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The Application of Frailty to the Modern Cardiac Risk Assessment: a Case-Based Review

Matthew Finn^{1,2} and Philip Green¹

¹Department of Cardiology, Columbia University Medical Center, New York, NY, USA

²Division of Cardiology, 622 West 168th Street, PH 3-347, New York, NY 10032, USA

Abstract

Cardiac risk assessment in aging patients poses a significant challenge to the practicing clinician, particularly when evaluating the use of invasive procedures. Frailty is a valuable risk marker that has been associated with worse outcomes in patients with coronary artery disease, heart failure, and aortic stenosis. Integrating the available frailty studies into cardiac risk assessments can help improve shared decision-making between physicians and their patients. In this review, we provide an up-to-date, case-based appraisal of the available clinical trial data focusing on the impact of frailty in patients with cardiovascular disease.

Keywords

Frailty; Cardiac risk assessment; Aging; Geriatric; Elderly; Aortic stenosis; Transcatheter aortic valve replacement; Coronary artery disease; Heart failure

Introduction

The evolution of modern medicine has enabled many individuals to approach their “natural life span,” the maximum age one could expect to live under optimal conditions. Longer life spans have lead to a higher incidence of disability, comorbidity, and diminished functional independence in older adults [1•]. The term frailty has been utilized to encompass this clinical phenotype. Frailty is defined as a state of overall susceptibility in which a person has decreased physical reserve, resulting in a greater possibility of unfavorable outcomes when a stressor is applied.

The idea of frailty as a clinically significant predictor of outcomes was originally proposed and tested by Fried et al. in the Cardiovascular Health Study. In the study, frailty was evaluated based on five parameters: overall physical activity level, unintentional weight loss, slow walking speeds, fatigue, and degree of weakness [2]. Subsequent studies have used a

Matthew Finn, mtf2129@cumc.columbia.edu.

Compliance with Ethics Guidelines

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variety of alternative markers for frailty including cognitive impairment, number of comorbid conditions, albumin level, and loss of independent living (Table 1) [3, 4].

The bio-pathologic basis of frailty is thought to comprise aging-associated “wear and tear” coupled with aging-related biologic changes that lead to subclinical multi-system dysfunction. The existence of a stressor (in the form of an illness) transforms “subclinical” disease into “clinical” disease and results in significant unfavorable effects [5•, 6].

Epidemiology of Frailty

Frailty is highly prevalent in the population over 65 with an estimated 10–20 % of individuals in this age group affected. In older patients with cardiovascular disease, the prevalence may approach 60 % [7, 8]. Frailty is even more pervasive in patients with valvular heart disease. In one recent study of high-risk patients with calcific aortic stenosis, the incidence of frailty was 86 % [9].

Case Studies in Frailty

We will provide four sample cases to illustrate clinical scenarios in which knowledge of frailty outcome data will assist the provider in clinical decision-making or prognostication. Case I will examine “pre-frailty” as a risk factor for the development of coronary artery disease. Case II will appraise the role of frailty in surgical risk assessment. Case III will evaluate frailty risk markers on the prognosis of transcatheter aortic valve replacement for severe aortic stenosis. Finally, case IV will demonstrate the relationship between frailty markers and coronary artery disease.

Case I

A 70-year-old woman with a history of hypertension and breast cancer with mastectomy who has been in remission for 11 years presents to her internist for a new patient assessment. A frailty assessment is performed based on the Fried scale and demonstrates slower than expected 5-m walking time and high levels of chronic fatigue [10, 11]. Do these risk factors increase her risk of developing cardiovascular disease (CVD) in the coming decade?

Pre-frailty

Recently, the concept of “pre-frailty” has been evaluated to ascertain its impact on CVD risk. Sergi et al. performed frailty screening on 1567 individuals over the age of 65 with follow-up for a mean of 4.4 years. The study showed that “pre-frail” patients (defined as those having one to two Fried frailty markers) had a significantly higher risk of developing coronary artery disease (CAD) (hazard ratio of 1.23 for 1 frailty marker, 95 % confidence interval 1.02–1.59, and hazard ratio of 1.78 for 2 frailty markers, 95 % confidence interval 1.28–2.40) [12•]. Low physical activity levels, high levels of fatigue, and slow gait speed were significantly associated with increased risk of new-onset CVD. These results were driven by new diagnoses of heart failure (HF), which comprised over half of CVD events in the study. This finding is of particular interest as “pre-frailty” may be more easily modifiable through treatment and risk modification than frailty [2].

Case II

An 86-year-old man with a history of hypertension, CAD with stents placed 7 years ago, and heart failure with preserved ejection fraction is hospitalized for severe lower back pain and new-onset lower extremity weakness. Inpatient workup reveals prostate cancer with metastatic disease to the spine. The patient and his family are debating proceeding with an urgent spinal cord decompression surgery. What impact would a pre-operative diagnosis of frailty pose on the overall risk of adverse complications related to the procedure?

Frailty Risk in Surgery

Several studies have evaluated the association of frailty on outcomes after surgical procedures. Makary et al., in the largest analysis to date, screened for frailty in 594 patients planned for general surgical procedures [13]. Frail patients were shown to have a significantly increased risk of post-procedural adverse outcomes (odds ratio 2.54, 95 % confidence interval 1.12–5.77) and increased length of stay for both minor (1.5 vs. 0.7 days) and major procedures (7.7 vs. 4.2 days). A similar, more recent study by Reveling et al. evaluated patients undergoing intra-abdominal surgery and found that frail patients had a greater, adjusted, 30-day mortality rate than the non-frail patients (23 % complication rate with Fried score of 0, a 27 % complication rate with a Fried score of 1–2, and 59 % complication rate with a Fried score of 3–4) [14].

Lee et al. analyzed the risk of frailty specifically in patients undergoing cardiac surgery and demonstrated that frail patients have a higher odds of post-procedural death (odds ratio 1.8, 95 % confidence interval 1.1–3.0) and discharge to a facility (odds ratio 6.3, 95 % confidence interval 4.2 to 9.4) than non-frail patients [15]. Afilalo et al. assessed whether gait speed alone could predict adverse outcomes after cardiac surgery and found that slow walkers had a higher adjusted in-hospital morbidity and mortality than faster walkers on 5-m gait testing (odds ratio 3.5, 95 % confidence interval 1.23 to 7.54) [16]. Furthermore, a recent systematic review evaluating six studies, including 4756 patients undergoing cardiac surgical procedures, showed that patients who were deemed frail had a higher likelihood of experiencing major adverse cardiac and cerebrovascular events, mortality, and functional decline following surgery [17].

Case III

A 78-year-old woman with chronic kidney disease and rheumatoid arthritis presents with worsening chest pain and dyspnea on exertion. Her transthoracic echocardiogram reveals critical aortic stenosis, and coronary angiography shows non-obstructive CAD. On frailty assessment, she is noted to have slow walking speed, chronic fatigue, weak grip strength, and a serum albumin of 3.1 g/dl. How will her diagnosis of frailty affect her prognosis if she is referred for transcatheter aortic valve replacement (TAVR)?

Frailty Risk in TAVR

The majority of data in frailty in cardiac care has come from patients undergoing TAVR procedures. The high prevalence of frailty and comorbidity in this cohort naturally lends itself to evaluation of these parameters [5•, 6, 18, 19]. These studies have established a clear

relationship between adverse outcomes and frailty status prior to TAVR. In 2015, a multicenter study within the Placement of Aortic Transcatheter Valve Trial evaluated frailty in 244 patients undergoing TAVR who were deemed either high risk or inoperable for surgical aortic valve replacement. At 1 year, poor outcomes occurred in 50 % of frail patients and 31.5 % of non-frail patients ($p=0.02$). Mortality was noted to be 32.7 % in the frail cohort and 15.9 % in the non-frail cohort at 1 year ($p=0.004$) [20•].

Additional studies have supported these results. A recent publication out of Germany demonstrated that mortality was significantly increased in frail patients undergoing TAVR compared to non-frail patients (in-hospital mortality, 5.5 vs. 1.3 %, $p=0.04$, and 1 month mortality, 17 vs. 5.8 %, $p=0.002$, respectively).

Another very recent study evaluating the Medtronic CoreValve® system sought to understand which patients undergoing TAVR were least likely to benefit. The trial showed an overall improvement in quality of life and subjective symptoms after TAVR; however, a significant proportion of the enrolled cohort (39 %) did not experience benefit. Two factors were predictive of lack symptomatic improvement with TAVR: wheelchair-bound status (odds ratio 2.6, 95 % confidence interval 1.3–5.2) and serum albumin <3.3 g/dl (odds ratio 1.8, 95 % confidence interval 0.9–3.5) [21].

Case IV

An 86-year-old man with multiple comorbidities presents with progressively worsening chest pain and a high-risk pharmacologic nuclear stress test. In discussions with the patient and his family, the decision is made to proceed with diagnostic coronary angiography. How could a pre-procedural diagnosis of frailty predict findings on coronary catheterization and outcomes after a potential intervention?

Frailty-Associated Risk of CAD and HF

Studies assessing the association of frailty with CAD have not only shown poor outcomes and higher mortality in the frail but have also been predictive of the extent of CAD seen on angiography. The Established Populations for Epidemiologic Studies of the Elderly trial demonstrated that impaired mobility alone significantly correlated with CAD-related mortality (adjusted relative risk, 1.9; 95 % confidence interval 1.4–2.4) [22]. Gharacholou et al. evaluated the prevalence and degree of CAD in 629 patients greater than 65 years of age undergoing cardiac catheterization using the Fried criteria. Frailty was seen in 19 % of the studied cohort and was independently associated with increased frequency of left main CAD and/or multi-vessel CAD after adjustment (74 vs. 60 %, $p<0.05$) but was not associated with a significant increase in cardiac catheterization-related complications [23]. A third study by Ekerstad et al. evaluated short-term mortality after non-ST elevation myocardial infarction and found that frailty was associated with a significantly increased adjusted mortality at 1 month (odds ratio 4.7, 95 % confidence interval 1.7–13.0) [24].

Studies in HF, unsurprisingly, have also demonstrated the connection between frailty and adverse outcomes [5•, 25]. An Italian study screened patients for frailty prior to hospital discharge for HF exacerbation. After adjustment, higher frailty scores were significantly

associated with increased risk of death in a graded manner across quartiles of frailty score (based on the Short Physical Performance Battery Scale frailty assessment) [26]. Moreover, frailty has also been shown to be a risk factor for developing HF over time. The Health ABC study published in 2013 showed a significantly increased probability of developing HF over an 11-year follow-up in patients who were diagnosed with frailty (moderate frailty: hazard ratio 1.36, 95 % confidence interval 1.08–1.71, and severe frailty: hazard ratio 1.88, 95 % confidence interval 1.02–3.47) [27•].

Conclusions

Frailty is a powerful risk marker that can predict increased morbidity, mortality, and loss of functional status across the spectrum of cardiovascular diagnoses. Despite this knowledge, frailty is frequently overlooked and is rarely objectively measured in day-to-day clinical practice. Also, frailty has not yet been integrated into the major cardiac risk evaluation tools. For example, the Society of Thoracic Surgeons (STS) score, commonly used for risk assessment in TAVR and surgical aortic valve replacement (SAVR), has not incorporated frailty risk markers. The STS study group has recognized this shortcoming and is now collecting 5-m walk speed data for potential addition to the risk model.

Several studies are underway to answer important outstanding questions regarding the role of frailty in cardiac risk assessment [28] (Table 2). The question of which frailty assessment tools best predict outcomes in patients undergoing TAVR and SAVR will be addressed by the FRAILTY-AVR study (NCT01845207). The ongoing SILVER-AMI trial (NCT01755052) will further evaluate frailty-associated outcomes in older persons with acute myocardial infarction (AMI). This SILVER-AMI study will create a risk model to assist clinicians and their patients in decision-making following AMI. The study is expected to be completed in 2016 and will substantially add to our understanding of outcomes in the elderly with AMI.

Risk prognostication in frail, older patients poses a significant challenge, particularly when facing decisions regarding the use of invasive procedures. Frailty is a valuable risk marker associated with worse outcomes in patients with HF, CAD, and aortic stenosis. Incorporating the currently available frailty studies and soon-to be published trials into cardiac risk assessments will help improve shared decision-making between physicians and their aging patients.

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Abbreviations

AMI	Acute myocardial infarction
CVD	Cardiovascular disease
CAD	Coronary artery disease

HF	Heart failure
SAVR	Surgical aortic valve replacement
STS	Society thoracic surgeons
TAVR	Transcatheter aortic valve replacement

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Table 1

Components of the most commonly utilized frailty assessment tools

Scale	Component	Frailty scoring cut-off
Fried scale		Each item is scored 0 or 1. Frailty is defined as 3 of 5
	5-m gait speed	Slow is >6 s
	Handgrip strength	<30 kg in men <20 kg in women
	Weight loss	>10 lbs in past year (self-reported) or albumin <3.3 g/dl
	Physical activity questionnaire (commonly used is Minnesota Leisure Time Activities Questionnaire)	Convert weekly activities to kilocalories <383 kcal/week in men <270 kcal/week in women
Short physical performance battery	Exhaustion: commonly measured with the CES-D or anergia questionnaire	For CES-D, 2 questions: considered positive if answer is "yes" to either question
	Chair rise	Scored 0–4 based on time to stand up 5 times quickly
	5-m gait speed	See above
	Balance	Scored 0–4 based on balance

CES-D Center for Epidemiologic Studies Depression Scale

Table 2Important ongoing frailty studies (clinicaltrials.gov)

Planned completion date	Primary investigator	Trial name	Study variables/outcomes evaluated
Presented ACC Conference March 2015	Albertson, P	Over Eighty Study	Patients with NSTEMI: coronary angiography with PCI vs. medical management
December 2015	Afilalo, J	FRAILTY-AVR	Evaluate frailty tools in patients undergoing SAVR/TAVR
January 2016	Campo, G	FRASER	Handgrip strength and SPPB effect on mortality in patients >70 admitted to the hospital
March 2016	Maciej, K	FRAILTY	Response to CRT in frail patients
June 2016	Chaudry, S	SILVER-AMI	Outcomes in patients >75 with acute MI
October 2017	Belman, J	Eva-G-TAVI	Assessment of functional independence after TAVR
December 2018	Mejia, O	FRAGILE	On-pump vs. off-pump CABG in frail patients

ACC American College of Cardiology, *NSTEMI* non-ST segment myocardial infarction, *PCI* percutaneous coronary intervention, *SAVR* surgical aortic valve replacement, *TAVR* transcatheter aortic valve replacement, *SPPB* short physical performance battery, *CRT* cardiac resynchronization therapy, *AMI* acute myocardial infarction, *CABG* coronary artery bypass grafting