

Evaluation and Treatment of Frailty in Hospitalized Older Adults with Acute Cardiac Conditions

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August 2021

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

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Table of Contents

English Abstract		4
French Abstract		6
Acknowledgements		8
Contribution of Authors		9
Chapter 1	Thesis Introduction	11
Chapter 2	Literature Review: Evaluation and Management of Frailty in Acute Cardiac Care Settings	14
Chapter 3	Commentary on Literature Review	30
Chapter 4	Transition to Cohort Study	32
Chapter 5	Cohort Study: Manuscript Submitted “Prognostic Value of Handgrip Strength in Older Adults Undergoing Cardiac Surgery”	34
Chapter 6	Commentary on Cohort Study	61
Chapter 7	Transition from Cohort Study to Randomized Clinical Trial	64
Chapter 8	Randomized Clinical Trial: Manuscript to be Submitted “Rationale and Design of the TARGET-EFT trial: A Multicomponent Acute Intervention in Frail Geriatric Patients	66

with Cardiovascular Disease using the Essential Frailty
Toolset”

Chapter 9	Commentary on Randomized Clinical Trial	94
Chapter 10	Thesis Conclusion	97
Appendices		100
References		107

English Abstract

Background: After an acute cardiac event or cardiac surgery, frail older adults are at risk of poor quality of life, nonfatal and fatal adverse events. Measuring frailty in acute cardiac care settings can provide valuable prognostic information to guide clinical decision-making and therapeutic interventions. To understand the benefits of screening and intervening on frailty in this setting, the objectives of this thesis were to determine the predictive value of rapid frailty screening tools (handgrip strength) and to design a pragmatic multidimensional intervention to improve functional recovery in frail hospitalized patients.

Methods: The first project was a cohort study using data from the prospective McGill Frailty Registry to determine the predictive value of a rapid frailty screening tool (i.e. handgrip strength) in patients undergoing cardiac surgery. The second project was a randomized clinical trial to determine the therapeutic value of an intervention targeting deficits identified by a frailty screening tool in patients hospitalized for acute cardiac conditions (“TARGET-EFT”: The Multicomponent Acute Intervention in Frail Geriatric Patients with Cardiovascular Disease using the Essential Frailty Toolset).

Results: The cohort study consisted of 1,245 cardiac surgery patients with a mean age of 74.0 ± 6.6 years. Weak handgrip strength was associated with higher risk of adverse outcomes and was predictive of 1-year and 30-day mortality (odds ratios of 2.44 (CI 1.39, 4.29) and 2.83 (CI 1.38, 5.81), respectively). The TARGET-EFT randomized trial consists of 130 frail hospitalized cardiac patients (out of a planned sample size of 144). Preliminary data analysis on the initial 77 patients with a mean age of 80 years showed that average length of stay was 8 days. Of the 39

intervention patients, 94% of patients requiring exercise, 100% of patients requiring cognitive stimulation, 86% of patients requiring intravenous iron sucrose and 81% patients requiring protein supplementation, received the minimum dose of interventions by discharge. Patients received an average of 6 exercise sessions, with 46% of sessions not being performed due to hospitalization-associated factors. We did not report intervention-related adverse events or injuries. The TARGET-EFT trial appears to be safe and feasible for frail patients hospitalized with acute cardiac conditions.

Conclusions: The assessment of frailty with rapid screening tools can easily identify patients who would benefit from a comprehensive geriatric assessment and multicomponent in-hospital interventions that aim to treat frailty and improve patient-centered outcomes. The results of the TARGET-EFT trial will inform practice guidelines on therapeutic interventions and frailty management in older adults with acute cardiac conditions.

French Abstract

Contexte: Après un événement cardiaque aigu ou une chirurgie cardiaque, les personnes âgées fragiles sont à risque de mauvaise qualité de vie, d'événements indésirables non mortels et mortels. La mesure de la fragilité dans les établissements de soins cardiaques aigus peut fournir des informations pronostiques précieuses pour guider la prise de décision clinique et les interventions thérapeutiques. Pour comprendre les bénéfices du dépistage et de l'intervention sur la fragilité dans ce contexte, les objectifs de cette thèse étaient de déterminer la valeur prédictive des outils d'évaluation rapide de la fragilité de (force de préhension) et de concevoir une intervention multidimensionnelle pragmatique pour améliorer la récupération fonctionnelle chez les patients fragiles hospitalisés.

Méthodes: Le premier projet était une étude de cohorte utilisant les données du registre de fragilité de McGill pour déterminer la valeur prédictive d'un outil de dépistage rapide de la fragilité (la force de préhension) chez les patients subissant une chirurgie cardiaque. Le deuxième projet était un essai clinique randomisé pour déterminer la valeur thérapeutique d'une intervention ciblant les déficits identifiés par un outil de dépistage de la fragilité chez les patients hospitalisés pour d'affections cardiaques aiguës (« TARGET-EFT » : The Multicomponent Acute Intervention in Frail Geriatric Patients with Cardiovascular Disease à l'aide de l'ensemble d'outils essentiels pour la fragilité).

Résultats: L'étude de cohorte portait sur 1 245 patients ayant subi une chirurgie cardiaque avec un âge moyen de $74,0 \pm 6,6$ ans. Une force de préhension faible était associée à un risque plus

élevé de résultats indésirables et était prédictive de mortalité à 1 an et 30 jours (rapports de cotes de 2,44 (IC 1,39, 4,29) et 2,83 (IC 1,38, 5,81), respectivement). L'essai randomisé TARGET-EFT se compose de 130 patients cardiaques fragiles hospitalisés (sur un échantillon prévu de 144). L'analyse des données préliminaires sur les 77 premiers patients avec un âge moyen de 80 ans a montré que la durée moyenne de séjour était de 8 jours. Sur les 39 patients de l'intervention, 94 % des patients nécessitant l'exercice, 100 % des patients nécessitant une stimulation cognitive, 86 % des patients nécessitant du fer saccharose par voie intraveineuse et 81 % des patients nécessitant une supplémentation en protéines, ont reçu la dose minimale d'intervention à la sortie. Les patients ont reçu en moyenne 6 séances d'exercices, dont 46 % des séances n'ont pas été effectuées en raison de facteurs liés à l'hospitalisation. Nous n'avons pas signalé les événements indésirables ou les blessures liées à l'intervention. L'essai TARGET-EFT semble être sûr et réalisable pour les patients fragiles hospitalisés pour des problèmes cardiaques aigus.

Conclusions: L'évaluation de la fragilité à l'aide d'outils de dépistage rapide peut facilement identifier les patients qui bénéficieraient d'une évaluation gériatrique complète et d'interventions en milieu hospitalier à plusieurs composantes visant à traiter la fragilité et à améliorer les résultats centrés sur le patient. Les résultats de l'essai TARGET-EFT éclaireront les directives de pratique sur les interventions thérapeutiques et la gestion de la fragilité chez les personnes âgées atteintes de maladies cardiaques aiguës.

Acknowledgements

I would like to firstly thank my supervisor Dr. Jonathan Afilalo, for the countless hours of mentorship and guidance throughout the completion of my master's degree. Dr. Afilalo has provided me an inspiring research environment and the skillset necessary to progress in my future research endeavors. I would like to thank the members of my thesis committee, Drs. Mark Eisenberg, Olivier Beauchet and Marc Fabian for their feedback and advice through the progression of my thesis. I would also like to thank those who had contributed to the review and editing of the manuscripts included in this thesis.

I would like to also thank the Cardiovascular Unit at the Jewish General Hospital for providing the infrastructure and resources to support the TARGET-EFT trial. I would like to thank the many cardiologists, nutritionists, physiotherapists, and nurses who have played integral roles in support of this trial. I would like to thank the Centre for Clinical Epidemiology at the Lady Davis Institute for providing me a workspace and learning environment to conduct my research. I would like to lastly thank the frailty research team for helping in the recruitment and collection of data for the TARGET-EFT trial.

I would like to acknowledge the Gordon Phillips Fellowship and Graduate Excellence Fellowship valued at \$10,000 from the McGill Faculty of Medicine and Health Sciences, the McGill Perseverance Scholarship valued at \$1,200 and the two travel awards granted by the Division of Experimental Medicine, for financially supporting me throughout my research endeavors. These awards allowed me to share my research at international scientific conferences. Most importantly, this recognition validated my research endeavors towards improving patient-centered outcomes in hospitalized frail older.

Contribution of Authors

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Thesis candidate. Performed literature review for this thesis. Co-initiated and designed the TARGET-EFT randomized clinical trial which consisted of writing the study protocol, questionnaires, consent forms and submitting the study documentation to the institutional research ethics boards. Constructed the REDCap database for data collection. Responsible for patient recruitment, conducting frailty assessments and administering exercise-based interventions as part of the randomized clinical trial. Wrote four abstracts presented at major international conferences. Wrote thesis document, and initial and revised manuscripts of cohort study and the randomized clinical trial.

Jonathan Afilalo, MD MSc

Thesis supervisor. Regularly provided support and guidance throughout the progression of my thesis. Developed the study design of TARGET-EFT trial and contributed to data analysis for cohort study. Contributed to the data analysis of the cohort. Reviewed and evaluated the thesis document in addition to the two manuscripts it contains.

Mark J Eisenberg, MD MPH

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Chapter 1: Thesis Introduction

Over the past decade, the progressive increase in the aging population and the high clinical complexity of older adults has posed many challenges to cardiovascular medicine (1). Geriatric syndromes such as frailty are necessary for risk prediction and to align care towards a patient-centered approach (2, 3). Frailty is a multidimensional geriatric syndrome characterized by the decreased physiological capacity and resilience to stressors (4). Following an acute cardiac event or surgery, frail older are at higher risk of poor health-related quality of life and are at higher risk of fatal and nonfatal adverse events.

The prevalence of frailty ranges from 20 to 60% in older patients with cardiovascular disease (CVD) and more than half of cardiac surgeries today are performed on older adults (5, 6). An acute hospitalization can pose a major threat to frail patients' physiological capacity. Frail older patients have an anabolic insufficiency to respond to the physiological stress and catabolic response initiated from the acute cardiac event (7). Hospitalization-associated stressors such as immobility, bedrest and undernutrition exacerbate frailty and increase acute and systemic inflammation, resulting in decreased muscle protein synthesis and muscle mass, especially in the lower limb extremities (8, 9). Compared to healthy young adults, after two weeks of immobilization older adults experienced 3- to 6-fold greater losses of muscle strength and mass (10). Ten days of bedrest caused knee extensor strength to be 13% lower and VO₂max to be 12% lower (11). The compounded effects of hospitalization-associated stressors and the acute cardiac event, render the patient into a vulnerable state that persists beyond discharge better known as the "post-hospital syndrome" (12).

The post-hospital syndrome stems from an inability to withstand the increased allostatic load from an acute illness in a hospital environment not conducive for recovery (12). Conditions

such as low mobility and bedrest has also been shown to increase disability in basic activities of daily living (ADLs) by discharge in hospitalized older patients (13, 14). During hospitalization, it has been shown that 40% of older adults lose the ability to self-care (15). Older adults discharged with one new disability in ADLs are known to be at risk of poor prognosis and recovery (16). The acquisition of one or more new disabilities in ADLs following hospital discharge is known as “hospital acquired disability” (HAD) (15, 17). In a study of older adults hospitalized for general medical services, of the 41% who developed HAD died at one year post-hospitalization and 29% retained an acquired disability after one year (16). With more than 50% of adults over the age of 85 years acquiring one new disability in ADLs upon discharge (8), there is a need to identify frail patients who would benefit from hospital-based interventions that promote safe passage from acute care settings to home.

Despite the recognition of frailty as a vital part in the evaluation of older adults with CVD, integration in routine clinical practice has been limited due to time and personnel constraints. The medical instability of patients adds an extra challenge to the application of frailty assessment tools in acute care settings. In addition, the various frailty assessment tools available have resulted in ambiguity on a gold standard measure. Following the examination of frailty assessment tools in acute care settings, the subsequent goal would be to implement these tools to guide therapeutic interventions and improve patient-centered outcomes.

Identification of the nonphysical and physical frailty domains can guide patient-tailored care and disease management to prevent risk of poor outcomes and readmission (18). Physical, nutritional, and cognitive interventions should be at the center of frailty management in acute care settings to prevent the rapid deconditioning from delirium, loss of muscle mass and strength. Multidimensional frailty therapeutic interventions emphasize a patient-centered approach rather

than disease-specific approach. To our knowledge, there have been no randomized clinical trials on multidimensional frailty interventions in cardiology (19). Optimizing care for frail older adults may result in shorter length of stay, in addition, empower better quality of life, functional independence and self-efficacy after an acute hospitalization for CVD.

Thus, the objective of this thesis was to perform a literature review on the current understanding of the evaluation and treatment of frailty in hospitalized older adults with acute cardiac conditions, to subsequently test the prognostic value of a pragmatic frailty assessment tool (handgrip strength) in older adults undergoing cardiac surgery and lastly to design and initiate a randomized clinical trial on a multicomponent frailty intervention to improve functional recovery in older adults hospitalized for acute cardiac conditions.

Chapter 2: Literature Review: Evaluation and Management of Frailty in Acute Cardiac Care Settings

Definition of Frailty

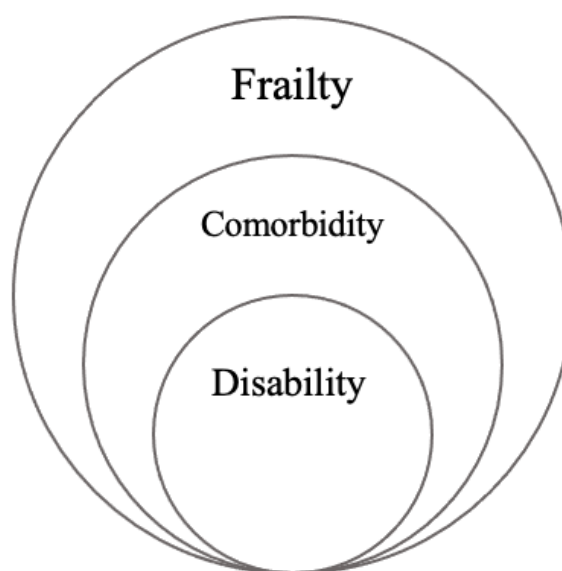
Frailty is a geriatric syndrome defined by a decreased resilience to stressors due to age-related decline in multiple organ systems (20). Frailty is recognized in the patient as a combination of muscular weakness, mobility limitations, physical inactivity, weight loss, mood disturbances, and cognitive impairment (21). Exogenous stressors, such as a fall, or iatrogenic stressors, such as cardiac surgery, can increase frail patients' vulnerability to adverse events (22). Compared to robust patients, these stressors will result in functional loss, deconditioning, increased dependency, procedural complications, poor quality of life and mortality (21, 23, 24).

There is a lack of consensus surrounding the definition of frailty, however, three factors have remained key to conceptualize the frailty syndrome. Firstly, frailty is multidimensional and is defined by the interaction of physical and psychosocial factors (25). Secondly, frailty is an extreme response to the normal aging process (26). Thirdly, frailty is dynamic and progressive, meaning the accumulation of injuries triggers continuous functional decline and state of vulnerability (25). Two main schools of thought have contributed to operationalizing frailty. The accumulation of deficits model was brought forth by Rockwood et al. which is measured by the Frailty Index (FI) (27). This model defines frailty by the number of accumulated deficits (signs, symptoms, diseases, disabilities, laboratory, radiographic or electrocardiographic abnormalities and social characteristics) during life. FI is calculated as a ratio of the number of deficits present to the number of potential deficits (28). The second model is the frailty phenotype. The Fried scale defines frailty as a biological syndrome based on five criteria: unintentional weight loss, self-report exhaustion, weakness, slow gait speed and low physical activity (29). Regardless of

the conceptual definition used, accumulated evidence consistently shows that frail individuals are vulnerable to illnesses and have worse clinical outcomes (20, 25, 30).

Frailty is multidimensional based on an interaction of biopsychosocial domains (31, 32). Physical frailty is characterized by low muscle mass and strength known as sarcopenia (33). Psychosocial domains of frailty include cognition, mood, and disability (34-36). Age-related comorbidities such as anemia, anorexia, dysregulation in hormonal and endocrine systems, decreased testosterone and increased insulin resistance and inflammation with an upregulation of cytokines, have been implicated in the etiology of frailty (37, 38). Inflammation triggers a catabolic response that leads to muscle loss. Since muscle houses the main supplies of amino acids necessary for muscle repair, muscle loss leads to an inability to repair in response to a stressor. Compounded by physical inactivity and malnutrition, this perpetuates a vicious cycle, leading to further deterioration (1). Frailty, comorbidity and disability are separate but related entities that are implicated in the progressive functional decline of older adults (4) (Figure 1).

Figure 1: Interaction of frailty, comorbidity, and disability

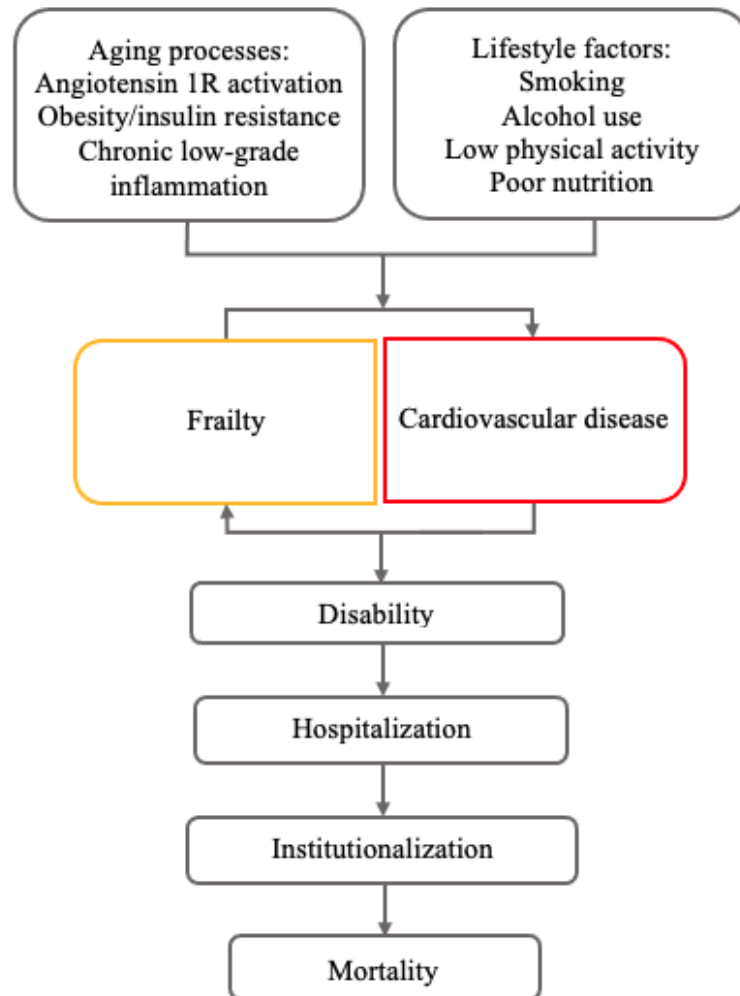


Frailty and Cardiovascular Disease

Through the interaction of lifestyle risk factors and multisystem biomarkers, there are shared pathways underlying CVD and frailty. Lifestyle-related cardiovascular factors such as obesity, poor nutrition, have been associated with cumulative disability with age (39). An important risk factor for frailty and CVD is low physical activity (40). In a large cohort study, frailty was associated with cardiovascular risk factors such as diabetes, hypertension, low HDL cholesterol, smoking and obesity (40).

Chronic low-grade inflammation resulting from the aging processes such as lifelong antigen exposure, redox imbalance, angiotensin type-1 receptor (1R) activation, obesity, and insulin resistance known as “inflammageing (41).” Inflammageing is also a known risk factor for common age-related conditions like chronic kidney disease, diabetes mellitus, cancer, depression, dementia, and sarcopenia (42). Inflammatory markers such as neutrophils, high sensitivity C-reactive protein and interleukin-6 (IL-6) are found in higher concentrations in frailty and CVD (43). Inflammation in CVD is known to lead to the oxidation of lipoproteins and the activation of plaques in atherosclerosis. Inflammation in frailty is responsible for the progressive muscle loss which inhibits amino acid mobilization for protein synthesis. In addition, insulin resistance has been shown to be involved in both CVD and frailty. Insulin resistance also discourages protein breakdown, further impairing amino acid mobilization for repair functions (43). These pathophysiological, immunological, and inflammatory processes are responsible for the progressive functional decline of older adults (44) (Figure 2).

Figure 2: Frailty and Cardiovascular Disease



Epidemiology of Frailty and Cardiovascular Disease

With the aging patient population increasing, there are more patients today living with CVD that are frail (20, 45). Observational studies have shown the association between frailty in CVD and morbidity and mortality in older adults (1, 6, 46, 47). The Cardiovascular Health Study (CHS) on 4,735 community-dwelling older adults showed that CVD was associated with a 3-fold increased prevalence of frailty (OR 2.79 9% CI 2.12-3.67). The Women's Health Initiative Observational Study (WHI-OS) was a large study that showed CVD (coronary artery disease, stroke and hypertension) was a risk factor for developing of frailty over the span of 3 years (48).

Subclinical abnormalities from testing (echocardiography, brain infarcts on magnetic resonance imaging, abnormal ankle-brachial index, carotid stenosis, pre-hypertension, and left ventricular hypertrophy) were also associated with frailty (49).

Numerous studies have examined the prevalence and prognostic impact of frailty in hospitalized older adults with CVD. Systematic reviews and meta-analyses have synthesized the evidence of frailty and its prediction of mortality and morbidity in acute cardiac settings, including heart failure, coronary syndromes, cardiac surgery, transcatheter aortic valve replacement (TAVR) (50-53). Frail patients with chronic heart failure were shown to have increased risk of mortality at 1-year (17 vs. 5%) and impaired quality of life (54). In patients admitted for acute decompensated heart failure, frailty defined by the Short Performance Physical Battery (SPPB), was associated with prolonged length of stay, higher risk of disability in ADLs and mortality (55). One of the first prospective studies on frailty and CVD was conducted by Purser et al. and showed that 27% to 50% of older adults admitted to cardiology wards were frail (56). The study also showed that older adults with severe coronary artery disease and slow gait speed were 3-times more likely to die at 6-months compared to non-frail patients (adjusted OR 4.0 95% CI 1.1-6.1) (56). The Frailty ABCs (Frailty Before Cardiac Surgery) study showed that slow gait speed was associated with a 3-fold increase in post-operative mortality or major morbidity (57). In TAVR patients, Schoenenberger et al. demonstrated that frailty was predictive of 3- to 4-fold increase in functional decline (as measured by disabilities in ADLs) and major cardiac adverse events at 1-year (58). In a recent systematic review and meta-analysis, objective frailty measures in older patients undergoing transcatheter aortic valve interventions (TAVI) were predictive of poor outcomes (59). The

accrual of these studies has provided influential evidence to incorporate frailty in risk assessments to improve the outcomes of older adults with acute cardiac conditions.

Challenges, Burden and Costs of Frailty in Acute Cardiac Care Settings

Frail patients have diminished physiological capacity (anabolic insufficiency) to fully recovery from an acute cardiac event or surgery (catabolic stressors) (7). Hospitalization-associated stressors such as bedrest and undernutrition exaggerate the catabolic response (7). Therefore, following an acute cardiac event or cardiac surgery, frail older adults are at risk of poor recovery, low self-efficacy, poor quality of life, risk of nonfatal and fatal adverse events (39). Goldfarb et. al. showed that frailty was associated with a marked increase in hospitalization costs after coronary artery bypass grafting or heart valve surgery and that the higher expenditures were related to major complications and prolonged length of hospital stay (60). Older patients who have undergoing cardiac surgery are shown to be at greater risk of delirium and cognitive decline at 1-month, due to sleep deprivation, dehydration, anxiety, pain, bedrest and polypharmacy experienced during hospitalization (10). Identifying patients who are at increased risk for morbidity, mortality and increased healthcare costs will enable clinicians to make informed medical decisions to provide patient-centered care.

Management of Frail older Adults in Acute Cardiac Care Settings

Optimal care management for frail older adults with acute CVD revolves around addressing geriatric risks. Early mobilization, minimized sedation, deprescription of medication, orientation, are all critical elements to provide a patient-centered approach in critical care settings (61-65). In recent years, a heart team approach has been suggested which includes a multidisciplinary team of physicians, pharmacists, physiotherapist, and nutritionists (66). The

gold standard approach for the management of frail older adults in hospital is the Comprehensive Geriatric Assessment (CGA), other methods include Acute Care for Elders (ACE) Units, delirium prevention and careful attention to hospitalization-associated stressors (low physical activity, malnutrition, polypharmacy) (67, 68). For the management of critically ill patients, healthcare professionals have suggested the application of the ABCDEF bundle (Assess, prevent, and manage pain; Both spontaneous awakening and breathing trials; Choice of sedation; Delirium monitoring and management; Early mobilization and exercise; Family engagement/empowerment) (69). The goal of the ABCDEF bundle is to minimize delirium and increase physical activity in hospitalized older frail adults. However, these strategies have mostly been applied to intensive care settings. How accurately these strategies are implemented in day-to-day clinical practice has yet to be explored (70, 71). Table 1 outlines the recommended components to integrate in the management of frail older adults during hospitalization (10, 72).

Table 1: Components of Hospital Care for the Management of Frail Older Adults

Components	Evidence	Implementation Strategies
Early mobilization	• Reduced weakness and improved functional recovery and walking distance before discharge • Shorter length of stay in intensive care units	• Interdisciplinary communication to assess patient's readiness to mobilize • Limit physical restraints (lines, drains and tubes)
Minimization of sedation	• Without benzodiazepines, patients are increasingly ventilator-free and have no delirium	• Use a tapered dexmedetomidine dosage routine

	• Low dose dexmedetomidine decreases incidence of delirium	• Use the sedation-agitation scales to assess need for sedation
Reducing Polypharmacy	• Deprescription resulted in less decline in functional and cognitive status	• Complex drug routines can be minimized by physician and pharmacists
Orientation	• Verbal and visual orientation lowered delirium occurrence • Sensory checks (hearing aids and glasses) are valid ways to reduce delirium	• Cognitive stimulation through activities • Memory clues through family engagement • Availability of hearing aids and glasses • Orient to time and place
Nutrition	• Malnutrition can be associated with adverse outcomes and mortality	• Nutritionist consultation • Increase and optimize feeding and protein intake
Physiotherapy	• Exercise is associated with independent functional at discharge	• Include resistance training (i.e., chair rises)

Medical decisions for frail patients depend on the benefits and risks inherent to specific treatments and procedures. Conventional cardiovascular therapies are more likely to cause adverse side effects in frail older adults. For example, diuretic therapy in frail patients with heart failure is more likely to lead to urinary incontinence, and progression of renal dysfunction, delirium and falls (73). Vasodilators have also been shown to lead to orthostatic hypotension in frail older adults (73). Attention to antithrombotic and anticoagulants dosage over the age of 75 years old is important to minimize the risk of bleeding (74). Studies have also shown frail patients are less likely to receive catheterization or cardiac surgery because they are at increased

risk of complications from these procedures (75). Therefore, these patients are recommended to undergoing less invasive surgeries such as transcatheter rather than surgical aortic valve replacements or percutaneous coronary intervention (PCI) rather than coronary artery bypass grafting (CABG) (75).

Assessment of Frailty

To date, there are over 60 developed frailty assessment tools that have shown to be predictive of adverse outcomes (76). Most instruments focus on one of two models (1) the frailty phenotype: slowness as measured by gait speed, weakness as measured by handgrip strength, and low physical activity, exhaustion, and shrinking measured by questionnaires (2) accumulation of deficits model which consider comorbidities, social and psychological factors. With most instruments focusing on the former, frailty instruments focus on either a combination of the domains or consider them individually.

The common phenotypic scales focus on physical frailty and sarcopenia. The Fried scale consists of all 5 of these domains and the presence of ≥ 3 of 5 criteria will lead to a diagnosis of frailty (77). Physical performance measures such as Guralnik's SPPB consists of gait speed, chair rise and tandem balance, each section is scored out of a possible 4 and a total score of ≤ 5 of 12 suggests a diagnosis frailty (78). A systematic review determined the associated between SPPB and increased risk for mortality (79). Single-item physical measures such as 5-meter gait speed, handgrip strength using a dynamometer, chair rise test, have also been shown as incremental predictors of poor outcomes and disability, falls and mortality (57, 80-82).

Other frailty tools include the psychosocial domain of frailty to capture mood and cognition. Mood is commonly assessed with Geriatric Depression Scale (83). Cognition is assessed with Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment, or the Mini-Cog (84-86). Multidimensional scales such as the Essential Frailty Toolset (EFT) capture physical, cognitive, and nutritional frailty (87). Other similar tools include Edmonton Frail Scale (EFS) and the FRAIL scale (88). The accumulation of deficits model includes the Frailty Index (FI) which is a calculation based on the presence of "deficits" (i.e., symptoms,

signs, diseases and disabilities) and the Clinical Frailty Scale (CFS), which is based on the evaluation of the patient's symptoms, level of mobility, disabilities in ADLs and IADLs (89, 90). Commonly used frailty assessment tools are summarized in table 2.

Table 2: Summary of Frailty Assessment Tools

Instrument	Criteria	Frailty
Physical Frailty Scales		
Fried Scale	Weight loss, low physical activity, exhaustion, slowness, weakness	Frail ≥ 3 items; pre-frail = 1–2 items; robust = none
SPPB	Combination of performance on gait speed, balance, and chair rise time	Score ≤ 8 out of 12
Single-Item Frailty Assessment Tools		
Handgrip strength	Maximal strength as measured by handheld dynamometer	<26 kg for men, < 16 kg for women
Chair rise	Time to complete 5 chair rises	>15 seconds to complete 5 or inability to complete 5
Gait speed	Measured gait speed > 5 m	Frail ≤ 0.8 m/s
Multidimensional Frailty Assessment Tools		
FRAIL	Self-reported fatigue, resistance, ambulation, illnesses, loss of weight	Frail ≥ 3 items; Pre-frail = 1–2 items; robust = 0 items
EFT	Lower extremity weakness, cognitive impairment, anemia, hypoalbuminemia	Frail ≥ 3 -5; pre-frail = 1-2; robust = 0
CFS	Visual and written chart for frailty with 9 pictures	1 = very fit; 9 = terminally ill A continuous score. Frailty ≥ 5

Assessment of Frailty in Acute Cardiac Care Settings

A literature review was conducted to synthesize the evidence on frailty and outcomes in patients hospitalized for various cardiac conditions and cardiac surgeries. The following cardiac cohorts were explored: 1) acute coronary artery syndrome, 2) heart failure, 3) heart valve surgery and 4) cardiac surgery.

Acute Coronary Syndrome

Studies have demonstrated that frail older adults are at increased risk of coronary artery disease, risk of major bleeding when catheterization was performed, and at increased risk of mortality compared to non-frail older adults (91, 92). A post hoc analysis of the SILVER-AMI trial demonstrated a great heterogeneity in outcomes of older adults ≥ 80 years of age with myocardial infarction. When the multivariable model was further adjusted for mobility impairment, measured by Timed Up and Go (TUG) test, the increased odds of 6-month case fatality rate of the oldest-old (≥ 85 years) relative to middle-old (75-84 years) decreased from 44% to 29%, and the association was no longer statistically significant, suggesting that these differences are driven by mobility impairment, a marker of frailty (93). In a large study of 2,640 nonagenarians with acute myocardial infarction undergoing PCI, 40% were frail, as defined by the Rockwood definition, at admission and frailty progressively worsened during the course of hospital stay (94). A prospective cohort study on 552 patients with a diagnosis of acute coronary syndrome, demonstrated that frailty, defined by CFS, was associated with higher rates of readmission (HR 2.832, 95% CI 1.140, 7.037) (95). In another prospective study, patients with higher CFS had much longer length of stay after PCI compared to non-frail patients (14.1 ± 26.7 vs. 3.5 ± 8.8 days, $p < 0.001$) and were 5- and 6-times more likely to die within 30-days and 1-

year, respectively, compared to non-frail patients (HR 4.8, 95% CI 1.4, 16.3, $p = 0.01$; HR 5.9, 95% CI 2.5, 13.8, $p < 0.001$) (96).

Heart Failure

Frailty has been shown to coexist and be highly prevalent in heart failure (HF) patients and has been shown to be associated with adverse outcomes in many studies (97, 98). In patients with acute decompensated HF, low SPPB score at admission was associated with increased risk of disabilities in ADLs, mortality, and readmission (OR 5.4, 95% CI 1.82, 15.0) (55, 99). In a similar study, patients with an SPPB score of 0 compared to 9-12, had rates of 1-year mortality of 62% versus 9%, respectively (100). Chaudhry et. al. found that frailty as defined by slow gait speed was associated with 28% greater risk of hospitalization in patients newly diagnosed with HF (101). The authors also found that grip strength was associated with a 19% increased risk of hospitalization. Older patients with acute HF have a worse short-term prognosis and these worse outcomes were mostly due to comorbidity, frailty, and disability than to age (102). A study showed that frail patients, measured by the Fried phenotype, admitted to the emergency department for acute HF, had higher rates of 30-day mortality compared to non-frail patients (adjusted HR 2.5, 95% CI 1.0, 6.0; $p = 0.047$) (103). Lastly, mortality at 6-months in patients admitted for HF seemed to be modulated by the presence of disability as measured by Barthel Index and dementia as measured by the Mini-Mental Status Examination (MMSE) (104).

Heart Valve Surgery

Patients with heart valve diseases (aortic, mitral, and tricuspid valve diseases) undergoing surgery are at increased postoperative risk including mortality (105). Specifically, in patients

with severe aortic stenosis, assessment of frailty has played a central role in clinical decision-making for transcatheter aortic valve replacement (TAVR) versus surgical approaches (105, 106). Growing evidence has shown that preoperative frailty predicted functional decline, longer length of stay, postoperative complications, short-term and long-term mortality in patients undergoing TAVR (107-112). A sub study on the PARTNER trial, found that frailty (defined by serum albumin, dominant handgrip strength, gait speed, and Katz activity of daily living survey) was associated with increased mortality and poor quality of life at 6-months (OR 2.21, 95% CI 1.09, 4.46, $p = 0.03$) and 1-year (OR 2.40, 95% CI 1.14, 5.05, $p = 0.02$) after TAVR (113). The FRAILITY-AVR study was a prospective multi-center study that evaluated the prognostic value of 7 frailty tools in older adults undergoing TAVR. The main findings showed that the Essential Frailty Toolset (EFT) had the highest predictive value, the highest c-statistic, Bassein information criterion (BIC), and improvement in the discrimination slope (IDI) beyond the Society of Thoracic Surgeons (STS) score prediction of 1-year mortality and worsening disability (87).

Though data on frailty in patients undergoing mitral valve repair or replacement surgery is limited, there are a few studies that have examined transcatheter and surgical mitral valve replacement. In a large retrospective cohort study of 50,410 patients undergoing surgical mitral valve replacement, frailty was associated with postoperative complications, discharge destination other than home, longer length of stay, 30-day readmission and in-hospital mortality (114). In a prospective study of 213 patients admitted for percutaneous mitral valve repair, 46% were defined as frail by the Fried scale were at increased risk of mortality at 1-year, even after adjustment for European System for Cardiac Operative Risk Evaluation (EuroSCORE) II (HR: 2.88; 95% CI: 1.45, 5.73; $p = 0.003$) (115). Cost of hospitalization has been reported to be higher

in frail mitral valve patients, indicating that frailty has an important place in preoperative decisions for surgical candidates (116).

Cardiac Surgery

Preoperative frailty assessments have been seen to provide valuable prognostic information alongside operative risk scores, such as STS score and EuroSCORE II risk models (117, 118). In patients undergoing CABG or valve surgery, the addition of frailty to the EuroSCORE II resulted in a statistically significant improvement in the risk of poor 1-year functional survival when compared with the EuroSCORE II alone, indicated by an absolute IDI improvement of 6.7% and a category-free net reclassification index (NRI) classification improvement of 59.6% (119). Presence of preoperative frailty (defined as SPPB ≤ 9 or CFS ≥ 4) was associated with a 2- and 3.5-fold higher risk of poor functional survival 1-year after cardiac surgery (OR 2.08, 95% CI 1.050, 4.12 and OR 3.44, 95% CI 1.69, 7.00).

Two landmark studies have focused on the relationship between frailty and mortality in cardiac surgery settings. Sündermann et al. showed that frailty, defined by the comprehensive assessment of frailty (CAF), increased 30-day ($p = 0.05$) and in 1-year mortality rates ($p = 0.01$) (120, 121). Lee et al. demonstrated frailty, characterized by disability, ambulation dependence and dementia, increased the risk of postoperative mortality (OR 1.8, 95% CI 1.1-3.0) and institutional discharge (OR 6.3, 95% CI 4.2, 9.4) (122). In a prospective study, presence of frailty at baseline, as measured by SPPB was associated with a 8-fold higher risk of postoperative delirium (123). A recent systematic review demonstrated that even with the variety of frailty assessment tools used in cardiac surgery settings, frailty remains predictive of poor post-operative outcomes (124).

Conclusion

Although the above studies explored a variety of frailty assessment tools, the consensus is that frailty predicts poor patient outcomes in older adults hospitalized for acute cardiac conditions. After an acute cardiac event or cardiac surgery, frail adults are at risk for nonfatal, fatal events and poorer quality of life (43). The presence of frailty can lead to the selection of appropriate treatment options such as TAVI or implantable cardioverter-defibrillator (CDI) insertion versus surgical options (39). Frailty assessments in day-to-day clinical practice can provide prognostic information and can assist clinicians in determining optimal care pathways. Addressing the unique risk profile of frail patients in hospital can prevent deterioration in physical capacity. A care plan incorporating a multidisciplinary team of cardiologists, geriatricians, physiotherapists, occupational therapists, pharmacists, and nutritionists can provide targeted interventions and closer follow-up to mitigate adverse outcomes.

Chapter 3: Commentary on Literature Review

The literature review revealed that frailty is associated with decreased functional status, longer length of stay, major complications, increased morbidity, and mortality in patients with various acute cardiac conditions. Due to the recognized impact of frailty on patient outcomes and the healthcare system, many international guidelines have recommended the screening of frailty during healthcare encounters to improve patient management (125). However, despite the abundant studies emphasizing the predictive value of frailty in older adults with acute cardiac conditions, the applicability of frailty assessment tools in acute cardiac settings are limited. The low level of utilization in clinical decision-making is due to the (1) lack of direction on how to integrate frailty information in clinical settings and (2) confusion over which frailty assessment tool to select (19).

Frailty assessment tools are not easy to interpret by non-geriatricians, therefore, the information that frailty assessment tools provide are limited to cardiologists. Applicability of multidimensional frailty tools in day-to-day clinical practice is limited by length and personnel requirements. In hospital settings, patients' medical status is also an important confounder to consider. Presence of disease-triggered changes in cognitive and physical status can hinder the validity of these assessments. Structured verbal questionnaires and interviews may overcome the influence of acute physical limitations and comorbidities; however, these are usually impractical because they rely on the patient's memory and cognitive status to accurately report which might be influenced by acute changes due to delirium. In terms of practicality, single-item measures such as 5-meter gait speed, chair rise time and handgrip strength, may be suitable for hospital settings since they are objective, quick and easy to integrate in day-to-day practice. A frailty assessment tool that can overcome the unique challenges encountered in acute cardiac settings

and that could be easily interpreted, will enhance the integration frailty assessments in the medical care of older patients with acute cardiac conditions.

Chapter 4: Transition to Cohort Study

After exploring the construct of frailty in various cardiac conditions and surgeries, cardiac surgery has been identified as a pertinent setting for frailty assessments since open-heart surgery represents a strong iatrogenic stressor to patients. In this context, frailty defines the patients' baseline resiliency that will determine their post-operative recovery and risk for complications. Therefore, in comparison to other less invasive cardiac surgeries such as transcatheter interventions, cardiac surgery is considered as a high-yield setting for frailty assessments (6).

Simple performance measures of frailty such as chair rise test, 5-meter gait speed have all been shown to predict adverse patient outcomes in patients undergoing cardiac surgery (126). Our cohort study aimed to explore the prognostic value of handgrip strength (HGS), a single-item frailty assessment tool. HGS is measured by a handheld dynamometer and does not rely on lower extremity muscle function and mobility which may be impacted by acute illness. HGS can also be easily measured in patients who are bedridden or unable to move due to physical restraints such as intravenous poles, nasal cannulas, and chest tubes (which are highly common in hospital settings). The utility and practicality of handgrip strength makes it an appropriate bedside measure of physical frailty in acute cardiac settings.

HGS is a widely used as a measure of muscle strength deterioration and it is an important index for diagnosing sarcopenia in geriatric medicine (127). HGS is a simple measure with high prognostic value and has shown to be an indicator of adverse outcomes, non-cardiovascular and cardiovascular mortality among older community-dwelling adults (128-130). Based on its predictive validity, the HGS has been recommended as a vital screening measure in various clinical settings (131). HGS was also shown to be associated with disabilities in ADLs, cognitive decline, and mobility limitation and longer length of stay in older adults hospitalized for

abdominal or general surgery (132-139). Frailty as a composite of walk test, Katz ADLs, preoperative serum albumin level and HGS, and the individual components have all been shown to be independent predictors of poor outcomes and all-cause mortality after TAVR (113). In patients with HF, impaired HGS was predictive of postoperative complications and increased mortality after ventricular assist device (AVD) (140). To date, the literature on HGS in patients undergoing cardiac surgery has been limited with small and inconclusive studies. Thus, the following study aims to explore the prognostic value of HGS, as a measure of the frailty, in older adults undergoing cardiac surgery.

Chapter 5: Cohort Study: Submitted Manuscript

“Prognostic Value of Handgrip Strength in Older Adults Undergoing Cardiac Surgery”

Our cohort study on the prognostic value of handgrip strength in older adults undergoing cardiac surgery are presented in the manuscript below.

This study was presented as an abstract at the Canadian Cardiovascular Congress on October 21-24, 2020. The manuscript was submitted to Canadian Journal of Cardiology on May 15, 2021.

Prognostic Value of Handgrip Strength in Older Adults Undergoing Cardiac Surgery

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Short title: Handgrip Strength in Cardiac Surgery

Conflicts of interest: none to disclose

Key words: frailty, handgrip strength, cardiac surgery, outcomes

Word count: 5206

Abstract

Background: While multi-dimensional frailty scales have been proven to predict mortality and morbidity in cardiac surgery, there is need for rapid tools that could be easily administered at point-of-care. Handgrip strength (HGS) is an attractive option which can be measured in acutely ill and bedbound patients, although it has yet to be validated in a large cardiac surgery cohort.

Methods: This is a post-hoc analysis of a multicenter prospective study in older patients undergoing coronary artery bypass grafting (CABG) and/or valve surgery between 2011 and 2019. HGS was measured before surgery and classified by sex-stratified cutoffs. The primary outcome was 1-year mortality and secondary outcomes were 30-day mortality, discharge disposition, and prolonged length of stay.

Results: There were 1,245 patients included in the analysis (mean age 74.0 ± 6.6 years; 30% females). Weak HGS was associated with advanced age, heart failure, kidney disease, malnutrition, and various frailty scales. In those with weak vs. normal HGS, 1-year mortality was 17% vs. 6%, 30-day mortality was 10% vs. 3%, prolonged length of stay was 34% vs. 19%, and discharge to a healthcare facility was 45% vs. 26% (all $P < 0.001$). After adjustment, HGS was predictive of 1-year and 30-day mortality, with odds ratios of 2.44 (CI 1.39-4.29) and 2.83 (CI 1.38-5.81), respectively. The HGS cutoff <26 kg in men and <16 kg in women had the highest predictive performance.

Conclusions: HGS is a simple and effective tool to identify patients at higher risk of mortality and protracted recovery after cardiac surgery.

Brief Summary

Frailty has been proven to predict mortality and morbidity in older adults undergoing cardiac surgery, however, there remains a need for a rapid and simple frailty tool in acute care settings. A post-hoc analysis on a multicenter prospective study was conducted, including patients over the age of 60 undergoing cardiac surgery with recorded preprocedural handgrip strength. Handgrip strength proved to be an effective measure at predicting all-cause mortality and protracted recovery.

INTRODUCTION

As the global population ages, more than half of cardiac surgeries are performed in patients aged 75 years and older (1). Older patients face greater risks of mortality and morbidity after cardiac surgery, and risk prediction is necessary to align care with patients' preferences and values (2-4). Frailty is a geriatric syndrome of decreased physiological reserve and resistance to stressors – such as cardiac surgery – resulting in adverse health outcomes (5-7). Evidence has consistently shown that objective markers of frailty are pervasive and predictive of adverse health outcomes and increased healthcare expenditures following cardiac surgery (8-15). While frailty is increasingly evaluated in clinical and research settings, integration in real-life remains suboptimal due to time and personnel required, and the limited applicability of these assessments in bed-bound patients in cardiovascular intensive care settings (16).

HGS has been extensively validated as a screening tool for frailty and sarcopenia (17). It is an objective measure of frailty that can be assessed in patients irrespective of acuity and mobility (18). In community-dwelling older adults, HGS has been associated with mortality and disability (19-21). In abdominal surgery cohorts, HGS has been associated with operative mortality and length of stay (22, 23). In cardiac surgery cohorts, studies with HGS as the independent variable have been small and inconclusive, and studies with HGS within a composite frailty score have been unable to clarify its contribution to risk prediction. Also, no study to date has compared published HGS cutoffs in this cohort (24-26). Thus, the objective of this study was to analyze HGS as a predictor of mortality and morbidity following cardiac surgery.

METHODS

Study Design

A post hoc analysis was performed of the McGill Frailty Registry and surgical subset of the Frailty-AVR Study. The McGill Frailty Registry prospectively enrolled patients undergoing cardiac surgery at two tertiary care academic centers in Montreal, Canada. The Frailty-AVR Study prospectively enrolled patients undergoing aortic valve replacement at 14 centers in Canada, the United States and France. The study design has been previously described (27). Frailty and other geriatric domains were evaluated preoperatively using questionnaires and physical performance batteries including HGS. Vital status and adverse events were evaluated after surgery using electronic medical records and telephone questionnaires at 12 months. The study was approved by the institutional review boards at participating hospitals and patients signed informed consent forms prior to participating.

Study Population

Inclusion criteria for the analysis were: (1) age 60 years or older, (2) urgent or elective CABG and/or heart valve surgery, (3) surgery performed between October 2011 and December 2019, and (4) HGS measured and recorded preoperatively. Exclusion criteria were: (1) emergency surgery, (2) clinical instability (unstable vital signs, refractory ischemia, or actively decompensated heart failure), (3) severe neuropsychiatric impairment, or (4) prohibitive language barrier.

Handgrip Strength Assessment

HGS was measured by trained observers using a Jamar hydraulic handheld dynamometer. The dynamometer was adjusted to grip size, and the patient was seated with their elbow bent at

90 degrees. The patient was asked to squeeze the dynamometer on three separate trials – once with each hand and then with the strongest hand – allowing time for rest between trials. The highest of the three measurements was retained and recorded to the nearest kilogram. HGS was classified as weak based on the following cutoffs: (i) <26 kg in men and <16 kg in women according to the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project (28), (ii) <30 kg in men and <20 kg in women according to the European Working Group on Sarcopenia in Older Persons (EWGSOP) (17) (iii) <29-32 kg in men and <17-21 kg in women according to the Fried Scale body mass index (BMI)-stratified cutoffs (29), (iv) <1.002 kg/m² in men and <0.557 kg/m² in women according to the FNIH Sarcopenia Project BMI-indexed cutoffs (28).

Covariates

Concurrently with HGS assessment, weight was measured using a calibrated scale and height was measured using a stadiometer. Comorbidities, cardiac status, and surgical information were extracted from the electronic medical records. Frailty was represented with the Essential Frailty Toolset (EFT), Short Physical Performance Battery, Clinical Frailty Scale (CFS), and Fried Scale. Nutritional status was assessed using the Mini-Nutritional Assessment Short Form. Depression was assessed using the Geriatric Depression Scale Short Form.

Outcomes

The primary outcome was 1-year all-cause mortality following surgery. Vital status was ascertained by a combination of medical records, death certificates, linkage to administrative data, and telephone interviews with patients and family members. Secondary outcomes were 30-

day all-cause mortality, prolonged postoperative length of stay defined by the Society of Thoracic Surgeons as ≥ 14 days, and discharge to a healthcare facility (location other than home).

Statistical Approach

HGS was analyzed primarily in its dichotomous form based on *a priori* cutoffs for clinically relevant weakness, and secondarily in its continuous form. Continuous variables are presented as means $\pm$ SD and compared between HGS groups using the student t-test. Categorical variables are presented as counts and percentages and compared between HGS groups using the chi-square test. Multivariable logistic regression was used to determine the association between HGS and mortality, adjusting for the following covariates: age, sex, BMI, diabetes, atrial fibrillation, cerebrovascular disease, peripheral artery disease, myocardial infarction, heart failure, left ventricular ejection fraction (LVEF), pulmonary hypertension, chronic obstructive pulmonary disease (COPD), glomerular filtration rate (GFR), prior cardiac surgery, urgency, and type of cardiac surgery. Models were repeated with the different HGS cutoffs to compare their Area Under the Receiver Operating Characteristics Curve (AUC) and Bayesian Information Criterion (BIC) performance metrics. Study data was managed using the REDCap electronic data capture tools held at the Lady Davis Institute's Centre for Clinical Epidemiology (30). Statistical analyses were performed using STATA version 16 (College Station, Texas).

RESULTS

Baseline Characteristics

Our cohort consisted of 1,245 patients, of whom 530 underwent isolated CABG surgery, 366 underwent isolated valve surgery and 349 underwent heart valve and CABG surgery. The mean age was 74.0 ± 6.6 years with 22% octogenarians and 30% females. The mean HGS was 35.9 ± 8.6 kg in men and 20.4 ± 5.8 kg in women. A comparison of priori cutoffs favoured the FNIH cutoff (<26 kg in men and <16 kg in women), therefore, this was used for the presentation of baseline characteristics (see section below). Patients with weak HGS were more likely to be older women with higher rates of heart failure, pulmonary hypertension, kidney disease, and anemia. They were also more likely to be frail according to the EFT, CFS, and Fried Scale, with higher rates of depression, malnutrition, slow gait speed, and disability in basic and instrumental activities of daily living. Baseline characteristics stratified by HGS are presented in Table 1.

Unadjusted Outcomes

At the time of data analysis, 1,143 complete cases had accrued at least 1 year of follow-up for ascertainment of the primary outcome measure. A total of 89 (8%) patients had died, with higher rates of 1-year mortality observed in those with weak HGS (17% vs. 6%; $p < 0.001$). Secondary outcome measures stratified by HGS are presented in Figure 1, with higher rates of 30-day mortality, prolonged postoperative length of stay, and discharge to healthcare facilities observed in those with weak HGS.

Adjusted Analyses

In the multivariable logistic regression model, the predictors of 1-year mortality were: weak HGS (OR 2.44; 95% CI 1.58, 4.50), pulmonary hypertension (OR 2.54, 95% CI 1.33, 4.85), prior stroke (OR 2.56; 95% CI 1.21, 5.41), and mitral valve surgery (OR 2.70, 95% CI:

1.30, 5.61) (Table 2). The predictors of 30-day mortality were: weak HGS (OR 2.83; 95% CI 1.38, 5.81), female sex (OR 2.24, 95% CI 0.99, 1.11), heart failure (OR 2.93, 95% CI 1.48, 5.81), peripheral artery disease (OR 2.47; 95% CI 1.02, 5.93), and mitral valve surgery (OR 3.14, 95% CI 1.2, 8.17) (Table 3). HGS was similarly predictive of prolonged postoperative length of stay (OR 1.88, 95% CI 1.26, 2.83) and discharge to healthcare facilities (OR 1.82, 95% CI 1.21, 2.74) (Supplementary Tables S1 and S2).

Comparison of HGS Cutoffs

The prevalence and predictive value of the different HGS cutoffs are presented in Table 4. Depending on the cutoff chosen, 12-33% of patients were classified as having weak HGS. When the main multivariable logistic regression model was re-analyzed with each of the HGS cutoffs, the FNIH cutoff achieved the highest adjusted odds ratio and the optimal BIC performance metric for the prediction of 1-year mortality. When re-analyzed with HGS in its continuous form, each 5-kg decrement in HGS was associated with a 20% increase in 1-year mortality (OR 1.038 per 1-kg, 95% CI 1.003, 1.075) with no evidence of effect-modification by sex (interaction $p = 0.20$).

DISCUSSION

This multicenter study has elucidated the prevalence and prognostic value of weak HGS in a large sample of older adults undergoing diverse types of coronary and heart valve surgery. Our results can be summarized as follows: (1) weak HGS is reflective – albeit not diagnostic – of frailty as measured by multi-item scales, (2) weak HGS is independently predictive of short and midterm mortality as well as hospital length of stay and disposition, (3) the FNIH cutoff

performs well to predict midterm mortality. Thus, HGS is an efficient bedside tool, and is the first step to identify vulnerable patients who may need further risk stratification and geriatric assessment.

HGS has previously been validated as a predictor of cardiovascular and non-cardiovascular mortality in medical populations (20, 31-34). In a meta-analysis of 39 studies focusing on patients with critical illnesses or chronic diseases, each 5-kg decrement in HGS was associated with a 39% increase in mortality (35). In another meta-analysis of 7 studies focusing on patients with stable cardiac disease (ischemic heart disease, chronic heart failure, cardiomyopathies, valvulopathies, and arrhythmias), each 5-kg decrement in HGS was associated with a 14% increase in heart failure hospitalization and a 19% increase in cardiovascular mortality (24); similar in magnitude to our results.

HGS has been validated as a predictor of postoperative morbidity in surgical populations (36) but studies in cardiac surgery have been small and single-centered. A study of 50 cardiac surgery Brazilian patients showed that HGS was inversely correlated with age, EuroSCORE, length of mechanical ventilation, and length of hospital stay and directly correlated with fat-free mass (25, 37). A Chinese study of 212 cardiac surgery patients, showed that pre-to-postoperative weakening in HGS was associated with 30-day complication rate (38). A study of 312 vascular surgery patients at a American academic center showed that HGS was associated with 30-day complications, mortality and disposition to healthcare facilities (39).

The aforementioned studies used different cutoffs for “weak HGS,” which varied by up to 20% between studies. Thus, there exists variability in clinical implementations of HGS. The most comprehensive evaluation of HGS cutoffs to date was led by the FNIH group that sought to identify clinically relevant weakness in a cross-sectional sample of 20,847 community-dwelling

adults, validating the HGS cutoff of <26 kg in men and <16 kg in women (40). The FNIH cutoff, when compared to other cutoffs, identified fewer patients as weak but demonstrated greater predictive value for all-cause mortality in our cohort. Indexation of HGS to BMI did not appear to add predictive value.

Our practice is to measure HGS as part of a frailty assessment to inform risk prediction and guide decision making in older adults referred for cardiac surgery. Complementary physical performance tests assess lower-extremity strength, namely chair rise time and 5-meter gait speed, but these may not be feasible in non-mobile or acutely ill patients. Similarly, self-reported questionnaires may not be feasible in confused or acutely ill patients. HGS, by virtue of its simplicity and portability, can overcome these challenges, yielding an objective biomarker for physical frailty that can be rapidly and repeatedly measured in almost any patient. In surgical candidates with weak HGS, our next step is often to consult physical therapy to perform a complete assessment and initiate pre- or post-operative strengthening interventions as indicated.

Measuring HGS is a first step to identify patients standing to benefit from various forms of strengthening interventions and cardiac rehabilitation. Given the association of weak HGS with mortality and morbidity, prehabilitation is likely to be beneficial to mitigate undesirable health outcomes. The preoperative period should be viewed as a window of opportunity to de-frail patients prior to surgery. In a pilot randomized clinical trial, 4 weeks of prehabilitation exercises resulted in improved frailty as measured by 5-meter gait speed (41). Early mobilization after cardiac surgery resulted in shorter length of stay and fewer complications (42). Considering the correlation between HGS and non-physical domains of frailty, multi-component interventions addressing nutrition and cognition are likely to be of even greater relevance (43).

HGS offers prognostic information operative risk stratification before cardiac surgery, however, is not specific or sensitive enough to use as a single-item diagnostic test for frailty or screening test for case-finding, respectively. Accordingly, in patients thought to be robust based on normal HGS, 30% would be reclassified as frail based on slow gait speed and 10% based on EFT score ≥ 3 . Conversely, in patients found to be frail based on weak HGS, 27% would be reclassified as robust based on normal gait speed and 62% based on EFT score < 3 . The potential disagreement between HGS and EFT is not unexpected given that the latter requires more than just the physical domain of frailty to be impaired (22). Combining HGS and EFT is synergistic in identifying multiple facets of frailty encompassing upper and lower extremity strength, cognition, nutrition, and anemia.

LIMITATIONS

Several limitations merit discussion. Firstly, HGS measurements in outpatients were reflective, for the most part, of frailty at a baseline while those in hospitalized patients were dynamically influenced by illness severity and acuity. That said, HGS should be less influenced by illness than other physical tests which rely on walking ability (44), and it was systematically measured after medical stabilization. Secondly, characteristics for non-enrolled patients were not readily available for the McGill Frailty Registry, although they were for the FRAILTY-AVR Study and did not suggest systematic differences between enrolled and non-enrolled patients (with the main reason for non-enrollment being logistical in relation to research assistant availability). Thirdly, this study was not designed to test the incremental value of HGS in addition to the EFT, but rather to examine the prognostic value of HGS under the assumption that broader frailty scales were not immediately accessible.

CONCLUSION

Handgrip strength is a practical and objective test to identify older adults undergoing cardiac surgery at greater risk of fatal and nonfatal adverse events. Patients with weak HGS, irrespective of age and comorbidities, were found to have higher rates of prolonged hospital length of stay, discharge to locations other than home, and death. HGS is ideally implemented alongside comprehensive frailty assessments, although in certain acutely ill or non-mobile patients, HGS may be the only accessible physical performance test. While there are various validated cutoffs, our comparison of four indexed and nonindexed cutoffs favored the FNIH cutoff. Patients with weak HGS should be further assessed for evidence of physical frailty and sarcopenia, in which case they would be likely to benefit from strengthening interventions to support their recovery and preserve their functional status.

Acknowledgements

The authors thank the research assistants at the participating sites for the recruitment of patients and the collection of data.

Funding Sources

Rosie Fountotos holds the Gordon Phillips Fellowship and Graduate Excellence Fellowship from the McGill Faculty of Medicine and Health Sciences.

Disclosures

None.

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Figure Legend

Figure 1

Title: Postoperative Outcomes According to HGS Cutoff

Legend: Based on HGS cutoffs of 26 kg in men and 16 kg in women. Asterix represents $p < 0.01$. Bar height represents incidence of outcomes. OR and CI represent adjusted odds ratio and 95% confidence interval. Other abbreviations as in Table 1.

Figure 1. Postoperative Outcomes According to HGS

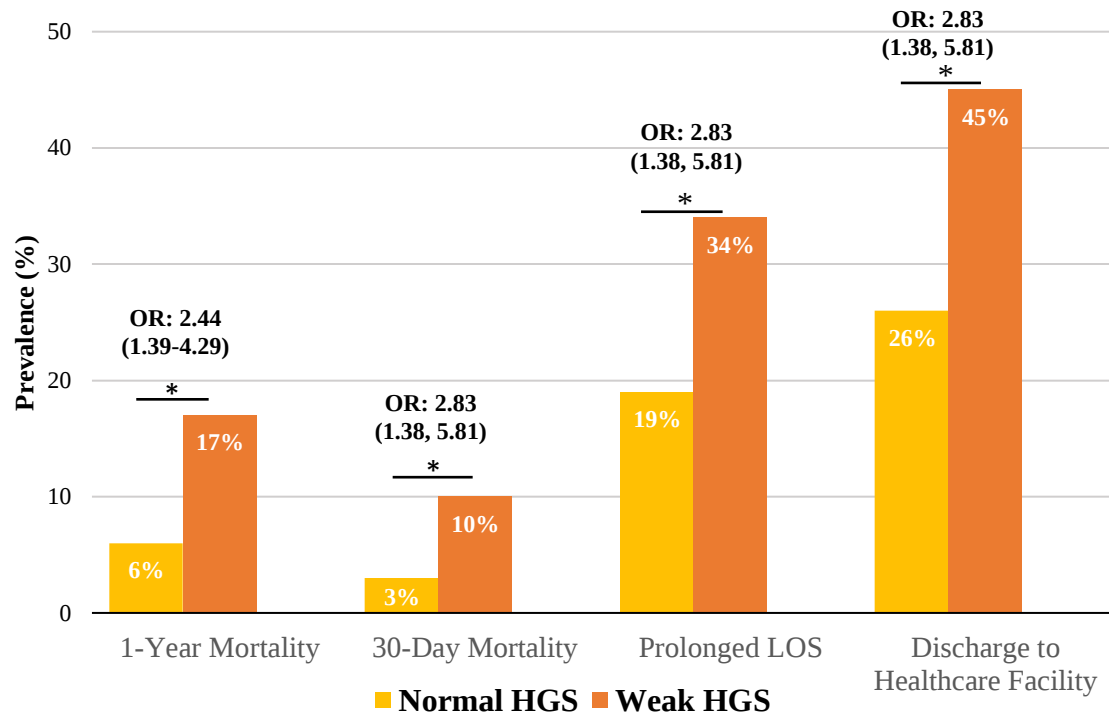


Table 1. Baseline Characteristics According to HGS

	Overall N=1,245	Normal HGS N=1088	Weak HGS N=157	p-Value
Age, years	74 ± 6.6	73.7 ± 6.6	76.5 ± 6.6	<0.001
Female sex	379 (30)	314 (29)	65 (41%)	0.001
BMI, kg/m ²	28.2 ± 5.4	28.3 ± 5.3	27.3 ± 6.1	0.04
Diabetes	442 (36)	383 (35)	59 (38)	0.56
Stroke	81 (7)	72 (7)	9 (6)	0.67
Atrial fibrillation	240 (19)	207 (19)	33 (21)	0.55
Myocardial infarction	410 (33)	366 (34)	44 (28)	0.16
Peripheral arterial disease	144 (12)	127 (12)	17 (11)	0.76
COPD	166 (13)	148 (14)	18 (11)	0.46
Heart failure	308 (25)	258 (24)	50 (32)	0.03
LVEF, %	55 ± 13.2	55.0 ± 13.2	55.0 ± 13.1	0.99
PASP, mmHg	37.0 ± 15.0	36.3 ± 14.7	41.9 ± 16	<0.001
GFR, mL/min/1.73 m ²	64.5 ± 16.2	65.1 ± 16	60.7 ± 17.1	0.002
Procedural				
STS PROM, %	2.6 ± 2.6	2.5 ± 2.4	3.6 ± 4.0	<0.001
EuroSCORE II, %	4.4 ± 4.8	4.2 ± 4.5	5.9 ± 6.5	<0.001
Prior cardiac surgery	86 (7)	77 (7)	9 (6)	0.53
Urgent surgery	271 (22)	230 (21)	41 (26)	0.16
Isolated CABG	530 (43)	483 (44)	47 (30)	0.002
Isolated valve surgery	366 (29)	308 (28)	58 (37)	
Combined surgery	349 (28)	297 (27)	52 (33)	
Frailty Markers				
Frail by EFT ≥3/5	208 (17)	150 (14)	58 (38)	<0.001
Frail by CFS ≥5/9	93 (8)	65 (6)	28 (18)	<0.001
Frail by SPPB ≤8/12	609 (49)	495 (45)	114 (73)	<0.001
Frail by Fried ≥3/5	268 (22)	184 (17)	84 (54)	<0.001
Depressed by GDS ≥2/5	296 (24)	246 (23)	50 (32)	0.01

Malnourished by MNA $\leq 7/14$	79 (6)	58 (5)	21 (13)	<0.001
Dependent by OARS $\geq 1/14$	286 (23)	216 (20)	70 (45)	<0.001
Albumin, g/dL	39.1 $\pm$ 5.2	39.4 $\pm$ 5.1	37.6 $\pm$ 5.6	<0.001
Hemoglobin g/dL	128.1 $\pm$ 17.9	129.3 $\pm$ 17.7	119.8 $\pm$ 17.1	<0.001

Based on HGS cutoffs of 26 kg in men and 16 kg in women. Values are mean $\pm$ SD or N (%).

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CFS, Clinical Frailty Scale; COPD, chronic obstructive pulmonary disease; EFT, Essential Frailty Toolset; GDS, Geriatric Depression Scale; GRF, glomerular filtration rate; LVEF, left ventricular ejection fraction; MNA, Mini-Nutritional Assessment; OARS, Older Americans Resources and Services; PASP, pulmonary artery systolic pressure; SPPB, Short Physical Performance Battery; STS PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 2. Multivariable Logistic Regression Model for 1-Year Mortality

	OR (95% CI)	p-Value
Age, per 1 year	1.06 (1.01, 1.10)	0.01
Female sex	1.32 (0.78, 2.23)	0.23
BMI, per 1 kg/m ²	0.98 (0.94, 1.03)	0.53
Diabetes	1.17 (0.68, 1.99)	0.56
Stroke	2.56 (1.21, 5.41)	0.01
Atrial fibrillation	1.10 (0.61, 1.98)	0.75
Myocardial infarction	1.31 (0.77, 2.24)	0.32
Peripheral artery disease	1.39 (0.70, 2.77)	0.35
COPD	1.30 (0.67, 2.54)	0.45
Heart failure	1.47 (0.87, 2.48)	0.15
LVEF, per 1 %	1.00 (0.98, 1.01)	0.68
PASP ≥50 mmHg	2.54 (1.33, 4.85)	0.005
GFR, per 1 mL/min/1.73m ²	0.98 (0.96, 0.99)	0.008
Prior cardiac surgery	1.49 (0.65, 3.41)	0.35
Urgent surgery	1.77 (1.01, 3.10)	0.04
CABG	1.76 (0.94, 3.27)	0.08
AV Surgery	1.23 (0.69, 2.20)	0.48
MV Surgery	2.70 (1.30, 5.61)	0.008
Weak HGS	2.44 (1.39, 4.29)	0.002

Based on HGS cutoffs of 26 kg in men and 16 kg in women. AV, aortic valve; MV, mitral valve.

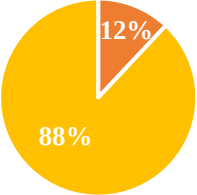
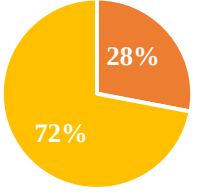
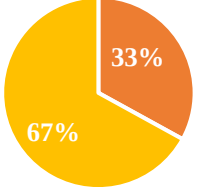
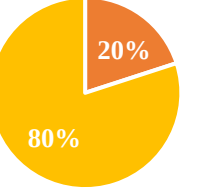
Other abbreviations as in Table 1.

Table 3. Multivariable Logistic Regression Model for 30-Day Mortality

	OR (95% CI)	p-Value
Age, per 1 year	1.05 (1.00,1.11)	0.06
Female sex	2.24 (1.12, 4.50)	0.02
BMI, per 1 kg/m ²	1.00 (0.95, 1.07)	0.85
Diabetes	0.52 (0.24, 1.15)	0.11
Stroke	3.20 (1.23, 8.28)	0.02
Atrial fibrillation	0.70 (0.31, 1.58)	0.39
Myocardial infarction	0.89 (0.41, 1.92)	0.78
Peripheral artery disease	2.47 (1.02, 5.93)	0.04
COPD	0.63 (0.22, 1.76)	0.38
Heart failure	2.93 (1.48, 5.80)	0.002
LVEF, per 1 %	1.00 (0.98, 1.03)	0.90
PASP ≥50 mmHg	1.97 (0.85, 4.57)	0.12
GFR, per 1 mL/min/1.73m ²	0.98 (0.96, 1.00)	0.38
Prior cardiac surgery	2.12 (0.75,5.99)	0.15
Urgent surgery	1.49 (0.68, 3.27)	0.32
CABG	1.53 (0.71, 3.31)	0.28
AV Surgery	1.20 (0.540, 2.68)	0.65
MV Surgery	3.14 (1.21, 8.17)	0.02
Weak HGS	2.83 (1.37, 5.81)	0.005

Based on HGS cutoffs of 26 kg in men and 16 kg in women. Other abbreviations as in Table 1 and 2.

Table 4. Prevalence and Predictive Value of Weakness According to Different HGS Cutoffs

	FNIH Cutoff	EWGSOP Cutoff	Fried Cutoff	FNIH Cutoff
Men	<26 kg	<30 kg	<29-32 kg $\propto$ BMI	<1.002 kg/BMI
Women	<16 kg	<20 kg	<17-21 kg $\propto$ BMI	<0.557 kg/BMI
HGS Normal (%) Weak (%)				
OR (95% CI)	2.44 (1.39, 4.30)	1.55 (0.94, 2.56)	1.19 (0.73, 1.95)	1.73 (0.95, 3.12)
AUC higher is better	0.778	0.771	0.765	0.775
BIC lower is better	645	651	654	651

Abbreviations: AUC, area under the receiver operating characteristics curve; BIC = Bayesian Information Criterion; BMI, body mass index; CI = confidence interval; EWGSOP, European Working Group for Sarcopenia in Older People; FNIH, Foundation for National Institutes of Health; OR, odds ratio (adjusted)

Supplementary Table S1: Multivariable Logistic Regression Model for Discharge to Healthcare Facility

	OR (95% CI)	p-Value
Age, per 1 year	1.08 (1.05, 1.11)	0.000
Female sex	2.59 (1.90, 3.52)	0.000
BMI, per 1 kg/m ²	1.01 (0.98, 1.04)	0.451
Diabetes	1.42 (1.05, 1.91)	0.022
Stroke	1.00 (0.56, 1.77)	0.993
Atrial fibrillation	1.33 (0.93, 1.92)	0.121
Myocardial infarction	1.20 (0.87, 1.66)	0.261
Peripheral artery disease	1.21 (0.78, 1.87)	0.394
COPD	1.20 (0.80, 1.79)	0.373
Heart failure	0.96 (0.68, 1.34)	0.808
LVEF, per 1 %	0.98 (0.97, 0.99)	0.005
PASP ≥50 mmHg	1.15 (0.70, 1.87)	0.578
GFR, per 1 mL/min/1.73m ²	0.99 (0.98, 1.00)	0.207
Prior cardiac surgery	0.58 (0.30, 1.10)	0.095
Urgent surgery	1.13 (0.78, 1.52)	0.472
CABG	1.67 (1.15, 2.43)	0.007
AV Surgery	1.27 (0.89, 1.82)	0.177
MV Surgery	1.98 (1.14, 3.44)	0.016
Weak HGS	1.82 (1.21, 2.74)	0.004

Based on HGS cutoffs of 26 kg in men and 16 kg in women. Abbreviations: AV, aortic valve; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; GRF, glomerular filtration rate; LVEF, left ventricular ejection fraction; MV, mitral valve; PASP, pulmonary artery systolic pressure.

Supplementary Table S2. Multivariable Logistic Regression Model for Prolonged Length of Stay

	OR (95% CI)	p-Value
Age, per 1 year	1.03 (1.00, 1.06)	0.034
Female sex	1.60 (1.15, 2.23)	0.005
BMI, per 1 kg/m ²	1.03 (1.01, 1.06)	0.014
Diabetes	1.18 (0.85, 1.63)	0.311
Stroke	1.74 (1.01, 2.98)	0.046
Atrial fibrillation	1.29 (0.88, 1.88)	0.192
Myocardial infarction	1.39 (0.99, 1.95)	0.059
Peripheral artery disease	1.79 (1.16, 2.75)	0.008
COPD	1.21 (0.82, 1.81)	0.372
Heart failure	1.29 (0.92, 1.82)	0.142
LVEF, per 1 %	0.99 (0.98, 1.00)	0.351
PASP ≥50 mmHg	1.84 (1.14, 2.94)	0.011
GFR, per 1 mL/min/1.73m ²	0.99 (0.98, 1.00)	0.013
Prior cardiac surgery	0.66 (0.35, 1.25)	0.203
Urgent surgery	1.11 (0.77, 1.60)	0.570
CABG	1.83 (1.23, 2.71)	0.003
AV Surgery	1.64 (1.31, 2.38)	0.009
MV Surgery	2.56 (1.48, 4.04)	0.001
Weak HGS	1.88 (1.25, 2.83)	0.002

Based on HGS cutoffs of 26 kg in men and 16 kg in women. Other abbreviations as in Table S1.

Chapter 6: Commentary on the Cohort Study

Our cohort study on a cardiac surgical subset from the McGill Frailty Registry revealed the strong prognostic value of HGS in an acute cardiac care setting. The measurement of HGS prior to cardiac surgery can identify patients at risk for post-operative mortality at 30-days and 1-year. HGS is a good approximate of overall muscle function and can be easily administered in acute care settings. HGS can avoid many of the pitfalls of physical performance tests that rely on lower limb muscle groups, since hospital-acquired deconditioning can lower patients' physical capacity to mobilize. HGS is a single-item measure of physical frailty with strong prognostic value of mid- and long-term mortality that requires minimal equipment, time and is well-tolerated even in wheelchair- and bed-bound patients. In preoperative populations, assessing frailty can guide the surgical approach taken, risk-stratify patients, predict likely adverse outcomes, and guide preoperative or postoperative interventions (141).

Routinely screening for frailty in older adults hospitalized for acute cardiac conditions or cardiac surgery can guide clinicians on medical decision-making that favors an uncomplicated postoperative recovery pathway. The commonly used "eyeball test" of frailty is subjective to interpretation, has low reproducibility, and is susceptible to miscommunication (142). The gold standard for frailty assessments is the CGA in hospitalized patients. In patients with HF, the CGA outperformed cardio-centric assessments and identified actionable items of frailty such as physical functioning, cognition, malnutrition, and disability (143). The CGA shows promising results in identifying those who would benefit from interventions targeting the physical and non-physical domains of frailty, however, they were proven to be neither feasible or cost effective (144). Physical performance measures of frailty have been validated in critical care, cardiology and cardiac surgery settings and are deemed more practical for day-to-day clinical practice,

which are in line with our results of our cohort study on HGS. However, these physical measures capture physical frailty and alone they may be limited in their role to guide therapeutic interventions designed to treat the multidimensionality of the frailty syndrome.

To achieve better discrimination and capture the frailty syndrome, multidimensional tools should then be considered. The Essential Frailty Toolset (EFT) (Appendix A) can capture an accurate picture of frailty and guide multicomponent interventions that support cognitive function, nutrition and exercise during hospitalization (145). The components of the EFT make the scale the most actionable frailty assessment tool (87). Each of these frailty deficits can be specifically targeted to using in-hospital interventions such as exercise, delirium prevention, nutritional support, and anemia correction. The EFT can be easily integrated into clinical practice since it is quick to perform at bedside, requires no equipment and is easy to interpret by clinicians.

With accrual of diagnostic and prognostic evidence of frailty in older adults with acute cardiac conditions, investigation of therapeutic trials are now required to improve care (146). During hospitalization, frail patients are at an increased need for care optimization to counteract the increased physiological stress from the acute cardiac condition that they are faced with. Frailty is marked by impairments in cognition, mood, muscle mass, strength and mobility which are all further compromised after an acute hospitalization (147). After 10 days of bedrest during hospitalization, older adults can loss up to 16% of muscle strength and 6% of muscle mass (148). The deconditioning during hospitalization can lead to decreased physical function at discharge with the acquisition of new disabilities in ADLs. This newly acquired vulnerable state can precipitate to conditions known as hospital-acquired disability and post-hospitalization syndrome. Thus, frail patients are more likely to be discharged from an index hospitalization

with lower physical independence and health-related quality of life. Multicomponent interventions targeting the physical and non-physical frailty deficits will ultimately empower patients to achieve full recovery and improve health-related quality of life after hospitalization.

Chapter 7: Transition to Randomized Clinical Trial

To our knowledge, there are no randomized clinical trials (RCTs) on multicomponent interventions addressing the needs of frail older adults in acute cardiac settings (149). Goldfarb et al. showed that early mobilization in cardiac intensive units are a feasible and effective strategy to minimize bedrest (150). In-hospital exercise programs on geriatric wards has shown to improve physical performance and ability to perform ADLs by time of discharge (151). “Prehabilitation” is a new concept that takes advantage of the waiting times before cardiac surgery that have been identified as opportunistic periods to intervene on frail patients. Prehabilitation provides exercise training, nutritional support and correctional interventions for other modifiable risk factors and has been shown to decreased length of stay in intensive care units, increase 6-MWT and increased quality of life (152).

Half of the registered RCTs have so far been on exercise training and/or nutritional supplementation and primarily in geriatric medicine and these studies were not conducted in-hospital and instead in outpatient settings (153, 154). Two recent RCTs showed that the implementation of a comprehensive geriatric assessment (CGA) to identify modifiable factors for frailty as targets for interventions resulted in significant reductions in functional decline and readmissions (18, 155). Though these CGA-guided multicomponent interventions improved clinical outcomes, they were proven to be resource intensive (144, 156). Therefore, a knowledge gap exists for a feasible multicomponent intervention to improve patient-centered care in older adults with acute cardiac conditions.

The next manuscript is the rationale and design of our randomized clinical trial (RCT) for a multicomponent intervention in hospitalized older patients with acute cardiac conditions. The multicomponent intervention aims to de-frail patients while combating hospitalization-associated

stressors that exacerbate frailty. Key elements in the care of older adults such as exercise, mobilization, nutritional support, and delirium prevention will be the focus of our interventions (65, 157-165). Besides objective clinical endpoints such as mortality, hospitalizations, and hospital length of stay, our primary outcome will be self-reported health-related quality of life and level of disability as measures of patient-centered outcomes. Given the absence of multicomponent frailty interventions in cardiology, we broadened our sample population to include older adults admitted with various forms of CVD to increase the applicability of our results to the field of geriatric cardiology.

Chapter 8: Randomized Clinical Trial: Manuscript in Submission

“Rationale and Design of the TARGET-EFT trial: A Multicomponent Acute Intervention in Frail Geriatric Patients with Cardiovascular Disease using the Essential Frailty Toolset”

The trial design of our randomized clinical trial on a multicomponent intervention in frail geriatric patients with cardiovascular disease is presented in the manuscript below.

The manuscript is currently in submission.

Rationale and design of the TARGET-EFT trial: A multicomponent acute intervention in frail geriatric patients with cardiovascular disease

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Running title: TARGET-EFT trial: Rationale and Design

Conflicts of interest: none to disclose

Key words: frailty, intervention, cardiovascular disease, outcomes

Word count: 5934

ABSTRACT

Background: Frailty is a primarily geriatric syndrome that can be exacerbated during hospitalization, resulting in protracted recovery, decompensation, and readmission. Measuring frailty in clinical practice can provide valuable prognostic information and guide decision-making. There is minimal evidence on frailty-based interventions for geriatric cardiac patients in the acute care setting. Thus, this trial aims to identify frailty using the Essential Frailty Toolset (EFT) and provide an acute, in-hospital, multicomponent intervention to correct identified frailty components. By focusing on physical activity, delirium prevention and nutrition, we provide a patient-centered approach to improve outcomes.

Methods: This is a single-center randomized clinical trial at a tertiary hospital in Montreal, Canada. Patients ≥ 65 years of age admitted to the cardiovascular unit will be screened for evidence of pre-frailty or frailty. The EFT will identify frailty deficits based on four criteria: physical weakness, cognitive impairment, hypoalbuminemia, and anemia. Patients will be randomly allocated to receive either usual care (control group), or targeted intervention based on the frailty deficits identified (intervention group). Patients will be followed 30-days post-hospital discharge to assess their recovery and health-related quality of life.

Conclusions: The randomized clinical trial will provide patients with multicomponent care by targeting physical and non-physical aspects of frailty. The aim of this trial is to support optimal recovery of frail patients and improve quality of life after hospitalization.

INTRODUCTION

Frailty is a multidimensional geriatric syndrome, characterized by an increased vulnerability to stressors, observed in 20-60% of patients with prevalent cardiovascular disease (CVD) (1). Frailty is a major risk factor for adverse events in cardiac patients, including protracted recovery, functional decline, poor health-related quality of life (HrQoL) and death (1).

With today's aging population and rising rates of CVD, cardiologists and cardiac surgeons are encountering a growing number of frail older patients that have complex cardiac and non-cardiac issues. Measuring frailty in clinical practice provides valuable prognostic information to help personalize treatment decisions (2). The Essential Frailty Toolset (EFT) is one of several tools that has been validated to predict death and functional decline in older patients undergoing cardiac surgery and transcatheter aortic valve replacement (3, 4). In addition to being among the most predictive tools and easiest-to-administer, the EFT was conceived to be actionable via practical interventions aimed at correcting the elicited deficits (5).

During the course of a hospital admission for CVD, frailty can be exacerbated by both illness-related and hospitalization-related stressors such as sleep deprivation, undernutrition, pain, anxiety, polypharmacy, and immobility (6). These compounding stressors exceed the frail patient's homeostatic reserves and thus lead to decompensation in the form of functional decline, complications, and readmissions, which have been termed "post-hospitalization syndrome" (6, 7). The ensuing physical deconditioning can also precipitate to disabilities in activities of daily living (ADLs), known as hospital-acquired disability (HAD) (8, 9). With more than 50% of adults over the age of 85 acquiring one new disability in ADLs upon discharge (8), frail older adults are at risk of losing functional independence after a single acute illness. In a study of older

adults hospitalized for general medical services, 41% of those who developed a HAD died within the first year post-hospitalization and 29% retained an acquired disability after one year (10).

Therapeutic de-frailing interventions, such as inpatient mobilization, nutritional supplementation, and cognitive stimulation, can mitigate the effect of hospitalization-related stressors. Consequently, these interventions prevent iatrogenic complications, such as deconditioning and delirium. Ultimately, these contribute to avoiding HAD and improving patients' health-related quality of life (HrQoL). Nevertheless, there is minimal evidence on targeted multicomponent interventions addressing frailty in geriatric patients within acute cardiac care settings (10). The Multicomponent Acute Intervention in Frail Geriatric Patients with cardiovascular disease using the Essential Frailty Toolset (TARGET-EFT) randomized clinical trial aims to address this knowledge gap in patients with CVD. Through a patient-centered approach that focuses on physical activity, nutrition, and delirium prevention, this trial aims to improve HrQoL of frail older patients hospitalized with CVD.

The primary objectives of the trial are:

1. To determine whether a multicomponent, targeted intervention to improve frailty, as measured with the EFT, will improve HrQoL at hospital discharge and 30-days post-discharge.
2. To determine whether this multicomponent, targeted intervention will reduce HAD measured at 30-days post-discharge.

The secondary objectives of the trial are to determine whether the intervention will 1) reduce 30-day readmission, 2) improve physical performance and frailty status, and 3) reduce in-hospital anxiety and depression.

METHODS

Study Design

The TARGET-EFT trial is a single-center parallel randomized clinical trial that compares a multicomponent, targeted intervention to usual clinical care. Participants are older adults admitted to the cardiovascular unit (CVU) at the Jewish General Hospital (JGH), an academic tertiary care center in Montreal, Quebec. The study aims to recruit 144 patients (72 individuals per allocation arm).

Patients who meet the inclusion criteria and consent to the trial will be randomly allocated to the control group for usual clinical care, or the intervention group for targeted treatments depending on the EFT deficits identified. Outcomes of interest in both groups will be assessed at three time points: 1) study enrollment, 2) discharge from the CVU and 3) 30 days after discharge. The study flowchart is illustrated in Figure 1. Figure 2 is a conceptual diagram outlining how the TARGET-EFT interventions aim to counteract frailty deficits and hospitalization-related stressors that exacerbate frailty.

The study is registered on the National Institutes of Health's clinical trials database ClinicalTrials.gov (NCT04291690). The study is funded by the principal investigators' research funds. The Research Ethics Board of the Jewish General Hospital has approved this study.

Participant Selection

Inclusion criteria

1. Patients aged 65 years or older
2. Frail or pre-frail patients, defined by an EFT score ≥ 1 at the time of enrollment
3. Patients admitted to the JGH cardiovascular unit
4. Patients who have provided written informed consent

Exclusion criteria

1. Patients with an expected discharge of < 3 days.
2. Clinically unstable patients, defined as those with:
 - a. Unstable vital signs
 - b. Low-threshold coronary ischemia
 - c. Uncontrolled heart failure
 - d. Hospitalizations for uncontrolled arrhythmias
3. Patients awaiting cardiac surgery within 3 days of the index hospitalization
4. Patients with severe dementia as defined by a score of $\leq 10/30$ on the Mini-Mental Status Examination (MMSE)
5. Patients with severe delirium as defined by a positive Confusion Assessment Method (CAM) score
6. Patients with psychiatric conditions precluding cooperation
7. Patients with Parkinson's disease
8. Patients who have had a recent stroke (< 7 days)
9. Patients who have physical limitations or are bed-bound, precluding participation in exercise interventions

10. Patients with an end-of-life care plan
11. Patients who are positive or have not been ruled-out for COVID-19
12. Patients who do not speak English or French

Screening Process

Research personnel will liaise daily with the clinical nursing staff and allied health professionals in the CVU to discuss potential patients for the trial. Patients' care needs, level of mobility, clinical status and discharge plan will be discussed with the treating team. Next, stable patients aged 65 years and older will be rapidly screened for frailty using the EFT, followed by a more in-depth frailty assessment. The EFT measures four frailty components: physical weakness (measured by the time to complete five chair rises), cognitive impairment (measured by the MMSE), malnutrition (measured by serum albumin) and anemia (measured by serum hemoglobin). An EFT score of ≥ 1 -2 will be indicative of pre-frailty and a score of 3-5 will be indicative of frailty. While severe frailty is not exclusionary, bedridden patients with severe physical limitations will be excluded, as the exercise interventions cannot be administered to these individuals. Consenting patients fulfilling the eligibility criteria will be randomized and allocated to one of two study arms.

Frailty Assessment

The baseline assessment consists of an interviewer-guided self-reported questionnaire, anthropomorphic measurements, and physical performance tests. The following covariates of interest will be recorded: age, sex, height, weight, reason for hospital admission, comorbidities, cardiac investigations, and treatments. Physical and cognitive frailty will be further measured by

the Clinical Frailty Scale (CFS), Short Performance Physical. Battery (SPPB) and MMSE. Malnutrition will be measured by the Mini-Nutritional Assessment (MNA) and by the Preoperative Nutrition Score (PONS), a scoring system that reflects low body mass index, weight loss, low dietary intake, and a low albumin level (11, 12).

Randomization and Blinding

Participants will be allocated to the intervention or usual care groups randomly on a 1:1 rate in blocks (using block randomization). The randomization allocation sequence was derived in consultation with a database manager at the McGill University Health Center (MUHC) Research Institute in Montreal, Quebec. Patients are only allocated to an arm of the study after the baseline assessment is complete and consent has been obtained. Given that the researchers administering the interventions cannot be blinded to the allocation group, the primary outcome at discharge will be assessed by a blinded nurse. The 30-day telephone follow-up calls will also be performed by blinded assessors to minimize bias.

Interventions

A. Usual Care

Patients randomized to the control group will receive usual clinical care as prescribed by their treating clinicians. In addition to treating the patient's heart condition, usual care may or may not include physiotherapy, geriatric consultation, nutritional consultation and supplementation, and treatment of anemia – including prescription of oral or intravenous iron replacement therapy for patients diagnosed with iron-deficiency anemia.

B. Intervention

Patients randomized to the intervention group will receive a multi-component intervention to improve in-hospital physical functioning, cognition, and nutrition. The intervention will be tailored to each patient based on their areas of frailty; exercise training will be provided for all patients with physical weakness, cognitive stimulation for those with cognitive impairment, an oral nutritional supplement for malnourished individuals, and intravenous iron replacement therapy for those with iron-deficiency anemia.

Intervention patients will receive two daily visits in their hospital room to partake in the intervention(s) as shown in Table I. Researchers will visit once in the early morning and once in the afternoon. In the case of prolonged hospital stays, the frequency of visits is reduced to once daily during the 3rd and 4th weeks of hospitalization, and once every other day thereafter. If patients are not feeling well or have scheduled tests during the planned visits, appointments are rescheduled or deferred at the patients' convenience.

B.1 Exercise component

Intervention patients identified as physically frail will be encouraged and assisted to walk around the ward, as tolerated and approved by their treating team, to maximize the time spent out of bed (i.e., up in chair for all meals) and minimize the time spent in bed. They will also be encouraged and assisted to perform the chair rise exercise to build lower extremity strength. For selected intervention patients with greater physical weakness, defined as an SPPB score ≤ 9 , a clinical exercise physiologist will administer a supervised, multicomponent exercise program combining strength, flexibility, balance, and gait for the prevention of weakness and falls. The exercise intervention is adapted from the *Vivifrail* program, an European Union-funded initiative

to prevent frailty, physical deconditioning, and incident disability in older persons (13). The exercise program is comprised of two daily sessions of 20 minutes each. The morning session will include strength and flexibility exercises, and the afternoon session will target balance and walking. The exercise intervention will be tailored according to the patients' SPPB scores and their individual physical capabilities.

B.2 Cognitive component

All intervention patients will be encouraged and assisted to wear hearing and visual aids (if applicable). Patients will be regularly oriented by the research staff to time and location, both verbally and in writing, on a clearly visible whiteboard in their hospital room. Furthermore, family members and caregivers will be encouraged to do the same. The research team will also inquire about their sleep quality and communicate with the clinical team to reduce sleep disturbances. For selected intervention patients with greater cognitive impairments, defined as an MMSE score ≤ 26 , cognitive stimulation is provided twice daily during the scheduled visits. Cognitive stimulation will be comprised of activities with the patient, including, but not limited to, discussion or updates about current news, trivia, crossword puzzles, and memory games. These cognitive interventions are adapted from the *Hospital Elder Life Program* (HELP) that targets risk factors for delirium (14).

B.3 Nutritional component

For all nutritional intervention patients, the research team will reinforce proper eating habits, and encourage and assist patients to wear their dentures (if applicable). Researchers will also inquire about food preferences and eating barriers, which will be communicated to the

dietician to address any issues. For intervention patients with greater nutritional deficits, defined as a positive PONS score, a prescription for MedPass supplementation will be recommended to the treating clinician. MedPass is a 60 mL, calorically dense, oral nutritional supplement consumed between meals four times daily. It is a cost-effective supplement for age-related nutritional problems, such as difficulties related to food intake and digestion of nutrients (15). Moreover, it has been demonstrated to be well-tolerated in older adults compared to other, high-volume protein supplements (16). If MedPass supplementation is contraindicated, the treating team will have full discretion to avoid its prescription and/or to consider alternative supplementation strategies.

B.4 Anemia component

According to the Canadian Cardiovascular Society Guidelines for Heart Failure (17), iron-deficiency anemia (IDA) is characterized by: (i) hemoglobin <130 g/L in men or <120 g/L in women with (ii) ferritin <100 µg/L or ferritin <300 µg/L with a saturation <20%. When intervention patients are diagnosed with IDA, the research team will recommend treating clinicians to prescribe Venofer, an intravenous iron replacement therapy. The use of intravenous iron replacement therapy is strongly recommended by the Canadian Cardiovascular Society Guidelines (17). Due to the rapid rate of iron repletion in the body, intravenous delivery is the preferred method of administration for iron supplements, and hospitalization is an opportune moment for its easy administration (18). Venofer is prescribed at a dosage of 300 mg daily for a total of three doses. If Venofer supplementation is contraindicated, the treating team will have full discretion to avoid its prescription and/or to consider alternative strategies.

At discharge, intervention patients will be encouraged to continue good physical and nutritional habits as instituted during their hospital stay, with the support of their family members and caregivers.

Outcomes

The primary outcome is HrQoL as measured by the EQ-5D-5L scale at the time of hospital discharge and at 30 days post-discharge. The EQ-5D-5L scale quantifies HrQoL in five dimensions of health: 1) mobility, 2) self-care, 3) usual activities, 4) pain/discomfort, and 5) anxiety/depression. Each dimension has five response options ranging from no problems to severe problems (19). The EQ-5D-5L scale is self-reported and administered by an observer. For the TARGET-EFT trial, the observer will be the patient's treating nurse for the in-person hospital assessment and a trained research assistant for the 30-day telephone assessment.

The co-primary outcome is hospital-acquired disability (HAD) as measured by the Older Americans Resources and Services (OARS) questionnaire at 30 days post-discharge. The OARS scale quantifies dependencies in seven basic (ADLs) and seven instrumental activities of daily living (IADLs). Each activity has four response options to evaluate the capacity of the patient to complete them: without help, with some help, unable, and not applicable. The OARS scale is self-reported and administered by a trained research assistant blinded to the patient's allocation group at the 30-day telephone assessment.

The secondary outcome is physical function as measured by the Short Physical Performance Battery (SPPB) scale at the time of discharge. The functional impact of sarcopenia will be measured by the SARC-F questionnaire at 30 days post-discharge. Lastly, hospital anxiety and depression will be measured by the Hospital Anxiety and Depression Scale (HADS)

at time of discharge. Table II summarizes the outcomes and the time points at which they are obtained.

Statistical Analysis

Using the web-based REDCap platform, permuted block randomization (with block sizes of four) will be concealed and stratified by sex. Data will be analyzed according to the intention-to-treat principle. The EQ-5D-5L and OARS scores are continuous endpoints. A multivariable linear regression analysis will be used to determine the effect of the intervention, after adjusting for baseline scores and other relevant covariates including age, sex, body mass index, cardiac diagnosis, comorbidity burden, and duration/intensity of the intervention delivered. Effect-modification with these covariates will also be examined. Missing data will be imputed using multiple imputation.

Sample Size Calculation

The sample size calculation was based on the primary objective of the study: health-related quality of life. A sample size of 72 patients per group (N=144) is required for an alpha value of 0.05 and a beta value of 0.2. This sample size is powered to detect a clinically meaningful change of 0.14 points in the EQ-5D-5L scale (20). The sample size calculation accounts for a 10% loss of patient data to follow-up, a conservative estimation given that the primary outcome is assessed in-hospital.

Data Collection and Management

Only data relevant to this study, as outlined herein, will be collected by the research personnel. All the information collected during the study will remain confidential to the extent required and provided by law. Patient data will be de-identified and codified using a 3-digit number followed by a 2-letter monogram via REDCap, a secure, web-based application for managing databases. The code will be kept by the principal investigator on a secure server located at the Centre for Clinical Epidemiology at the Lady Davis Institute. Study results published in peer-reviewed journals or shared during scientific meetings will not allow identification of the participants.

Ethics Approval

The Jewish General Hospital (JGH) Research Ethics Board has approved this study. This trial is conducted in accordance with the Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans (2014), as well as in respect of the requirements set out in the applicable standard operation procedures of the JGH Research Ethics Board.

Participation in the TARGET-EFT trial will be entirely voluntary, and patients will have the right to refuse or withdraw from the trial at any time. Regardless of a patient's enrolment in the study, they will be entitled to receive mobilization, physiotherapy, nutritional supplementation, and anemia treatments as clinically indicated by the treating physicians and allied health professionals.

Trial Monitoring and Oversight

The number of interventions delivered, exercise-related symptoms and adverse events will be recorded. Chest pain, dyspnea, palpitations, desaturation, lightheadedness, syncope, falls,

musculoskeletal pain or discomfort, worsening heart failure or coronary ischemia will be considered adverse events. All serious or minor potentially study-related adverse events will be reported and reviewed by the Research Ethics Board.

To minimize the risk of adverse events, heart rate and oxygen saturation will be monitored during exercise. Exercise intensity will be limited as a function of the patients' SPPB level, current health status, and perceived exertion using the Borg scale (21). The clinical exercise physiologist will consult the clinical team daily to ensure that the patients are safe to undergo the respective exercise interventions, deferring exercise sessions or reducing exercise intensity when patients are not physically capable of completing them.

DISCUSSION

The TARGET-EFT trial aims to rapidly identify frail patients in an acute cardiac care setting, and subsequently, provide a multicomponent intervention, targeting physical and non-physical aspects of frailty to optimize care (4). Our trial has implemented a two-step process to facilitate the integration of frailty assessments in a clinical setting: 1) a rapid, initial frailty screening using the EFT, followed by 2) a targeted, in-depth frailty assessment for deficits identified by the EFT screening. The EFT can be quickly administered and easily interpreted by clinicians to guide clinical decision-making and identify patients who may benefit from targeted frailty interventions. These interventions can mitigate the impact of hospitalization-associated stressors, thereby improving recovery, and minimizing the risk of developing post-hospitalization syndrome and hospital-acquired disability (HAD). After an index hospitalization, we postulate that patients who received the multicomponent intervention will have better health-related quality of life (HrQoL) and shorter recovery times than those receiving usual care.

Previous systematic reviews examining the treatment of frailty show the benefit of physical activity, nutritional supplementation, and cognitive training; however, these interventions were delivered in primary care, community, or home settings, rather than in acute, hospital settings (22-24). A recent systematic review and meta-analysis identified a total of seven randomized clinical trials (RCTs) on frailty interventions in hospitalized older adults, with only one study evaluating HrQoL as a primary outcome (25). A scoping review reports that more than 50% of patients in acute care settings are frail, yet there continues to be a paucity of evidence on interventions to improve frailty and guide decision-making (10, 26). The TARGET-EFT trial addresses this knowledge gap by evaluating a multicomponent intervention addressing of frailty and hospitalization-related stressors to improve HrQoL after index hospitalization for acute cardiac conditions.

A systematic review of in-hospital exercise interventions found inconsistent outcomes on physical performance, an effect driven by low sample size, and lack of standardization in exercise intensity and frequency between studies (27). Nonetheless, early mobilization of critically ill adults was found to benefit patients' functional recovery (28, 29). Furthermore, a seminal RCT by Martínez-Velilla shows that in-hospital resistance training administered to acutely-ill older patients improved functional status, independence in ADLs and HrQoL at discharge (13). Another systematic review and meta-analysis found that nutritional support in frail and pre-frail in-patients significantly decreased mortality rates and is associated with a reduction in non-elective hospitalizations compared to standard care (30). In the NOURISH study, malnourished hospitalized older adults who received high-protein nutritional supplements had a significantly lower risk of mortality at 90 days (31, 32). In another RCT, MedPass was shown to significantly improve the HrQoL of malnourished geriatric patients (14). Given the

evidence supporting the benefits of exercise and nutritional programs on HrQoL, our trial aimed to integrate these interventions in hospital while maintaining feasibility. Therefore, our exercise intervention can be conducted with simply a chair (which is always found in patients' rooms). Our nutritional intervention uses existing resources already available in hospitals.

A systematic review and meta-analysis of various delirium prevention programs found that they successfully reduced the incidence of delirium in older patients undergoing elective surgery. Consequently, the authors recommend these programs as “prehabilitation” prior to surgery (33). Geriatric patients who received a tailored Hospital Elder Life Program (HELP) postoperatively maintained or improved physical and cognitive function and had shorter lengths of hospital stay (34). The HELP program has been studied in cardiac intensive care units, however, it has not been studied in cardiology units (35-37). Therefore, TARGET-EFT will be the first RCT to evaluate HELP in older frail patients admitted to the CVU.

Intravenous iron therapy is associated with improved HrQoL and reduced hospitalizations in heart failure patients with iron deficiency (38, 39). In a prospective randomized wait-list trial, older outpatients with unexplained anemia that received intravenous iron for five weeks significantly increased the distance walked in the 6-minute walk test (18). While deemed safe and more efficacious than oral supplementation for older adults, intravenous iron administration is underutilized by clinicians (40). Since older adults with anemia are twice as likely to be frail, treatment of iron deficiency anemia can lower the adverse events associated with both frailty and anemia (41). The TARGET-EFT trial will use intravenous iron supplementation to treat anemia and improve patient recovery from acute illness or cardiac surgery.

To our knowledge, there are no RCTs evaluating a multicomponent intervention in frail older adults with CVD, which includes exercise, nutritional support, cognitive stimulation and

delirium prevention, and treatment for anemia (42). The results of the study will inform future practice guidelines for patient-centered therapeutic interventions and frailty management in older adults with CVD. In doing so, frail patients will be supported in during their recovery process which, in turn, will improve their quality of life after hospitalization.

CURRENT STATUS

To date, 130 patients have been randomized and the study is actively recruiting participants. The first patient was recruited in March 2020 and recruitment is expected to be complete by August 2021. The final 30-day telephone follow-ups are expected to be completed by September 2021. The primary analysis is expected to be completed by October 2021.

ACKNOWLEDGMENTS

The authors would like to acknowledge the Cardiovascular Unit and the Lady Davis Medical Research Institute at the Jewish General Hospital for the infrastructure supporting this trial.

FUNDING

RF is supported by the Gordon Phillips Fellowship and the Graduate Excellence Fellowship from the McGill University Faculty of Medicine and Health Sciences. HM was supported through a grant provided by the Fonds de Recherche du Québec—Santé (FRQS). FA is supported by the Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best Canada Graduate Scholarship.

DECLARATIONS OF INTEREST

None.

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Figure Legend

Figure 1

Title: Study Design Flow Chart

Abbreviations: EFT, Essential Frailty Toolset; HADS; Hospital Anxiety and Depression Scale; OARS; Older Americans Resources and Services; SPPB, Short Physical Performance Battery.

Figure 2

Title: Conceptual Diagram

Legend: Frail older patients are at risk of hospital-acquired disability and poor quality of life following index hospitalization. The interaction of hospitalization-associated stressors and pre-existing frailty deficits negatively impact the capacity to recover after an acute illness. The TARGET-EFT interventions aim to simultaneously counteract hospitalization-associated stressors and frailty deficits to improve patient-centered outcomes. Abbreviations: BMI, body mass index; HAD, hospital-acquired disability; HrQoL, health-related quality of life; IDA, iron deficiency anemia; IV, intravenous.

Table 1. Usual Care and TARGET-EFT Multicomponent Intervention

	Physical Weakness	Cognitive Impairment	Malnutrition	Anemia (Iron-Deficient)
Usual care	• RN encouragement to mobilize early and often • Physiotherapy PRN	• RN orientation • RN screening for delirium • Geriatrics consult PRN	• RN encouragement to eat hospital meals • Nutritionist PRN • MedPass PRN	• MD investigation for diagnosis of anemia • MD prescription for oral or intravenous iron PRN
Intervention	• Additional encouragement to mobilize between and during visits BID • Chair rises at least BID • If SPPB ≤ 9: Vivifrail program x BID	• Put on hearing/vision aids • Additional orientation on board and during visits BID • Address sleep promotion • If MMSE $\leq 26/30$: cognitive stimulation BID	• Put on dentures • Additional encouragement to eat during visits BID • Address food likes/barriers • If PONS +: prescription of MedPass QID	• Verification of iron studies according to established diagnostic criteria • If iron deficient anemia: prescription of intravenous iron QD x 3

Abbreviations: BID, twice a day; MD, medical doctor; MMSE, Mini-Mental Examination; PONS, Preoperative Nutrition Score; PRN, when necessary; RN, registered nurse; SPPB, Short Physical Performance Battery; QD, once a day; QID, four times a day.

Table 2. Clinical Outcomes of interest and Ascertainment Time Points

Outcomes	Measured by	Baseline (T0)	Discharge (T1)	30-Days (T2)
Primary Outcome				
Health-related quality of life	EQ-5D-EL	X	X	X
Secondary Outcomes				
Hospital-acquired disability in basic ADL	OARS	X	X	X
Length of stay	Number of days		X	
Lower extremity physical performance	SPPB	X	X	
Functional impact of sarcopenia	SARC-F	X		X
All-cause death, delirium, fall, infection, pressure ulcer	Composite safety		X	
All-cause death, discharge to healthcare facility, unplanned repeat hospital visit	Composite benefit			X

Abbreviations: OARS; Older Americans Resources and Services. Other abbreviations as in table

1.

Figure 1: Study Flowchart

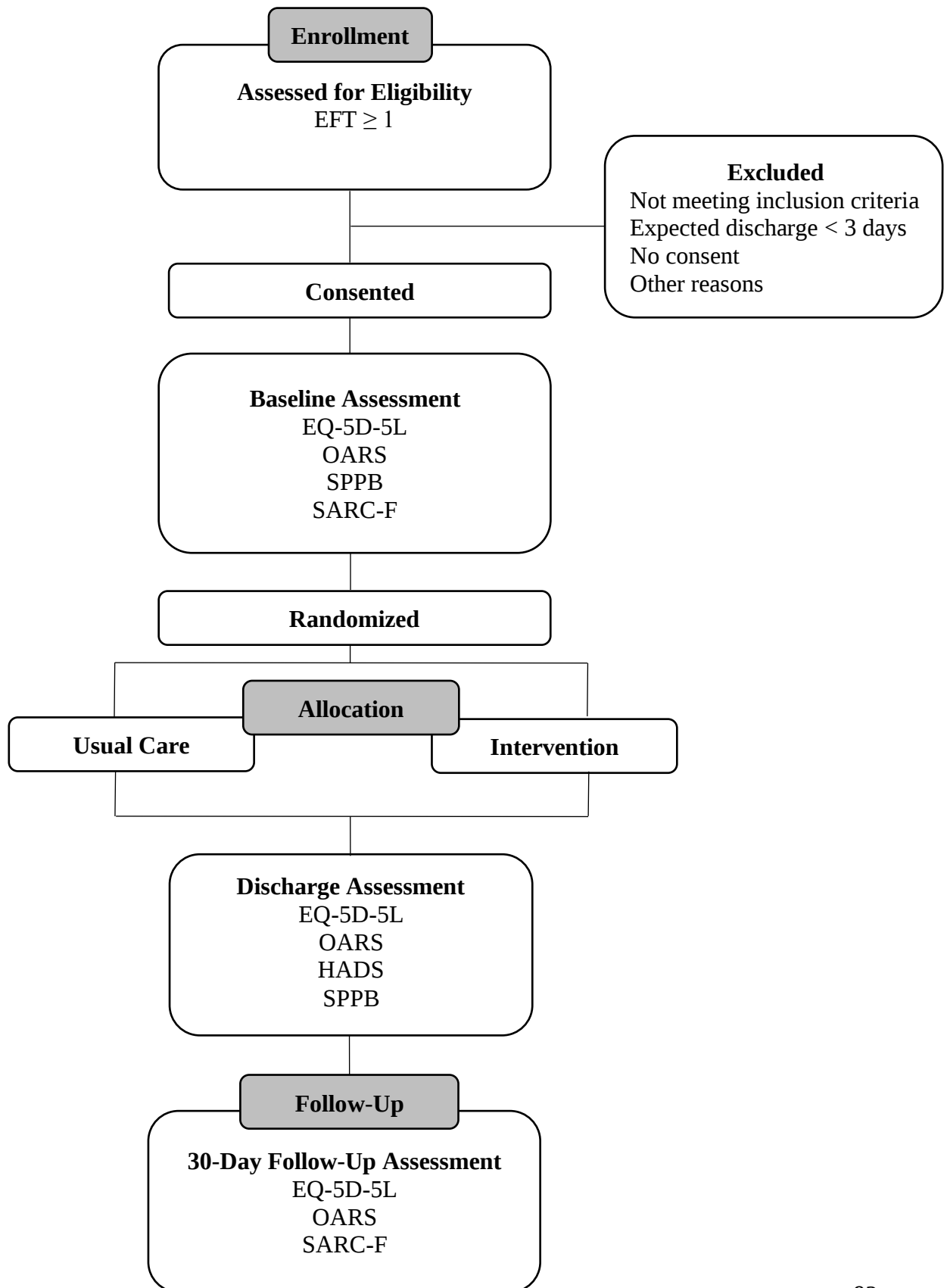
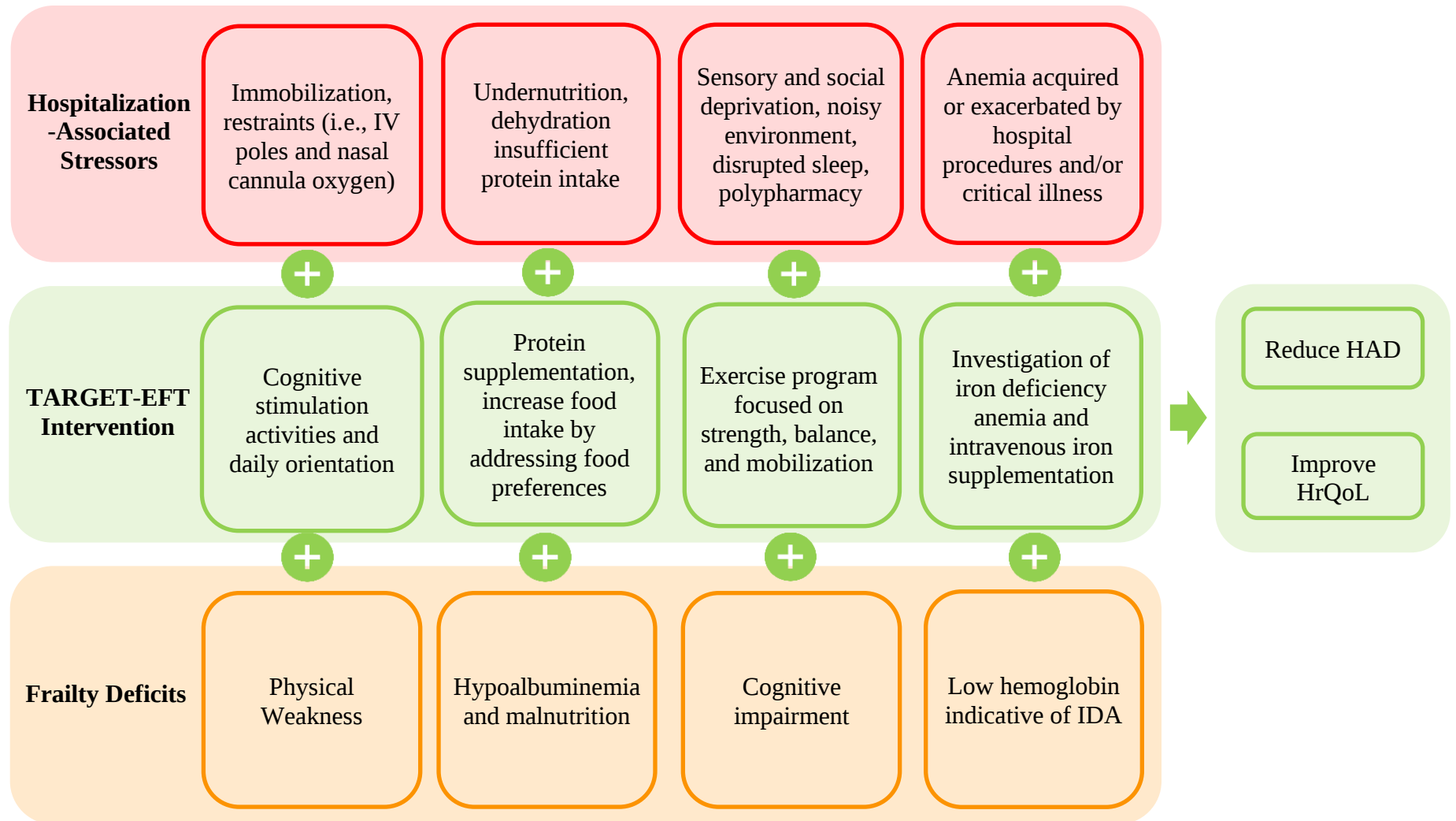


Figure 2: Conceptual Diagram



Chapter 9: Commentary on Randomized Clinical Trial

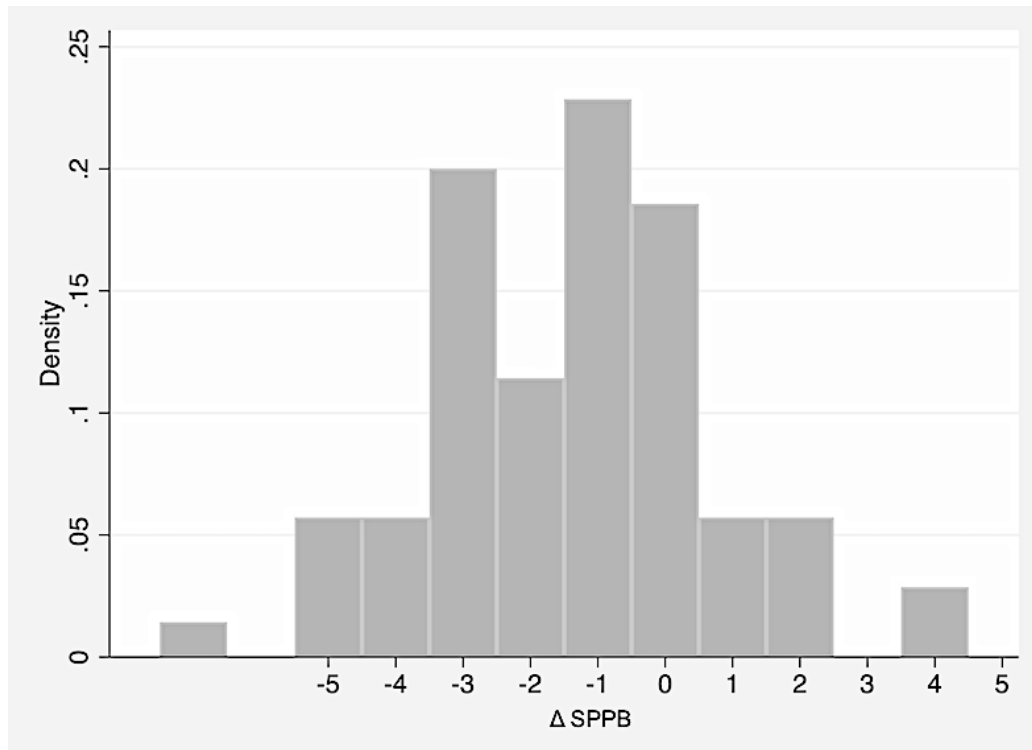
Frailty underlines the rapid functional decline during hospitalization in older adults with acute cardiac conditions (4). Hospitalization leads to loss of muscle mass and strength and ultimately the exacerbation of frailty. Aside from the stress of the cardiac illness, hospitalization-factors including delirium and disorientation, undernutrition and hospital-acquired anemia are key contributors to worsening patient outcomes. Gill et. al. has reported that the chances of becoming less frail were reduced by 50% with each hospitalization (166). Therefore, hospitalization is a major threat to frail older adults, leading to deconditioning, the post-hospitalization syndrome and hospital-acquired disability (12). There is a present need for RCTs with adequate sample sizes to establish whether multicomponent in-hospital frailty interventions improve patient-centered outcomes and reduce the negative consequences of an acute hospitalization. As the first RCT evaluating this hypothesis in a cardiac patient, our findings from the TARGET-EFT trial can provide clinically meaningful information on the association of multicomponent frailty interventions and post-hospitalization HrQOL.

Presently, the trial is nearing completion, with 130 of the planned 144 patients randomized. The complete analysis of the trial has not been conducted yet since we presently do not have the adequately powered sample size to achieve clinically meaningful change in our primary objective of HrQoL. However, we have conducted preliminary feasibility analysis on the first half of patients randomized ($n = 77$). We found that the most common reasons for exclusion were age <65 years and expected discharge within <3 days. The median age was 80 years and length of stay was 8 days. In each group, we reported that 1 patient withdrew and 1 had died. We have reported no intervention-related adverse events or injuries. Of 39 intervention patients, 36 qualified for exercise and received an average of 6 sessions (46% of sessions were not performed due to tests,

mandatory bedrest, or patient refusal). For the other interventions, we showed that 94% of 36 patients who required exercise, 100% of 18 patients that required cognitive stimulation, 86% of 15 patients that required intravenous iron sucrose and 81% of 16 patients who required protein supplementation, received the interventions by hospital discharge. Lastly, we analyzed patients' change in SPPB scores from baseline (time of enrollment) to discharge. Change in SPPB is calculated by subtracting the baseline score from discharge score. A positive change in SPPB score indicates a decrease in SPPB score by discharge (worse) and a negative change in SPPB score indicates an increase in SPPB score by discharge (improved). We concluded that SPPB increased by the time of discharge in our cohort, as shown by the negative change in SPPB scores (Figure 2).

Our preliminary analysis of baseline characteristics and feasibility data has revealed that the TARGET-EFT trial appears to be beneficial, practical, and safe for frail and pre-frail patients hospitalized with acute cardiac conditions. Our interventions reflect a multidisciplinary care approach thus they can be easily implemented into clinical practice through geriatricians, physiotherapists, occupational therapists, nutritionists and social workers and family. As the TARGET-EFT interventions aim to concurrently counteract frailty and the debilitating effects of hospitalization-associated stressors that can exacerbate frailty, older adults will be empowered to achieve better HrQoL after an acute hospitalization.

Figure 2: Histogram for Change in SPPB Scores



Change in SPPB amongst our cohort, calculated as baseline score minus discharge score.

Abbreviations: Δ, delta; SPPB, Short Performance Physical Battery.

Chapter 10: Thesis Conclusion

The literature review revealed that the prevalence of frailty was 20% to 60% in older adults with acute cardiac conditions. The impact of frailty on adverse clinical outcomes has been shown repeatedly across various cardiac cohorts. Frailty has been associated with decreased functional status, longer length of stay, increased readmissions, major complications, and mortality in patients with cardiovascular diseases. The role of frailty assessment tools in clinical practice can enhance shared decision-making amongst physicians and guide better management. Regardless of the assessment tool used, frailty has negative consequences on patient outcomes and prognosis for survival. Even with the accrual of evidence, the integration of frailty in day-to-day clinical practice has remained limited by the (1) lack of consensus over which frailty assessment tool is most optimal for acute care settings (2) the practicality of these frailty assessment tools in acute care settings. Therefore, there remains a need to identify pragmatic frailty assessment tools in this setting and determine their prognostic value.

Our cohort study explored the use of handgrip strength as a simple measure of frailty and predictor of mortality in older adults undergoing cardiac surgery. A multicenter prospective cohort of 1,245 older patients undergoing coronary artery bypass grafting (CABG) and/or valve surgery was analyzed. HGS was measured prior to surgery and classified by sex-stratified cutoffs. Weak HGS was associated with various comorbidities and various frailty scales. Those with weak HGS were more likely to experience 1-year mortality, 30-day mortality, prolonged length of stay, and discharge to a healthcare facility (all $p < 0.001$). After adjustment, HGS was predictive of 1-year and 30-day mortality, with odds ratios of 2.44 (CI 1.39-4.29) and 2.83 (CI 1.38-5.81), respectively. In our cohort, we found that the FNHIH cutoff of <26 kg in men and <16 kg in women had the highest predictive performance.

This was the first study to evaluate the predictive value of HGS in older adults undergoing cardiac surgery. HGS thus proved to be a simple and effective tool to identify patients at higher risk of mortality and protracted recovery after cardiac surgery. HGS is a good approximate of overall muscle function and overcomes many of the challenges that have limited the integration of frailty assessments in acute care settings. HGS requires minimal equipment, time and is well-tolerated even by wheelchair- and bed-bound patients. Following this cohort study, we recognized that there is a need to pragmatically identify frailty in patients who would benefit from treatment optimization and therapeutic interventions to improve post-operative recovery and patient-centered outcomes after an acute cardiac illness.

With the evidence on the impact of frailty and adverse patient outcomes, the recommended next step is the exploration of feasible therapeutic interventions to redefine care for frail cardiac patients. With the aging population, cardiologists and cardiac surgeons are increasingly faced with older frail patients with acute cardiac conditions where care is more complex. There are currently no randomized clinical trials evaluating the effects of in-hospital multicomponent interventions targeting frailty in older frail adults with acute cardiac conditions to improve a patient-centered outcomes.

To address this knowledge gap, we designed the TARGET-EFT trial. This is a single center randomized clinical trial at the Jewish General Hospital. Patients ≥ 65 years old admitted to the cardiovascular unit with evidence of frailty or pre-frailty defined by the EFT will be randomized into one of two groups, intervention, or usual care. The intervention group will receive a multicomponent frailty intervention that addresses patient needs in four domains, physical weakness, cognitive impairment, malnutrition, and iron-deficiency anemia. The intervention will correct frailty deficits and combat hospitalization-associated stressors such as

physical inactivity, sleep deprivation, social isolation, cognitive impairment, delirium, and undernutrition that further challenge patients' resilience. By targeting these areas, we aim to combat physical deconditioning that results in post-hospitalization syndrome and hospital-acquired disability. Our primary objective is to improve patient-centered outcomes such as change in HrQoL and hospital-acquired disability at hospital-discharge and 30-days. We have conducted preliminary analysis of baseline characteristics and feasibility data that shows our interventions are well-tolerated, safe, and practical for older frail adults. To date, 130 of 144 patients have been randomized and we aim to complete recruitment in July 2021 with study completion in August 2021.

Frailty proves to play an integral role in risk assessment of older adults with acute cardiac conditions. Frailty assessment tools that are pragmatic and actionable (handgrip strength and the Essential Frailty Toolset) can be easily implemented in acute care settings to reduce the risk of fatal and nonfatal adverse events. These frailty assessment tools can subsequently identify frail patients who would benefit from a deeper geriatric assessment and therapeutic interventions during acute hospitalization. The TARGET-EFT trial aims to examine the effects of a multicomponent frailty intervention in reducing the burden of hospitalization-associated stressors. We hope that the findings from the TARGET-EFT trial will provide clinically meaningful information to practice guidelines in the near future. In-hospital therapeutic interventions truly have the potential to provide patient-centered care and promote older frail patients to maintain physical independence in activities of daily living and to achieve improved health-related quality of life after hospital discharge.

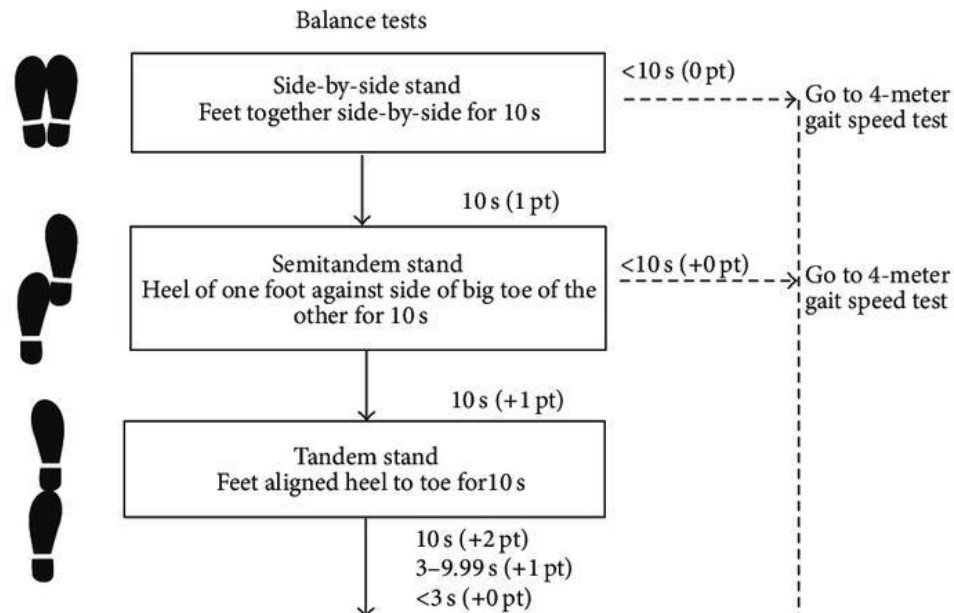
Appendices

Appendix A: Essential Frailty Toolset (EFT)

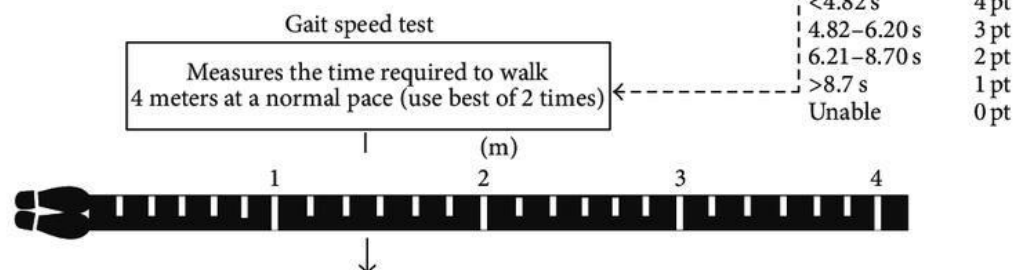
	Five chair rises <15 seconds	0 Points
	Five chair rises ≥15 seconds	1 Point
	Unable to complete	2 Points
	No cognitive impairment	0 Points
	Cognitive impairment	1 Point
	Hemoglobin ≥13.0 g/dL ♂ ≥12.0 g/dL ♀	0 Points
	Hemoglobin <13.0 g/dL ♂ <12.0 g/dL ♀	1 Point
	Serum albumin ≥3.5 g/dL	0 Points
	Serum albumin <3.5 g/dL	1 Point

Appendix B: Short Performance Physical Battery (SPPB)

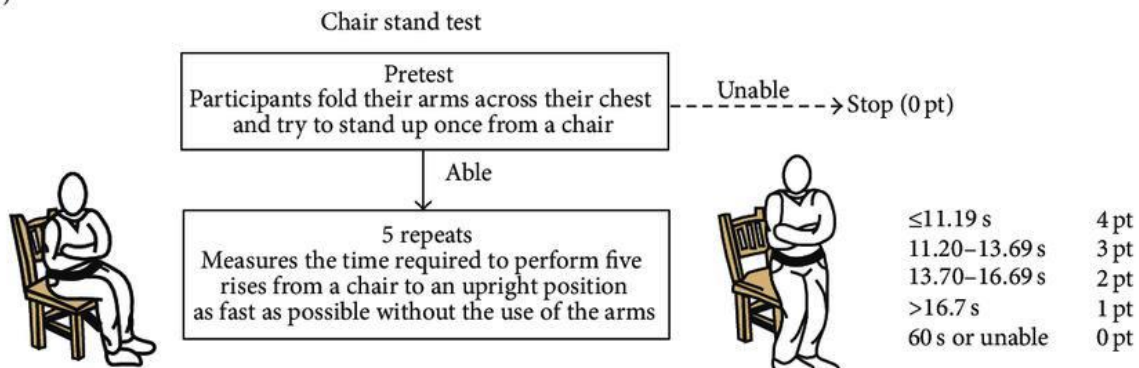
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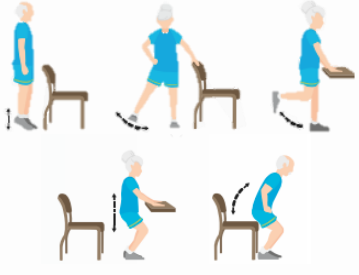
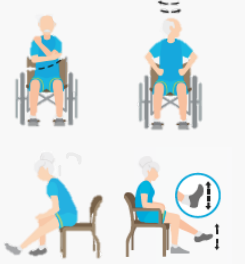
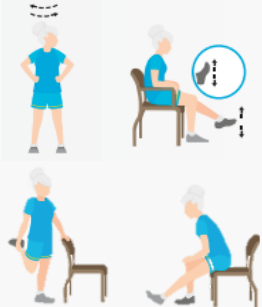
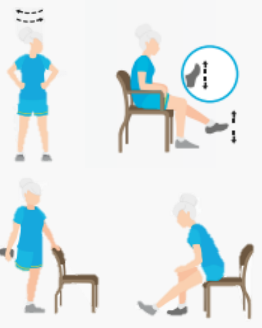
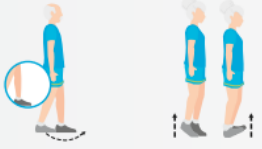
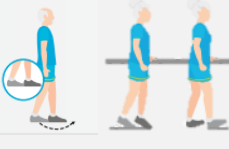
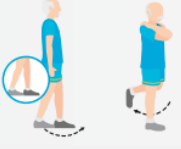
(2)



(3)



Appendix C: Exercise Intervention (Adapted from the Vivifrail Progra

SPPB 0-3	SPPB 4-6	SPPB 7-9
These exercises will increase functionality, like getting out of the chair.	These exercises will show improvements in patients' physical capacity.	These exercises will develop endurance and improve walking.
STRENGTH		
		
FLEXIBILITY		
		
BALANCE		
		
MOBILITY		
		

Appendix D: Mini-Mental Examination (MMSE)

Orientation

1. What year is this? _____/1
2. What season is this? _____/1
3. What month of the year is this? _____/1
4. What is today's date? _____/1
5. What day of the week is this? _____/1
6. What country are we in? _____/1
7. What province are we in? _____/1
8. What city are we in? _____/1
9. What is the name of this hospital? _____/1
10. What floor of the building are we on? _____/1

Registration

11. I am going to name 3 objects. After I have said all 3 objects, I want you to repeat them.
Remember what they are because I am going to ask you to name them again in a few minutes: _____/3
Ball Car Man
Please repeat the 3 items for me

Attention and Calculation

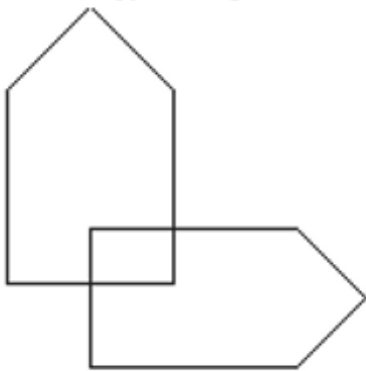
12. Subtract 7 from 100 and keep subtracting seven from what's left until I tell you to stop
or spell the word "world" backward _____/5

Recall

13. Now what were the three objects that I asked you to remember? _____/3

Language

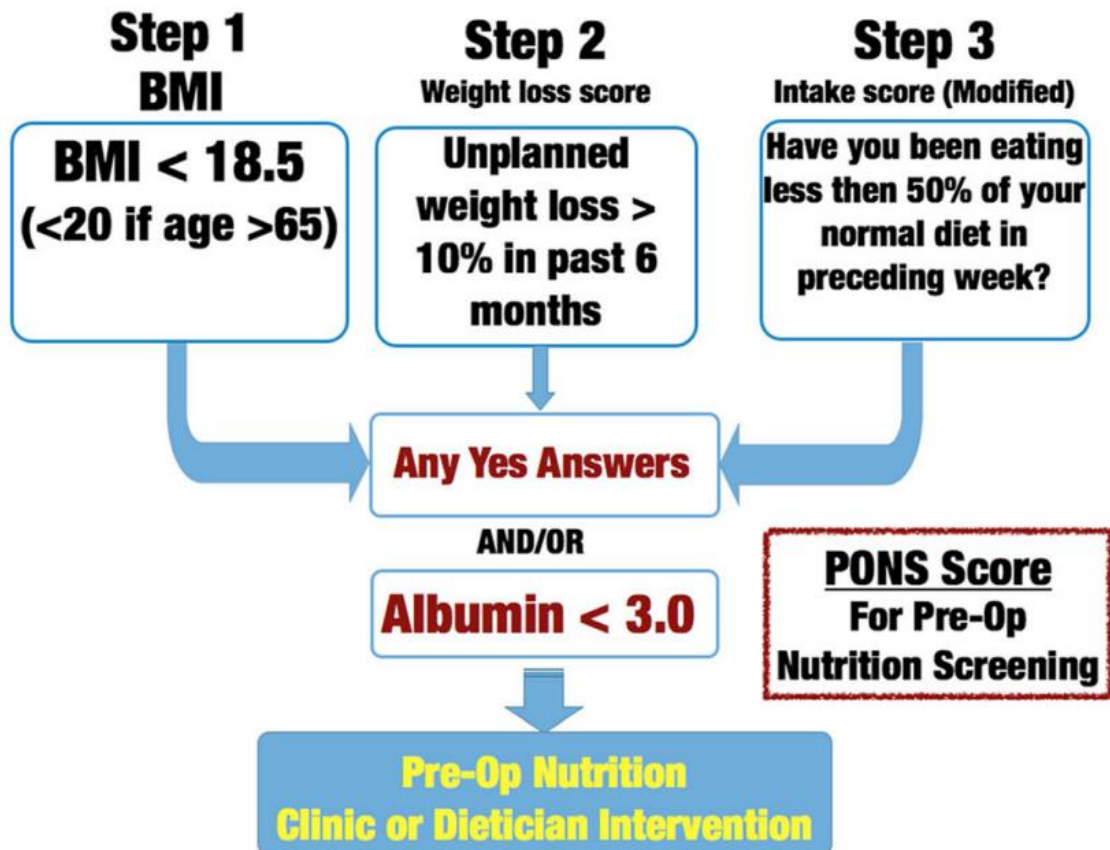
14. What is this called (a watch) _____/1
15. What is this called (a pencil) _____/1
16. Repeat the following phrase: "No ifs, ands, or buts" _____/1
17. Follow a 3-stage command: "Take a paper in your right hand, fold it in half, and put it on the floor" _____/3
18. Read the words on this paper and do what it says: Close your eyes _____/1
19. Write a complete sentence on this piece of paper _____/1
20. Copy the design shown _____/1



CLOSE YOUR EYES

MMSE Total Score: ____ / 30

Appendix E: Preoperative Nutrition Score (PONS)



Appendix F: 5Q-5D-5L Scale

EQ-5D-5L	
1. Mobility	☐ I have <u>no problem</u> walking about ☐ I have <u>slight</u> problems in walking about ☐ I have <u>moderate</u> problems in walking about ☐ I have <u>severe</u> problems in walking about ☐ I am <u>unable to</u> walk about
2. Self-care	☐ I have <u>no problem</u> washing or dressing myself ☐ I have <u>slight</u> problems washing or dressing myself ☐ I have <u>moderate</u> problems washing or dressing myself ☐ I have <u>severe</u> problems washing or dressing myself ☐ I am <u>unable to</u> do my usual activities
3. Usual activities (i.e., work, study, housework, family or leisure activities)	☐ I have <u>no problem</u> doing my usual activities ☐ I have <u>slight</u> problems doing my usual activities ☐ I have <u>moderate</u> problems doing my usual activities ☐ I have <u>severe</u> problems doing my usual activities ☐ I am <u>unable to</u> do my usual activities
4. Pain/Discomfort	☐ I have <u>no pain or discomfort</u> ☐ I have <u>slight</u> pain or discomfort ☐ I have <u>moderate</u> pain or discomfort ☐ I have <u>severe</u> pain or discomfort ☐ I have <u>extreme</u> pain or discomfort
5. Anxiety/Depression	☐ I am <u>not anxious or depressed</u> ☐ I am <u>slightly</u> anxious or depressed ☐ I am <u>moderately</u> anxious or depressed ☐ I am <u>severely</u> anxious or depressed ☐ I am <u>extremely</u> anxious or depressed
Visual Analogue scale	
<u>Worst</u> health you can imagine <u>Best</u> health you can imagine 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100	

Appendix G: Older Americans Resources Services (OARS) Scale

<i>ADLs</i>	Without help	With some help	Completely unable	Not applicable
1. Can you eat?	1	2	3	4
2. Can you dress and undress yourself?	1	2	3	4
3. Can you take care of your own appearance? (comb your hair, shave)	1	2	3	4
4. Can you walk? (without help includes walking with a cane, but not with a walker)	1	2	3	4
5. Can you get in and out of bed?	1	2	3	4
6. Can you take a bath or shower?	1	2	3	4
7. Do you ever have trouble getting to the bathroom on time?	1	2	3	4
<i>IADLs</i>				
8. Can you use the telephone? (without help includes looking up a # and dialing)	1	2	3	4
9. Can you get to places out of walking distance? (drive car, take bus or taxi)	1	2	3	4
10. Can you go shopping for groceries or clothes?	1	2	3	4
11. Can you prepare your own meals?	1	2	3	4
12. Can you do your housework?	1	2	3	4
13. Can you take your own medicine?	1	2	3	4
14. Can you handle your own money? (write checks, pay bills)	1	2	3	4

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