albumin with all-cause mortality. Multiple imputation was used to assess for the missing albumin values**.** A sensitivity analysis was used for missing data. Survival analysis was performed using the Kaplan-Meier method and the log-rank test was used to determine the statistical difference in terms of survival. Statistical significance was assumed when the p-value was rejected at $p<0.05$. Statistical analysis was performed using STATA (StataCorp, College Station, Texas).

Results

399 out of 489 patients had a documented pre-TAVR serum albumin and were included in the analysis (Table 1). One centre did not collect preprocedural albumin levels and was excluded from the analysis. Serum albumin levels followed a normal distribution (Figure 1) and were categorized into tertiles. Median follow-up was 1.1 years. 65 patients (16.3%) died during the follow-up period. At baseline, there were no significant between group differences in age, gender or co-morbid diseases. Patients in the lowest albumin group had the lowest preprocedural levels of hemoglobin and physical activity and the highest levels of disability, frailty and femoral approach for TAVR. Patients in the lowest albumin group had the highest preprocedural weight loss and predicted mortality.

For the primary outcome, patients in the lowest albumin group compared to the highest albumin group had a higher 30-day mortality (6.4% vs. 0%), 6-month mortality (17.4% vs. 4.0%) and 12-month mortality (25.8% vs. 7.0%) (Table 2). Lower serum albumin levels had high specificity but low sensitivity for 6-month mortality with the converse for higher serum albumin levels (Figure 2). Our model showed high specificity (87%) at albumin levels ≤ 30g/L and high sensitivity (83%) at albumin levels ≥ 39g/L.

For the multivariate analysis, 90 serum albumin levels were added by multiple imputation. Albumin levels predicted mortality at 30 days (odds ratio (OR) 0.88) (Supplemental Table 1), 6 months (OR 0.90) (Table 3) and 12 months (hazard ratio (HR 0.94))(Supplemental Table 2). Non-femoral TAVR access was a strong predictor of mortality at 6-months (OR 3.60). The receiver operating characteristic (ROC) curve for the model including albumin had a C-statistic of 0.8835 for 30 day mortality and 0.7995 for 6 month mortality (table 4). In the survival analysis, the lowest albumin group showed significantly lower post-TAVR survival at 1-month,

6 months and 12 months (Figure 3). In the sensitivity analysis, when imputed serum albumin values were excluded, there were no significant differences in the HR for mortality prediction (Supplemental Tables 3-5).

Discussion

Our study was one of the largest cohort of TAVR patients with preprocedural serum albumin levels, frailty measures and outcome data to date. We found that serum albumin level is a strong predictor of all-cause mortality post-TAVR at 30-days, 6 months and 12 months and is an incremental predictor to frailty measures. In terms of 6-month mortality prediction, our model showed high specificity at lower albumin levels and high sensitivity at higher albumin levels. Most significantly, there was a graded increase in mortality with decreasing albumin levels below 40g/L. Risk discrimination was excellent in our model, particularly when albumin was included. We also found significant, clinically relevant differences in baseline characteristics based on albumin group membership in the level of disability and amount of daily physical activity.

Proper patient selection is of critical importance in TAVR due to the increased morbidity and mortality in this higher risk population, as well as considerable peri-procedural costs.[14] Important clinical factors to define TAVR success include both quality of life and survival.[15] Mortality risk prediction in the TAVR patient population commonly uses surgical risk prediction models such as the Society of Thoracic Surgeons Predicted Risk of Mortality score or logistic EuroSCORE, both of which do not include preprocedural albumin as a predictor variable in their models.[16] Yet studies in TAVR populations have demonstrated the importance of albumin as a predictor of mortality.[11-13] Green *et al*. showed that the mortality rate differed considerably based

on the results of a frailty score which included serum albumin level as one of its components.[8] Yamamoto *et al*. used a dichotomous albumin cut-off of 35 g/L to demonstrate that hypoalbuminemia was a predictor of 30-day and 1-year all-cause mortality.[17] However, most TAVR-specific mortality risk prediction models have yet to incorporate albumin and frailty measures and these risk scores have shown only fair predictive ability (C-statistics of 0.62-0.67).[18, 19] In addition, there are minimal data on using serum albumin as a predictor in post-TAVR quality of life outcomes.[20]

There are several mechanisms which may explain the pathophysiological link between frailty and serum albumin levels. Studies have consistently shown an association of frailty, low serum albumin and elevated inflammatory markers.[21-23] Inflammatory cytokines such as interleukin-6 and tumor necrosis-alpha are associated with low serum albumin levels and are negatively correlated with the rate of muscle synthesis.[24, 25] Chronic low grade inflammation has been implicated in the pathogenesis of sarcopenia, the accelerated age-related decline of muscle mass.[26] Low albumin levels are also strongly associated with anemia due to chronic inflammation in the elderly.[27] Oxidative stress may also play a direct causal role in the decrease in skeletal muscle mass seen in frailty.[28] Albumin is a modulator of glutathione, one of the main antioxidants, and low serum levels may result in excessive damage at the cellular and organ level.[29] In frail patients, serum albumin levels may reflect the degree of subclinical organ dysfunction.

Albumin circulates in the plasma as the most abundant visceral protein ("serum albumin") and is also found in somatic protein stores such as skeletal muscle. Serum albumin is a complex marker which reflects a number of nutritional, such as inadequate protein intake, and non-nutritional factors, such as hepatic synthetic dysfunction, renal disease, infection, dilution

and inflammation. The serum albumin level is also modulated by the dynamic balance between body compartments and will decrease in response to an acute stressor, such as TAVR, due to increased vascular permeability, increased visceral protein breakdown and/or impaired anabolic responses.[12]

Poor nutritional status has also been implicated in both frailty and hypoalbuminemia.[7, 11, 30] Yet serum albumin levels are a poor marker of nutritional status in individuals with inflammation and/or disability[9, 10] and when assessed by Subjective Global Assessment, the gold standard of nutritional screening tools.[27] Indeed, overall nutritional status is better assessed by considering both visceral albumin concentration and somatic protein stores since they are not necessarily correlated.[31] Thus, lower baseline serum albumin in older adults may be understood as a marker of decreased total body protein reserve and a chronic inflammatory state associated with muscle catabolic processes. Lower serum albumin levels in older adults are predictive of future appendicular skeletal muscle mass loss.[32]

Including serum albumin measurement as part of the pre-TAVR risk assessment has a number of potential advantages. Firstly, serum albumin levels improve risk discrimination beyond the use of traditional risk factors and frailty status. Second, low serum albumin levels assist the clinician in identifying older adults who may need additional post-procedural support in terms of supervised exercise programs or physiotherapy to prevent further disability. Third, serum albumin is easy to obtain, low cost and readily understandable. Fourth, low serum albumin levels are a potentially modifiable marker. Preprocedural interventions such as comprehensive nutritional, psychological and physical support aimed at improving the underlying etiology of frailty may decrease the underlying inflammatory state and improve frailty status – and possibly lead to a corresponding increase in serum albumin levels. However, there are no studies to date

which demonstrate improved outcomes with correction of serum albumin levels or intravenous albumin administration. Further studies are required to assess whether pre- and post-TAVR interventions can improve outcomes in an elderly patient population.

There were several limitations to our study. The study was retrospective in nature, although the collection of data, including preprocedural serum albumin levels, was pre-specified. Missing albumin levels were determined by multiple imputation. However, no significant differences in outcomes were observed in the sensitivity analyses. The study was observational registry based and the participants were not subject to randomization. We adjusted for potential confounders in the analysis, although there could still have been residual confounding factors that were not accounted for.

Conclusion

Lower serum preprocedural albumin levels are associated with a graded increase in mortality in older adults undergoing TAVR and add incremental predictive ability beyond other markers of frailty. Risk prediction models which include albumin and frailty have improved short and longer-term mortality prediction. Serum albumin levels should be part of the pre-TAVR assessment and be incorporated into TAVR mortality risk prediction models.

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Table 1. Baseline Demographics and Clinical Factors According to Albumin Group

	Albumin ≤ 35g/L (n = 140)	Albumin 35-40 g/L (n=132)	Albumin ≥ 40g/L (n=127)	p-value
Age, years	84.4 ± 6.1	83 ± 5.9	83.1 ± 5.8	0.16
Female sex	45.7%	49.2%	45.7%	0.99
Body Mass Index (kg/m^2)	26.2 ± 5.7	26.9 ± 5.8	27.1 ± 5.6	0.16
Weight loss in previous 12 months (kg)	4.0 ± 6.9	2.2 ± 3.7	1.4 ± 3.2	<0.001
Congestive Heart Failure	57.1%	43.9%	53.5%	0.57
Chronic Obstructive Pulmonary Disease	23.6%	22.0%	21.3%	0.65
Diabetes Mellitus	25.0%	28.0%	27.6%	0.57
Hemoglobin (g/L)	116.0 ± 17.0	119.0 ± 15.0	124.0 ± 15.9	<0.001
White blood cell count (x10^9/L)	7.2 ± 2.3	7.8 ± 8.1	7.1 ± 2.3	0.38
Glomerular filtration rate (mL/min)	51.4 ± 18.1	53.9 ± 16.5	54.1 ± 17.2	0.21
Mini-Mental Status Exam	25.6 ± 3.9	26.0 ± 3.3	26.8 ± 3.1	0.01
MNA score	10.5 ± 2.7	11.2 ± 2.5	11.9 ± 1.8	<0.001
MNA score ≤7 (malnourished)	15.0%	8.3%	3.2%	0.001
Activities of Daily Living	1.2 ± 1.7	0.5 ± 1.2	0.3 ± 0.7	<0.001
Instrumental Activities of Daily Living	2.0 ± 2.0	1.6 ± 1.8	1.0 ± 1.3	<0.001
Short Performance Physical Battery	5.2 ± 3.5	5.7 ± 3.4	6.4 ± 3.1	0.003
Max Handgrip Strength	23.8 ± 10.1	22.8 ± 9.7	25.8 ± 9.2	0.07

Clinical Frailty Scale	5.1 ± 1.5	4.6 ± 1.4	4.4 ± 1.5	<0.001
Daily Physical Activity (kcal/day)	237.1 ± 436.9	254.3 ± 439.7	463.7 ± 824.3	<0.001
STS Predicted Mortality	7.9 ± 5.6%	6.7 ± 4.5%	6.0 ± 3.7%	0.002
Femoral TAVR Approach	82.7%	81.7%	70.9%	0.02

Legend

Values are mean ± SD or %

MNA, Mini-Nutritional Assessment; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement

Mini-Mental Status Exam: Score range 0-30; ≤23 indicates cognitive impairment

Mini-Nutritional Assessment: Score range 0-14; ≤7 indicates malnutrition, 8-11 indicates at-risk for malnutrition.

Activities of Daily Living and Instrumental Activities of Daily Living: OARS score range 0-6. A higher score indicates increased disability.

Physical activity was measured using the Paffenbarger scale and reported in kilocalories of energy expenditure per day (kcal/d).

Short Performance Physical Battery: Score range 0-12; lower scores indicating decreased functional capability

Clinical Frailty Scale: Score range 1-9; higher scores indicating increased frailty

Table 2. Outcomes According to Albumin Group

Primary Outcome	Albumin ≤ 35g/L	Albumin 35-40 g/L	Albumin ≥ 40 g/L	p-value
Mortality at 30 days	9 (6.4%)	5 (3.8%)	0 (0%)	0.005
Mortality at 6 months	24 (17.4%)	12 (9.2%)	5 (4.0%)	<0.0001
Mortality at 12 months	32 (25.8%)	25 (19.7%)	8 (7.0%)	<0.0001

Table 3. Multivariate Analysis for Predictors of 6-Month Mortality Post-TAVR

	Odds ratio (95% CI)	p-value
Age	1.01 (0.95-1.08)	0.77
Female	1.70 (0.88-3.29)	0.11
BMI	0.93 (0.87-1.00)	0.04
GFR	0.97 (0.95-0.99)	0.003
COPD	1.33 (0.62-2.88)	0.46
Diabetes	1.36 (0.63-2.92)	0.43
Atrial fibrillation	1.99 (1.02-3.86)	0.04
Mean aortic gradient	0.99 (0.97-1.01)	0.28
MMSE	0.92 (0.84-1.00)	0.04
Fried	0.97 (0.74-1.27)	0.80
ADL	1.10 (0.88-1.38)	0.10
Femoral TAVR access	2.40 (1.17-4.95)	0.02
Albumin	0.90 (0.85-0.95)	<0.0001

Legend

ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MMSE, mini-mental status exam; TAVR, transcatheter aortic valve replacement

Table 4. Performance of Models With and Without Albumin for Mortality Prediction

	C-statistic	AIC	IDI	p-value
Predicting 30-day mortality (logistic regression model)				
With albumin	0.8835	95.5	0.1322	0.01
Without albumin	0.8348	107.0		
Predicting 6-month mortality (logistic regression model)				
With albumin	0.7995	217.8	0.0414	0.03
Without albumin	0.7738	226.7		
Predicting 12-month mortality (Cox proportional hazards model)				
With albumin	0.7117	735.0	0.0229	0.04
Without albumin	0.6835	741.8		

Legend

AIC, Akaike Information Criterion ; IDI, Integrated Discrimination Index

Figure 1. Distribution of Serum Albumin Levels

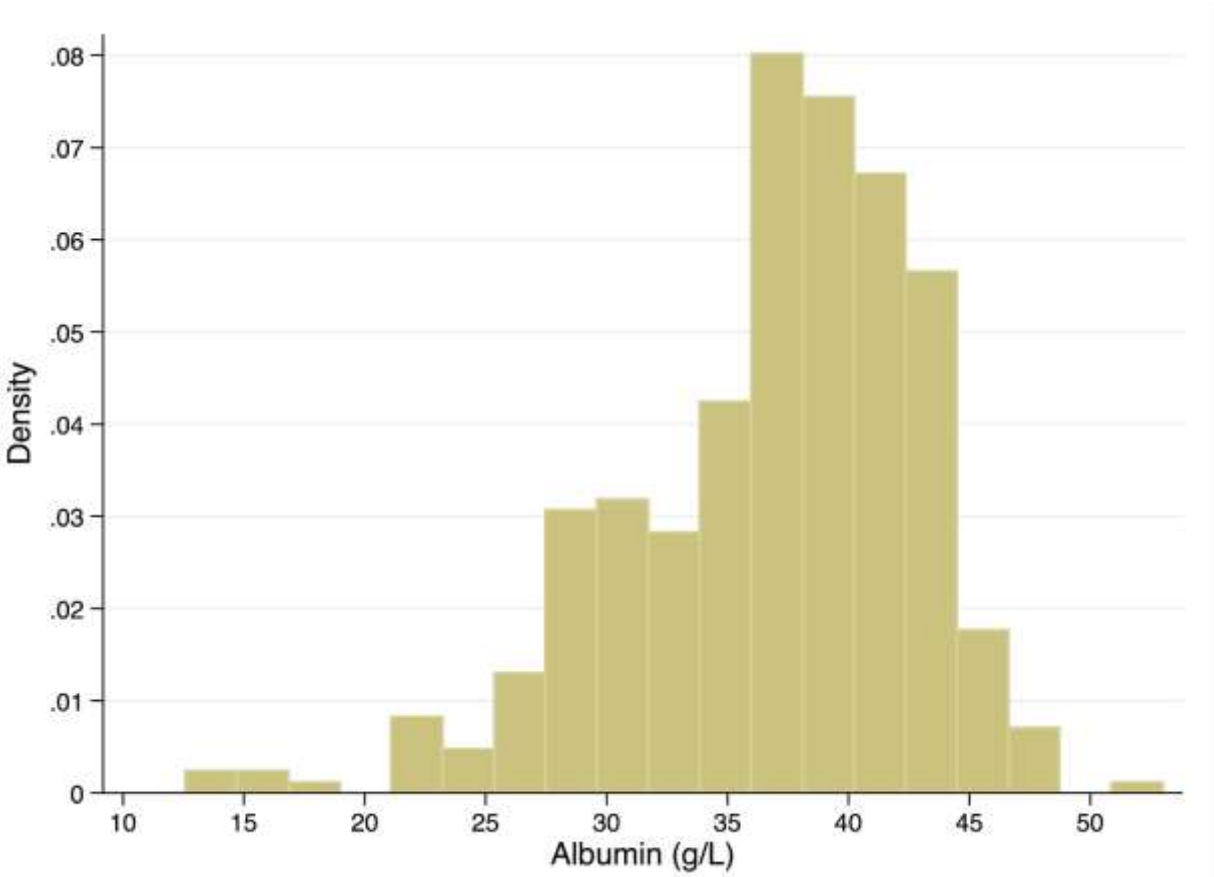


Figure 2. Sensitivity and Specificity for 6-Month Mortality by Serum Albumin Level

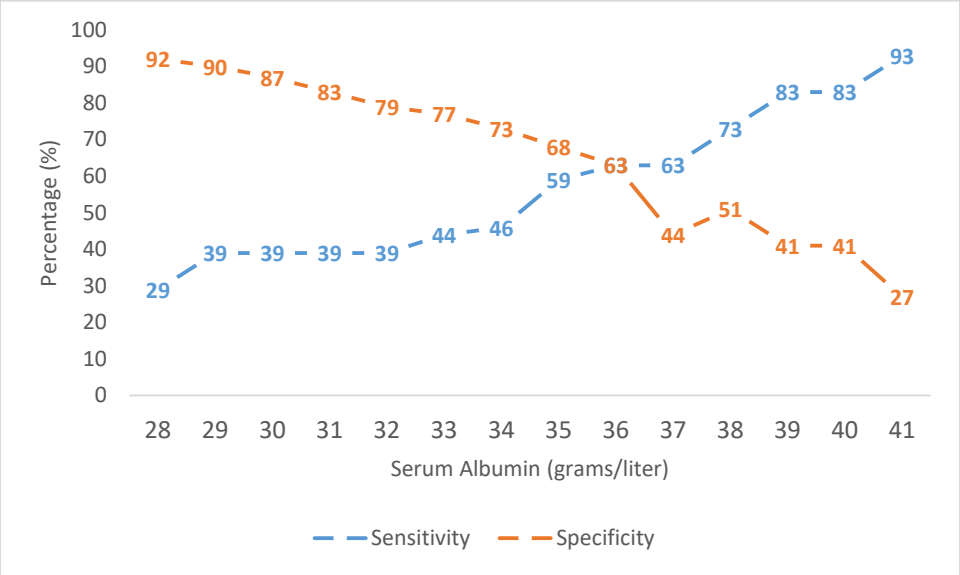
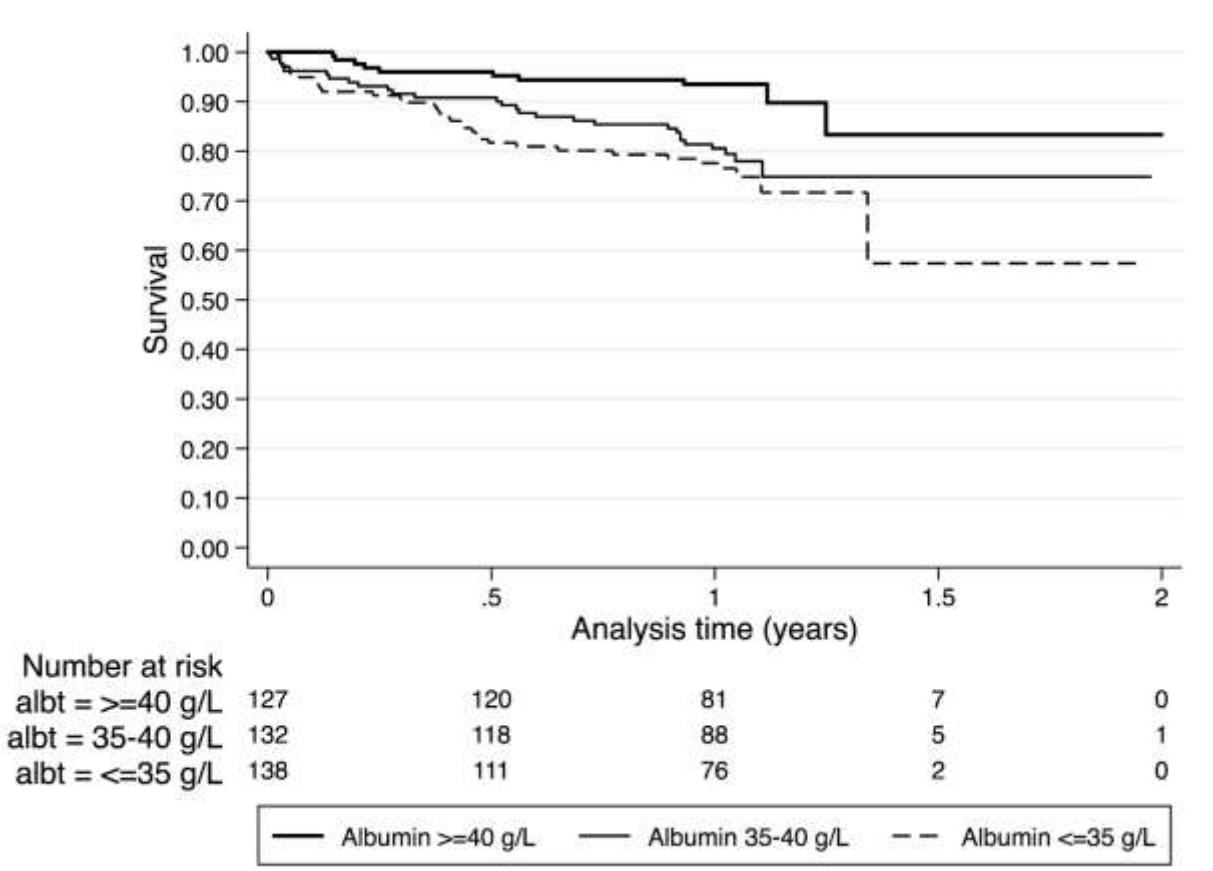


Figure 3. Survival Curves by Albumin Group



Supplemental Table 1. Multivariate Analysis for Predictors of 30-day Mortality Post-TAVR

	Odds ratio (95% CI)	p-value
Age	1.09 (0.98-1.21)	0.12
Female	1.60 (0.58-4.43)	0.36
BMI	0.95 (0.85-1.06)	0.33
GFR	0.98 (0.95-1.01)	0.13
COPD	1.32 (2.50-4.38)	0.65
Diabetes	0.67 (0.17-2.71)	0.58
Atrial fibrillation	1.30 (0.47-3.63)	0.61
Mean aortic gradient	0.99 (0.95-1.02)	0.48
MMSE	1.01 (0.88-1.16)	0.92
Fried	0.93 (0.61-1.43)	0.75
ADL	0.97 (0.97-1.80)	0.08
Non-femoral TAVR access	3.60 (1.16-11.21)	0.03
Albumin	0.88 (0.81-0.96)	0.004

Legend

ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MMSE, mini-mental status exam; TAVR, transcatheter aortic valve replacement

Supplemental Table 2. Multivariate Analysis for Predictors of 12-month Mortality Post-TAVR

	Hazard Ratio (95% CI)	p-value
Age	1.02 (0.98-1.07)	0.31
Female	1.16 (0.75-1.80)	0.51
BMI	0.98 (0.93-1.02)	0.27
GFR	0.98 (0.97-0.99)	0.001
COPD	1.18 (0.70-2.00)	0.53
Diabetes	1.28 (0.77-2.13)	0.34
Atrial fibrillation	1.79 (1.16-2.76)	0.01
Mean aortic gradient	0.98 (0.97-1.00)	0.04
MMSE	0.94 (0.89-0.99)	0.03
Fried	1.03 (0.86-1.23)	0.76
ADL	1.12 (0.96-1.29)	0.14
Non-femoral TAVR access	1.72 (1.05-2.81)	0.03
Albumin	0.94 (0.90-0.97)	0.001

Legend

ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MMSE, mini-mental status exam; TAVR, transcatheter aortic valve replacement

Supplemental Table 3. Multivariate Analysis for Predictors of 30-day Mortality Post-TAVR

	Odds ratio (95% CI)	p-value
Age	1.07 (0.92-1.24)	0.39
Female	0.85 (0.83-3.56)	0.83
BMI	0.84 (0.69-1.04)	0.11
GFR	0.98 (0.94-1.03)	0.44
COPD	0.69 (0.13-3.77)	0.67
Diabetes	0.90 (0.13-6.19)	0.92
Atrial fibrillation	0.94 (0.21-4.15)	0.94
Mean aortic gradient	0.98 (0.93-1.04)	0.51
MMSE	0.92 (0.75-1.12)	0.40
Fried	0.84 (0.46-1.54)	0.57
ADL	1.32 (0.83-2.11)	0.24
Femoral TAVR access	9.92 (1.72-57.08)	0.01
Albumin	0.84 (0.76-0.92)	<0.0001

Legend

ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MMSE, mini-mental status exam; TAVR, transcatheter aortic valve replacement

Supplemental Table 4. Multivariate Analysis for Predictors of 6-Month Mortality Post-TAVR

	Odds ratio (95% CI)	p-value
Age	0.98 (0.91-1.06)	0.60
Female	1.40 (0.63-3.12)	0.41
BMI	0.85 (0.77-0.94)	0.001
GFR	0.97 (0.95-0.99)	0.01
COPD	1.40 (0.56-3.49)	0.47
Diabetes	1.44 (0.55-3.77)	0.45
Atrial fibrillation	1.73 (0.77-3.87)	0.19
Mean aortic gradient	0.99 (0.96-1.01)	0.30
MMSE	0.92 (0.83-1.03)	0.14
Fried	0.94 (0.68-1.30)	0.71
ADL	1.16 (0.88-1.53)	0.29
Femoral TAVR access	2.61 (1.05-6.47)	0.04
Albumin	0.91 (0.85-0.96)	0.001

Legend

ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MMSE, mini-mental status exam; TAVR, transcatheter aortic valve replacement

Supplemental Table 5. Multivariate Analysis for Predictors of 12-Month Mortality Post-TAVR

	Odds ratio (95% CI)	p-value
Age	1.07 (0.92-1.24)	0.39
Female	0.85 (0.83-3.56)	0.83
BMI	0.84 (0.69-1.04)	0.11
GFR	0.98 (0.94-1.03)	0.44
COPD	0.69 (0.13-3.77)	0.67
Diabetes	0.90 (0.13-6.19)	0.92
Atrial fibrillation	0.94 (0.21-4.15)	0.94
Mean aortic gradient	0.98 (0.93-1.04)	0.51
MMSE	0.92 (0.75-1.12)	0.40
Fried	0.84 (0.46-1.54)	0.57
ADL	1.32 (0.83-2.11)	0.24
Femoral TAVR access	9.92 (1.72-57.08)	0.01
Albumin	0.84 (0.76-0.92)	<0.0001

Legend

ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MMSE, mini-mental status exam; TAVR, transcatheter aortic valve replacement

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Chapter 5: Actual Postoperative Nutrition Following Cardiac Surgery in Older Adults

Our study demonstrated that preprocedural serum albumin level was a strong predictor of mortality at 30 days, 6 months, and 12 months post-TAVR. We also found that serum albumin was an incremental predictor of mortality to frailty measures. We delineated an upper limit of 30 grams per litre as a highly specific cutoff for an increased mortality risk. Lower albumin levels were also associated with preprocedural weight loss, anemia, inactivity, disability, and frailty.

There are a number of important implications to our findings. Our results suggests that serum albumin is a biomarker that can identify patients in the preprocedural period who are at increased risk for comorbid illness and disability, as well as for poor postprocedural outcomes, beyond traditional preoperative risk determination. Serum albumin is easy to obtain, inexpensive, and understandable for most clinicians. Low serum albumin levels are also a potentially modifiable marker.

Both the MNA-SF screening tool and preprocedural serum albumin levels could serve as actionable triggers for more aggressive perioperative nutrition in the identified patient. In the preoperative period a comprehensive nutritional, physical, and psychological support aimed at improving malnutrition and comorbid disease could improve both the underlying frailty and the nutritional status, and result in increased serum albumin levels. In the intraoperative period, there may be a role for amino acid infusions to maintain the serum levels of amino acids in order to diminish catabolism and reduce the inflammatory response. In the postoperative period, extensive catabolism continues due to ongoing inflammation and prolonged bedrest. Higher levels of protein intake in the postoperative period may reduce this catabolic state and there is evidence in surgical population that early nutrition interventions decreases hospital resource use.[89-91] However, a number of barriers exist to adequate nutritional intake in the immediate postoperative period, such as mealtime interruptions, missed meals, and decreased appetite.

Minimal data exists on the actual intake of protein in older adults in the postoperative cardiac surgery period and whether older adults meet their recommended protein intake requirements after cardiac surgery. Older adults not consuming adequate amounts of protein to meet their needs may be a potential target for dietary interventions to improve protein intake. Thus, we designed and implemented a pilot observational study to evaluate actual protein intake in older adults in the postoperative cardiac surgery period. Our objectives were to quantify

postoperative protein intake in older adults after cardiac surgery and to identify predictors of low protein intake in older adults after cardiac surgery. The following manuscript presents the research protocol and results for our pilot study of nutrition in the postoperative cardiac surgery period in older adults.

Actual Postoperative Nutrition Following Cardiac Surgery in Older Adults

Goldfarb M,[a,b] Marcano Y,[c] Schafer D,[c] Afilalo J[a,b,d]

[a] Division of Experimental Medicine, Faculty of Medicine, McGill University, Montreal, QC;
[b] Division of Cardiology, Jewish General Hospital, Montreal, QC;
[c] Division of Clinical Nutrition, Jewish General Hospital, Montreal, QC;
[d] Centre for Clinical Epidemiology, Lady Davis Institute, Montreal, QC.

Abstract

Background

Older adults undergoing major surgery have increased protein requirements in the postoperative period, but there are limited data describing actual protein intake in the perioperative cardiac surgical period.

Methods

We will perform a prospective, observational nutrition substudy of the Frailty-AVR multi-centre study at a single academic tertiary care centre. We will enroll 110 older adults prior to undergoing cardiac surgery who will undergo nutritional screening by a nutritionist during three phases of care: preoperatively, during the early postoperative period, and postdischarge. Nutritional screening will be done with a food frequency questionnaire preoperatively and postdischarge and with a nutritionist-recorded food log over 3 days during the early postoperative period. The primary outcome measure will be the mean protein intake per kilogram of body weight per day (g/kg/d) during the three phases of care compared to the recommended daily allowance (1.2 g/kg/d for the preoperative and post-discharge periods and 2.0 g/kg/d for the early postoperative period).

Results

There were 23 patients enrolled in the study (female, n=8 [34.8%]; mean age 72.0 $\pm$ 7.8 years old). In the preoperative, early postoperative, and postdischarge periods, respectively, the mean protein intake was 1.3 ± 0.5 g/kg/d with a mean protein excess of 0.2 g/kg/d, 0.8 ± 0.3 g/kg/d with a mean protein deficit of 1.2 g/kg/d, and 1.4 ± 0.6 g/kg/d with a mean protein excess of 0.2 g/kg/d ($P<0.0001$ for early postdischarge compared to each of the other phases). No patients in the early discharge period met the recommended targets for protein intake compared

to 65.5% (n=13/23) preoperatively and 46.7% (n=7/15) postdischarge. The most frequent cited barriers to food intake in the early postoperative period included low appetite (95.7%, n=22) and dislike of the food served (82.6%, n=19).

Conclusion

There was a considerable protein deficit in the early postoperative period. Strategies to improve protein consumption in older adults following cardiac surgery should be considered as a therapeutic target.

Keywords: Nutrition, Protein, Cardiac Surgery, postoperative

Background and Rationale

Older adults require a higher amount of protein intake (1.5-2g/kg/d) than younger people (0.8 g/kg/d)[1, 2] due to a decreased ability to synthesize protein, yet only a quarter of older adults meet this amount with dietary intake.[3] In addition, during period of severe stress, such as cardiac surgery, metabolic demands and muscle breakdown are accelerated due to surgical stress, bedrest and poor oral intake resulting in substantial lean tissue loss.[4] A mean weight loss of 5% has been reported in older patients undergoing coronary artery bypass grafting (CABG) at 6 weeks postoperatively and those who lost more weight were more likely to be readmitted.[5]

Nutritional society guidelines vary as to the amount of protein required in the critically ill patient. The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends a protein intake of 2.0 grams per kilogram of body weight per day (g/kg/d)[6] whereas the European Society for Parenteral and Enteral Nutrition (ESPEN) recommends 1.5g/kg/d in the critically ill patient.[7] A recent systematic review of protein requirement in the critically ill suggests that based on the evidence this amount may be too conservative and a daily protein intake of 2.0-2.5 g/kg/d is safe and may be a more appropriate target.[8] These guidelines recommend aggressive postoperative nutrition, including early tube feeding when necessary in order to achieve postoperative caloric and protein goals.

There are limited data describing actual protein and caloric intake in the postoperative cardiac surgery population. Practice patterns of nutritional support following cardiac surgery also likely vary considerably between centres. In addition, little is known about the impact of muscle mass loss on functional outcomes following cardiac surgery. We hypothesize that frail older adults do not consume an adequate amount of calories and protein following cardiac surgery. If protein intake is indeed insufficient, improving protein consumption in older adults following cardiac surgery could be a practical and achievable therapeutic target.

Methodology

Trial Design

The Frailty-AVR study is a multi-centre, international prospective cohort study assessing the role of frailty assessment prior to surgical and transcatheter aortic valve replacement. This nutrition substudy will enroll 110 older adults prior to undergoing cardiac surgery at the Jewish General Hospital, an academic tertiary care centre in Montreal, Canada. Inclusion criteria are: (1)

age ≥70 years, (2) undergoing cardiac surgery via median sternotomy, (3) providing informed consent. Exclusion criteria are: (1) not English or French speaking, (2) not able to write, (3) moderate or severe cognitive impairment, (4) or significant dysphagia or GI condition restricting food intake, (5) persistent critically ill postoperative status, (6) pacemaker/ICD (contraindication to bioimpedance scale).

A member of the research team will present the study to the patient and obtain consent before surgery. We will obtain food intake data during 3 phases of care: preoperatively, during the early postoperative period, and postdischarge. Prior to the operation, demographics, baseline nutritional status, strength, physical activities, and mood will be collected and the nutritionist will administer a food frequency questionnaire (Appendix A). Starting on postoperative day #2 (or as soon as in step-down unit and receiving oral and/or enteral feeding), a nutritionist will record daily food intake in a meal log and continue for a total of 3 days. One to four months postdischarge, the nutritionist will again administer a food frequency questionnaire by telephone. A nutritionist will analyze the calorie and protein content of foods ingested, and calculate mean daily calorie and protein intake. Medical charts will be reviewed to extract comorbidities and postoperative outcomes.

Outcome Measures

The primary outcome measure is the mean protein intake (g/kg/d) preoperatively, during the early postoperative period, and postdischarge. The mean protein intake will be compared to the recommended daily allowance (RDA) to calculate the mean protein deficit or excess. The RDA of protein prior to hospitalization and postdischarge is 1.2 g/kg/d. The RDA of protein during the early postoperative period is 2.0 g/kg/d.[6] The secondary measure is percentage of patients achieving recommended protein intake preoperatively, during the early postoperative period, and postdischarge.

Data Analysis

Descriptive statistics about the mean daily protein intake will be presented for the 3 phases of care and also expressed as a proportion of patients meeting the recommended daily protein intake. Continuous data are presented as mean ± standard deviation and differences between groups were tested with the student's t test (when 2 groups) or ANOVA one-way test (when 3 or more groups). Multivariable linear regression models will be used to identify predictors of postoperative protein intake (expressed as g/day). Statistical significance was

assumed when the p-value was rejected at $p \leq 0.05$. Data were analyzed using SPSS 22.0 software (Armonk, New York: IBM Corp). The study was approved by the Research Ethics office of the participating institution.

Results

There were 23 patients included in the initial analysis (Table 1). Eight patients did not have the 1-4 month postoperative nutritional assessment. Eight patients were female (34.8%) and the mean age was 72.0 $\pm$ 7.8 years old.

Preoperatively, the mean protein intake was 1.3 ± 0.5 g/kg/d with a mean protein excess of 0.2 g/kg/d (Figure 1). In the early postoperative period, the mean protein intake was 0.8 ± 0.3 g/kg/d with a mean protein deficit of 1.2 g/kg/d. During the postdischarge period, the mean protein intake was 1.4 ± 0.6 g/kg/d with a mean protein excess of 0.2 g/kg/d for the 15 patients with data available. The between group difference was significant between the preoperative and early postoperative periods ($P<0.0001$), between the early postoperative period and the postdischarge period ($P<0.001$), but not between the preoperative and the postdischarge period ($P=0.67$). There were no differences in mean protein intake per kilogram of body weight per day in women compared to men in the preoperative, early postoperative, and postdischarge periods (all $P>0.05$).

The number and percentage of patients meeting recommended targets for protein intake were 13 (65.5%), 0 (0.0%), and 7 (46.7%) in the preoperative, early postoperative, and postdischarge periods, respectively. Only one patient in the early postoperative period consumed more protein than 1.2 g/kg/d.

Mean calorie intake (in kcal/d) was 2553 ± 851, 1211 ± 447, and 2395 ± 645 for the preoperative, early postoperative, and postdischarge periods, respectively ($P<0.0001$ for between group difference). The mean percentage of calories from protein of the total caloric intake was 14.6%, 17.0%, and 11.2% for the preoperative, early postoperative, and postdischarge periods, respectively.

For patients with data available for all 3 phases of care (n=15), patients who did not meet the preoperative protein RDA (n=7, mean protein deficit 0.3 g/kg/d) compared to patients who met or exceeded the preoperative protein RDA (n=8; preoperative mean protein excess 0.5

g/kg/d, P<0.002) had no difference in the early postoperative protein deficit (1.5 g/kg/d vs. 1.2 g/kg/d, P =0.1) or the postdischarge protein excess (0.1 g/kg/d vs. 0.3 g/kg/d, P=0.42).

The most frequent cited postoperative barriers to food intake included low appetite (95.7%, n=22) and dislike of the food served (82.6%, n=19; Figure 2).

Discussion

Due to the lack of data describing actual protein and caloric intake in the perioperative cardiac surgery period and the importance of understanding whether older adults are meeting protein requirements following cardiac surgery, we performed a prospective observational pilot study to assess the actual protein intake post-cardiac surgery at a single academic tertiary care hospital centre. We found that there was a considerable mean protein deficit in early postoperative period, but that there was a small mean protein excess in the preoperative and postdischarge period. The early postoperative period mean protein deficit was mediated by both insufficient protein intake and increased protein requirements. No patients met the recommended protein intake in the early postoperative period. Adequate preoperative protein intake did not identify patients who were more likely to have lower protein intake in the early postoperative and postdischarge periods. Mean caloric intake was also lower in the early postoperative period. A number of barriers to food intake in the early postoperative period were also identified.

The most important finding of our initial analysis is that there was insufficient protein intake during the early postoperative period. Inadequate protein intake in the early postoperative period is associated with worse outcomes. A study in surgical intensive care unit patients found that patients with a postoperative protein deficit were 29% as likely to be discharged home compared to patients without a postoperative protein deficit.[9] A large multi-centre international nutrition database reported that consuming close to the recommended protein intake was associated with a reduction in 60-day mortality and more ventilator free days.[10] A prospective interventional study in the surgical intensive care unit reported that patients who received aggressive protein supplementation had a reduced protein deficit during their critical unit stay and a 66% reduced risk of late infections compared to a historical cohort.[11] A retrospective study of 1007 postsurgical patients at 8 hospitals found that sufficient protein intake, which was defined as >60% of the recommended protein intake, was associated with decreased length of stay and hospital costs compared to patients without sufficient protein intake.[12] The Nutrition

Care in Canadian Hospitals (NCCH) study reported that surgical patients who ate less than half of the provided food had an increased length of stay and that poor food intake during hospital stay can lead to iatrogenic malnutrition, even in previously well-nourished patients.[13]

As a result of the emerging evidence for the importance of protein in the postsurgical diet, professional nutritional societies, such as ESPEN, strongly promote the need to start oral feeds as soon as feasible postoperatively.[14] In addition, surgical quality of care programs, such as the Enhanced Recovery after Surgery (ERAS) program, include nutritional supplementation in the early postoperative period as a fundamental component of the plan to promote functional recovery in surgical populations. The ERAS program is designed to reduce postoperative catabolism and support anabolism and allow for faster and better recovery and has been shown to be beneficial and safe in older adults.[15, 16] ERAS guidelines recommend the use of oral nutritional supplements in the pre- and postoperative phases of care.[17]

When comparing patients who met preoperative recommended protein intake with those who did not, there was no significant difference in early postoperative and postdischarge protein intake. There was trend toward a lower protein deficit in the group of patients with adequate preoperative protein intake. However, with a sample size of only 15 patients it is highly possible that that these findings were underpowered to detect a real difference between the two groups. Inadequate preoperative protein presents a potential modifiable target for nutritional supplementation in the preoperative and postoperative periods. Additional data are needed to see if patients who consume inadequate protein intake preoperatively are at risk for inadequate protein intake postoperatively.

Based on the available metabolic, physiologic, and clinical evidence, there is a consensus amongst nutritional professional societies that there are increased protein intake requirements in the postoperative and critical illness phase of case, although these groups differ on the exact protein requirements.[6, 7] Older adults may also require more protein per kilogram of body weight than their younger people.[18] Even if we had chosen a lower protein intake target for the early postoperative period, such as 1.2 or 1.5 g/kg/d, only one patient in our cohort would have met these targets and there would still have been a considerable mean overall protein deficit.

While nutritional supplementation is likely a key treatment modality to improve protein consumption, there is a need to concurrently address barriers to food intake. In our cohort, low appetite was present in nearly all patients (22 out of 23 patients). Low appetite is probably the

result of the complex metabolic, hormonal, and physiological changes experienced in the post-cardiac surgical state. However, there is likely a contribution from a number of the other barriers reported by patients, such as a dislike of the food served (82.6% of patients), pain, and nausea. Patients are given food options prior to meals at our institution, but the food offered may differ considerably from the patient's typical diet at home and there may be certain cultural food preferences that are not being addressed with hospital diets. Systems of care can also be implemented to reduce mealtime interruptions and to ensure that patients do not miss meals. Food brought from home may be considered as a means to improve protein intake.

There are several limitations to our study that should be noted. This was a single-centre study and our results may not be generalizable to other centres. This pilot study had a small sample size and large scale studies are needed to assess the validity of our findings. In addition, while the early postoperative nutritional evaluation was a detailed in-hospital assessment of actual food intake, the food frequency questionnaire administered by the nutritionist on admission and postdischarge may be subject to recall bias by the patient. It is possible that patients systematically overestimated food consumption during these two periods, although the nutritionist attempted to ensure that stated food intake reflected actual food consumption.

Conclusion: In the early postoperative period, patients had a considerable protein deficit. Larger scale studies are needed to confirm this finding. Strategies to improve protein consumption in older adults following cardiac surgery should be considered as a therapeutic target.

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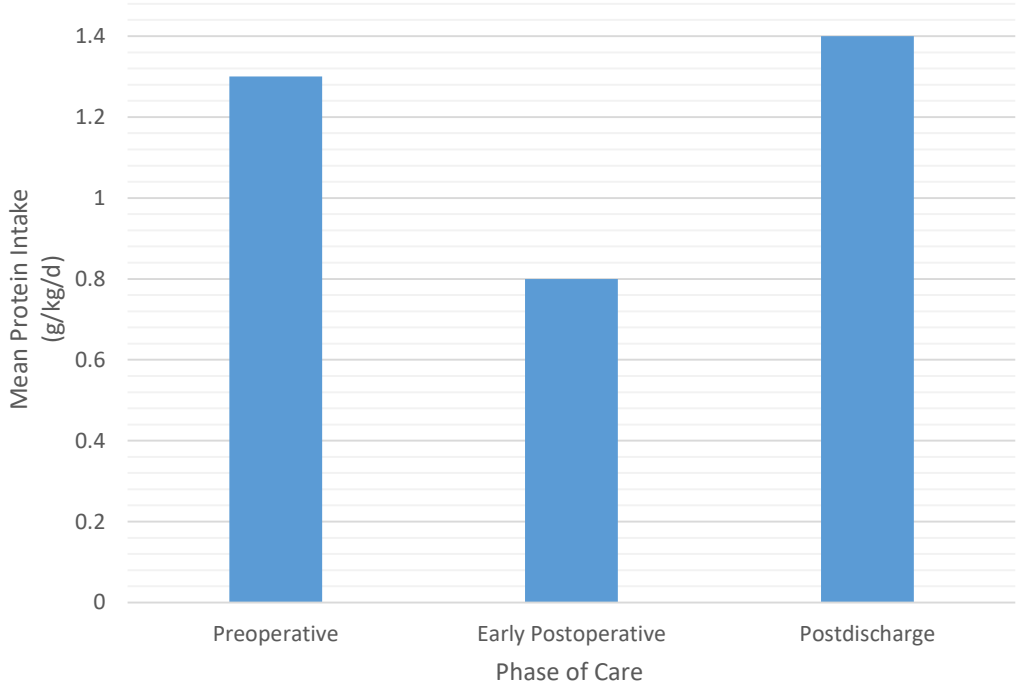
Table 1. Calorie and Protein Intake in the Perioperative Cardiac Surgery Period

			Preoperative				Early postoperative				Postdischarge			
Case	Age/Sex	Weight	Calories / day	Total protein intake	Protein/ weight/ day	Protein deficit	Calories / day	Total protein intake	Protein/ weight/ day	Protein deficit	Calories / day	Total protein intake	Protein/ weight/ day	Protein deficit
			kcal/d	g/d	g/kg/d	g/kg/d	kcal/d	g/d	g/kg/d	g/kg/d	kcal/d	g/d	g/kg/d	g/kg/d
1	67M	61.3	2165	63.5	1.0	-0.2	1533.0	58.3	1.0	-1.1	N/A	N/A	N/A	N/A
2	77M	81.7	2796	83.7	1.1	-0.1	1263.7	49.5	0.6	-1.4	2670.0	126.0	1.6	0.4
3	69M	69.8	2231	78.0	1.1	-0.1	1683.7	76.3	1.1	-0.9	2762.0	141.0	2.0	0.8
4	77M	78.1	2977	115.0	1.8	0.6	865.5	31.6	0.5	-1.5	1562.0	67.0	1.0	-0.2
5	77M	92.6	3420	128.0	1.7	0.5	865.7	27.9	0.4	-1.6	3010.0	75.0	1.0	-0.2
6	77M	118.0	2843	125.2	1.5	0.3	1483.7	71.5	0.8	-1.2	N/A	N/A	N/A	N/A
7	54M	85.8	2406	50.0	0.6	-0.6	616.0	24.0	0.3	-1.7	1480.0	89.0	1.0	-0.2
8	85M	126.0	1474	50.4	0.6	-0.6	908.5	37.3	0.4	-1.6	1734.0	73.0	0.9	-0.4
9	59M	54.3	2208	82.3	1.5	0.3	1317.0	70.5	1.3	-0.7	3041.0	174.8	3.2	2.0
10	61M	75.0	2473	95.0	1.4	0.2	1743.0	70.3	1.1	-0.9	2705.0	119.2	1.8	0.6
11	66M	79.2	2973	112.0	1.4	0.2	1869.0	78.0	1.0	-1.0	2936.0	112.7	1.4	0.2
12	77M	101.8	3191	99.9	1.2	0.0	1460.3	51.6	0.6	-1.4	2720.0	95.1	1.1	-0.1
13	84M	73.0	3238	105.0	1.4	0.2	1442.7	63.8	0.9	-1.1	N/A	N/A	N/A	N/A
14	71M	101.0	4960	243.8	2.8	1.6	1352.3	78.9	0.9	-1.1	3595.0	152.1	1.7	0.5
15	71M	98.5	3692	140.3	1.8	0.6	1450.3	71.6	0.9	-1.1	N/A	N/A	N/A	N/A
16	84F	69.3	1461	61.4	1.0	-0.2	883.3	32.2	0.5	-1.5	N/A	N/A	N/A	N/A
17	74F	64.7	1615	58.9	0.9	-0.3	878.0	37.5	0.6	-1.42	1718.0	70.0	1.1	-0.1
18	72F	62.6	1915	62.2	1.0	-0.2	162.3	7.9	0.1	-1.87	2493.0	68.6	1.1	-0.1
19	67F	50.1	2451	83.2	1.7	0.5	901.0	33.9	0.7	-1.32	1884.0	49.7	1.0	-0.2
20	64F	63.6	1384	65.5	1.1	-0.1	865.3	35.3	0.6	-1.41	1617.0	70.4	1.2	0.0
21	75F	38.4	1193	42.2	0.8	-0.4	1654	74.9	1.5	-0.55	N/A	N/A	N/A	N/A
22	74F	84.5	2826	104.6	1.5	0.3	1976	77.2	1.1	-0.91	N/A	N/A	N/A	N/A
23	75F	56.6	2842	97.0	1.7	0.5	687.3	26.9	0.5	-1.53	N/A	N/A	N/A	N/A

Legend. Abbreviations. d, day; F, female; g, gram of protein; kg, kilogram of body weight; M, male; N/A, not available

Figure 1. Mean Protein Intake during Different Phases of Care



Legend

Abbreviations: d, day; g, grams of protein; kg, kilogram of body weight

Figure 2. Barriers to Food Intake in the Early Postoperative Period

Food Barriers (n=23)		
	N	**%**
Low appetite	22	95.7
Nauseas	5	21.7
Tiredness	4	17.4
Pain	3	13.0
Breathing difficulties	3	13.0
Dislikes	19	82.6
Interrupted by staff	3	13.0
Other*	10	43.5

*Discomfort with lines, afraid of constipation, missing food on tray, change in taste, late meal due to transfer, afraid of high blood sugar, food variety, food temperature, received food from home, afraid of diarrhea, hard to chew

Chapter 6: Transition from a Prospective Pilot Observational Study to a Randomized Controlled Trial

The data from the "Actual Postoperative Nutrition Following Cardiac Surgery in Older Adults" pilot observational study suggests that protein intake in the preoperative and postdischarge periods is adequate, but that protein intake in the early postoperative period is insufficient to meet patient's needs. The marked protein deficit in the early postoperative period is due to both the decreased intake, as well as the considerable increase in protein requirements during this phase of care. In addition, the majority of the patients reported low appetite and a dislike for the food choices available. Other noted barriers included nausea, fatigue, discomfort, changes in taste, and missing food. Addressing these barriers is necessary when trying to improve protein intake in the early postoperative period.

Given the poor protein intake and increased protein requirements in older adults in the postoperative period, the responsiveness to higher levels of protein intake in older adults, and the association of inadequate nutrition with poor outcomes in older adults following surgery, we designed a randomized controlled trial to test the hypothesis whether protein supplementation can prevent postoperative loss of muscle mass and strength after cardiac surgery in frail older adults with sarcopenia.

The study was designed to achieve three specific aims: (1) to determine the effect of a leucine-enriched whey protein beverage on muscle mass and strength, as compared to a placebo beverage, given for 8 weeks after cardiac surgery; (2) to compare the daily amount of caloric and protein intake from food sources in older adults randomized to the protein or placebo beverage after cardiac surgery; and (3) to identify predictors of muscle mass and strength gain in older adults randomized to the protein beverage after cardiac surgery.

The trial will enrol patients aged ≥70 years that meet criteria for sarcopenia or pre-sarcopenia at the time of their pre-operative assessment. On postoperative day 2 patients will be randomized to ingest a leucine-enriched whey protein beverage twice daily for 8 weeks following cardiac surgery or a matching placebo beverage. The primary outcome will be change in muscle performance measured by the short physical performance battery score 8 weeks post-surgery. The study results will inform whether postoperative whey protein supplementation improves muscle mass, strength, and physical performance in older adults post-cardiac surgery.

Chapter 7: Protocol for a Randomized Controlled Trial of Nutritional Supplementation

A "Study Protocol for a Randomized Trial of Protein Nutritional Supplementation to Prevent Loss of Muscle Mass and Strength in Older Adults after Cardiac Surgery" is presented here.

Funding: This randomized controlled trial was awarded a $25,000 Lady Davis Institute Clinical Research Pilot Project (Montreal, Canada) grant.

Principal Investigator: Jonathan Afilalo, MD, MSc, Divisions of Cardiology and Clinical Epidemiology

MSc Candidate: Michael Goldfarb, MD, Divisions of Cardiology and Experimental Medicine

Co-Investigators:
Paule Bernier, RD, MSc, Division of Clinical Nutrition
Louis-Francois Côté, RD, Division of Clinical Nutrition
Yves Langlois, MD, Division of Cardiac Surgery
Felix Ma, MD, Division of Cardiac Surgery
Shannon MacNamara, RN, Division of Cardiac Surgery
John Marsala, RN, MSc, Division of Cardiac Surgery
Jean-Francois Morin, MD, Division of Cardiac Surgery
Emmanuel Moss, MD, Division of Cardiac Surgery
Lawrence G. Rudski, MD, Division of Cardiology (JGH Department Head)
Donna Schafer, RD, MSc, Division of Clinical Nutrition

Study Protocol for a Randomized Trial of Protein Nutritional Supplementation to Prevent Loss of Muscle Mass and Strength in Older Adults after Cardiac Surgery

Goldfarb M,[a] Bernier P,[b] Côté L-F, [b] Langlois Y,[c] Ma F,[c] MacNamara S,[c] Marsala J,[c] Morin J-F,[c] Moss E,[c] Rudski L, [a] Schafer D,[b] Afilalo J.[a]

[a] Division of Cardiology, Jewish General Hospital, Montreal, Quebec, Canada

[b] Division of Clinical Nutrition, Jewish General Hospital, Montreal, Quebec, Canada

[c] Division of Cardiac Surgery, Jewish General Hospital, Montreal, Quebec, Canada

Abstract

Background

Frail older adults require more protein than their younger counterparts but only one-quarter of older adults meet their requirements with dietary intake. The decline in muscle is accelerated during periods of stress such as cardiac surgery. Whey protein supplementation has been shown to prevent this muscle loss and help preserve strength.

Methods

A total of 168 patients aged ≥70 years that meet criteria for sarcopenia or pre-sarcopenia at the time of their pre-operative assessment will be recruited. Patients will be randomized on postoperative day 2 to ingest a leucine-enriched whey protein beverage twice daily for 8 weeks following cardiac surgery or a matching placebo beverage. The amino acid composition will be optimized to stimulate muscle synthesis in older adults, and has a low-volume (200 mL) low-calorie (120 calories) profile intended to supplement rather than replace food intake. Patients and outcome assessors will be blinded. The primary outcome will be change in muscle performance measured by the short physical performance battery score 8 weeks post-surgery.

Discussion

Results of this trial will help evaluate whether, compared with a placebo beverage, a whey protein beverage enriched with leucine will improve muscle mass, strength, and physical performance in older adults post-cardiac surgery.

Background & Rationale

Sarcopenia is defined as age-related decline in muscle mass and strength – a core domain of the geriatric syndrome known as *frailty*. The pathophysiology of sarcopenia is multi-factorial, including catabolic stimuli and anabolic resistance. To overcome this, frail elders require more protein (1.2 – 2 g/kg/d) than their younger counterparts (0.8 g/kg/d)[1, 2] but only 28% meet these targets with dietary intake.[3] The decline in muscle is accelerated during periods of stress such as cardiac surgery, due to the vicious cycle of (1) upregulated catabolic stimuli, (2) low oral dietary intake, and (3) bedrest. Under experimental conditions, 10 days of bedrest results in a substantial 2 kg loss of muscle mass.[4] Whey protein supplementation has been shown to prevent this muscle loss and help preserve strength.[4] Whey protein provides essential amino acids such as leucine and is superior to other protein sources for stimulating muscle protein synthesis in older adults.[5] We hypothesize that, compared with a placebo beverage, a whey protein beverage enriched with leucine will improve muscle mass, strength, and physical performance in older adults post-cardiac surgery. If our hypothesis is correct, the improvements in physical performance and frailty have been shown to translate into reduced postoperative morbidity, repeat hospital visits, incident disability, and loss of autonomy in this population of vulnerable older adults.[11]

Methodology

Trial Design

The CONSORT flow diagram for this trial is shown in Figure 1. This interdisciplinary prospective double-blind randomized clinical trial will be conducted at two tertiary care academic centres in Montreal, Quebec (Jewish General Hospital and McGill University Health Centre).

Selection Criteria

Patients aged ≥70 years undergoing coronary artery bypass graft surgery, valve replacement or repair surgery, transcatheter valve implantation, or any combination of these procedures will be screened. Those that provide informed consent and meet criteria for sarcopenia or pre-sarcopenia (Figure 2) will be included. Exclusion criteria are: allergy to any ingredient in the protein or placebo beverage, severe renal insufficiency with glomerular filtration rate <30, cirrhosis, pacemaker/ICD (contraindication to bioimpedance scale), emergency surgery, unable to safely ingest liquids by oral route or tube feed, anticipated difficulty returning for follow-up, severe neuropsychiatric impairment, not English or French speaking.

Data Collection

A member of the clinical team will introduce the study to the patient, and if they accept to be approached, a research assistant will invite them to participate when they are admitted to hospital before their surgery. The research assistant will administer a questionnaire and physical performance tests aimed at measuring sarcopenia and frailty. Physical performance tests include the SPPB (5-meter gait speed, chair rise time, tandem balance), handgrip strength and isometric hip flexion and knee extension strength using a portable dynamometer. Body composition parameters include skeletal muscle mass and fat mass measured with the InBody segmental multi-frequency bioimpedance scale. Covariates of interest include frailty status, height, weight, physical activity, cognition, mood, comorbidities, and importantly, dietary intake, which will be recorded using calorie counts and patient-kept food diaries in the hospital and at home.

Intervention and Control Groups

On postoperative day 2, the allocated beverage will be given to the patient twice daily via oral intake (or tube feed). The intervention beverage is composed of 200 mL of water with 30 g of purified whey protein isolate powder enriched with leucine and non-caloric natural flavouring and sweetener (120 cal). The placebo control beverage is composed of 200 mL of water with a matching powder that contains 30 g of nonessential amino acids. Both are packaged in identical disposable plastic bottles, and are manufactured in a Good Manufacturing Practice (GMP) kosher-certified facility. The end date for consuming the study beverage will be 56 days after the start date.

Follow-Up Procedures

Patients will be asked to return for a study visit 4 and 8 weeks after surgery, at which time physical performance tests and body composition parameters will be reassessed. The research assistant will review the patient's medical chart to obtain information about postoperative complications and readmissions, and contact them by telephone at 2 weeks and 6 months to administer a 10-minute questionnaire about food intake, physical activity, and quality of life.

Outcome Measures

The primary outcome is change in SPPB score from pre-op to 8 weeks post-op. The SPPB is a responsive and clinically meaningful endpoint that is endorsed by a major task force.[6] Secondary outcomes are change in skeletal muscle mass from pre-op to 8 weeks post-op (measured by bioimpedance) and change in quality of life, physical activity level, disability, and frailty from pre-op to 8 weeks and 6 months post-op (measured by the SF-36 scale). Compliance will be monitored by bottle counts and intake logs.

Sample Size Calculation

A total of 168 patients would be required to demonstrate a pre-post improvement in SPPB score from +0 in controls to +1.5 in intervention, given a SD of 3.2 and 10% loss to follow-up. The value of +1.5 was chosen because the clinically meaningful change has been estimated to be +0.5 to +1.5.

Availability of Subjects

Within the scope of our frailty cohort study, we recruited 3 cardiac surgery patients aged ≥70 at the JGH and 5 at the MUHC per week, of which 50% are expected to meet criteria for sarcopenia or pre-sarcopenia. Accordingly, it should conservatively take 1 year to recruit the desired sample size if a two-centre design is maintained. Additional centres from the 13 centres that participated in the recently completed frailty cohort study may be added if recruitment is slower than expected.

Analytic Approach

Block randomization (block size of 6) will be stratified by type of surgery and site, and allocation of treatment will be concealed. Patients, physicians, nurses, researchers, outcome assessors, and statisticians will be blinded to the allocation. The primary analysis will be performed according to intention-to-treat with change in SPPB as a paired continuous outcome measure. Protein intake from food sources will be compared between groups using the non-parametric Wilcoxon rank sum test. Predictors of increased muscle gains in patients receiving protein supplementation will be identified by linear regression models with interaction terms for potential synergistic covariates, notably – dietary intake and frailty status.

Safety

An independent DSMB will review all adverse events. The safety profile of protein supplements has been extensively documented,[7] with the only potentially serious risk being glomerular hyperfiltration and worsening kidney function in patients with severe kidney disease – who will be excluded from this trial.[8] Minor risks include rare occurrence of increased bowel movements, nausea, thirst, bloating, cramps, reduced appetite, tiredness, and headache, which are observed with high doses of whey protein (higher than those being used in this study). Patients will be given symptom logs packaged in a study folder along with their food diaries to record the occurrence and frequency of such symptoms. This type of supplement does not have a Drug Identification Number (DIN). There are no risks associated with the bioimpedance scale with the exception of patients that are pregnant or have a permanent pacemaker or defibrillator – who will also be excluded from this trial (the reason being that bioimpedance scale currents may disrupt the functioning of pacemakers or defibrillators).

Ethics & Confidentiality

Participation in this study is voluntary, and patients may refuse or withdraw at any time. Patient ID will be coded according to a consecutive 3-digit number and 2-letter monogram. All of the information will be kept strictly confidential. The Research Ethics Committee and legal authorities will have access to the collected data without compromising confidentiality. Patients will not be identified in any publication. Study documents will be kept in secured files by the investigators until the study is concluded.

Organizational Timeline

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
IRB approval	X	X																						
Recruitment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Follow-up		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Data analysis & manuscript writing																						X	X	X
KT plan												X											X	X

Implementation Plan

The physical workspace and trained personnel needed to conduct this trial are already in place. There are research coordinators for the Frailty-AVR cohort study who will transition over to this trial, which has a similar target population and case report forms. The Clinical Epidemiology Centre at the JGH will manage data, including the set-up of a REDCap-based electronic database and randomization platform.

Knowledge Translation Plan

The results of this trial will be presented at a LDI/JGH event, a major cardiology conference, and published in a high-impact cardiology journal. An email synopsis of the trial will be shared with practitioners via membership lists of collaborating professional societies: Canadian Cardiovascular Society, American College of Cardiology (ACC), Canadian/American Geriatrics Societies, Canadian Council of Cardiovascular Nurses. Dr. Afilalo is co-director of the ACC Geriatric Cardiology Research Group, and will leverage this group's communication channels to efficiently disseminate results. Lastly, if our results are positive, the Divisions of Cardiac Surgery and Dietetics have expressed a commitment to implement this protein supplementation intervention in routine clinical practice.

Figure 1. Trial Flow

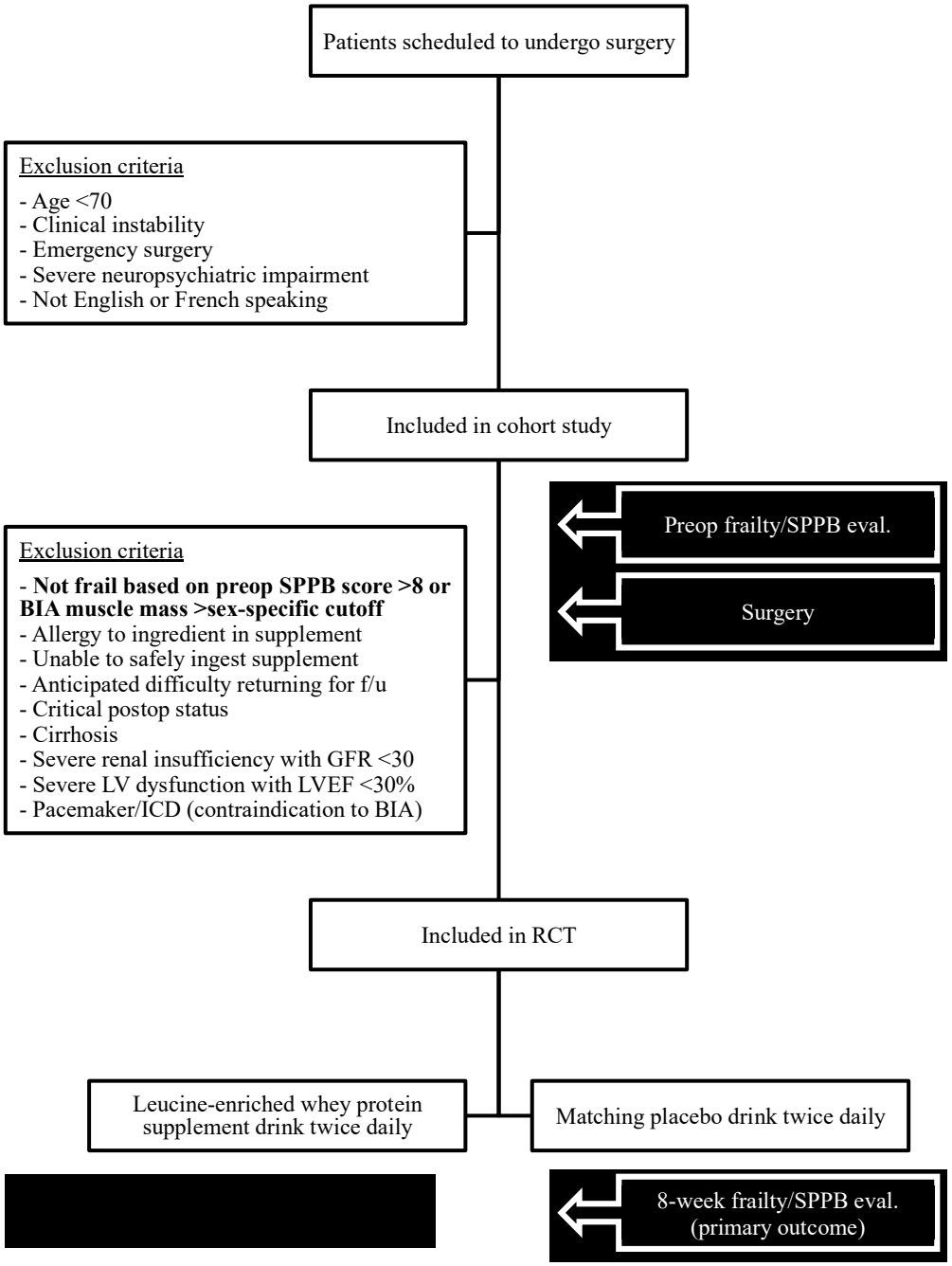
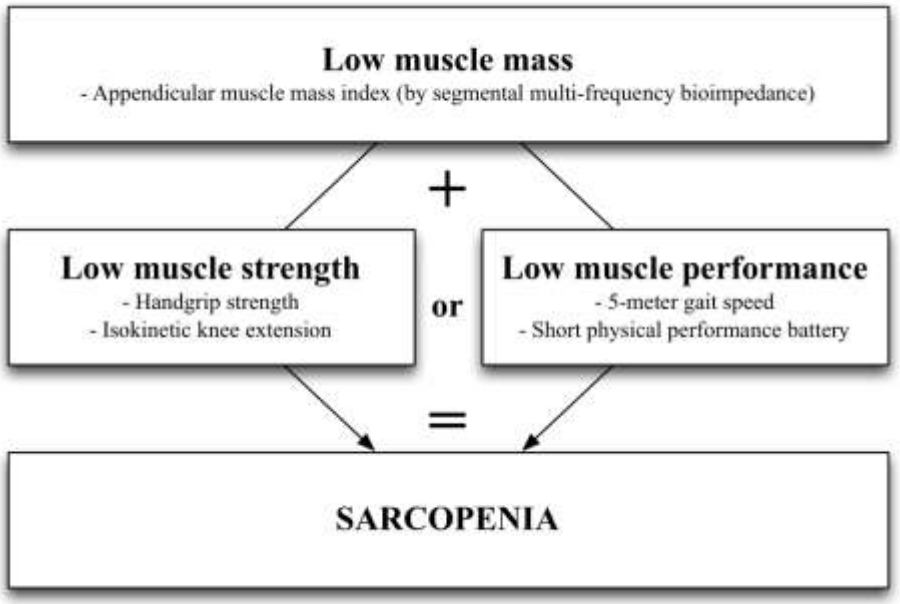


Figure 2. Definition of Sarcopenia



* In addition to the sarcopenia phenotype depicted above, pre-sarcopenia – defined as low muscle mass without low strength or performance, or low strength or performance without low muscle mass – is also an inclusion criteria for this trial

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Chapter 8: Frailty and the Costs of Cardiac Surgery

The randomized controlled trial of protein supplementation in the postoperative period was designed to evaluate whether protein supplementation with a whey protein beverage enriched with leucine improves outcomes such as muscle mass, strength, and physical performance in older adults following cardiac surgery. The trial will assess whether frailty, preoperative nutritional status, and preoperative serum albumin levels identity patients who may benefit more from protein supplementation in the postoperative period. Frail older adults, as compared to non-frail older adults, have potentially more to gain as sarcopenic muscle appears to be inordinately affected by iatrogenic stressors and bedrest.

Frailty is associated with prolonged mechanical ventilation, longer intensive care and hospital unit stays, higher rates of discharge to healthcare institutions, and higher rates of readmission; each of which are associated with increased costs healthcare costs.[8, 10, 11, 133-135] With frail older adults comprising 25-50% of patients undergoing cardiac surgery, the implications on frailty on healthcare costs are potentially considerable.

Despite the link between preoperative malnutrition and frailty and postoperative morbidity and the association between morbidity and costs, there are limited data on the direct link between frailty and costs following cardiac surgery. With an improved understanding of the costs associated with frailty in this population, stakeholders would be better suited to make informed decisions about perioperative interventions in frail older adults and overall healthcare resource utilization. In addition, implementing perioperative interventions aimed at improving nutrition and/or frailty could impact postoperative morbidity, mortality, and improve outcomes. Thus, we determined the impact of preoperative frailty status on postoperative hospitalization costs in a two-centre cohort of older adults undergoing cardiac surgery.

Chapter 9: Cost of Cardiac Surgery in Frail Compared to Non-Frail Older Adults

Our post-hoc analysis on the additional cost of frailty on the index hospitalization following cardiac surgery is presented in manuscript form.

The study was presented as an abstract at the American Heart Association's Scientific Sessions on November 15, 2016.

The manuscript was published in the Canadian Journal of Cardiology as:

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Clinical Research

Cost of Cardiac Surgery in Frail Compared With Nonfrail Older Adults

Michael Goldfarb, MD,[a,b] Melissa Bendayan, BSc,[a,b] Lawrence G. Rudski, MD,[c] Jean-Francois Morin, MD,[d] Yves Langlois, MD,[d] Felix Ma, MD,[d] Kevin Lachapelle, MD, MSc,[e] Renzo Cecere, MD,[e] Benoit DeVarennes, MD, MSc,[e] Christo I. Tchervenkov, MD,[e] James M. Brophy, MD, PhD,[f] and Jonathan Afilalo, MD, MSc[a,b,c]

[a]Division of Experimental Medicine, Faculty of Medicine, McGill University, Montreal, Quebec, Canada
[b]Centre for Clinical Epidemiology, Lady Davis Institute, McGill University, Montreal, Quebec, Canada
[c]Division of Cardiology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada
[d]Division of Cardiac Surgery, Jewish General Hospital, McGill University, Montreal, Quebec, Canada
[e]Division of Cardiac Surgery, McGill University Health Centre, McGill University, Montreal, Quebec, Canada [f]Department of Medicine, McGill University Health Centre, McGill University, Montreal, Quebec, Canada

See editorial by Yanagawa et al., pages 959e960 of this issue.

ABSTRACT

Background: Frailty is a risk factor for mortality, morbidity, and prolonged length of stay after cardiac surgery, all of which are major drivers of hospitalization costs. The incremental hospitalization costs incurred in frail patients have yet to be elucidated.

Methods: Patients aged 60 years were evaluated for frailty before coronary artery bypass grafting or heart valve surgery at 2 academic centres between 2013 and 2015 as part of the McGill Frailty Registry. Total costs were summed from the date of the index surgery to the date of hospital discharge. Mutivariable linear regression was used to determine the association between preoperative frailty status and total costs after adjusting for conventional surgical risk factors.

Results: Among 235 patients included in the analysis, the median age was 73.0 years (interquartile range [IQR], 70.0-78.0 years) and 68 (29%) were women. The median cost was $32,742 (IQR, $23,221-$49,627) in 91 frail patients compared with $23,370 (IQR, $19,977-$29,705) in 144 nonfrail patients. Seven extreme-cost cases > $100,000 were identified,

RESUME

Contexte : La fragilite est un facteur de risque de mortalite, de morbidite et de sejour prolonge après une intervention chirurgicale cardiaque, lesquels contribuent de façon importante aux coûts d'hospitalisation. Les coûts croissants d'hospitalisation des patients fragiles n'ont pas encore ete elucides.

Methodologie : Des patients de 60 ans ou plus ont subi des evaluations visant à determiner leur degre de fragilite avant un pon-tage aortocoronarien ou une intervention chirurgicale valvulaire dans deux centres d'etude entre 2013 et 2015; les resultats ont ete con-signes dans le registre de fragilite McGill (McGill Frailty Registry). Les coûts totaux ont ete calcules à partir de la date de l'intervention chirurgicale de reference jusqu'à la date de sortie de l'hôpital. Une regression lineaire à variables multiples a servi à determiner l'association entre l'etat de fragilite preoperatoire et les coûts totaux après correction tenant compte des facteurs de risque chirurgicaux conventionnels.

There are > 250,000 coronary artery bypass grafting (CABG) operations and 67,500 surgical aortic valve replacement operations performed annually in North America, with a mean cost per operation of $30,000 to > $150,000 depending on case mix, institution, and geographic region.[1-3] At the patient level, chronologic age is a suboptimal predictor of costs after cardiac surgery,[4-7] which are largely driven by postoperative complications that consume excessive resources and prolong length of stay.[8]

Frailty, a geriatric syndrome of reduced resiliency to stressors, is a foremost predictor of postoperative complications in cardiac and noncardiac surgery.[9] In a recent study of 15,171 older adults from the Society of Thoracic Surgeons (STS) cardiac surgery database, frailty was associated with a 2-fold increase in operative mortality and major morbidity.[10]

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Corresponding author: Dr Jonathan Afilalo, 3755 Cote St. Catherine Rd, E-222, Montreal, Quebec H3T 1E2, Canada. Tel.: þ1-514-340-8232; fax: þ1-514-221-3785.
E-mail: jonathan.afilalo@mcgill.ca

See page 1025 for disclosure information.

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and all of the patients in these cases exhibited baseline frailty. In the multivariable model, total costs were independently associated with frailty (adjusted additional cost, $21,245; 95% confidence interval [CI], $12,418-$30,073; P < 0.001) and valve surgery (adjusted additional cost, $20,600; 95% CI, $9,661-$31,539; P < 0.001).
Conclusions: Frailty is associated with a marked increase in hospitalization costs after cardiac surgery, an effect that persists after adjusting for age, sex, surgery type, and surgical risk score. Further efforts are needed to optimize care and resource use in this vulnerable population.

Resultats : Parmi les 235 patients inclus dans l'analyse, l'âge median etait de 73,0 ans (intervalle interquartile [IIQ] : 70,0-78,0 ans) et 68 (29 %) femmes etaient presentes. Le coût median etait de 32 742 $ (IIQ : 23 221 $-49 627 $) chez 91 patients fragiles comparativement à 23 370 $ (IIQ : 19 977 $-29 705 $) chez 144 patients non fragiles.
Sept cas de coûts extrêmes superieurs à 100 000 $ ont ete recenses, tous chez des patients qui presentaient une fragilite au depart. Dans le modèle à variables multiples, les coûts totaux etaient independamment associes à la fragilite (coût supplementaire corrige : 21 245 $; intervalle de confiance [IC] à 95 % : 12 418 $-30 073 $; p < 0,001) et à l'intervention chirurgicale valvulaire (coût supplementaire corrige : 20 600 $; IC à 95 % : 9 661 $-31 539 $; p < 0,001).
Conclusions : La fragilite est associee à une augmentation marquee des coûts d'hospitalisation après une intervention chirurgicale cardiaque; cet effet persiste après correction tenant compte de l'âge, du sexe, du type d'intervention chirurgicale et du score de risque chirurgical. Des efforts supplementaires sont necessaires pour optimiser les soins et l'utilisation des ressources au sein de cette population vulnerable.

Moreover, frailty has been associated with prolonged mechanical ventilation, longer intensive care unit stays, longer hospital stays, higher rates of discharge to rehabilitation facilities, and higher rates of readmission, all of which are cost intensive.[11-16] With the prevalence of frailty estimated to be 25%-50% in older adults undergoing cardiac surgery, and the oldest patients representing the fastest growing group of patients, the population attributable risk and downstream implications on health and health care costs are substantial.

Despite the clear connection between frailty and morbidity and between morbidity and costs, there has yet to be a study directly examining the link between frailty and costs after cardiac surgery. Thus we sought to determine the impact of preoperative frailty status on postoperative hospitalization costs in a 2-centre cohort of older adults undergoing cardiac surgery.

Methods

Study design

We conducted a post hoc analysis of the McGill Frailty Registry, which prospectively enrolled older adults undergoing cardiac surgery at 2 tertiary care academic centres in Montreal, Canada. Patients aged 60 years were evaluated before elective and urgent CABG or heart valve surgery. Costing data were available from April 1, 2013-March 31, 2014 for the Jewish General Hospital (JGH) and from April 1, 2014-March 31, 2015 for the Royal Victoria Hospital (RVH) based on the date of implementation of the electronic cost-accounting platform at the respective institutions. Exclusion criteria included emergency surgery, clinical instability, severe neuropsychiatric impairment, or significant language barriers. The study was approved by the institutional review boards at the participating centres, and patients signed informed consent to participate.

Before cardiac surgery, we administered a structured questionnaire and physical performance tests to measure indices of frailty. Frailty was defined as a Fried score of 3 of 5 or a Short Performance Physical Battery score (SPPB) of 5 of 12. The Fried score reflects unintentional weight loss, self-reported exhaustion, weak handgrip strength, slow 5-m gait speed, and low physical activity.[17] The SPPB reflects standing balance, 5-m gait speed, and the time it takes to rise from a chair 5 times.[18]

After the index hospitalization, we reviewed electronic medical records and extracted data concerning clinical variables, operative variables, and postoperative mortality and major morbidity using data definitions from the Society of Thoracic Surgeons (STS) adult cardiac surgery database.[19] At 6 months and 12 months, we contacted patients to determine their vital status.

Cost determination

We captured costs incurred from the index operation date to the hospitalization discharge date at the treating institution. We used the Med-GPS (MediaMed Technologies, Mont-St-Hilaire, Canada) costing platform, which uses diagnosis-related groups (DRGs) to estimate the cost of care. DRG-based cost estimation has been shown to reflect actual costs incurred by hospitals and is used in many health care systems for payer reimbursement.[20,21] The Med-GPS data are validated for accuracy and consistency at each hospital. Physicians' fees are remunerated by the provincial health care system and are therefore not included in hospital-level financial data. Thus we used the provincial health services ministry fee schedule to estimate the costs of physician visits and services.[22] Included in these costs are the fees of the cardiac surgeons, anesthetists, radiologists, consultants, and attending physicians in the intensive care unit, stepdown unit, and hospital wards.

Costs were subdivided according to the following categories: physician fees, nursing, pharmacy, imaging, laboratory, operating room, and other costs (including allied health professionals such as physiotherapy, occupational therapy, occupational therapy, social work, and respiratory therapy, as well as blood bank and hospital fixed costs). Laboratory costs were

Table 1. Characteristics and outcomes stratified by cost

Variable	Cost < $20,000 (n ¼ 43)	Cost $20,000-$39,999 (n ¼ 146)	Cost $40,000 (n ¼ 46)	P value
Preoperative variables				
Age, y	71 (68-77)	73 (70-77)	78 (72-83)	0.004
Female sex	9 (21%)	38 (26%)	21 (46%)	0.38
BMI, kg/m^2	26.5 (23.6-28.1)	27.1 (24.1-31.3)	25.7 (23.4-29.4)	0.41
Previous stroke	4 (9%)	10 (7%)	4 (9%)	0.92
COPD	10 (23%)	20 (14%)	5 (11%)	0.42
Chronic kidney disease	12 (28%)	59 (40%)	19 (41%)	0.97
Diabetes	17 (40%)	55 (38%)	16 (35%)	0.93
Previous MI	14 (33%)	56 (38%)	17 (37%)	0.13
AF	3 (7%)	29 (20%)	16 (35%)	0.2
Heart failure	8 (19%)	41 (28%)	23 (50%)	0.07
LVEF	59% (47.5%-64%)	60 (45%-63%)	58 (40%-60%)	0.29
Geriatric domains				
Frail (by Fried or SPPB)	7 (16%)	51 (35%)	33 (72%)	0.04
Fried score, 5 possible (higher ¼ frail)	1 (0-2)	1 (0-2)	2 (1-3)	0.14
SPPB score, 12 possible (lower ¼ frail)	9 (7-10)	8 (5-9)	4 (2-7)	0.01
Gait speed, m/s	1 (0.8-1.2)	0.9 (0.7-1)	0.6 (0.2-0.8)	0.006
ADL disability	2 (5%)	20 (14%)	10 (22%)	0.65
Dementia	3 (7%)	12 (8%)	7 (15%)	0.34
Depressed mood	6 (14%)	36 (25%)	10 (22%)	0.62
Operative variables				
Isolated CABG	38 (88%)	71 (49%)	10 (22%)	< 0.001
Valve surgery without CABG	4 (9%)	39 (27%)	14 (30%)	< 0.001
Valve surgery with CABG	1 (2%)	36 (25%)	22 (48%)	< 0.001
Elective surgery	35 (81%)	133 (91%)	37 (80%)	0.78
STS-PROM, %	1.2 (0.8-1.6)	1.7 (1.1-2.9)	3.7 (2.0-5.1)	< 0.001
Postoperative events				
1-y mortality	3 (7%)	11 (8%)	10 (22%)	0.11
30-d mortality	1 (2%)	3 (2%)	4 (9%)	0.13
In-hospital mortality/morbidity	6 (14%)	30 (21%)	28 (61%)	< 0.001
Reoperation	2 (5%)	11 (8%)	14 (30%)	0.04
Stroke	0 (0%)	3 (2%)	3 (7%)	0.5
Sepsis	0 (0%)	2 (1%)	6 (13%)	0.01
Prolonged ventilation	2 (5%)	10 (7%)	20 (43%)	< 0.001
Acute kidney injury	1 (2%)	10 (7%)	9 (20%)	0.008
Postoperative AF	13 (33%)	36 (31%)	19 (63%)	0.003
Delirium	4 (9%)	27 (21%)	20 (54%)	0.03
Length of stay, d	6 (5-7)	8 (6-10)	22.5 (16-32)	< 0.001

Data are presented as n (%) or median (interquartile range).

ADL, activities of daily living; AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SPPB, Short Performance Physical Battery, STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

not available for the RVH site and were inferred by simple imputation. We adjusted for an annualized 1.55% rate of inflation from 2013 (the JGH cohort) to 2014 (the RVH cohort) based on the consumer price index.[23]

Statistical analysis

We used medians, interquartile range (IQR), and Spearman correlation coefficients to describe and compare continuous variables. We used frequencies, percentages, and Cuzick trend tests to describe and compare categorical data. For the multivariable analysis, we used linear regression to determine the association between frailty status and the total hospitalization cost after adjusting for age, sex, type of operation, and the STS predicted risk of mortality (STS-PROM). To account for the possibility of nonhomoscedasticity, we performed a sensitivity analysis treating the total hospitalization cost as a log-transformed variable. We used logistic regression to determine the association between frailty and postoperative events. We performed all analyses with the Stata 12 software package (StataCorp, College Station, TX).

Results

A total of 235 patients were included in the analysis. The median age was 73.0 years (IQR, 70.0-78.0 years), and 68 (29%) patients were women. We were able to extract costing data for all patients who underwent cardiac surgery during the calendar years studied. Baseline demographics, clinical characteristics, geriatric domains, and operative data are shown stratified by total cost < $20,000 (corresponding to the 20th percentile), $20,000-$39,000, and $40,000 (corresponding to the 80th percentile) (Table 1) and by frailty status (Supplemental Table S1). Patients in the highest cost category were older, more likely to be frail, more likely to undergo valve surgery, and had higher STS-PROM scores.

The distribution of total costs was right-skewed with a median value of $25,361 (IQR, $21,126-$34,180) and a

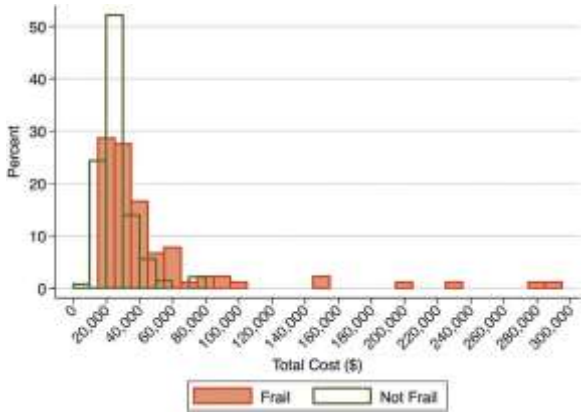

Figure 1. Hospitalization cost by frailty status.

mean value of $35,002 $34,109. The median costs were $32,742 (IQR, $23,221-$49,627) for the 91 frail patients compared with $23,370 (IQR, $19,977-$29,705) for the 144 nonfrail patients (Fig. 1, Table 2). Frail patients incurred greater direct and indirect costs and greater costs across all subcategories: in descending order of magnitude nursing, operating room, physician fees, pharmacy, laboratory, and imaging services (Fig. 2). Increasing levels of frailty were associated with increased index hospitalization costs (Supplemental Fig. S1). Compared with patients with an SPPB score > 5, patients with an SPPB score 5 had a higher rate of readmission or discharge to a rehabilitation, convalescent, or longer term care facility at 1 year (80% vs 52%).

In the multivariable model, total costs were independently associated with frailty (adjusted additional cost, $21,245; 95% CI, $12,418-$30,073; P < 0.001) and operations other than isolated CABG, ie, valve surgery with concomitant CABG (adjusted beta $20,600; 95% CI, $9661-$31,539; P ¼ 0.005) and valve surgery without concomitant CABG (adjusted beta, $14,819; 95% CI, $4555-$25,083; P < .001) (Table 3). Sensitivity analysis yielded similar results when we examined log-transformed total costs as a function of frailty and when we removed outliers (adjusted beta, $6247; 95% CI, $2572-$9,922; P < 0.001).

Seven extreme-cost cases were identified, representing patients who incurred total costs of $100,000 or more (Table 4). All 7 patients in the extreme-cost cases were frail at baseline, experienced a major bleeding episode and at least 1 other postoperative complication, and had a prolonged length of hospital stay. Overall, frailty was associated with a high risk of fatal and nonfatal major postoperative complications (adjusted odds ratio, 2.44; 95% CI, 1.31-4.57; P < 0.001) and with prolonged length of stay (> 14 days) (adjusted odds ratio, 5.67; 95% CI, 2.73-11.77; P < 0.001).

Discussion

To our knowledge, this is the first study to investigate the incremental cost associated with preoperative frailty in older adults undergoing cardiac surgery. We found that frail pa-tients incurred, on average, an additional $21,245 in total hospitalization costs. This sizeable cost difference was related to a marked increase in major postoperative complications and hospital length of stay. Frailty remained a powerful predictor of hospitalization costs even after adjusting for potential confounders, and the effect was consistent at both hospitals and across all cost subcategories. In addition, once frailty was accounted for, age and STS score were no longer predictive of hospitalization costs.

Our findings are in line with those of Robinson et al.,[16] who found that colorectal surgery hospitalization costs were $76,363 in frail older adults compared with $27,731 in nonfrail older adults. The absolute cost difference widened in the ensuing 6-month period because of a higher rate of readmissions, reaching $110,702 in frail older adults compared with $33,453 in nonfrail older adults. At least 20% of older adults are readmitted within 30 days of discharge after cardiac surgery[24]; since our study did not capture readmission costs, our estimated incremental cost associated with frailty is likely to be conservative when considering lifetime cost trajectories. In acute medical pop-ulations, hospitalization costs have been correlated with slow gait speed and low handgrip strengthd2 frailty markers that
were evaluated as part of composite frailty scales in our study.[25,26]

The impact of extreme-cost cases should not be understated, because a small number of cases may disproportionately influence global expenditures and result in considerable differences between patient costs and payer reimbursements. Similar to our results, Riordan et al.[27] found that the cost of CABG had a near-normal distribution, but that 21 of 628 patients had a cost that was 5.3 times the median. At the population-based level, administrative data have shown that 15% of the population accounts for 50% of the health care expenditures and resource use.[28] In our study, the 7 extreme-cost cases represented 3% of the population, yet they accounted for 17% of the aggregate costs.

Previous studies have demonstrated that frailty is effective in predicting survival and quality of life after cardiac surgery. The current study has demonstrated the effectiveness of frailty in also predicting the financial burden associated with surgical treatment. Accordingly, stakeholders (regulatory agencies, hospital administrators, insurance payers, clinicians, and patients advocates) should seek to integrate frailty to gauge the cost-effectiveness of major cardiac operations in an increasingly complex and aged referral base. By quantifying the economic impact of frailty, stakeholders would be better equipped to forecast costs and judiciously allocate resources. Attempts at predicting hospitalization costs using age alone or surgical risk models have had limited success, as is confirmed in the present study.[27,29] Arnaoutakis et al. showed that for every 1% increase in STS-PROM, hospitalization costs increased by $3,000.[30] Our unadjusted results similarly

Table 2. Total and distribution of costs by frailty status

Costs	Frail (n ¼ 91)	Nonfrail (n ¼ 144)
Total hospitalization cost, $	32,742 (23,221-49,627)	23,370 (19,977-29,705)
Direct costs, $	28,641 (20,356-43,059)	20,528 (17,486-25,796)
Indirect costs, $	4,139 (3,065-6,371)	2,966 (2,523-3,827)

Data are presented as median (interquartile range). Frailty defined as Short Performance Physical Battery score 5 of 12 or Fried score 3 of 5.

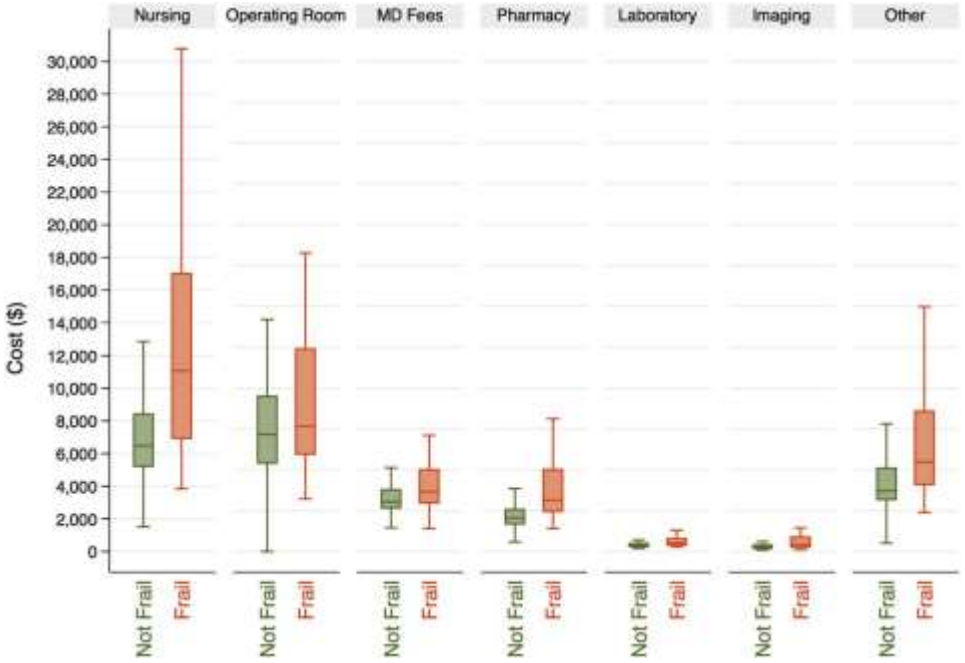

Figure 2. Cost categories by frailty status.

showed that for every 1% increase in STS-PROM, costs increased by $3131, although this was attenuated after adjustment for frailty.

Identification of frail patients who are at risk for increased surgical morbidities and costs empowers clinicians and patients to make more informed decisions about their care and tailor therapy toward less risky or resource-intensive options. Transcatheter aortic valve replacement is 1 such option that may minimize the procedural risks in high-risk patients, although costs are slightly higher with the transcatheter approach compared with the surgical approach at the present time (this is expected to change as the cost of transcatheter valves diminishes).[31] Alternative surgical approaches such as robot-assisted CABG may reduce length of stay and decrease variable costs.[32] Multidisciplinary optimization and prehabilitation programs may improve outcomes and accelerate functional recovery, thus reducing length of stay and resource use in the hospital setting.[33] In particular, malnutrition appears to be a high-yield target that is modifiable and associated with prolonged length of stay and postoperative morbidity.[34 -38] One study evaluated a preoperative nursing intervention to optimize frail older adults for cardiac surgery and found that the intervention would be cost-effective if it reduced the risk of postoperative complications by only 1%.[39] Given the uncertainty of the net therapeutic benefit of less invasive approaches in frail patients with cardiovascular disease and the challenge in predicting cost outliers, patient selection based on cost considerations should be approached with caution at the present time. Further studies are needed to determine the optimal management strategy in frail patients.

Our study has a number of limitations. First, the study is a post hoc analysis of a prospective registry and is subject to unmeasured confounding. We did capture and adjust for important confounders (age, sex, operation type, STS-PROM) and purposefully did not adjust for postoperative complications because these represent intermediate variables between frailty and costs rather than confounders. Second, patients from 2 centres in a single province were included; a broader cohort would be required to achieve widespread generalizability. Third, physician fees were estimated by using standardized billing codes, because actual billing data are not collected at the hospital level. This estimation is unlikely to have introduced meaningful measurement bias because physicians in Quebec must use these provincially mandated billing codes for all patients. Fourth, postdischarge costs were not directly available in our data set; however, we did observe that the principal drivers of postdischarge costs (ie, a need for specialized facilities and readmissions) were significantly increased in frail patients. Finally, laboratory costs were imputed at 1 of the sites where they were not available in the costing platform, although at the site where they were

Table 3. Multivariable analysis of hospitalization cost

Variable	Adjusted Beta	95% CI	P value
Age, per decade	e43	e846 to 759	0.92
Female sex	e2064	e11,639 to 7511	0.67
Frailty	þ21,245	12,418 to 30,073	< 0.001
STS-PROM, %	þ446	e1817 to 2710	0.39
Type of surgery			
Isolated CABG	Referent		
Valve surgery without CABG	þ14,819	4555 to 25,083	0.005
Valve surgery with CABG	þ20,600	9661 to 31,539	< 0.001

Frailty defined as Short Performance Physical Battery score 5 of 12 or Fried score 3 of 5.

CABG, coronary artery bypass graft; CI, confidence interval; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 4. Characteristics of Cases Costing More than $100,000

Case	Total cost*	Age/sex	Comorbidities	STS-PROM	Frail	Operation	Postoperative morbidity	LOS (d)	Disposition	Readmission
¼	¼1$100,17079/MCAD,CKD,previousstroke5.Yes(Fried2;SPPB 0)					Elective CABG3%	Prolonged ventilation, major bleed	32	Transferred to another hospital	Yes (1-6 mo)
¼	¼0%2$151,83182/FAF,CAD,CKD,PH,14.Yes(Fried1;SPPB 4)					Elective MVR	Prolonged ventilation, major bleeding episode, reoperation	<24	TransferredtoanotherYes(30 d) hospital, died at 11 mo	
anemia, visual impairment, falls										
¼	¼	þ7%3$151,90884/MAF,CAD,anemia,visual3.Yes(Fried2;SPPB0)				ElectiveCABG SAVR	Prolonged ventilation, major bleeding episode,	75	Transferred to a rehabilitation facility	Yes (6-12 mo)
impairment										
¼	¼	þ5%4$195,25782/MAF,CAD,anemia,dementia,5.Yes(Fried4;SPPB0)				UrgentCABG SAVR	reoperation, sepsisMajorbleedingepisode, sepsis	74	Transferred to another hospital, died at 3 mo	No
hearing impairment, falls										
¼	¼	þ	þ5$228,08773/MAF,CKD,previousstroke,2.Yes(Fried5;SPPB6)			ElectiveMVATVA8%	Prolonged ventilation, major bleeding episode, reoperation	134	Died in hospital at 4 mo	e
anemia, depression, visual impairment			aortic surgery							
¼	¼2%6$284,10365/MAF,CAD,depression1.Yes(Fried4;SPPB 9)					Elective MVR	Prolonged ventilation, major	156	Home	No
¼	¼	þ6%7$289,40169/FCAD1.Yes(Fried2;SPPB4)				ElectiveCABG	bleeding episode,reoperation,sepsis, AKIMajorbleedingepisode, reoperation, AKI, dialysis	<103	TransferredtoaYes(30 d) rehabilitation facility	
þSAVR aortic surgery										

AF, atrial brillation; AKI, acute kidney injury; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD,fi chronic kidney disease; LOS, length of stay; MVA, mitral valve annuloplasty; MVR, mitral valve replacement; PH, pulmonary hypertension; SAVR, surgical aortic valve replacement; SPPB, Short Performance Battery; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; TVA, Physicalfrailtyandvalveannuloplasty.*Costingdatadonotincludecostsincurredatthecovalescenthospital,rehabilitationfacility,ordatingreadmission.

available we found that they represented a very small proportion (1%-3%) of total hospitalization costs.

Conclusions

Frail older adults undergoing cardiac surgery incur substantially higher hospitalization costs than do their nonfrail counterparts. Our study has added to the emerging body of evidence linking frailty with increased costs in noncardiac surgery and inpatient medical care. Given the expansion of the frail older adult population and their growing need for cardiovascular care, these findings have considerable implications for our constrained health care system. Further research is needed to better allocate resources and contain costs by improving patient selection and pre- and postoperative optimization of frail patients to prevent deleterious and costly health outcomes.

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Disclosures

The authors have no conflicts of interest to disclose.

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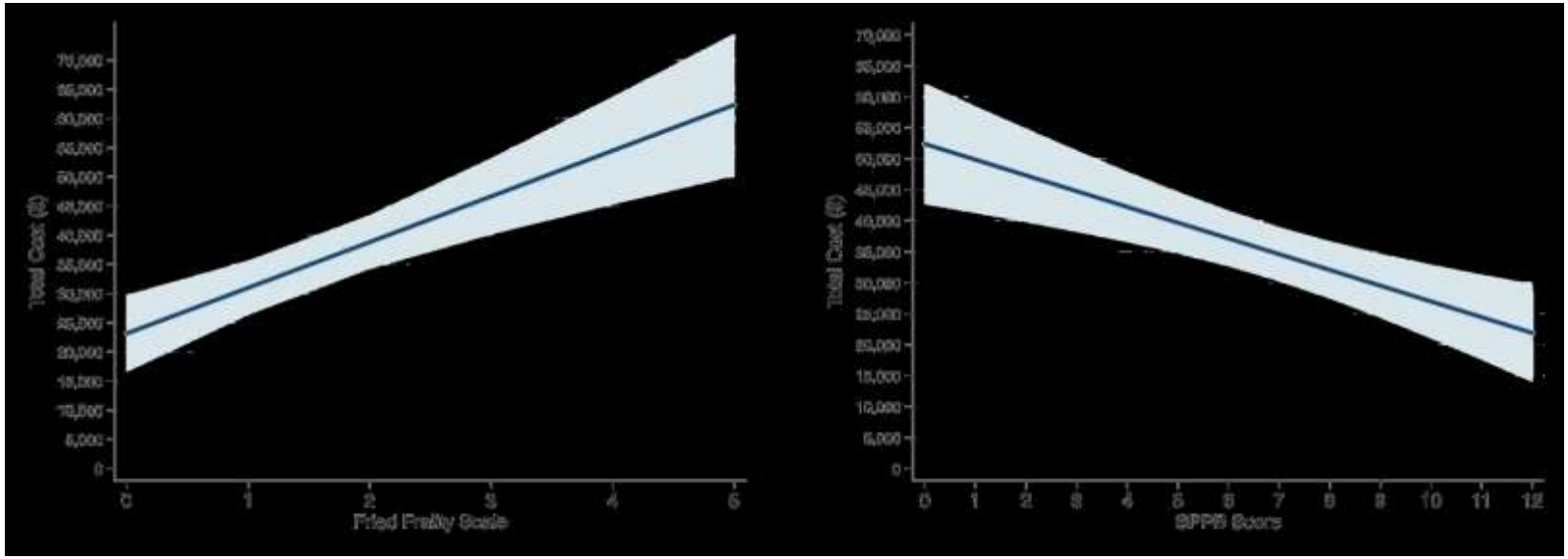
Supplemental Table S1. Characteristics and Outcomes Stratified by Cost

	Non-Frail (N=144)	Frail (N=91)	P-value
PREOPERATIVE VARIABLES			
Age, years	73 (68, 77)	75 (71, 79)	0.008
Female	29 (20%)	39 (43%)	<0.001
BMI, kg/m2	26.4 (24, 29)	27.3 (23.5, 31.3)	0.28
Prior stroke	6 (4%)	12 (13%)	0.01
COPD	22 (15%)	13 (14%)	0.84
Chronic kidney disease	49 (34%)	41 (45%)	0.09
Diabetes	44 (31%)	44 (48%)	0.006
Prior MI	51 (35%)	36 (40%)	0.52
AF	17 (12%)	31 (34%)	<0.001
Heart failure	31 (22%)	41 (45%)	<0.001
LVEF	60 (50, 65)	55 (42.5, 60)	0.009
Geriatric Domains			
Fried score, /5 (higher=frail)	1 (0, 1)	3 (2, 3)	<0.001
SPPB score, /12 (lower=frail)	9 (8, 10)	4 (1, 5)	<0.001
Gait speed, m/s	1.0 (0.9, 1.1)	0.7 (0.5, 0.8)	<0.001
ADL disability	6 (4%)	26 (29%)	<0.001
Dementia	7 (5%)	15 (16%)	0.003
Depressed mood	19 (13%)	33 (36%)	<0.001
OPERATIVE VARIABLES			
Isolated CABG	77 (53%)	42 (46%)	<0.44
Valve surgery without CABG	30 (21%)	25 (27%)	
Valve surgery with CABG	37 (26%)	24 (26%)	
Elective surgery	123 (85%)	82 (90%)	0.29
STS-PROM, %	1.4 (1.0, 2.4)	2.9 (1.4, 4.5)	<0.001
POSTOPERATIVE EVENTS			
1-year mortality	10 (7%)	14 (16%)	0.03
30-day mortality	3 (2%)	5 (6%)	0.15
In-hospital mortality/morbidity	28 (19%)	36 (40%)	<0.001
Reoperation	11 (8%)	16 (18%)	0.02
Stroke	3 (2%)	3 (3%)	0.57
Sepsis	3 (2%)	5 (5%)	0.16
Prolonged ventilation	11 (8%)	21 (23%)	<0.001
Acute kidney injury	6 (4%)	14 (15%)	0.003
Postoperative AF	47 (37%)	21 (35%)	0.79
Delirium	23 (18%)	28 (35%)	0.007
Length of stay, days	7 (6, 10)	11.5 (8, 22)	<0.001
Need for readmission (1-year)	52 (36%)	43 (47%)	0.09
Discharge to healthcare facility	33 (23%)	47 (52%)	<0.001

Data are presented as n (%) or median (interquartile range)

Supplemental Figure S1. Relationship between Frailty Level and Total Cost. More advanced levels of frailty (lower SPPB scores, higher Fried scores) were associated with a greater total cost of hospitalization. Abbreviations: SPPP, Short Physical Performance Battery.



Conclusions

There are a number of important changes to protein and muscle metabolism that occur with aging. Older adults have both increased muscle catabolism and impaired anabolic responses. Acute and chronic comorbid disease in older adults further exacerbate the altered catabolic and anabolic responses that occur with increasing age. There is also evidence that older adults do not consume sufficient protein to meet their needs. As a result, up to half of hospitalized older adults with cardiovascular disease are malnourished or are at-risk for malnourishment. Malnourished older adults are at-risk for worsened clinical outcomes during hospitalization.

However, a large amount of protein intake can counteract the age-related changes in protein metabolism since the anabolic response to a large amount of protein ingestion remains intact in older adults. Protein intake of more than 2 g/kg/day has been shown to be safe and may be justified in older adults under severe physical stress, such as cardiac surgery. Dietary protein supplementation in older adults has been shown to improve physical performance including measures of leg strength, physical functioning, and disability scores.

Approximately half of older adults undergoing cardiac surgery and TAVR are frail and frailty is independently associated with worse outcomes for these procedures. Frailty is also associated with malnutrition and there have been proposed pathophysiological mechanisms underlying inadequate nutrition and the frailty syndrome. Given the need to understand the role of nutrition and frailty in older adults undergoing invasive cardiac procedures, we looked at the preoperative use of the MNA-SF, a nutritional screening tool, and the preoperative serum albumin concentration, to predict longer-term mortality and other adverse events. We observed the actual postoperative protein intake in older adults undergoing cardiac surgery in order to understand current practice. We then designed a randomized controlled trial to evaluate whether a protein-rich supplement could improve outcomes in older adults following cardiac surgery. We also explored the impact of frailty status on postoperative costs of care in order to understand the potential implications on healthcare resources.

Key findings

In our prospective cohort analysis of more than 1,000 patients in the FRAILTY-AVR registry, a multi-center international prospective study of older adults undergoing aortic valve replacement, we found that malnourished older adults (8.7% of the cohort) had a nearly 3-fold increased risk of 1-year mortality compared to those with normal nutritional status (28% vs 10%). Furthermore, nearly 1 in 3 older adults were at-risk for malnutrition and these patients had a 50% higher 1-year mortality than those with normal nutritional status. These findings suggest nutritional status assessment with the MNA-SF is a useful prognostic tool for longer-term mortality in older adults undergoing transcatheter and surgical aortic valve replacement.

Lower serum albumin levels were also found to be associated with poor outcomes following TAVR. Hypoalbuminemia was found to be a powerful predictor of post-TAVR mortality and added incremental discrimination beyond traditional risk models and frailty scores. A serum albumin concentration of 30 grams per liter was determined as an optimal cutoff for prediction of both shorter-term and longer-term mortality.

In our prospective observational pilot study to assess the actual protein intake post-cardiac surgery, we found that there was a mean protein deficit in the early postoperative period, but a small mean protein excess in the preoperative and postdischarge periods. The mean protein deficit in the early postoperative period was mediated by both inadequate protein intake and higher protein needs. Preoperative protein intake did not identify patients who were more likely to have inadequate postoperative protein intake. We also identified a number of barriers to food intake in the early postoperative period.

Our study was also the first to evaluate the additional cost associated with frailty in older adults undergoing cardiac surgery. We found that frailty was associated with a considerable increase in index hospitalization cost following cardiac surgery. In our two center cohort, frail patients cost on average $21,245 more than non-frail patients in total hospitalization costs, which was mainly driven by increased hospital length of stay and postoperative complications.

Implications of Our Findings and Future Directions

Malnutrition, low serum albumin levels, and frailty were strong predictors of poor outcomes following cardiac surgery and TAVR. Importantly, clinicians can readily identify each

of these factors preoperatively using simple bedside or laboratory testing. Malnutrition, albumin, and frailty are also potentially modifiable targets.

One of the most important questions raised by our findings is whether perioperative nutritional support improves outcomes. While malnourished older adults have shown the capacity to respond to protein supplementation with increased protein synthesis and lean body mass, there is currently limited evidence whether nutritional support in the perioperative period improves clinical outcomes in malnourished, at risk, and/or frail older adults undergoing invasive cardiac procedures. The initial results from our prospective observational study on perioperative protein intake suggest that the early postoperative period may be an opportune time for nutritional intervention. During this phase of care, older adults have reduced protein intake despite increased protein intake requirements. As a result of the considerable protein deficit during the early postoperative period, muscle catabolism may be accelerated in older adults predisposing them to lean muscle loss and functional impairment. Frail older adults have potentially more to gain with nutritional supplementation than non-frail older adults since sarcopenic muscle may be more affected by bedrest and other physical stressors.

There is a need to determine the optimal patient selection and perioperative care to improve outcomes in frail and malnourished older adults. Our prospective, double-blind randomized controlled trial is designed to evaluate whether leucine-enriched whey protein supplementation initiated during the early postoperative period in older adults improves muscle mass, strength, and physical performance in older adults post-cardiac surgery. The study will also assess whether preoperative nutritional status, serum albumin, and frailty status can identity patients who may benefit more from protein supplementation postoperatively. We hypothesize that improvements in physical performance and frailty will translate into decreased postoperative morbidity, re-hospitalizations, disability, and functional independence in vulnerable older adults. There may also be a role for mobility exercises in addition to nutritional supplementation. A combined exercise and nutrition strategy may have a synergistic impact on the maintenance of muscle mass, strength, and functional recovery in critically ill patients and this treatment strategy also needs to be further explored.

Our pilot data suggests that adequate preoperative protein intake does not identify patients who were more likely to have insufficient protein intake in the early postoperative and postdischarge periods, although our sample size was underpowered to conclude whether there is

a relationship between preoperative dietary protein intake and postoperative protein deficits. Additional data are needed to evaluate the relationship between preoperative and postoperative protein intake.

We also identified a number of barriers to food intake in the early postoperative period. The vast majority of respondents listed poor appetite and dislike of offered food as barriers to food intake. However, it is also likely that pain, nausea, meal interruptions – all of which are potentially addressable – play a role in inadequate food consumption. Further research is needed to identify strategies to address these barriers and improve dietary intake of protein in the early postoperative period.

Lastly, the increased cost of hospitalization post-cardiac surgery could have tremendous implications to our healthcare system. Older adults comprise the majority of patients undergoing cardiac surgery and TAVR. The older adult population, especially the oldest old, is increasing at a fast rate. The majority of older adults undergoing TAVR and up to half of older adults undergoing cardiac surgery are frail and frailty is associated with increased postoperative morbidity and resource utilization. Identifying frail patients prior to cardiac interventions who are at risk for increased postoperative morbidity and costs helps patients and clinicians to make more informed decisions about their care and consider less invasive, lower risk, and less costly management options.

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