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Perioperative Frailty

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Introduction

Elderly patients comprise over 40% of all surgical patients in the United States per year and generate a very large proportion of healthcare costs ^{1–3}. Studies suggest that frailty, a health condition which predisposes an individual to worsening health status and death, is common in elderly patients prior to surgery^{45–7}. For a frail patient relatively minor stressors (e.g. UTI, minor surgery) may result in major consequences such as increased dependence on caregivers, need for nursing care, and predisposition to falls and delirium⁸. Therefore frailty is a condition which affects a large proportion of all surgical patients and is a major health concern in the perioperative arena.

The risk of anesthesia related complications and death is significantly elevated in patients over the age of 55–64 and highest in patients over 85 years old ⁹. The concept of frailty transcends comorbidity alone to include strength, function, and cognition, and in many types of surgery predicts postoperative complications better than traditional risk scores ^{10–12}. Because of the large magnitude of the elderly surgical population and their propensity toward complications, the idea that a clinical entity could be prospectively identified and targeted for treatment is very attractive.

In this chapter we discuss frailty in the surgical patient, and the underlying pathophysiology. We review methods of identification, and provide evidence that assessment and treatment of frailty is of emerging importance. While there is a growing body of frailty literature specific to the perioperative setting, much of our knowledge is derived from geriatric community-based research. Throughout the chapter, we will therefore indicate where we are extrapolating from medical literature. Finally, we will discuss future directions for research including biomarkers to identify patients and treatments including pharmacologic, physical conditioning and multimodal therapy.

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Defining Frailty

Frailty can be defined as a physical condition, a psychological condition, or both. Historically, there was some disagreement regarding whether frailty was a single syndrome consisting of a combination of fatigue, weight loss, low activity, social withdrawal, cognitive change and vulnerability to stressors or multiple entities which have similar “clusters” of traits (e.g. weight loss and weakness)^{13–17}. Despite this, a 2012 consensus conference defined frailty as an important and potentially treatable medical syndrome. Additionally, the consensus committee recommended frailty screening for all patients over the age of 70 as well as any individual with chronic disease or weight loss⁴.

In general, the concept of frailty transcends weakness and sarcopenia alone, and does not per-se classify all disabled patients as frail^{18–20}. The diagnosis of frailty is one conferred by a geriatrician after a formal evaluation, however some simple screening tools are available to recognize frailty which are amenable to use by other practitioners. An example would be the FRAIL screening tool which asks 5 simple questions based on items from the Medical Outcomes Study 36-item Short Form Survey (SF-36)^{21,22}:

Fatigue – Are you fatigued?

Resistance- Do you have difficulty walking up one flight of steps?

Aerobic- Are you unable to walk at least one block?

Illness: Do you have more than 5 illnesses?

Loss of weight: Have you lost more than 5 percent of your weight in the last 6 months?

The two major formal approaches to classifying a patient as frail are the Frailty Index and Fried et al’s Frailty Phenotype. The Frailty Index considers frailty to be a state of “accumulated deficits,” and multiple comorbidities and disabilities are added together to determine an individual’s overall frailty score. In contrast, the frailty phenotype operationalizes functional impairment in 5 domains: reduced activity, slowness, weakness, exhaustion, and weight loss^{16,23}. Both scales discriminated between non-frail, pre-frail, and frail. Many other definitions and manners of assessment have evolved, most based on one of the two aforementioned approaches²⁴ (Table 1).

The Frailty index was created from a 5 year prospective cohort study of greater than 10,000 elderly patients in Canada²⁵. 92 signs, symptoms, lab values, diseases, and disabilities were scored to define frailty. The index is calculated as the presence or absence of each over the total number possible, which creates a continuous variable where patients with higher scores are more likely to be frail. The ten year adjusted hazard ratio for mortality was 1.57 for the frail group (CI 1.41–1.74), i.e. death is more likely for frail patients over time. While this scale was well validated, it was also found to be somewhat unwieldy, and a smaller subset of characteristics was also found to be predictive (30)⁸. Much of the retrospective surgical literature regarding frailty has used an 11- item modified version of the Frailty Index (mFI)

which uses routine predictors collected for the National Surgical Quality Improvement Program^{26,27,28}.

The phenotype model described by Fried et al was created from a secondary analysis of data obtained from the Cardiovascular Health Study. This involved more than 5200 men and women over the age of 65 and used 5 variables for classification: weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. Frailty was defined as having 3/5 characteristics and pre-frailty as 1–2 characteristics. The incidence of frailty in the original cohort was 7% and pre-frailty was 47%; mortality for these groups was 43% and 23% respectively compared to 12% for the robust group. For the frail group the hazard ratio of mortality over 7 years was 1.63 (1.27–2.08) which is relatively consistent with the Frailty Index. Another phenotype model by Robinson et al combined these characteristics with lab values and created a composite index based on comorbidity, function, cognition, a history of falls, presence of anemia, and low serum albumin²⁹.

Additionally, multiple studies have attempted to use single measures as a surrogate for a frailty assessment. These include gait speed, grip strength, walking speed, and a history of falls^{30–34}. Single measures have been shown to predict morbidity and mortality. For example the “Timed Up and Go Test”, a gait speed measure, had an AUC of .775 for predicting 1 year complications and mortality in colorectal patients⁷. Similarly, patients with a history of falls within 6 months prior to surgery were shown to be more than ten times more likely to experience postoperative complications.³⁴

The Prevalence of Frailty

A recent systematic review by Collard et al described the weighted average prevalence of frailty in community dwelling elderly as 9.9% (CI 9.6–10.2) and 44.2% (44.2–44.7) for pre-frailty³⁵. Frailty was generally more prevalent in women and increased with age. Elderly patients undergoing surgery generally have been found to have a higher prevalence of frailty (25–56 %) ^{5,29,36}. Notably most studies were performed in white patients in Canada and the United States, and therefore frailty scores may have limited external validity (cutoff values, incidence, hazard ratios) for Hispanic and/or African-American people. Interestingly, the simple FRAIL screening tool was shown to predict outcomes in African-Americans²².

Frailty and the risk of surgery

The basic tenet of frailty is that it confers vulnerability to stress, and the perioperative period is a time of physiologic (especially inflammatory) and psychological stress. The prospective and retrospective surgical literature has used the construct of frailty defined as a single measure or composite score to assess risk for death and postoperative complications in a variety of surgeries (Table 2).

A recent review of the cardiac and thoracic surgery literature and frailty found that overall there are 9 studies as of 2013 which demonstrated the connection of preoperative frailty with poor outcomes³⁷. However, only 4 of the 9 studies found that the addition of frailty measures increased predictive ability in comparison to other cardiac or thoracic risk indices. In general, single measures were less helpful than studies which added multiple frailty

predictors. For example, the single measure of gait speed did not seem to increase prediction of mortality or major morbidity compared to the routine Society of Thoracic Surgeons risk calculator. However, adding additional functional impairments did increase the ability to predict in-hospital morbidity and mortality³¹. Lee et al found that patients who were classified as frail by the presence of need for assistance with ambulation or activities of daily living (ADL), and presence of dementia had a higher risk of in-hospital mortality (OR 1.8, 95% CI 1.1–3.0) and mortality at 2 years (HR 1.5, 95% CI 1.1–2.2)³⁸. Sunderman et al found that comprehensive frailty assessment in patients undergoing cardiac surgery did predict 3-day mortality (AUC 0.71) but did not out predict other cardiac risk calculators³⁹. There are also studies which suggest that frailty markers may have predictive value for patients undergoing traditional and percutaneous aortic valve replacement^{40,41,42}.

In a combined colorectal and cardiac surgical population, Robinson et al showed that a frailty index consisting of gait speed, comorbidity, cognition, a history of falls, and the presence of anemia and low albumin predicted longer hospital stays and higher readmission rates.²⁹ Frailty markers, especially functional dependence and gait speed, were able to predict the need for postoperative institutionalization⁴³. In another study, gait speed alone was associated with 1-year mortality and major morbidity⁷. Preoperative frailty has been shown to predict prolonged hospital stays and postoperative complications in elderly patients after elective cholecystectomy³⁶. In surgical oncology patients undergoing pancreaticoduodenectomy, frailty predicts postoperative complications, institutionalization, and 30 day readmission rates⁴⁴.

The surgical subspecialties of urology, otolaryngology, and orthopedics have also produced prospective and retrospective studies on frailty and postoperative outcomes⁴⁵. In the case of otolaryngology, the modified frailty index (mFI) was able to predict postoperative complications and death. Patel et al showed that the mFI could predict mortality at 1 and two years after femoral neck fracture^{46,47}. Preoperative frailty has been shown to increase the odds of postoperative delirium⁴⁸.

Pathophysiology of Frailty

The aging process is characterized by changes in almost all organ systems and is a combination of genetic and environmentally determined physiology and pathology^{14,49}. The state of frailty is a rapid decline of several systems and is the result of a synchronous decline which reaches a critical threshold of deterioration^{15,50}. Indeed the likelihood of frailty increases with the number of abnormal organ systems more than the amount of abnormality in a single organ system¹⁵. Homeostatic reserve is limited in the elderly, and the rapid change associated with the frail state is a risk factor for perioperative complications and mortality¹⁴.

The pathophysiology of frailty continues to be elucidated, and two major areas are the role of a pro-inflammatory state and the link between inflammation and endocrine systems⁵¹. Aging is associated with changes in the immune system including immunosenescence characterized by an altered distribution of cytokine secreting T-cells and higher levels of cytokines secreted by adipose tissue^{52,53}. Elevated markers of inflammation including IL-6,

TNF- α , and CRP have found in frailty populations and are associated with the stigmata of frailty. For example, IL-6 has been associated with the development of sarcopenia, anemia, and insulin resistance^{54–56}. Increased levels of TNF- α is associated with a decrease in muscle mass over a period of 5 years in patients greater than 70 years old⁵⁷. The pattern of immune system alteration in frailty has a specific phenotype; for example high neutrophil and monocyte counts have been found in frail community dwelling elderly but not eosinophils or lymphocytosis⁵⁸.

In terms of the relationship between frailty, inflammation, and endocrine dysregulation, age related decreases in IGF-1, dehydroepiandrosterone (DHEAS), and gonadal steroids (testosterone and estradiol) have been associated with a decline in anabolic metabolism and leukocyte function⁵⁹. The interaction of endocrine and immune systems is further supported by the inverse relationship between IGF-1 and IL-6 in frail patients, not seen in the healthy elderly⁶⁰. Baylis et al demonstrated that elevated cortisol:DHEAS ratios were significantly correlated with frailty in a 10-year prospective study⁵⁰. Consistent with the overall concept of multisystem dysregulation, a study of elderly women showed that women with greater than one relative deficiency of DHEAS, IGF-1, and testosterone were associated with frailty, but a single deficiency was not⁵⁹.

The etiologic relationship of low vitamin D to frailty has been strongly suggested⁶¹. Vitamin D deficiency is common in the elderly, because of less exposure to sun and a relative inefficiency of vitamin D synthesis and metabolism. In the elderly, low vitamin D levels independently predict mortality^{62,63}. The mechanism behind the association has been postulated from a variety of human and animal studies as the following: low vitamin D is associated with high parathyroid hormone levels which result in a high level of the active metabolite of 1,25 D which has been shown to increase muscle metabolic activity, influence strength and contraction, and regulate protein synthesis^{64–66}. In humans this pathway may translate to sarcopenia, weakness, or the fatigue associated with frailty.

While some of the pro-inflammatory state and altered immunity is part of normal aging, basic science research continues to try and elucidate the triggers of the cellular cascade which predisposes a patient to frailty. One mechanism is the NF- κ B mediated pathway of transcription of biomediators and immune regulation⁶⁷. Another is the role of oxidative stress which may be particularly relevant in the perioperative period where patients are exposed to high concentrations of reactive oxygen species⁶⁸. Reactive oxygen species may alter protein expression, induce DNA damage, and have been associated with many conditions including Alzheimer's Disease and cancer. Metabolomics is the study of low molecular weight substances found in biological samples, and has been used to understand aging and frailty via its metabolic footprint. A recent study identified 163 metabolites which correlate with age⁴⁹.

Treatment of Frailty

Frailty is a dynamic condition which may worsen or improve in an individual, and has been shown to be amenable to treatment in medical and community dwelling elderly patients. Without intervention it is much more likely to transition to a state of worsening frailty than

to improve to lesser states of frailty or to non-frail states⁶⁹. To date, there are no studies which have examined interventions targeted toward preventing and treating frailty in the surgical population. The studies we will describe are from the general medical and community literature where three overlapping areas of treatment have emerged: physical exercise/rehabilitation, pharmacologic therapy, and multidisciplinary interventions.

Studies of geriatric medical patients suggest that exercise training can improve frailty and functional outcomes in frail individuals. A recent metaanalysis of 18 studies published in 2012 showed that patients who participated in exercise programs (vs. no exercise) had improved mobility and physical function⁷⁰. Overall, patients did not report increased physical activity or improved quality of life but this outcome was only measured in a small proportion of the studies. In general, high intensity exercise seemed to be most effective, and ideal duration of the exercise program was not well investigated but programs of longer duration and 3× week 30–45 minutes/session tended to have better outcomes⁷¹. A second metaanalysis in 2013 found that exercise improves gait speed and physical performance but did not find consistent improvement in balance and ADL⁷².

The role of pharmaceuticals to prevent or modify frailty is less clear⁷³. Some of the pharmaceutical trials to improve frailty attempt to address the loss of muscle mass and function. Angiotensin converting enzyme (ACE) -inhibitors are one class of drug which has been studied because of the relationship between low levels of ACE and better endurance training in young people⁷⁴. A cohort study from the Women's Health Initiative Observational Study found no difference in the incidence of frailty between women who took ACE-Inhibitors and those who did not⁷⁵. A prospective randomized study of ACE inhibitors vs. placebo in patients with limited mobility or functional impairment suggested that 6 minute walk time was improved after 20 weeks of treatment⁷⁶. However, a subsequent study which randomized patients to ACE inhibitor plus exercise or exercise alone found that ACE inhibitors did not confer an additional benefit⁷⁷. The use of growth hormone and testosterone has also been studied. A large retrospective study using the Third National Health and Nutrition Examination Survey (NHANES III) found that low free testosterone and high sex-hormone-binding-globulin (SHBG) was associated with almost 3 times the odds of frailty. However, the authors expressed concern regarding the potential of confounding influence of obesity, smoking and the higher prevalence of cardiovascular disease- i.e. low SHBG as the result of obesity and smoking and not the cause of frailty⁷⁸. The safety and effectiveness of testosterone replacement for improvement of muscle mass or symptoms of frailty has not been established. Overall, the literature suggests that testosterone and DHEAS generally are not beneficial; however there are some preliminary small studies which suggest that certain subsets of patients (hypogonadal hyperglycemic older men) may show some improvement of symptoms.⁷⁹ A systematic review of the effect of daily Vitamin D supplements (800–1000U/day) showed benefits in terms of gait (Time to Up and Go) and posture⁸⁰. Studies have been mixed regarding the efficacy of Vitamin D to prevent falls and fractures. One large trial of over 2000 patients actually found an increased risk of falls and fractures in patients randomized to receive a single yearly large oral dose of 500,000 IU⁸¹.

The Program of All Inclusive Care (PACE) is an example of a community multimodal program designed to generally improve the health and outcomes of elderly community dwelling patients⁸². These community based programs began in the 1970s in California and offer medical services, rehabilitation, and social services to frail chronically ill older adults. Multiple foundations including the John Hartford Foundation, Robert Wood Johnson and Medicare and Medicaid have supported these centers which exist across the United States. Participation in the PACE program has been shown to confer survival advantage in black participants, reduce admissions due to unmet ADL needs, and decrease admissions to a nursing homes for patients without an informal care giver (e.g. family, spouse)⁸³. While there has been some variation in success between PACE centers, some have improved patients mortality and functional status⁸⁴. To date, there are no studies which examine PACE program participants and postsurgical outcomes.

The Acute Care for Elders Program (ACE) is an in-hospital multimodal geriatric care approach for elderly medical patients. The ACE team consists of a nurse coordinator, geriatrician, nurses, physical and occupational therapists, dietician, pharmacist and social workers who work together to improve patient care. The ACE⁸⁵ team model has been shown to improve outcomes in the elderly and decrease costs. Other programs have used specially prepared environments designed to prevent falls, and increase orientation, and provide rehabilitation and prevent polypharmacy and have successfully reduced the number of patients who required long term nursing care placement after hospitalization⁸⁶. However, these programs were not designed to examine outcomes in frail surgical patients.

Conclusion

In conclusion, the medical literature has clearly established that frailty is a prevalent, morbid, and treatable condition of the elderly. Frailty is even more commonplace in elderly surgical patients and correlates with postoperative complications and mortality across surgery types. Surgery represents a time of stress and inflammation which may trigger a cascade of events which causes an elderly patient to transition to a worse state of frailty. Treatment for frailty has largely been studied in medical and community dwelling elderly and consists of physical rehabilitation, modest effects from pharmaceutical treatment, and community based and in-hospital multidisciplinary care. While the surgical and anesthesia literature has identified frailty as a risk factor for death and mortality, studies lack that examine the identification of frailty for risk stratification or the treatment of frailty to prevent complications. In the future, there is a need for studies in elderly surgical patients to reach across disciplines and identify frailty prior to surgery for the purpose of treatment and amelioration of risk. Adapting frailty screening and treatment for the perioperative patient will require significant effort in terms of assessments and partnering with non-surgical physicians and nonphysician providers. There is substantial evidence that these efforts are likely to be successful, cost effective, and in the best interest of patients.

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Table 1**Frailty Assessment Tools and Scoring Systems**

Frailty Measure	Description	Clinical Outcome	Source
Frailty Phenotype	Weight loss, grip strength, exhaustion, low physical activity, 15 ft. walking speed	30d postoperative complications, institutionalization, length of stay	Fried et al.
Frailty Index/Deficit Accumulation	30 to 70 measures of comorbidity, function plus, physical exam	Mortality, institutionalization	Rockwood et al.
Modified Frailty Index	History of diabetes; COPD or pneumonia; congestive heart failure; myocardial infarction; angina/PCI; hypertension requiring medication; peripheral vascular disease; dementia; TIA or CVA; CVA with neurological deficit; ADL	30d, 1yr and 2yr mortality, 30d major postoperative complications	Adams et al., Karam et al., Patel et al., Tsiouris et al., Velanovich et al.
Gait Speed	5 meter gait 6secs	Mortality, major postoperative complications, institutionalization, length of stay	Afilalo et al.
Timed Up and Go (TUG)	TUG 10secs, 11-14secs, 15secs	1yr mortality	Robinson et al.
Falls	6-mo history of falls	30d major postoperative complications, institutionalization, 30d readmission	Jones et al.
Robinson Score	Katz Score, Mini Cog, Charlson Index, Anemia <35%, Albumin <3.4, hx of falls	30d major postoperative complications, length of stay, 30d readmission, 6mo postoperative mortality	Robinson et al.

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Notes: ADL (activities of daily living), COPD (chronic obstructive pulmonary disease), CVA (cerebrovascular accident), PCI (percutaneous coronary intervention), TIA (transient ischemic attack), Cog (Cognition), d(day), mo(month), yr(year)

Table 2

Examples of recent frailty and outcomes studies in surgical patients

Surgery	Study Design	Frailty Measure	Clinical Outcome	Source
Cardiac (CABG)	Multicenter prospective	5-meter gait speed	Slow gait increased the risk of 30 day mortality, LOS, institutionalization, and 30 day mortality	Afilalo 2010 J Am Coll Cardiol
Cardiac (CABG)	Multicenter prospective	5-meter gait speed and Nagi disability scale	Frailty plus the Nagi disability scale increased the predictive power of cardiac risk scores for morbidity and mortality (AUC .76 vs. AUC .72)	Afilalo 2012 Circ Cardiovasc Qual Outcomes
Elective Cardiac Surgery	Single center retrospective	ADL, gait, or diagnosis of dementia	Impairment in any three measures predicted postoperative institutionalization and mortality	Lee 2010 Circulation
Elective Cardiac Surgery	Single center prospective	Gait speed, handgrip, IADL, balance, ability to rise from a chair, pick up an object, FEV1, serum albumin, creatinine, BNP	30 day mortality as predicted by frailty correlated well with established cardiac risk scores (EuroSCORE and STS)	Sundermann 2011 Eur J Cardiothorac Surg
Aortic Valve Replacement	Secondary analysis of a prospective multicenter study	Six-Minute Walk Test	Frequency of 1 year mortality, myocardial infarction, and stroke was higher in patients who walked <300m (23.8% vs. 4.7%)	de Arenaza 2010 Heart, Global
TAVI	Single center prospective	Mini-Mental State Exam, gait speed, functional measures	Frailty associated with 8x risk of 30 day mortality, and 3.5x risk of 1 year mortality	Stortecky 2011 J Am Coll Cardiol Interv
Percutaneous Valve Replacement	Single center prospective	Serum albumin, gait speed, handgrip, function (ADLs and IADLs)	Frailty predicted increased LOS and 1 year mortality. No difference in the rate of 30 day postoperative complication	Green 2012 JACC
Colorectal and Cardiac Surgery Patients	Single center prospective	Robinson Index	Frailty, slower Up and Go, and functional dependence predicted institutionalization	Robinson 2011 J Am Coll Surg
Colorectal and Cardiac Surgery Patients	Single center prospective	Timed Up and Go	Slower Timed Up and Go predicted increased postoperative complications and 1-year mortality	Robinson 2013 Ann Surg

Surgery	Study Design	Frailty Measure	Clinical Outcome	Source
Elective CCY	Single center prospective	Comprehensive Geriatric Assessment	Frail patients had a higher incidence of postoperative complications and a higher frequency of hospital stay >2 days	Lasthiotakis 2013
Colorectal and Cardiac Surgery Patients	Single center prospective	Robinson Index	Frailty associated with increased LOS and readmission. Predicted postoperative complication (AUC >.7)	Robinson 2013 Am J Surg
Urology	Single center retrospective	Braden Scale and Deficit Accumulation index	The Braden Scale, but not the Deficit Accumulation Index, predicted 30 day postoperative complications	Cohen et al 2012
Otolaryngology	Single center retrospective	mFI	Higher mFI scores were associated with increased 1 and 2 year mortality rates	Patel et al 2013
Femoral Neck Fracture	Retrospective cohort study (NSQIP data)	mFI	Higher mFI scores were associated with increased morbidity and mortality	Adams et al 2013

Abbreviations: ADL = Activities of Daily Living; CCY = Cholecystectomy; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IADL=Instrumental Activities of Daily Living; LOS = Length of Stay; mFI = Modified Frailty Index; NSQIP = National Surgical Quality Improvement Program; STS = Society of Thoracic Surgeons; TAVI = Transcatheter Aortic Valve Implantation;

Table 3**Biomarkers of Frailty**

Dihydroepiandrosterone (DHEAS)
Elevated White Blood Cell Counts
C-reactive protein
IL-6
C-glycosyl tryptophan
Vitamin D